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Allogenic hematopoietic cell transplant in hematological malignancies: controversies and perspective

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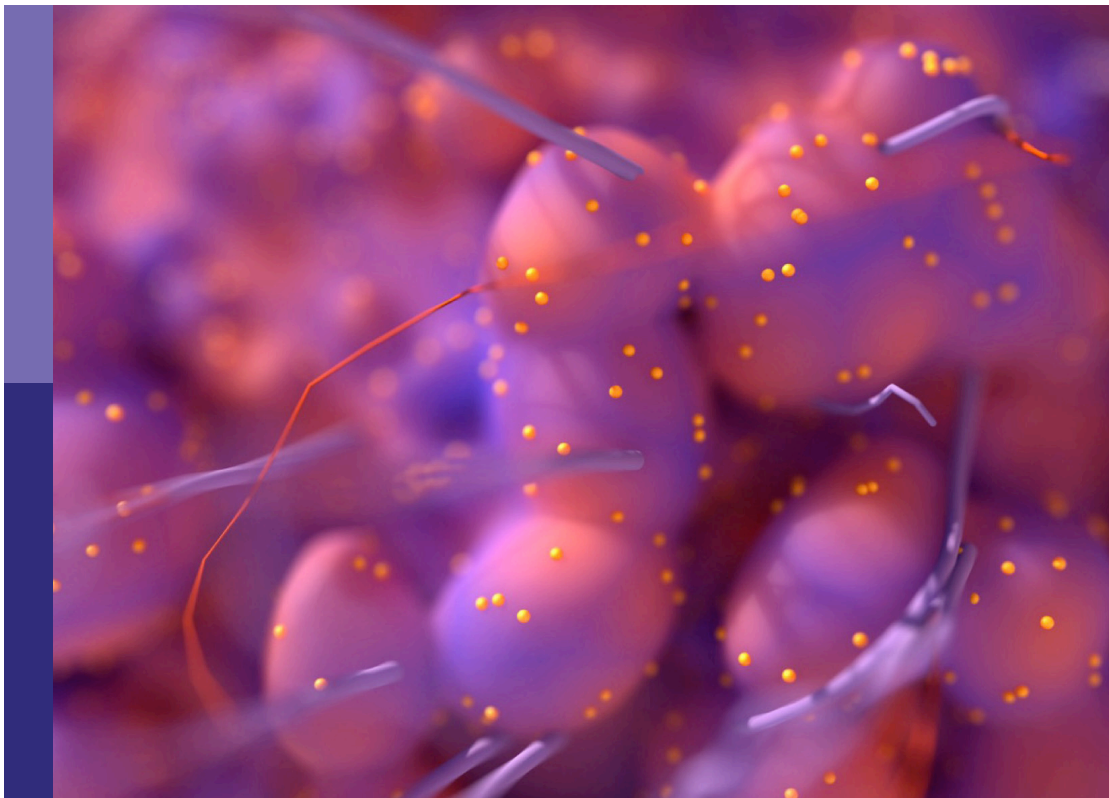

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Allogenic hematopoietic cell transplant in hematological malignancies: controversies and perspective

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Table of contents

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Editorial: Allogenic hematopoietic cell transplant in hematological malignancies: controversies and perspective

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Editorial on the Research Topic
Allogenic hematopoietic cell transplant in hematological malignancies: controversies and perspective

The Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) represents the unique chance of cure for patients affected by some hematologic malignancies and in particular for acute leukemias, myelodysplasia (MDS) and myelofibrosis. Several unmet needs are still on the table and are object of research.

First, transplant indications. The novel classification of acute leukemias, derived from a refinement of the knowledge of the bio-molecular patterns underlining the hematologic neoplasms, allowed a more precise risk-stratification (1, 2). Based on such stratification expert panels have identified high risk-categories for which the transplant approach in the front-line setting is mandatory (3). By converse for low and intermediate risk-categories the HSCT in 1st complete remission is more controversial and evaluation of minimal residual disease (MRD) in this setting plays a crucial role (4, 5).

Also for myelofibrosis and MDS the improvements in knowledge of the pathogenetic patterns refined the prognosis and the transplant's indications (6, 7). For multiple myeloma and lymphoma, given the advent of the bi-specific antibodies and CAR-T, the perspective of HSCT has become increasingly distant and remains confined to settings such as plasma cell leukemia, relapsed/refractory Hodgkin lymphoma and some T-cell non-Hodgkin lymphomas.

Second, If by one hand, HSCT can cure a relevant proportion of patients, for about half of the transplanted patients relapse of the hematological disease and treatment-related mortality are the main causes of transplant-failure.

In the last two decades significant improvements in conditioning regimens, graft-versus host disease (GVHD) prophylaxis, management of infections and maintenance therapies have increased the opportunity to perform transplantation for an even greater number of patients by reducing transplant-related mortality (TRM) and by preventing relapse.

The introduction of the novel reduced-toxicity conditionings (8, 9) and novel GVHD-prophylaxis regimens (10–12) contributed to reduce the TRM and to extend the transplant to an increasingly large population both in terms of age, co-morbidities and absence of an HLA fully-matched donor.

The introduction of the busulfan-fludarabine regimens (8) and of treosulfan (9) have reduced the impact of the conditioning on non-hematological toxicity and extended the HSCT up to 70 years-old patients or higher. Furthermore, different combinations of alkylating drugs and dosages generates a series of reduced-intensity conditionings (RIC). The RIC regimens, if by one hand are associated with lower TRM, on the other hand correlate with a greater risk of relapse (13) and experts recommend their use in an individualized approach that takes into account age, fitness and relapse-risk (14).

The application of the T-cell-replete HSCT based on the use of post-HSCT cyclophosphamide (PTCy) has made possible to extend the haploidentical transplantation in favor of a greater number of patients who lacks an HLA-compatible donor. Furthermore, also centers that do not perform expensive *ex vivo* T-depletion may perform such procedure.

Nowadays, the results of the T-replete transplantation with PTCy from haploidentical donors are comparable with those of HSCT from unrelated and related HLA-matched donors (10–12). PTCy has been proposed as a novel GVHD-Prophylaxis regimen also for transplants from HLA-compatible donors as an alternative to antithymocyte globuline (ATG) or anti-T- lymphocyte globulin (ATLG) that, together with calcineurin-Inhibitors and methotrexate, have been for years a cornerstone of GVHD-prophylaxis (15).

In patients with donor-specific anti-HLA antibodies strategies to overcome the donor-sensitization by combining immunosuppressive therapy and plasma-exchange allowed to achieve engraftment also in such challenging situation (16).

The scenario of the pre-remissional treatment has been enriched with novel targeted drugs such as hypomethylating agents and venetoclax that have made possible for elderly patient (> 60 years old) unfit for intensive chemotherapy, to achieve complete remission and HSCT (17). Other classes of targeted drugs, such as tyrosine-kinase inhibitors and blinatumomab have increased the number of patients who reach a deeper remission before transplantation (18–21).

At the same time the introduction of the targeted therapies improved the transplant outcome when applied as post-transplant maintenance and by synergizing with the Graft Versus Leukemia effect (22–27).

The GVHD, historically considered an "orphan disease", in the past ten years has been the subject of clinical trials that led to the approval of new agents such as ruxolitinib (FDA and EMA-approved for acute and chronic steroid-refractory GVHD) (28–29), ibrutinib (30) and belumosudil (31) (FDA-approved as second and third-line for chronic GVHD, respectively).

As regard to acute GVHD-prophylaxis, recently new drugs have undergone to investigation: vedolizumab (32), abatacept (33), fecal transplantation (34), begelomab (35), α1 antitrypsin (AAT) (36). A phase 2/3 study is evaluating the AAT as prophylaxis of acute GVHD (NCT03805789).

In regard of chronic GVHD, axatilimab, a CSF-R inhibitor, is under investigation in steroid-refractory chronic GVHD alone or in combination with Extracorporeal Photopheresis (NCT06821542, NCT06663722) following the promising results of a phase 1/2 study (37). Other studies are ongoing to investigate axatilimab as first line therapy in combination with other agents (steroids or ruxolitinib) (NCT06388564, NCT06585774).

Another line of research focuses on the use of anti-GVHD cellular therapies and the potential target represented by the T-regulatory lymphocytes (38).

Moreover, growing evidence supports the contribution of loss of the gut microbiome diversity and of the endothelial dysfunction to transplant morbidity, justifying studies aimed at developing novel therapies in these fields of application (39, 40).

The transplantation is the platform on which to add strategies aimed at preventing relapse. Novel studies evaluated the employment of post-transplant immunotherapy. Such interventions may be represented by conventional T-cells (prophylactic or pre-emptive DLI) (41), by selected subsets of T-cells (such as CD45RA-) (42) or by modified effector cells (either NK cells or T-cells redirected against leukemia antigens) (43). Results of these studies although promising, require further research.

Based on these assumptions we propose a Research Topic dedicated to HSCT. The purposes of the research-topic are:

providing transplant-physicians and hematologists with a description of the current "state of the art" in some particular settings such as HSCT from alternative donors, transplantation in multiple myeloma and primary myelofibrosis.

Furnishing experience about some topics such as transplantation from AB0- mismatched donors, impact of donor-parity on outcome of HSCT, transplantation in patients with immunological sensitization against the donor, post-transplant maintenance.

Specialists in the subjects selected and reviewed the Research Topics and we hope that it can be a valid tool to support the reader in improving the knowledge and the clinical practice.

Author contributions

SL: Writing – original draft, Writing – review & editing. SG: Writing – original draft, Writing – review & editing. JM: Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The outcome of acute leukemia patients with SET-NUP214 fusion after allogeneic stem cell transplantation

Yuyan Shen[1,2], Donglin Yang[1,2], Rongli Zhang[1,2], Xin Chen[1,2], Qiaoling Ma[1,2], Jialin Wei[1,2], Weihua Zhai[1,2], Aiming Pang[1,2], Yi He[1,2], Erlie Jiang[1,2] and Sizhou Feng[1,2]*

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SET-NUP214 fusion gene, also known as TAF-1-CAN and SET-CAN, is observed in acute myeloid leukemia (AML) and T-cell lymphoblastic leukemia (T-ALL). SET-NUP214 fusion in T-cell lymphoblastic leukemia is associated with chemotherapy resistance, but the prognosis of patients with AML with SET-NUP214 has rarely been reported. In the present study, we retrospectively analyzed all patients with acute leukemia including AML and T-ALL patients with SET-NUP214 fusion who underwent allogeneic stem cell transplantation (alloHSCT) in our center from July 2017 to November 2022. Of the total 11 patients, 5 patients were diagnosed with AML and 6 patients were diagnosed with T-ALL *de novo*. All patients received myeloablative regimens in CR1, and there were three (60%) AML patients who relapsed post-alloHSCT and three T-ALL (50%) patients who relapsed post-alloHSCT. Only one patient with AML who relapsed post-alloHSCT responded to subsequent chemotherapy plus donor lymphocyte infusion and survived the last follow-up. The estimated 1-year overall survival and 3-year overall survival for all these 11 patients were 69.3% and 38.5%, respectively. The estimated 1-year leukemia-free survival and 3-year leukemia-free survival for all patients were 69.3% and 38.5%, respectively. The research shows a high incidence of relapse for patients with acute leukemia with the SET-NUP214 fusion gene, even after alloHSCT. More clinical trials or research with larger samples are urgently needed for this group of patients.

KEYWORDS

acute myeloid leukemia, acute T lymphoblastic leukemia, allogeneic stem cell transplanation, SET-CAN/NUP214 fusion, del(9q)

Introduction

The SET-NUP214 fusion gene, which results from either cryptic t(9;9)(q34;q34) or del(9)(q34.11q34.13), was first described in a patient with acute undifferentiated leukemia (1). Subsequently, several researchers reported that the fusion gene was also found in patients with acute myeloid leukemia (AML) and T-cell lymphoblastic leukemia (T-ALL) (2–4). SET-NUP214 fusion in patients with T-ALL is associated with corticosteroid/chemotherapy resistance but may respond to hematopoietic stem cell transplantation (HSCT) (5). The impact of SET-NUP214 fusion on patients with AML has rarely been reported. Due to the limited occurrence of SET-NUP214, with the reporting occurrence varying from 4.9 to 6% in T-ALL (5, 6), the outcome of acute leukemia patients with SET-NUP214 after hematopoietic stem cell transplantation has rarely been reported. In the present study, we retrospectively analyzed 11 acute leukemia patients with positive SET-NUP214 fusion gene who underwent allogeneic stem cell transplantation in our center from July 2017 to Nov 2022. These patients' prognoses were rather poor despite the utilization of myeloablative conditioning.

Methods

Patient characteristics

Between July 2017 and Nov 2022, 11 patients with acute leukemia presenting SET-NUP214 who underwent allogeneic stem cell transplantation (alloHSCT) were enrolled in this study. Patients had a median age of 29 years (ranging from 17-43 years) at transplant. Seven of the patients were men and four were women. Five patients were diagnosed with AML, and six patients were diagnosed with T-ALL de nova, according to the fifth edition of the WHO classification. Of the 11 patients, 6 achieved hematological complete remission after one cycle of induction chemotherapy. Only 1 of the 11 patients achieved molecular complete remission after one cycle of induction chemotherapy. The median cycle of chemotherapy to achieve CR1 was one (ranging from one to four). All the patients received a median of four cycles (ranging from three to six) of chemotherapy before alloHSCT. The median time from diagnosis to transplant was 6 months (ranging from 6 to 8 months). All the patients underwent alloHSCT in CR1, but only three patients achieved negative SET-NUP214 fusion gene before alloHSCT. One patient with T-ALL presented with central nervous system leukemia involvement before HSCT and was in remission at transplant. The details of the patients before alloHSCT are summarized in Tables 1, 2.

TABLE 1 Patient and transplant related characteristics.

Median patient age, years (range)	29(17-43)
Patient sex,n	
Male	7
Female	4
Diagnosis	
T-ALL	6
AML	
AML-M5	1
AML without maturation	3
AML not specified	1
Mean WBC count at diagnosis ($\times10^9$/L) (range)	
AML	16.42 (1.63-50.00)
T-ALL	55.96 (0.26-223)
Cycles of chemotherapy to achieve CR1	
1	5
>1	6
MRD at transplantation	
Y	8
N	3
From diagnosis to transplant, mo	
≤6	6
>6-12	5
Donor type,n,	
HLA-identical sibling	3
10/10 matched unrelated	2
Related haploidentical	6
Donor sex, n,	
Female	6
Male	5
Donor/patient sex	
Female/male	4
Other combinations	7
Chromosome Type *de novo*	
Normal	6
46,XX,del(5)(q31(q35),del13(q12q14)	1
46,XX,add(16)(p13)	1
N/A	3

N/A, Not Available; ALL, Acute Lymphoblastic Leukemia; AML, Acute Myeloid Leukemia; MRD, Minimal Residual Disease.

Transplant procedures

All 11 patients received myeloablative conditioning and allogeneic stem cell transplantation. The conditioning regimens for patients with AML were as follows: four patients with AML received conditioning regimens consisting of Busulfan (Bu, 3.2 mg/kg, days -9 to -7), Cyclophosphamide (Cy, 40 mg/kg, days -3 to -2), and Cytarabine(Ara-C, 2 g/m^2, days -6 to -4) or Idarubicin (IDA,

TABLE 2 Characteristics of patients at transplant and prognosis.

Patient No.	Sex/ Age (Y)	Diagnosis	White blood cell count *de novo* ($\times10^9$/L	Chromosome type *de novo*	Concurrent gene mutations	Donor type/ Donor Sex	Months from diagnosis to transplant	GVHD prophylaxis	Conditioning regimen	MNC ($\times10^8$/kg)	CD34 +cell ($\times10^6$/kg)	aGVHD	cGVHD	Relapse (days post transplant)	Follow-up (month)
1	F/37	AML	50	46,XX[20]	KRAS exon2 mutation, CCND3 exon5 mutation	Haplo/ M	7	Tacrolimus +MTX +MMF	Bu+Flu+IDA +Cy+ATG	12	2.28	N	Y	Y(281)	DOD (25.7)
2	M/ 34	AML	1.63	46,XY[20]	JAK3 exon 15 mutation,TP53 exon8 mutation	MSD/ M	8	CsA+MTX +MMF	Bu+Cy+Flu +Ara-C	18.98	6.83	Y(II)	N/A	Y(90)	DOD (10.8)
3	M/ 29	AML	N/A	N/A	JAK3 mutation,SH2B3 mutation,KDM6A mutation, PHF6 mutation	URD/ M	6	Tacrolimus +MTX +MMF	TBI+Cy+Flu +Ara-C+ATG	13	4.03	Y(II)	Y	Y(89)	Alive (10.5)
4	M/ 43	T-ALL	47.63	46,XY[5]	FLT3-ITD mutation,BIRC3 exon2 mutation,SUZ12 exon8 mutation,PHF6 exon6 mutation,ASXL2 exon12 mutation	MSD/F	6	Tacrolimus +MTX	TBI+Cy+Flu +Ara-C+ATG	10	2.9	N	N	Y(456)	DOD (17.8)
5	M/ 31	T-ALL	26	46,XY[20]	SETBP1 EXON4,CREBBP EXON 19,EZH2 EXON 18	MSD/F	6	Tacrolimus +MTX	TBI+Cy+Flu +Ara-C	8.41	4.12	Y(IV)	Y	Y(1436)	DOD (53.2)
6	F/30	T-ALL	9.74	46,XX[2]	N/A	URD/F	6	CsA+MTX +MMF	TBI+Cy+Flu +Ara-C+ATG	10.52	4.2	Y(I)	N	Y(42)	DOD (2.6)
7	M/ 25	AML	12.26	N/A	N/A	Haplo/ F	6	CsA+MTX +MMF	Bu+Clad+Ara-C+Cy+ATG	16.54	2.64	Y(I)	N	N	Alive (18.3)
8	M/ 23	AML	1.81	N/A	ETV6 mutation,PHF6 mutation,RUNX1 mutation	Haplo/ M	8	Tacrolimus +MTX +MMF	Bu+Flu+IDA +Cy+ATG	13.74	2.41	Y(III)	N	N	TRM (8.1)
9	F/20	T-ALL	12.2	46,XX,del(5)(q31q35),del 13 (q12q14)	N/A	Haplo/ M	7	Tacrolimus +MTX +MMF	TBI+VP16+Cy +ATG	8.27	2.65	N	N	N	Alive (24.1)
10	F/29	T-ALL	223	46,XX,add(16)(p13)[3]/46,XX[3]	JAK1 exon19 mutation, NOTCH1 exon26 mutation, JAK3 exon13 mutation	Haplo/ F	7	CsA+MTX +MMF	TBI+Cy+Flu +Ara-C+ATG	11.6	3.44	Y(I)	Y	N	Alive (7.0)
11	F/17	T-ALL	8.88	46,XY	JAK3 exon15 mutation, NOTCH1 exon34 mutation, WT1 exon7 mutation	Haplo/ F	6	CsA+MTX +MMF	TBI+Cy+Flu +Ara-C+ATG	14.14	4.16	N	Y	N	Alive (27.1)

Y, yes; N, No; N/A, not applicable; F, Female; M, Male; AML, Acute Myeloid Leukemia; T-ALL, Acute T lymphocyte Leukemia; Haplo, Related Haploidentical Donor; MSD, Matched Sibling Donor; URD, matched Unrelated Donor; MTX, Methotrexate; CsA, Cyclosporin; MMF, Mycophenolate Mofetil; TBI, Total body irradiation; Bu, Busulfan; Flu, Fludarabine; Ara-C, Cytarabine; Cy, Cyclophosphamide; ATG, anti-thymocyte globulin; MNC, mononuclear cells.

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10mg/kg, days -6 to -4) and Fludarabine (Flu, 30 mg/m^2, days -6 to -4), or Cladribine (Clad, 5mg/m^2, days -6 to -4). One patient with AML received TBI instead of Bu. Patients with T-ALL mostly received conditioning regimens as follows: TBI (3.3 Gy, days −9 to −7), Cy (40mg/kg, days −6, −5), Flu (30 mg/m^2, days −4 to −2), and Ara-C (2 g/m^2, days −4 to −2) as previously described (n=5) (7). One patient with T-ALL received etoposide instead of fludarabine and cytarabine. Patients who received haploidentical donor and matched unrelated donor HSCT received an additional 2.5mg/kg/day anti-T lymphocyte globulin (ATG) on days -5 to -2 (n=9). ATG was also given to the patient who was older than 40 years old (n=1). Calcineurin inhibitors plus short-term methotrexate along with or without mycophenolate mofetil were used for acute graft versus host disease prophylaxis as previously described (7, 8). Three patients received stem cells from matched-sibling donors, six from related haploidentical donors, and two from matched unrelated donors. More details are shown in Table 2.

Statistical analysis

The primary endpoint was leukemia-free survival (LFS). Relapse or death were considered events. Overall survival (OS) was defined as the duration from stem cell administration to the last follow-up or death due to any cause. Transplant-related mortality (TRM) was defined as death in complete remission of leukemia after HSCT. Relapse was defined as any kind of morphological, cytogenetic, molecular disease recurrence, or extramedullary relapse. Minimal residual disease (MRD) was defined as any kind of molecular disease present without hematological relapse as follows: 1. Positive detection by real-time PCR of the SET-NUP214 fusion gene (ABL copies>10^4, target gene/ABL >0%), 2. 0%<morphological leukemia blast cells <5%, and 3. leukemia cells/mononuclear cells >0% by flow cytometry analysis (capture 500,000 total events). Neutrophil engraftment was defined as the first date of neutrophil count ≥0.5×10^9/L for three consecutive days. Platelet engraftment was defined as the first date of platelet count ≥20×10^9/L and sustained for seven consecutive days independent of transfusion. Acute graft-versus-host disease (GVHD) was based on a previous standard (9). All dates were calculated from the first day of stem cell infusion to the day of the event or censored at the last follow-up. The Kaplan–Meier curve was calculated using SPSS 22.0. P<0.05 were considered statistically significant.

Results

Patient, disease, and transplant characteristics

The SET-NUP214 fusion gene could be detected in both T-ALL and AML patients in our single center. Normal chromosome phenotypes were mostly seen in these patients (n=6) (Table 1). JAK mutation (n=4) and PHF6 mutation (n=3) were mostly observed in these patients as concurrent mutations. Of all the patients with AML, three were categorized as AML without maturation. One patient was categorized as acute monocytic leukemia, and one was not otherwise specified de novo, according to the fifth edition of the WHO classification. One patient with T-ALL was categorized as ETP-ALL. Of all the 11 patients with acute leukemia, only 1 patient achieved complete molecular remission after one cycle of chemotherapy, indicating that this cohort of patients is somehow resistant to chemotherapy and should take HSCT as a treatment option, which is consistent with a previous report (5). All the patients underwent alloHSCT in CR1 and received peripheral stem cell infusion with a median positive CD34 count of 3.44 (range 2.28-6.82) ×10^6/kg and median mononuclear cell count of 12.00 (range 8.27-18.98) ×10^8/kg. Median times of neutrophil and platelet recovery were 14 days (range 11-17 days) and 15 days (range 11-33 days), respectively. All the patients achieved hematopoietic engraftment and complete remission at the molecular level after alloHSCT.

OS and LFS

The estimated 1-year overall survival (OS) was 53.3% for patients with AML and the 3-year OS was 0% (Figure 1A). The estimated 1-year OS for patients with T-ALL was 83.3% and the 3-year OS was 62.5% (Figure 1A). There were no statistical differences between the two groups (p=0.676). The estimated 1-year and 3-year OS for all these 11 patients were 69.3% and 38.5%, respectively (Figure 1B). The 1-year and 3-year leukemia-free survival (LFS) for all patients were 69.3% and 38.5%, respectively. Of note, only one patient with T-ALL received regular chidamide as maintenance chemotherapy post-HSCT, and none of the others received any kind of maintenance chemotherapy post-HSCT. The patient taking chidamide was in LFS 814 days post-HSCT to the last follow-up.

Relapse incidence and non-relapse mortality

In total, six patients relapsed after HSCT and five patients died of leukemia at the last follow-up. Three out of five (60%) patients with AML relapsed post-HSCT (Figure 1C): one patient had extramedullary involvement, one patient relapsed in bone marrow, and both patients died due to leukemia. One patient relapsed presenting as MRD and received combined chemotherapy including venetoclax and donor lymphocyte infusion; the patient achieved CR and was alive with chronic graft-versus-host disease to the last follow-up, which was 226 days after relapse post-HSCT. This patient remains the only one who survived after relapse post-HSCT. Three out of six patients with T-ALL (50%) relapsed post-HSCT and died of leukemia (Figure 1C). Two patients received intensive chemotherapy and subsequent DLI but did not respond to treatment. One patient chose palliative care and died 1 month after relapse. One patient with AML died of infection and was the only patient who died of transplant in this cohort. The TRM rate was 9.1%. Of note, the only patient who achieved molecular complete remission after one cycle of chemotherapy was in leukemia-free survival 211 days post-HSCT

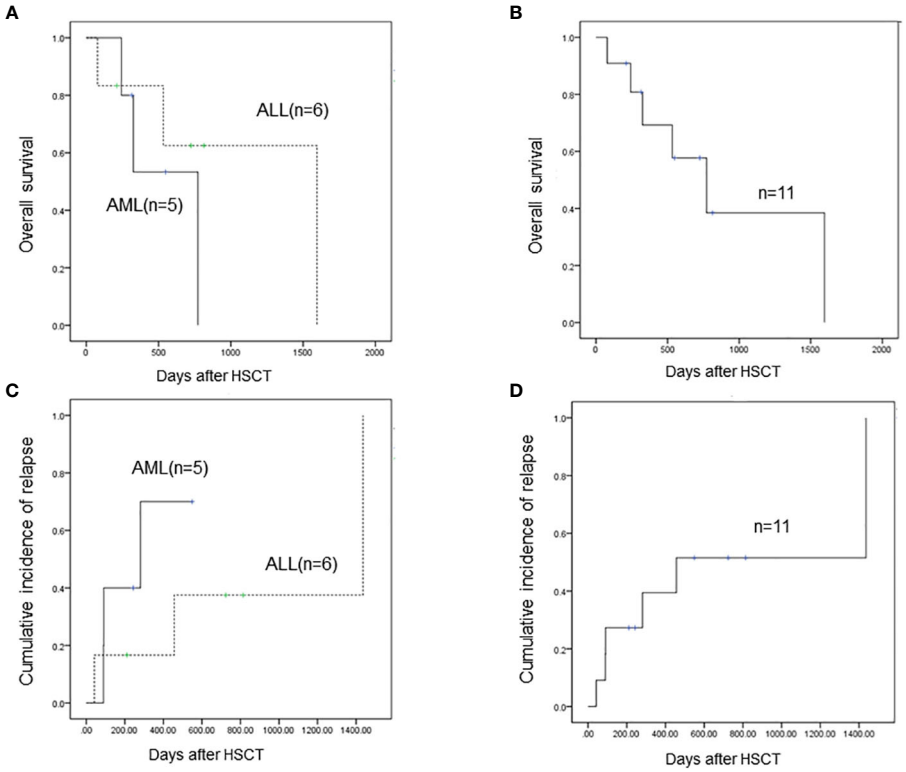

FIGURE 1
(A) The estimated 1-year overall survival (OS) is 53.3% for AML patients with SET-NUP214 fusion and the 3-year OS is 0%. The estimated 1-year OS for T-ALL patients with SET-NUP214 fusion is 83.3% and the 3-year OS is 62.5%. There are no statistical differences between the two groups (p=0.676). **(B)** The estimated 1-year and 3-year OS for all these 11 patients are 69.3% and 38.5%, respectively **(C)** Three of five (60%) patients with AML relapsed post-HSCT, and three of six patients with T-ALL (50%) relapsed post-HSCT. **(D)** For all 11 patients, the 1-year and 3-year cumulative incidence of relapse is 39.4% and 51.5%, respectively.

to the last follow-up. The six patients who relapsed post-HSCT never reached negative detection of the SET-NUP214 fusion gene before HSCT. In patients who did not relapse post-HSCT to the last follow-up, three out of five reached molecular remission before HSCT, and the number of cycles of chemotherapy to achieve negative fusion gene detection was 1,3, and 4, respectively. This indicates that patients with molecular remission before HSCT may achieve long survival after HSCT. Patients who never reach molecular remission have a high incidence of relapse rate (75%) post-HSCT but may still respond to HSCT. Thus, alloHSCT could be a salvage treatment option for these patients who are resistant to conventional chemotherapy. For all 11 patients, the 1-year and 3-year cumulative incidence of relapse was 39.4% and 51.5%, respectively (Figure 1D).

Discussion

The NUP214 mapping at chromosome 9q34 has been reported as significant to genes in leukemogenesis (10). SET was reported as an oncogene that plays a role in transcription by modulating chromatin organization (11). The SET-NUP214, also known as TAF-1-CAN and SET-CAN, as a gene fusion has previously been described as a result of a chromosomal translocation t (9;9)(q34; q34) and del(9)(q34.11q34.13) (2–4). The fusion gene regulated leukemogenesis partly by upregulating the HOXA gene (2, 6). This fusion can be found in patients with T-ALL. The incidence of this fusion in patients with T-ALL is 4.6%-6%, according to data from different centers (5, 6). SET-NUP214 fusion has also been reported in cell lines of AML and single clinical cases of AML and AUL (1, 12, 13). In our study, AML with SET-NUP214 fusion was mostly present as AML without maturation, which may lead to poor survival even after alloHSCT. In patients with T-ALL, SET-NUP214 was reported to be strongly associated with corticosteroid and chemotherapy resistance but did not negatively influence clinical outcomes after HSCT (5). It is indicated that mutations of PHF6 and JAK1 are associated with the rearrangement of SET-NUP214 in T-ALL. In our cohort, concurrent mutations including JAK (n=4) and PHF6 (n=3) were mostly observed in both T-ALL and AML patients. Of note, JAK3 (n=3) and PHF6 (n=2) mutations were also observed in patients with AML. Regarding the prognosis of T-ALL patients with SET-NUP214, a Korean study showed that among four adult patients with T-ALL who presented with the fusion gene, only one patient who underwent HSCT survived (4). Song Y reported that in 17 AML and T-ALL patients with SET-NUP214, the median OS of 6 patients in chemotherapy was 10.5 (3-41) months, indicating none of the patients could survive without further alloHSCT. The OS and

relapse-free survival of patients who underwent alloHSCT were better than those of the chemotherapy group (p=0.038) (14). In another study enrolling 11 T-ALL patients with SET-NUP214 fusion, the LFS and OS at 3 years of SET-NUP214–positive patients were 45% and 73%, respectively (5), which is somehow consistent with the prognosis of patients with T-ALL in our center. The present study and previous research all show disappointing LFS of these patients. The two patients with AML who were alive at the last follow-up did not exceed 3 years post-HSCT, thus we have no patients with AML who survived more than 3 years post-HSCT. However, regarding the high incidence of relapse, AML patients with SET-NUP214 fusion have a very poor prognosis even after alloHSCT. Bcl2 inhibitors such as venetoclax may be effective in patients with AML, as shown in our research but there is a need for further clinical trials with larger samples.

Recent research from Oka M linked NUP214 and NUP98, demonstrating that these two fusion proteins share some characteristics, including their nuclear bodies co-localized with CRM1 (also known as XPO1), and are both associated with aberrant activation of HOX genes. In addition, they are both physically and functionally associated with MLL1, which is also known as KMT2A (15). This suggests that treatment options for NUP98 rearranged acute myeloid leukemia may be adaptable to NUP214 rearranged acute myeloid leukemia patients but further evidence is needed. For patients with T-ALL, our previous research shows that maintenance of chidamide after alloHSCT did not significantly reduce the 1-year CIR of high-risk T-ALL but may improve the event-free survival (16). The one patient taking chidamide in our study is somehow in LFS to the last follow-up; there is a need for further investigation of the impact of chidamide on SET-NUP214 positive T-ALL.

Our research shows a very poor prognosis of acute leukemia patients with SET-NUP214 fusion even after alloHSCT. Despite all these patients undergoing alloHSCT in CR1 and achieving molecular remission shortly after HSCT, the major cause of death for these patients is still leukemia relapse. With very limited cases in our study, it is highly recommended that physicians should consider novel treatment strategies for these patients, including a stronger conditioning regimen and proper maintenance chemotherapy. Physicians should be alert of the high incidence of relapse for acute leukemia patients with SET-NUP214, even after alloHSCT. There is an urgent need for more clinical trials or research with larger samples for this group of patients.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

YS: Conceptualization, Data curation, Writing – original draft. DY: Validation, Writing – review & editing. RZ: Validation, Writing – review & editing. XC: Validation, Writing – review & editing. QM: Validation, Writing – review & editing. JW: Validation, Writing – review & editing. WZ: Validation, Writing – review & editing. AP: Validation, Writing – review & editing. YH: Validation, Writing – review & editing. EJ: Supervision, Validation, Writing – review & editing. SF: Conceptualization, Funding acquisition, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Allo-HSCT with TBI-based preconditioning for hepatosplenic T-cell lymphoma: two case reports and systematic review of literature

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Hepatosplenic T cell lymphoma (HSTCL) is a particularly difficult-to-treat form of lymphoma, with many patients exhibiting primary resistance to chemotherapy. At present, no effective strategy for treating relapsed and refractory HSTCL has been established, with treatment being hampered by questions of how best to overcome chemoresistance to allow patients to attain more durable therapeutic benefits. While there have been marked advances in immunotherapy, allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains one of the primary approaches to curing HSTCL. Of patients who undergo immunochemotherapeutic treatment, many are resistant to conventional chemotherapeutic drugs yet remain sensitive to radiotherapy. We selected to employ a transplant pretreatment regimen consisting of total -body irradiation (TBI) and administered this regimen to two patients with HSTCL. Both patients achieved complete remission (CR) after transplantation, demonstrating extended periods without disease recurrence. We systematic reviewed previously published instances involving allo-HSCT in patients with HSTCL. We have found a total of 67 patients who have received allo-HSCT. In general, age<45 and the status of CR at HSCT may have a more favorable prognosis. Although the impact of TBI on prognosis was not found to be substantial, patients in the TBI group had higher 3-year overall survival (66.7% vs. 71.1%) and 5-year overall survival (58.4% vs. 71.1%) compared to patients in the non-TBI group. In addition, the relapse rate of the TBI group is approximately half that of the non-TBI group. This regimen is well tolerated and associated with low recurrence rates or complications, suggesting that it represents a viable pretreatment regimen for young HSTCL patients undergoing allogeneic HSCT.

KEYWORDS

hepatosplenic T cell lymphoma, allogeneic hematopoietic stem cell transplantation, total body irradiation, preconditioning, prognosis, systematic review

Introduction

Hepatosplenic T cell lymphoma (HSTCL) is a rare and highly aggressive form of peripheral T cell lymphoma that is most commonly diagnosed in younger males, resulting in a disease characterized by systemic symptoms, thrombocytopenia, and hepatosplenomegaly without corresponding lymphadenopathy (1). Pathological examination of affected patients often revealed neoplastic cells in the splenic red pulp with infiltration of the hepatic, splenic, and bone marrow sinusoids (2). While γδ T cell receptor (TCR) expression is observed in most cases, some HSTCL cases exhibit αβ TCR expression, with both subtypes exhibiting a similar clinical course such that αβ HSTCL is generally regarded as an immuno-phenotypic variant (3). Approximately 20% of HSTCL cases develop in patients with a history of immunosuppression, and this disease is not related to infection with Epstein-Barr virus (EBV), in contrast with other forms of immune-mediated lymphoma (4, 5).

HSTCL exhibits a very aggressive clinical course, with poor chemotherapy response rates, an extremely low 7% 5-year survival rate, and a median overall survival duration of just 10 months across age groups (6). While there have been a few case reports documenting long-term survivors diagnosed with HSTCL, no standardized strategy for treating affected patients has yet been established (7). Most published data comprise case reports or case series in which CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone)-based regimens have been linked to poor long-term outcomes (6). Even among patients who achieve complete remission (CR) after induction, the median overall survival duration tends to be short as the duration of disease remission tends to be short (8). The only curative treatment option for HSTCL patients is allogeneic hematopoietic stem cell transplantation (allo-HSCT). This report describes two cases of patients diagnosed with HSTCL who underwent allo-HSCT with a TBI combined precondition regimen. In addition, a systematic review of literature on adults with HSTCL who underwent allo-HSCT is also provided.

Case presentation

Patient 1

In 2020, a 29-year-old man with ecchymosis of both lower limbs showed up with no obvious explanation. Despite corticosteroids, the patient continued experiencing splenomegaly and increasing thrombocytopenia, increasing the possibility of an ITP diagnosis. In February 2021, the patient reported to our hospital. At that time, physical examination revealed that the lower pole of the spleen was located two finger widths above the umbilicus and was palpable below the left costal margin. After a thorough assessment (Table 1), a splenectomy was performed, ensuring that there were no contraindications. Significant splenic enlargement was observed during the surgery (Figures 1A, B). The histological findings revealed cells of moderate size with oval-shaped nuclei, exhibiting abnormalities in their nuclear structure and small nucleoli. Immunohistochemistry results of spleen revealed these cells were CD2-, CD3+, CD5-, CD7+, CD20- PAX5-, CD79α-, CD23-, TIA-1 +, CD56-, granzyme B-, CD4-, CD8-, CD30-, CD138-, ALK-, Ki-67 + 60%. Cells were positive for TCRγ rearrangement. The splenic flow cytometry analysis was performed, which demonstrated abnormal T cells accounted for ~22.94% of total cells, and these cells were CD7++, CD16++, CD33-, CD13-, CD38-, CD117-, CD19-, CD34-, HLA-DR dim, CD56-, CD5-, CD 5-, CD25-, CD3++, CD99dim, CD2 minimal expression, CD4++, CD8-, TCRαβ-, TCRγδ+, CD335-, CD28dim, CD24, CD57-, CD94+, CD337-, CD158a,h-, CD158f-, CD158e1/e2-, CD158b1/b2j+, CD158i (46.00%). Therefore, a definitive diagnosis of stage IE Hepatosplenic T-cell Lymphoma (HSTCL) was made.

At approximately 3 weeks after surgery, the patient's platelet levels had recovered to within the normal range. Chemotherapy consisting of an ICE regimen (ifosfamide 2.7 g d1-3, etoposide 0.15 g d1-3. carboplatin 0.5 g d2) was administered on 2/23/2021, 3/15/2021, 4/12/2021, and 5/12/2021, and after treatment PET-CT results were negative and the patient was considered to have achieved CR. As HSCTL is an aggressive disease with a poor prognosis, it was recommended that the patient undergo allo-HSCT. A FACT conditioning regimen was initiated on 6/18/2021 consisting of TBI (6 Gy, d -10), Fludarabine (150 mg/m^2 in 5 days, d -9 to -6), Cytarabine (10 g/m^2 in 5 days, d -9 to -5), Cyclophosphamide (2 g/m^2 in 2 days, d -4 to -3), T -cell depletion with anti-human thymoglobulin (10 mg/kg in 4 days, d -4 to d -1). GVHD prophylaxis consisted of cyclosporine, mycophenolate mofetil, and low -dose methotrexate (MTX). Between 6/29/2021 and 6/30/2021, haplotypic hematopoietic stem cells were transfused (HLA matched 6/12 with blood type donor A+ for recipient A+, with mononuclear cell (MNC) counts of 8.08x10^8/kg and CD34+ cell count of 2.54x10^6/kg. On 6/28/2021, an auxiliary transfusion of cord blood was performed (HLA 7/10, O+ for A+), with a total nucleated cell (TNC) count of 2.2x10^7/kg and a CD34+ cell count of 1.34x10^5/kg. Leukocyte and platelet were engrafted on days +10 and +11, perspectively. Acyclovir was used as a precaution to prevent cytomegalovirus (CMV) activation. On day +46, the patient's CMV DNA levels had risen to 7.82x10^3 copies/mL but improved with ganciclovir antiviral treatment. On day +85, the patient developed nausea and vomiting after excluding CMV or EBV infection. This was considered an instance of grade I/II gastrointestinal graft-versus-host response. Glucocorticoid and cyclosporine were used for anti-rejection treatment and were effective. On day +443, the patient developed herpes zoster infection, which improved with valaciclovir antiviral therapy.

Abbreviations: HSTCL, Hepatosplenic T cell lymphoma; allo-HSCT, allogeneic hematopoietic stem cell transplantation; TBI, total body irradiation; CR, complete remission; TCR, T cell receptor; EBV, Epstein-Barr virus; CHOP, chemotherapy regimen consisting of cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete remission; PET-CT, positron emission tomography-computed tomography; FACT, conditioning regimen consisting of TBI, Fludarabine, Cytarabine, and Cyclophosphamide; HLA, human leukocyte antigen; ICE, a chemotherapy regimen consisting of ifosfamide, carboplatin, and etoposide; MTX, methotrexate; MNC, mononuclear cell; TNC, total nucleated cell; CMV, cytomegalovirus; DLI, Donor lymphocyte infusion; PTCL, peripheral T cell lymphoma; MAC, myeloablative preconditioning; RIC, reduced intensity conditioning.

TABLE 1 Clinical examination results of two patients.

Examination	Result of Patient 1	Result of Patient 2
Routine blood count	Platelet $27x10^9$/L	White blood cell count $0.7x10^9$/L, platelet count $47x10^9$/L, and hemoglobin 113 g/L.
Chest/abdominal CT	Splenomegaly	Splenomegaly with uneven density, increased liver volume, and limited effusion of the left chest and abdominopelvic cavity
PET-CT	Splenomegaly, with a SUVmax of 8.5.	Not performed.
Liver and kidney function	Lactate dehydrogenase level was elevated (368 U/L, normal range: 50-240 U/L) without other abnormal results.	Normal.
B ultrasonography	Splenic area of 14.5 x 6 cm.	Liver was normally sized, while the spleen was enlarged (23 x 12 cm) with full morphology, smooth contours, and uneven local parenchymal echo at the lower pole.
Bone marrow puncture	Clear evidence of hyperplasia, with 850 megakaryocytes in the entire film, primarily of the naïve and granular types and exhibiting poor functionality.	Clear hyperplasia, with 24.0% lymphocytes, some loose nuclear chromatin, and villi or pseudo-like processes at the margins of small lymphocytes.
Bone marrow flow cytometry	Normal.	T lymphocytes that were CD45+, CD3+, CD5-in accounted for ~11.2% of nucleated cells, and these cells were found to express CD2, CD3, CD7, CD45RO, and TCR γδ but not CD4, CD5, CD8, CD16, CD30, CD57, TCR αβ, or CD45RA.
Bone marrow biopsy	Consistent with the hypohyperplasia of bone marrow hematopoietic tissue and 10-20 megakaryocytes per low-powered field.	Presence of small- to intermediately-sized lymphoid cells in the medullary sinus, with slight irregularities, loose chromatin, and inconspicuous nucleoli.
Immunohistochemistry results of Bone marrow	Normal.	Lymphoid cells: MPO-, TDT-, CD34-, CD117-, CD10-, CD3+, CD5-, CD2 weak+, CD7+, CD4-, CD8-, CD43 weak+, CD20—, CD30–, CD56–, granzyme B–, TIA-1++, Ki-67+ 10-15%+, CD42b megakaryocytes+, Gomori 1+. The T cell receptor (TCR) rearrangement results showed TCRGA+, TCRGB+, and TCRD+.
Biopsy result of spleen	Cells were of intermediate size with ovoid nuclei, nuclear irregularities, and small nucleoli.	Not performed.
Immunohistochemistry results of spleen	CD2-, CD3+, CD5-, CD7+, CD20- PAX5-, CD79α-, CD23-, TIA-1+, CD56-, granzyme B-, CD4-, CD8-, CD30-, CD138-, ALK-, Ki-67+ 60%. Cells were positive for TCRγ rearrangement.	Not performed.
Splenic flow cytometry	Abnormal T cells accounted for ~22.94% of total cells, and these cells were CD7++, CD16++, CD33-, CD13-, CD38-, CD117-, CD19-, CD34-, HLA-DR dim, CD56-, CD5-, CD 5-, CD25-, CD3++, CD99dim, CD2 minimal expression, CD4++, CD8-, TCRαβ-, TCRγδ+, CD335-, CD28dim, CD24, CD57-, CD94+, CD337-, CD158a, h-, CD158f-, CD158e1/e2-, CD158b1/b2j+, CD158i (46.00%).	Not performed.

PET-CT scans (Figures 1G, H) revealed a substantially reduced number of lesions compared to the prior scans. Currently, the patient remains free from disease and has survived for 732 days following the transplantation procedure. The patient's overall health was good, as shown in Figure 2A.

Patient 2

A 30-year-old male received medical treatment at our hospital in July 2020 due to a 3-year history of an enlarged spleen and abdominal swelling without any other associated symptoms. Recently, he has been suffering from inexplicable fatigue, decreased appetite, increased abdominal distension, and a significant weight loss of approximately 10 kg in just 3 months.

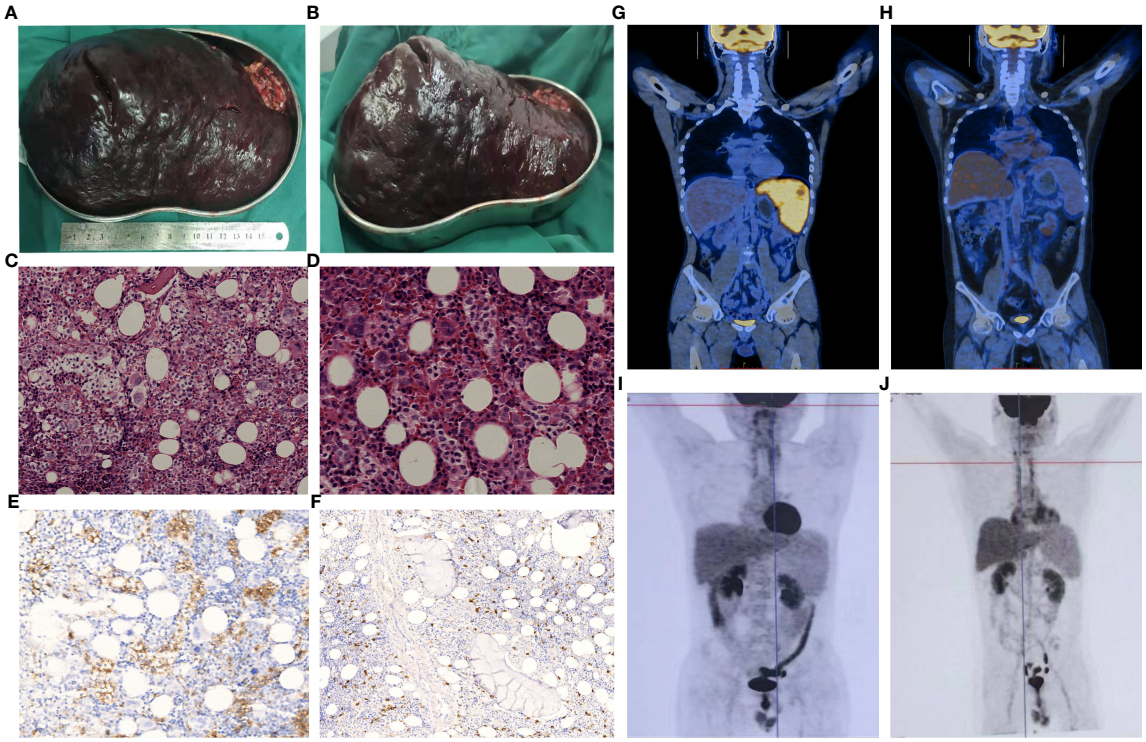

FIGURE 1
Clinicopathological features of the two patients. In patient 1, the splenectomy specimen revealed significant splenic enlargement, as demonstrated in images **(A, B)**. Bone marrow histology of patient 2, stained with HE **(C)**, x200; **(D)**, x400), exhibited infiltration of lymphoma cells. These cells appeared as small to intermediately sized lymphoid cells within the medullary sinus, displaying slight irregularities, loose chromatin, and inconspicuous nucleoli. Immunostaining indicated that these cells were positive for CD3 **(E)**, x400) and negative for CD5 **(F)**, x200). A PET-CT scan performed on patient 1 before **(G)**, 2/1/2021) and after **(H)**, 1/26/2022) allo-HSCT demonstrated complete remission. Post allo-HSCT, patient 2 showed no abnormalities on PET-CT scans conducted on 5/13/2021 **(I)** and 1/26/2022 **(J)**.

Systemic examinations were performed, as indicated in Table 1. Bone marrow biopsy revealed apparent hyperplasia, with 24.0% lymphocytes, some loose nuclear chromatin, and villi or pseudo-like processes at the margins of small lymphocytes. Bone marrow flow cytometry revealed T lymphocytes that were CD45+, CD3+, CD5- in accounted for ~11.2% of nucleated cells, and these cells were found to express CD2, CD3, CD7, CD45RO, and TCR γδ but not CD4, CD5, CD8, CD16, CD30, CD57, TCR αβ, or CD45RA. Bone marrow biopsy revealed small- to intermediately-sized lymphoid cells in the medullary sinus, with slight irregularities, loose chromatin, and inconspicuous nucleoli. Immunohistochemistry results showed that the lymphoid cells were MPO-, TDT-, CD34-,

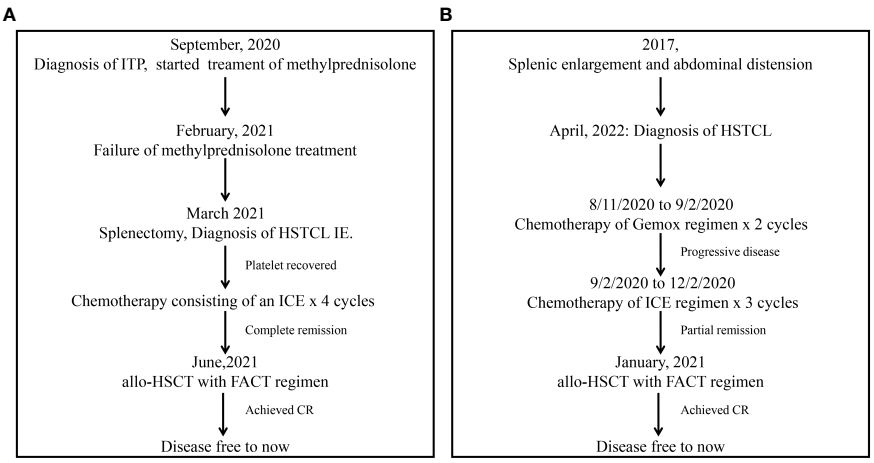

FIGURE 2
Clinical course of patients 1 **(A)** and 2 **(B)**.

CD117-, CD10-, CD3+, CD5-, CD2 weak+, CD7+, CD4-, CD8-, CD43 weak+, CD20—, CD30–, CD56–, granzyme B–, TIA-1++, Ki-67 + 10-15%+, CD42b megakaryocytes+, Gomori 1+. The T cell receptor (TCR) rearrangement results showed TCRGA+, TCRGB+, and TCRD+. The diagnosis of HSTCL was conclusively confirmed through a bone marrow biopsy (Figures 1C-F). The PET-CT scan was excluded because of its excessive cost. The diagnosis of HSTCL was considered based on these data.

After excluding contraindications, a P-Gemox chemotherapeutic regimen (gemcitabine needle [1.6 g d1, oxaliplatin [0.16 g d1], and Pegaspargase [3750 U d2]) was initiated on 8/11/2020. A P-Gemox regimen was repeated beginning on 9/2/2020, and after treatment, B ultrasonography revealed splenomegaly with localized infarction. In addition, the patient experienced a fever associated with the tumor, suggesting that the earlier chemotherapy was ineffective. An ICE chemotherapy regimen was administered on 10/16/2020, 11/14/2020, and 12/5/2020 consisting of etoposide (0.16 g d1-3), ifosfamide (2 g d1-3), and carboplatin (450 mg d1). After treatment, the spleen shrank, consistent with partial remission.

On 1/11/2021, allo-HSCT treatment was initiated using a FACT conditioning regimen. The drugs used for GVHD prophylaxis include cyclosporine, mycophenolate mofetil, and low-dose MTX. Between 1/21/2021 and 1/22/2021, haplotypic hematopoietic stem cells were transfused (HLA matched 6/12, blood type donor O+ for recipient O+) with MNC counts of $10.72x10^8$/kg and a CD34+ cell count of $7.63x10^6$/kg. Leukocytes and platelets were engrafted on days +16. Acyclovir was used to protect against CMV infection after transplantation. On day +59, blood tests for CMV DNA revealed a titer of $3.10x10^3$ copies/mL, and sodium foscarnet was provided for antiviral therapy. Due to the high risk of relapse, Donor lymphocyte infusion (DLI) was treated at day +84 and day +140.

On day +119, B ultrasonography of the liver revealed enlargement and echoic changes with an increase in splenic volume (18.1 x 6.9 cm), and the lower splenic pole was located two finger-widths above the umbilicus. The PET-CT scan (Figure 1I) showed no abnormal glucose uptake by the spleen. On day +182, the patient exhibited skin and oral mucosa grade I GVHD, which improved with glucocorticoid therapy. On day +243, Alanine aminotransferase levels were significantly elevated and improved following hormone administration and hepatoprotective treatment. On day +431, B ultrasonography suggested the presence of multiple hypoechoic nodules in the bilateral axilla, which were more prominent on the right side, being about 4.1x2.2x2.8 cm in size. Substantial splenic enlargement was noted (~4.8 cm thick). An axillary lymph node biopsy was performed, and pathology did not reveal any evidence of lymphoma. Repeat PET-CT (Figure 1J) scans were negative. The patient remains disease-free at day 902 after transplant (Figure 2B).

Systematic review

In order to provide a complete overview of the clinical features and outlook for patients with HSTCL who received HSCT, we systematically assessed the available literature. The included Supplementary Table S1 provides a comprehensive overview of our search methodology, with retrieval and outcome analyses being conducted by two independent researchers. Due to the primary statistical focus on the prognosis of transplant patients, material that did not include precise survival data, especially overall survival (OS), was excluded. We incorporated 30 research papers encompassing 67 patients (including two participants from this study). In cases where articles or attachments did not expressly include precise clinical details, we used the terms 'Not Available' or 'Not Defined' to indicate the absence of data. This was accomplished to avoid any later statistical analysis in survival assessments.

Among the individuals who underwent transplants were 41 males and 20 females. The majority of them, precisely 44 out of 61, were under the age of 45. 9 individuals suffered from having spleens removed, and 58 patients were classified as stage IV. During the transplantation process, 25 patients were found to be in a state of complete remission, 26 patients were in a state of partial remission, and 11 patients were not. The donor selection process consisted of 17 instances involving sibling donors, 7 cases involving haploidentical transplants, 18 cases involving unrelated donors, and 4 cases involving cord blood. The origins of the transplants consisted of 12 cases of bone marrow, 16 cases of peripheral blood stem cells, and 4 cases of cord blood. The transplant intensity was classified as MAC in 25 cases, RIC in 11 cases, and NMAC in 1. A total of 33 patients received transplant conditioning regimens involving TBI, with the majority being under the age of 45 (29 out of 33, P=0.002). Fourteen of these cases reported the dose and method of TBI application. Seven received >6GY, and 7 received ≤6GY. The majority (10/12) underwent fractionated radiation therapy. The predominant protocols implemented for GVHD prevention were CSA or FK506, and the GVHD incidence was 72.9%(27/37) (Table 2).

Eleven patients suffered a recurrence, accounting for 18.6% of the total (11/59). Before transplantation, patients who achieved complete remission (CR) appeared to have a decreased relapse rate (4.7% vs 25.7%, P=0.072). The number of recorded deaths was 22, resulting in a mortality rate of 32.8% (22 out of 67). Patients under 45 exhibited a reduced mortality rate (27.2% vs 52.9%, P=0.076). In addition, patients who achieved CR before transplantation had a significantly lower mortality rate compared to those who did not (16% vs 45.9%, P=0.027). Out of the 19 patients whose reasons for death were recorded, only 4 died as a result of disease progression (Tables 2, 3). No indicators were identified as affecting GVHD (Supplementary Table S2).

There were 53 patients with complete data documenting the use of TBI as a component of the transplant conditioning regimen. The groups had no substantial statistical disparities in prognosis or adverse outcomes. Patients who had TBI as part of their transplant preparation showed higher expected 3-year OS rates and 5-year OS rates compared to those who did not get TBI (71% vs 67%, 71% vs 58%). The group of individuals with TBI exhibited a decreased rate of relapse in comparison to the group without TBI (25% vs 40%). The incidence of GVHD was 66.7% in the TBI group and 83.3% in the non-TBI group. The group of individuals with TBI demonstrated a substantially lower rate of relapse in comparison

TABLE 2 Clinical characteristics of patients reviewed.

Clinical characteristics		Patients Number*
Gender	Male	41
	Female	20
Age	≥ 45	17
	<45	44
Stage	I	2
	III	5
	IV	58
Prior splenectomy	Yes	9
	NO	32
Status at HSCT	CR	25
	PR	26
	NR	11
Donor Source	Sibling	17
	Haplo	7
	MUD	18
	UBC	4
Graft Source	BM	19
	PB	16
	UCB	4
Conditioning intensity	MAC	24
	RIC	11
	NMAC	1
Conditioning include TBI	Yes	33
	No	20
TBI dose	≤6GY	7
	>6GY	7
TBI fraction	Yes	10
	No	2
GVHD prophylaxis	CSA+MMF+MTX	7
	CSA+MTX	2
	CSA+PTCY	2
	FK506	2
	FK506+MMF	1
	FK506+MMF+PTCY	1
	FK506+MMF+MTX	1
GVHD	aGVHD	18
	cGVHD	4
	aGVHD+cGVHD	3
	No GVHD	10
	Not defined	2
Relapse after HSCT	Yes	11
	NO	48
Status of patients	Alive	45
	Died	22
Main course of death	TRM	3
	Primary Disease	4
	Infection	1
	GVHD	3
	GVHD and Infection	3
	GVHD and VOD	1
	VOD	1
	Others	3

*Each group includes only the patients for whom data is available.
CR, complete remission; PR, partial remission; NR, no remission; TBI, total body irradiation; Haplo, haploidentical; MUD, matched unrelated donor; UCB, unrelated core blood; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; NMAC, non-myeloablative; BM, bone marrow; PB, peripheral blood; CSA, Cyclosporine; MMF, mycophenolate mofetil; MTX, methotrexate; PTCY, post-transplantation cyclophosphamide; FK506, tacrolimus; GVHD, graft versus host disease; TRM, treatment relate mortality; VOD, veno-occlusive disease.

to the group without TBI (12.9% vs 27.8%). The mortality rate was 24.2% among individuals with TBI and 40% among those without TBI.

We conducted additional studies of patients' OS and PFS (Supplementary Table S3). All patients who were enrolled in the study had OS data available. However, there were challenges in estimating PFS. We attempted to replace PFS nodes with post-transplant progression-free survival time, but only 25 patients reported explicit PFS durations. Prognosis may be affected by factors such as age (Figures 3A, D), the state of remission before a transplant (Figures 3B, E) and relapse after transplantation (Figures 3C, F) when considering the operating system. Before transplantation, attaining CR may affect patients' PFS, and after the transplant, the recurrence of the disease seems to be associated with a lower PFS (as shown in the Table). Furthermore, the prognosis does not appear to be affected by either splenectomy or the transplant conditioning regimen.

Discussion

HSTCL is a rare and aggressive type of peripheral T cell lymphoma (PTCL) that most frequently affects young males, with a median age at diagnosis of 32 years. First reported in 1990 (9), HSTCL accounts for < 1% of all PTCL cases and is a rapidly progressive disease that is poorly responsive to chemotherapy (8). An estimated 20% of patients with HSTCL exhibit underlying immunosuppression, and viral infections (including EBV and

TABLE 3 Clinical factors associated with survival status and relapse.

Clinical Chracteristics*		Status		P-value	Relapse*		P-value
		Alive	Died		NO	YES	
Age	45	32	12	0.076	31	9	0.708
	≥45	8	9		13	2	
Stage	I-III	5	2	1	1	2	0.328
	IV	38	20		7	0	
Status Before HSCT	PR+NR	20	17	0.027	26	9	0.072
	CR	21	4		20	1	
Prior splenectomy	NO	24	8	0.408	22	6	0.657
	YES	5	4		6	3	
Donor	SIB	8	9	0.179	14	2	0.52
	Haplo	6	1		7	0	
	MUD	12	6		15	3	
Graft	BM	12	7	1	13	5	0.18
	PB	10	6		15	1	
Conditioning include TBI	NO	12	8	0.355	13	5	0.259
	YES	25	8		27	4	
Conditioning intnsity	MAC	17	7	0.709	22	2	1
	RIC	7	4		10	1	
GVHD	NO	8	2	0.688	10	0	1
	YES	18	9		25	2	
Relapse	NO	34	14	0.042	–	–	–
	YES	4	7		–	–	–

*Each group includes only the patients for whom data is available.
CR, complete remission; PR, partial remission; NR, no remission; TBI, total body irradiation; SIB, sibling; Haplo, haploidentical; MUD, matched unrelated donor; UCB, unrelated core blood; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; NMAC, non-myeloablative; BM, bone marrow; PB, peripheral blood; GVHD, graft versus host disease.

hepatitis B virus) are rarely reported to be associated with HSTCL onset (10). Greater HSTCL incidence rates among inflammatory bowel disease patients undergoing TNF inhibitor treatment have been reported. Bernstein et al. (11) noted that the risk of this form of lymphoma was elevated among individuals with Crohn's disease. Kandiel et al. (12) conducted a meta-analysis in which they found that lymphoid malignancy risk was increased four-fold among patients receiving biologics. Ochenrider et al. (13) additionally surveyed reports about 28 HSTCL patients with Crohn's disease and found that all of these patients underwent azathioprine or thiopurine treatment. At the same time, 79% were treated with the biological infliximab.

HSTCL presents in a manner distinct from other more common lymphomas, with affected patients often exhibiting hepatosplenomegaly and prominent systemic symptoms without substantial lymph node involvement. Routine blood analyses may detect cytopenia without significant bone marrow infiltration (8). Other common presentations include Coombs-negative autoimmune hemolytic anemia and moderately elevated transaminase levels. Mild myeloid cell pathological hematopoiesis may be evident in the bone marrow, and significantly elevated lactate dehydrogenase levels are often detected. Both patients in this report exhibited thrombocytopenia when initially diagnosed, consistent with the fact that over 90% of patients reportedly develop thrombocytopenia that may be indicative of disease progression (14). Case 1 was initially diagnosed with immune thrombocytopenia, and the initial efficacy of hormonal treatment may have been attributable to a partial effect of this therapeutic intervention on lymphoma cells before the onset of hormone resistance.

HSTCL patients exhibit a 5-year OS rate of under 7%, with a median OS interval of just 10 months. Early induction therapy is essential when managing these patients, and while some patients undergo chemotherapeutic treatment, the response duration is generally short (8, 15). Thus, optimal patient outcomes depend on diagnosing patients and planning to perform HSCT early. In patients necessitating radical treatment, high-intensity chemotherapy is recommended, and given the absence of definitive guidelines for first-line chemotherapeutic regimens for these patients, approaches similar to those utilized for PTCL, such as CHOP or ECHOP regimens, can be implemented as initial treatments. In their single-center study of 14 HSTCL patients, Voss et al. (6) found that the

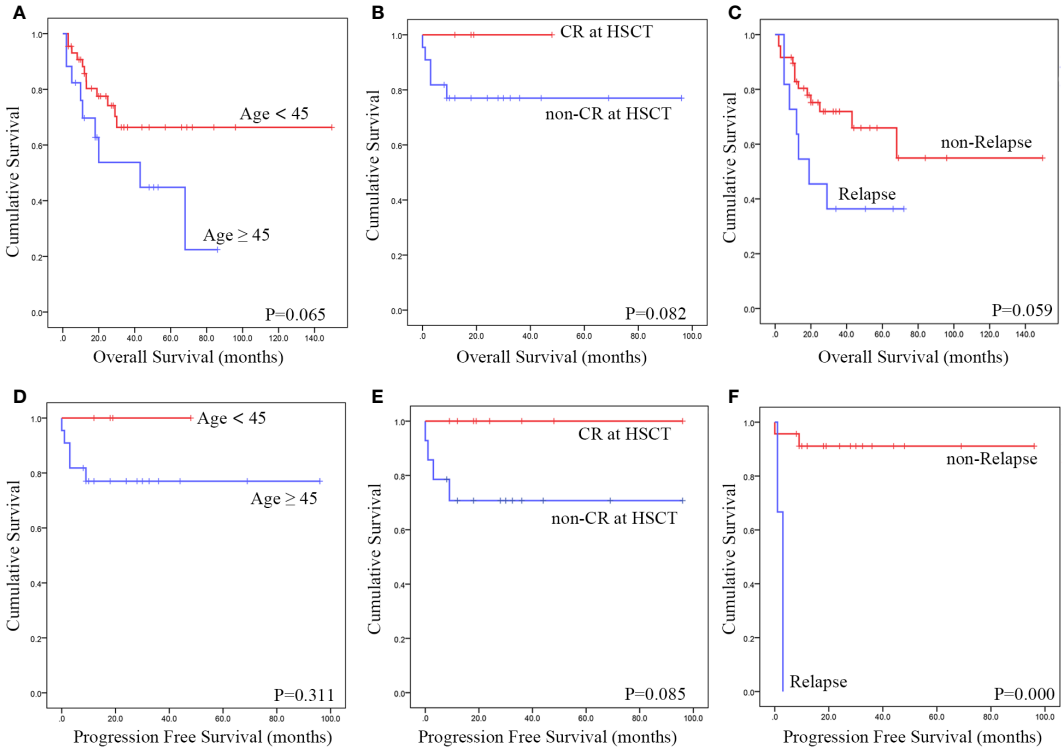

FIGURE 3
Using data from published cases, a Kaplan-Meier survival analysis was conducted to assess the impact of various risk factors. The findings revealed that Patients under 45 years of age **(A, D)**, transplant status of CR **(B, E)** and relapse after transplantation **(C, F)** exhibited a improved OS and PFS.

median patient age was 36 years, and all patients presented with stage IV disease. Non-CHOP induction therapies were used for most patients, with most receiving ifosfamide-based induction regimens and 8 receiving a non-CHOP regimen, of whom 5 achieved remission and underwent subsequent auto- or allo-HSCT. The prognosis of CHOP regimens was reportedly poor in two studies by Belhadj et al. (14) and Falchook et al. (16). As such, the two patients in the present report were initially treated with non-CHOP induction chemotherapy. In Case 2, the patient responded poorly to a GDP regimen but achieved therapeutic remission after switching to an ICE regimen and currently remains disease-free after bridging transplantation. In Case 1, initial ICE induction chemotherapy led to CR, and the patient remained disease-free after bridging allogeneic HSCT. These outcomes align well with prior evidence that ifosfamide-based regimens are associated with better patient treatment responses.

The value of HSCT as a form of consolidation therapy in HSTCL patients has yet to be established. As such, transplantation has the potential to be curative. Patients may experience better outcomes than those who undergo other forms of disease management. While CR can be achieved following induction therapy in some cases, given the short remission duration in most HSTCL cases, early transplantation is generally recommended. In a study of seven HSTCL patients at the Memorial Sloan-Kettering Cancer Center, of whom six had undergone autologous or allogeneic HSCT, the median OS was 65.5 months (6). In the European Bone Marrow Transplant Lymphoma Working Group Study of 25 HSTCL patients (17), 2/18 of the patients who underwent all-HSCT experienced subsequent relapse compared to 5/7 patients who underwent auto-HSCT. The graft-versus-lymphoma effects associated with allo-HSCT may thus provide benefits to treated patients.

Given that HSTCL primarily affects younger patients and is associated with poor outcomes, this suggests that allo-HSCT should be considered as an option for consolidation treatment in appropriate patients. Our comprehensive evaluation revealed that patients under 45 years who have a complete response at the time of transplantation may experience a more favorable prognosis than older patients. Although the impact of TBI on prognosis was insignificant, patients in the TBI group had improved 3-year and 5-year OS rates compared to those in the non-TBI group. Post-transplant relapse has a significant impact on OS. The prognosis was also not impacted by disease stage at the time of transplantation, indicating that even patients with advanced disease at the time of transplantation may attain benefits from HSCT.

One of the two patients in this report underwent allogeneic HSCT while in CR. In contrast, the other underwent this procedure in a stable disease state, with good efficacy in both instances. Limited data from prior studies suggest that myeloablative preconditioning (MAC) is not associated with any improvements in efficacy relative to reduced intensity conditioning (RIC), suggesting that the graft-versus-lymphoma effect is the primary advantage of allogeneic transplant preconditioning. Treatment

regimens incorporating TBI offer advantages for the management of relapsed and refractory lymphatic tumor patients, mainly as they provide a means of more effectively targeting sheltered tumor cells. The treatment regimen employed in this case report was between that of RIC and MAC (18), and these patients achieved deep remission following FACT pretreatment without any significant pretreatment-associated side effects. Patient 2 exhibited splenomegaly on the initial diagnosis, and while splenic enlargement was still evident on PET-CT scanning, the corresponding SUV value was low, and the patient exhibited no cytopenia or evidence of recurrent disease. This patient thus achieved CR, which continues to be accurate as of the most recent follow-up. In another report focused on HSTCL (19), four patients were identified as long-term survivors, with three of these patients having undergone splenectomy alone, including the patient with the longest survival duration of 137 months. Splenectomy may thus represent a viable alternative treatment strategy for patients with disease confined to the spleen who are refractory to chemotherapy or transplantation.

Conclusion

In conclusion, HSTCL has been associated with a very unfavorable prognosis, highlighting the necessity for further clinical trials to elucidate the significance and ideal timing of allo-HSCT in affected individuals. Younger patients can benefit significantly from allogeneic transportation due to the disease's tendency for rapid progression and brief remission periods; therefore, it is recommended that this procedure be executed shortly after remission is achieved, with a pretreatment regimen that includes TBI constituting a viable strategy. Even in patients with relapsed and refractory HSTCL, allo-HSCT can provide benefits. Nonetheless, considering that high treatment -related mortality may be evident even in the early phases, the patient's overall condition should be considered when determining the most suitable transplantation protocol.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

CC: Writing – original draft, Writing – review & editing. FY: Data curation, Investigation, Writing – review & editing. PM: Data curation, Formal analysis, Writing – review & editing. PS: Investigation, Writing – original draft. SQ: Project administration, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1345464/full#supplementary-material

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Determining the predictive impact of donor parity on the outcomes of human leukocyte antigen matched hematopoietic stem cell transplants: a retrospective, single-center study

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Introduction: Donor choosing remains to play a pivotal role in allogeneic hematopoietic stem cell transplantation (allo-HSCT). Numerous criteria beyond HLA compatibility impact the selection of a suitable donor.

Methods: We evaluated the effect of donor parity on transplant outcomes in a large homogeneously treated population that received an HLA-matched allo-HSCT between 2010 and 2021 at our center. All patients were transplanted from a peripheral blood stem cell source following a myeloablative Busulfan-based conditioning and an identical protocol for graftversus-host disease (GVHD) prophylaxis regimen.

Results: A total of 1103 allo-HSCT recipients were included. 188 (17%) had transplants from parous female donors, whereas 621 (56.30%) and 294 (26.70%) received transplants from male and nulliparous female donors, respectively. HSCTs from parous female donors compared to male and nulliparous females were associated with a significantly higher incidence of grade III-IV acute (a) GVHD (55.27% vs. 11.34 and 10.84%) and extensive chronic (c) GVHD (64.32% vs. 15.52 and 13.65%), as well as lower relapse incidence (RI).

Discussion: This study finds that while parous female donors are associated with higher incidences of grade III-IV aGVHD and extensive cGVHD post-allo-HSCT, the advantages, such as a lower RI, outweigh the risks. The results of our study provide valuable insights for donor selection.

KEYWORDS

graft-versus-host disease (GVHD), hematopoietic stem cell transplantation (HSCT), donor parity, overall survival, relapse incidence

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) stands out as one of the most efficacious therapeutic modalities for individuals with hematological malignancies and bone marrow failure syndromes (1). Nevertheless, this treatment approach is associated with substantial morbidity and mortality (2). Donor choosing remains to play a pivotal role in transplantation due to its importance in post-HSCT outcomes. Major histocompatibility antigens (MHC) matching is crucial for appropriate donor selection. However, numerous criteria beyond HLA compatibility including, age, sex, ABO compatibility, and parity (i.e., the history and number of prior pregnancies), impact the selection of a suitable donor (3–5). Typically, donors who are HLA-identical siblings are favored. But, some patients may possess multiple siblings who are HLA-matched. In addition, unrelated donors (URD) are being extensively used for allo-HSCT and have shown similar long-term survival when compared to matched related donors (MRDs) (6–9). Therefore, it is crucial to comprehend the impact of donor-related factors beyond HLA matching on outcomes following SCT.

Donor parity is often a debated non-human leukocyte antigen (non-HLA) factor that affects the outcome of HSCT. Various research studies indicate that individuals receiving grafts from parous female donors exhibit a significantly greater incidence of acute or chronic graft versus host disease (aGVHD or cGVHD) when compared to recipients of male or nulliparous donors (2, 4, 5, 10–14). Pregnancy frequently results in alloimmunization of T and B cells through the exchange of cells between the mother and the fetus via the placenta. There is substantial evidence that maternal T cells that are alloimmune and specific to neonatal inherited paternal antigens (IPA) persist for a lengthy amount of time after delivery (15, 16). Furthermore, certain studies have described that male recipients might face even greater risk due to the female donor's immune response to the H-Y antigen (2, 4, 13, 14). In contrast, some studies have not found any correlation between parity and the increased risk of developing GVHD (17).

In this investigation, we sought to determine the influence of donor parity on the incidence of high grade aGVHD and extensive cGVHD in a large homogeneously treated adult patients receiving an HLA-identical allo-HSCT.

Materials and methods

Ethical considerations and data collection

The current study was carried out in compliance with pertinent guidelines and regulations. Approval for this research was granted by the ethical committee of the Research Institute for Oncology, Hematology, and Cell Therapy (HORCSCT), as indicated by the reference number IR.TUMS.HORCSCT.REC.1400.023. All the participants submitted written informed consent, thereby authorizing the application of their data within the scope of the study. Patients' and donors' demographic, clinical, and laboratory data was gathered from their medical records using a checklist. The data was subsequently updated, and the patients were followed up until the end of 2022.

Study design and inclusion criteria

This retrospective cohort study was conducted at Research Institute for Oncology, Hematology and Cell Therapy of Shariati Hospital, affiliated with Tehran University of Medical Sciences, Tehran, Iran. All adult patients presenting to our institution with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) who underwent the first allo-HSCT in complete remission (CR) from an HLA-matched related donor following uniform busulfan (BU)-based myeloablative conditioning (MAC) regimen between Feb 2010 and Jan 2021 were included. Patients who received a graft of bone marrow or cord blood, those who underwent allo-HSCT from a matched unrelated donor, and those who received a reduced intensity conditioning regimen were excluded to make a more homogenous population and reduce confounding variables. The primary objective of this study was to investigate the predictive impact of donor parity on the incidence of grade III-IV aGVHD and extensive cGVHD, following HLA-identical allo-HSCT.

Transplant procedure

Every recipient was given an identical MAC regimen, which involved administering either oral busulfan (Bu) at a dosage of 4

mg/kg/day or intravenous Bu (Busilvex) of 3.2 mg/kg/day between days -6 to -3, along with cyclophosphamide with a dose of 60 mg/kg/day on days -3 and -2. The prophylaxis for GVHD consisted of cyclosporine A (CyA) that was initiated intravenously at a dosage of 1.5 mg/kg/day on day -2, followed by 3 mg/kg/day from day +7 until oral tolerance was attained, and methotrexate (MTX) with a dose of 10 mg/m^2 on day +1, followed by 6 mg/m^2 on days +3, +6, and +11.

All the patients received acyclovir, fluconazole, and trimethoprim/sulfamethoxazole for prophylaxis against herpes simplex virus (HSV), candida, and Pneumocystis jirovecii infections. Cytomegalovirus (CMV) reactivation was monitored through biweekly screening using DNA polymerase chain reaction. Ganciclovir was given as the preemptive treatment when CMV was reactivated.

Outcomes and definitions

The primary endpoints were grade III-IV aGVHD (at day-100) and 1-year extensive cGVHD. The secondary endpoints encompassed 5-year relapse incidence (RI), GVHD-free relapse-free survival (GRFS), and overall survival (OS) rates. GRFS was denoted as survival without grade III-IV aGVHD, extensive cGVHD, or relapse (18) and OS was characterized as the time until death. Diagnosis and grading of acute and chronic GVHD were under Glucksberg's criteria (18) and the National Institutes of Health consensus guidelines (19).

Statistical analysis

The between-group comparison of the demographic, clinical, and laboratory data was performed through the Mann-Whitney U and chi-squared tests for continuous and categorical variables, respectively. The median follow-up time was determined using the reverse Kaplan-Meier method. Also, the Kaplan-Meier method was implemented to estimate GRFS and OS, and their comparison was carried out among various categories of each covariate using the log-rank X^2 test. Moreover, the Fine and Gray tests were used to calculate and compare the cumulative incidences (CIs) of grade III-IV aGVHD, extensive cGVHD, and RI.

Using the Cox proportional hazard regression model, multivariable analyses were conducted to assess the effects of donor parity on outcomes considering confounding factors. The recipient and donor's age, sex matching, primary disease, and pre-transplant remission status were covariates that included in univariable analyses. Only variables that demonstrated a p-value below 0.2 in the univariable analyses were incorporated into the multivariate analysis. A p-value of less than 0.05 was considered as the statistical significance of the entire analyses. All statistical analyses were performed using STATA version 17 (StataCorp, LP, College Station, TX, USA).

Results

1103 patients made up this study, of whom 438 (39.70%) were female and 665 (60.30%) were male. 188 (17%) of these patients had transplants from female parous donors, whereas 621 (56.30%) and 294 (26.70%) of these patients received transplants from male and nulliparous female donors, respectively. The donors' and recipients' mean ages were 33.51 and 33.69 years, respectively, with a median age of 32 for both groups. Furthermore, as the primary disease, 415 (37.62%) of the recipients had ALL, and 688 (62.38%) had AML. All patients have been followed up for a median of 73.59 (95%CI: 69.78– 75.89) months. Table 1 summarizes the patients' and donors' baseline characteristics.

As shown in Table 2 and Figure 1, HSCTs from parous female donors were associated with a significantly higher incidence of grade III-IV aGVHD compared to male and nulliparous female donors (55.27% vs 11.34 and 10.84%, *P*= 0.00). Additionally, parous female donors showed a substantially higher incidence of extensive cGVHD (64.32% vs 15.52 and 13.65%, *P*= 0.00) than men and nulliparous female donors (Table 2, Figure 2).

In univariate analyses, factors apart from the parity status that were associated with an increased risk of grade III-IV aGVHD and extensive cGVHD were donor age (≥ 32 vs. < 32) and sex (male vs. female), recipient age (≥ 32 vs. < 32), and primary disease (AML vs. ALL). However, multivariate analysis showed that the greater age of the donor (HR= 1.53, P= 0.03), and parity history (HR= 3.90, P= 0.00) remained significant predictors of grade III-IV aGVHD; while, the parous female donors posed the sole significant risk for extensive cGVHD (HR= 4.62, P= 0.00) (Table 3).

As shown in Table 2 and Figure 3, the 5-year RI for parous female transplant recipients was significantly lower than for male and nulliparous female recipients (21.26% versus 39.24% and 46.51%, *P*= 0.00). Additional factors associated with higher RI in univariate analysis were recipient age and sex (male vs. female), as well as primary disease of AML and disease status of second complete remission and above (≥ CR2) before transplant. In multivariate analysis (Table 3), male recipients and disease status of ≥ CR2 were the predictive hazard factors (HR= 1.38, P= 0.01 and HR= 1.86, P= 0.00, respectively), whereas parous donors and primary disease of AML were the protective factors against RI (HR= 0.61, P= 0.02 and HR= 0.58, P= 0.00, respectively). Furthermore, RIs for patients transplanted from all three types of donors at CR ≥ 2 were significantly escalated compared to recipients at CR1 (results not shown).

HSCTs from females of parous type were also associated with significantly poorer GRFS of 5 years compared to male and nulliparous females (11.48% vs 41.41% and 36.01%, *P*= 0.00). Other characteristics associated with GRFS in univariate analysis were donor age and sex, recipient age, and primary disease. In Multivariate analysis, AML as the primary disease showed a significantly better probability of 5-year GRFS compared to ALL (HR= 0.83, P= 0.02), while the donor age of ≥ 32 and parous female donor significantly reduced the GRFS at 5-year (HR= 1.30, P= 0.00 and HR= 2.26, P= 0.00, respectively).

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TABLE 1 Baseline characteristics of donors and recipients.

Characteristic		Donor Sex/Parity			
		Parous female	Male	Nulliparous female	Total
Donor age, n (%)	< 32	36 (6.90%)	283 (53.90%)	206 (39.20%)	525 (47.60%)
	≥ 32	152 (26.30%)	338 (58.50%)	88 (15.20%)	578 (52.40%)
Recipients' age, n (%)	< 32	53 (10.20%)	283 (54.20%)	186 (35.60%)	522 (47.30%)
	≥ 32	135 (23.20%)	338 (58.20%)	108 (18.60%)	581 (52.70%)
Recipients' sex, n (%)	Female	80 (18.30%)	238 (54.30%)	120 (27.40%)	438 (39.70%)
	Male	108 (16.20%)	383 (57.60%)	174 (26.20%)	665 (60.30%)
Primary disease, n (%)	ALL	51 (12.30%)	221 (53.30%)	143 (34.50%)	415 (37.62%)
	AML	137 (19.90%)	400 (58.10%)	151 (21.90%)	688 (62.38%)
ABO matching, n (%)	Matched	104 (15.71%)	387 (58.46%)	171 (25.83%)	662 (60%)
	Minor mismatch	42 (22.82%)	94 (51.09%)	48 (26.09%)	184 (16.7%)
	Major mismatch	35 (18.14%)	96 (49.74%)	62 (32.12%)	193 (17.5%)
	Bidirectional	7 (10.94%)	44 (68.75%)	13 (20.31%)	64 (5.8%)
Disease status, n (%)	CR1	148 (17.67%)	471 (56.20%)	219 (26.13%)	838 (76%)
	CR≥ 2	35 (13.83%)	145 (57.31%)	73 (28.86%)	253 (22.9%)
Graft cell dose, mean ± SD	CD34 cells	5.29 ± 2.53	6.04 ± 6.44	6.26 ± 20.99	5.97 ± 11.84
	CD3 cells	292.39 ± 83.27	278.62 ± 101.91	307.20 ± 122.48	288.54 ± 105.71
Total, n (%)		188 (17.00%)	621 (56.30%)	294 (26.70%)	1103 (100%)

AML indicates acute myeloid leukemia; ALL, acute lymphoblastic leukemia, CR, complete remission.

TABLE 2 Post-transplant outcomes according to donor sex/parity.

	Donor sex/ parity	Probability (%)	95% CI	*P*
Grade III-IV aGVHD	Parous female	55.27	43.96-69.00	0.00
	Male	11.34	8.88-14.00	
	Nulliparous female	10.84	7.58-16.00	
Extensive cGVHD	Parous female	64.32	50.67-82.00	0.00
	Male	15.52	12.38-19.00	
	Nulliparous female	13.65	9.57-19.00	
GRFS	Parous female	11.48	7.19-16.87	0.000
	Male	41.41	37.32-45.43	
	Nulliparous female	36.01	30.17-41.87	
RI	Parous female	21.26	14.22-31.77	0.00
	Male	39.24	33.53-45.93	
	Nulliparous female	46.51	37.35-57.91	
OS	Parous female	49.17	41.57-56.31	0.039
	Male	56.32	52.12-60.29	
	Nulliparous female	48.61	42.48-54.45	

aGVHD indicates acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; CI, confidence interval; CR2, second complete remission; GFRS, graft-versus-host disease free relapse free survival; OS, overall survival; RI, relapse incidence.

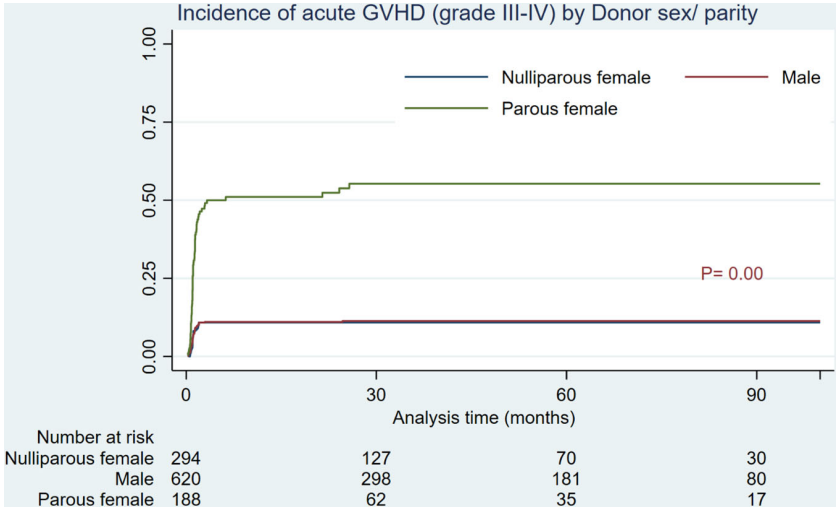

FIGURE 1
Cumulative incidence of grade III-IV acute GVHD by donor sex/parity.

On the other hand, the 5-year OS among individuals transplanted from parous female donors was comparable to those from nulliparous females but significantly reduced than recipients of male donors (Table 2). Donor age, recipient age and sex, disease status, and primary disease were all significantly associated with OS in univariate analysis. Moreover, in multivariate analysis, primary disease of AML (HR= 0.64, P= 0.00) was shown to be the only predictive factor for better OS, whereas donor's age of ≥ 32 and disease status of ≥ CR2 were significant predictors for a lowered OS (HR= 1.40 and HR= 1.59, respectively) (Table 3).

Considering sex matches, female donors for male recipients (F-M) were found to be associated with significantly higher incidences of grade III-IV aGVHD and extensive cGVHD when compared to the other sex matches that were combined into one group. However, there were no significant differences in 5-year RI (results not shown).

Discussion

Suitable donor selection is vital for reducing risks and improving outcomes, constituting an essential part of the clinical transplantation procedure. Numerous research has been conducted to evaluate the predictors of outcomes following allo-HSCT. Among the variables analyzed, donor parity is an aspect that has got the least attention, and its impact on HSCT outcomes and GVHD is disputed. Our study aimed to investigate the outcomes of allo-HSCT over a decade-long period, with a specific focus on

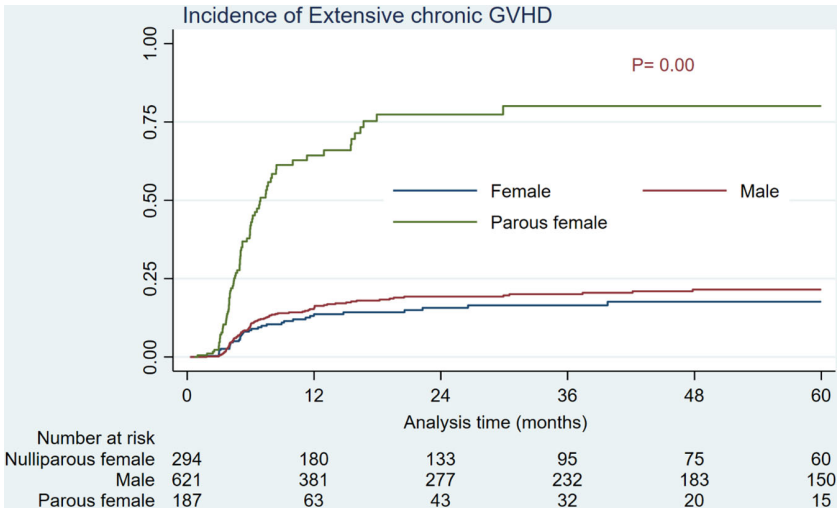

FIGURE 2
Cumulative incidence of extensive chronic GVHD by donor sex/parity.

TABLE 3 Multivariable Cox regression analyses for the outcomes.

Outcome	Variable	*P*	HR	95% CI
Grade III-IV aGVHD	Donor age (≥ 32 vs. < 32)	0.031	1.534	1.040-2.264
	Donor sex (male vs. female)	0.791	0.942	0.605-1.467
	Parous female donor vs. not	0.000	3.908	2.470-6.184
	Recipient age (≥ 32 vs. < 32)	0.907	0.979	0.684-1.401
	Primary disease (AML vs. ALL)	0.900	1.021	0.736-1.417
Extensive cGVHD	Donor age (≥ 32 vs. < 32)	0.939	1.013	0.724-1.417
	Donor sex (male vs. female)	0.499	1.146	0.772-1.701
	Parous female donor vs. not	0.000	4.623	3.024-7.067
	Recipient age (≥ 32 vs. < 32)	0.439	1.137	0.821-1.575
	Primary disease (AML vs. ALL)	0.202	1.219	0.899-1.651
RI	Parous female donor vs. not	0.020	0.616	0.410-0.928
	Recipient age (≥ 32 vs. < 32)	0.688	0.950	0.741-1.219
	Recipient sex (male vs. female)	0.011	1.388	1.079-1.785
	Primary disease (AML vs. ALL)	0.000	0.583	0.457-0.745
	Disease status (≥ CR2 vs. CR1)	0.000	1.861	1.449-2.391
GRFS	Donor age (≥ 32 vs. < 32)	0.004	1.305	1.089-1.565
	Donor sex (male vs. female)	0.207	0.887	0.737-1.068
	Parous female donor vs. not	0.000	2.266	1.802-2.850
	Recipient age (≥ 32 vs. < 32)	0.563	0.949	0.796-1.132
	Primary disease (AML vs. ALL)	0.023	0.834	0.713-0.975
OS	Donor age (≥ 32 vs. < 32)	0.001	1.405	1.141-1.729
	Parous female donor vs. not	0.147	1.189	0.941-1.502
	Recipient age (≥ 32 vs. < 32)	0.547	0.938	0.762-1.155
	Recipient sex (male vs. female)	0.080	1.179	0.981-1.418
	Primary disease (AML vs. ALL)	0.000	0.644	0.535-0.775
	Disease status (≥ CR2 vs. CR1)	0.000	1.592	1.309-1.937

aGVHD indicates acute graft-versus-host disease; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; cGVHD, chronic graft-versus-host disease; CI, confidence interval; CR2, second complete remission; GFRS, graft-versus-host disease free relapse free survival; HR, hazard ratio; OS, overall survival; RI, relapse incidence.

grafts obtained from female donors who had a history of previous pregnancy.

We observed that grade III-IV aGVHD and extensive cGVHD incidences were significantly higher in recipients who received the graft from parous female donors compared to the grafts from male and nulliparous donors. This finding lends credence to the concept that an alloimmunization induced during pregnancy may result in prolonged immune activation, which in turn might elevate the risk of acute and chronic GVHD. In contrast, the 5-year RI in recipients of parous female donors was approximately half that of recipients of male or nulliparous donors. Donor parity was also found to have no significant effect on survival, suggesting that the predictive effect of donor parity on higher incidences of grade III-IV aGVHD and extensive cGVHD can be compensated by the advantage of increasing graft-versus-tumor effect and a lower risk of relapse, leading to no noticeable impact on survival. However, the 5-year GRFS for allo-HSCT from parous donors was much lower compared to other donor types.

Reports regarding the impacts of donor parity on HSCT outcomes need to be more consistent. The study of Flowers et al. (20) on the patients with aplastic anemia who received the HSCT from HLA-identical siblings described the donor parity as a significant risk factor for the incidence of grade II-IV aGVHD compared to nulliparous female donors (RR= 2.5, P= 0.02). The research conducted by Loren et al. (2) also displayed an elevated risk for aGVHD in HSCT from parous women (unadjusted HR= 1.16, P= 0.04) compared to male or nulliparous female donors. In our study, the robust predictive impact of donor parity on grade III-IV aGVHD incidence, along with donor age, persisted regardless of other possible confounding factors (HR= 3.90, P= 0.00). On the other hand, Przepiorka et al. (17) observed that the gestation history of the donor did not affect the hazard for grade II-IV aGVHD incidence

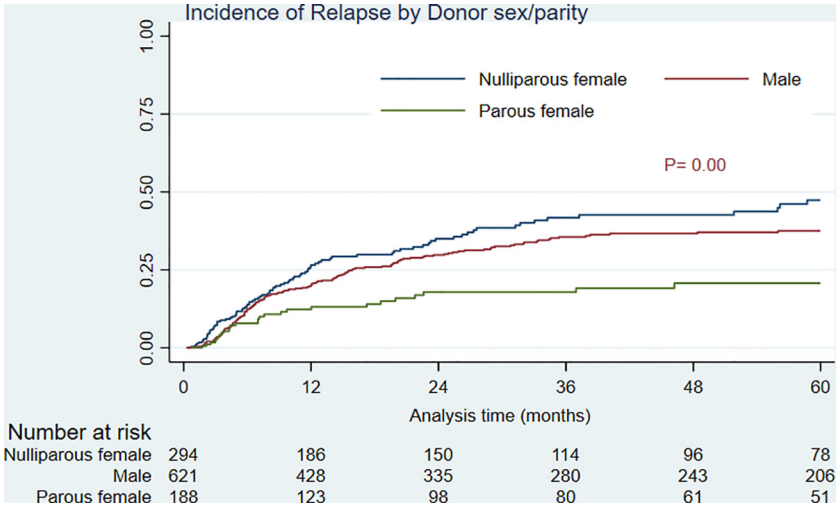

FIGURE 3
Relapse incidence by donor sex/parity.

in recipients of HLA-matched related donors. However, donor parity along with donor-recipient sex mismatch appeared to be significant risk factors for aGVHD of grades II-IV (P= 0.001) in the study by Nash et al. (21). Another study conducted by Gale et al. (11) also showed that compared with other donor-recipient sex combinations, the female-to-male combination was associated with significantly higher incidence of moderate to severe aGVHD especially in case of parous female donors.

Similar to the results of our analysis, the donor parity was not a significant risk factor for poor survival in the multivariate Cox regression model conducted by Flowers et al. (RR= 1.6, P= 0.30); however, they showed the survival rate was worse among the patients transplanted from parous females than the recipients from nulliparous females (47% vs 68%) (20). The analysis by Loren et al. (2) also did not find any effect of donor parity on OS among the patients who underwent the HSCT from HLA-identical siblings in the multivariate model fitted.

Data provided by the Center for International Blood and Marrow Transplant Research (CIBMTR) in a large cohort study revealed that donor sex, donor pregnancy history, and recipient age were significantly associated with the onset of cGVHD (2), while donor parity was the sole variable that significantly influenced the risk of extensive cGVHD in our study. Regarding the augmented risk of cGVHD, the predictive effects of other factors such as aGVHD grades I-IV, males receiving grafts from allo-immunized females, and donors age have all been recognized significant in the multivariate analyses by previous studies (10, 22–24).

Regarding the relapse incidence, we found donor parity was significantly associated with decreased relapse risk. This was inconsistent with the results obtained by Loren et al. (2), who failed to identify any relationship between donor parity and RI. In the case of GFRS, we did not find any study in the literature to assess the effect of donor parity post-HSCT.

The discrepancy between our findings and the results of other studies can be due to the different protocols and wide heterogenicity such as sources of graft, conditioning and GVHD prophylaxis regimens, as well as demographic characteristics of the donors and recipients. This study has several benefits and limitations. As an advantage, we selected a homogenous population of patients to minimize the effects of potential confounding variables as few as possible. For this goal, all included patients had undergone the HSCT from the peripheral blood as the single source of the graft, together with identical Bu-based MAC and GVHD prophylaxis regimens. However, the study was limited by its retrospective design, dearth of data regarding immune reconstitution, and absence of information regarding cytogenetic or molecular examinations. A further limitation is that the study's data was restricted to the donor's parity evaluation and lacked information about the number and sex of the children.

Conclusion

This study casts light on the influence of donor parity on outcomes following HLA-identical allogeneic HSCT. However, our data showed that the predictive impact of donor parity on higher incidences of grade III-IV aGVHD and extensive cGVHD can be counterbalanced by the benefit of increasing graft-versus-tumor effect and a lower risk of relapse, resulting in no significant effect on survival, although it led to poorer GRFS. The findings highlight the importance of non-HLA factors in shaping GVHD incidence, relapse rates, and overall survival. This information equips clinicians with valuable insights for making informed decisions about donor choice and effectively managing potential GVHD risks.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. The corresponding author can provide the datasets created during the current investigation upon reasonable request.

Ethics statement

The studies involving humans were approved by Research Institute for Oncology, Hematology, and Cell Therapy (HORCSCT), Tehran University of Medical Sciences, Tehran, Iran. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MA: Writing – original draft, Data curation. MB: Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & editing. TB: Conceptualization, Supervision, Investigation, Writing – review & editing. SR: Data curation, Writing – review & editing. HKF: Data curation, Writing – review & editing. SAM: Data curation, Writing – review & editing. STS: Data curation, Writing – review & editing. MA: Data curation, Writing – review & editing. PS: Writing – review & editing. MV: Data curation, Project administration, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case report: Difficult diagnosis of *Mycobacterium tuberculosis* infection in patients after allogeneic hematopoietic stem cell transplantation: two case reports and a literature review

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Background: *Mycobacterium tuberculosis* (MTB) is a relatively infrequent infection encountered during hematopoietic stem-cell transplantation (HSCT). The identification of MTB following HSCT remains a complex task, with delayed detection and misdiagnosis potentially resulting in unfavorable outcomes. Metagenomic next-generation sequencing (mNGS) represents a novel, highly sensitive, and rapid diagnostic tool in clinical settings for discerning intricate infections and detecting exceedingly rare pathogens

Methods: With the aid of mNGS, we diagnosed MTB in the lymph nodes and lungs of two patients with hematological diseases following allogeneic peripheral blood hematopoietic stem cell transplantation. Both patients presented with a fever, localized symptoms, and clinical signs. Following inconclusive results from routine tests, impractical biopsy procedures, and unsuccessful responses to empirical treatments, mNGS was employed as a final recourse, revealing DNA fragments of MTB in blood samples.

Results: The diagnoses were ultimately confirmed in conjunction with additional clinical evidence. The application of mNGS in MTB cases after allogeneic HSCT has rarely been reported. The mNGS technique can provide a prompt and highly sensitive indication leading to the definitive diagnosis of MTB in complex post-transplant scenarios.

KEYWORDS

MTB (*Mycobacterium tuberculosis*), mNGS (metagenomic next-generation sequencing), allo-HSCT, diagnosis, case report

1 Introduction

Due to transient or persistent deficiency in cellular and humoral immunity, recipients of hematopoietic stem cell transplantation (HSCT) are often vulnerable to infections caused by opportunistic and foreign microbes, especially in allogeneic HSCT. The incidence of *Mycobacterium tuberculosis* (MTB) in HSCT recipients varies, ranging from 0.4% in nonendemic areas to approximately 16% in endemic areas, which is higher than that in immunocompetent populations in the same region (1–4). Several retrospective analyses have indicated that HSCT recipients face a heightened susceptibility to MTB infection, especially in the presence of factors such as mismatched HLA transplantation, acute or chronic graft-versus-host disease (GVHD), and total body irradiation (TBI) (2, 5).

Due to atypical and nonspecific clinical presentations (2), along with the limitations of less sensitive tests and the impracticality of biopsy procedures due to associated risks such as bleeding and other complications, the diagnosis of MTB remains challenging in patients following allogeneic HSCT. A novel technique known as metagenomic next-generation sequencing (mNGS) has emerged as a sensitive and rapid method for detecting DNA and RNA fragments of various microorganisms present in clinically suspected samples without the need for *in vitro* culturing and amplification. This advanced approach has been increasingly utilized in cases of complex infections where conventional clinical microbiological assays have proven ineffective (6). In the context of two reported cases of MTB infection following allogeneic HSCT, the diagnosis heavily relied on the application of mNGS technology.

2 Transplantation protocol and mNGS protocol

2.1 Transplantation protocol

Case 1 was diagnosed with acute myeloid leukemia (AML) with myelodysplasia-related changes, while case 2 had classical Hodgkin's lymphoma. Both cases underwent peripheral stem cell transplantation from fathers who were five of 10 human leukocyte antigen (HLA)-matched. The conditioning regimen for case 1 was busulfan, fludarabine, cytarabine (BFA), which included busulfan 0.8 mg/kg every 6 h from days −8 to −5, fludarabine 30 mg/m^2 daily from days −8 to −4, and cytarabine 2 g/m^2 daily from days −8 to −4. Case 2 received a conditioning regimen of busulfan, fludarabine, melphalan (BFM), which consisted of busulfan 0.8 mg/kg every 6 h from days −9 to −7, melphalan 50 mg/m^2 daily from days −7 to −6, and fludarabine 30 mg/m^2 daily from days −6 to −2. The protocol for GVHD prophylaxis involved four drugs following the Beijing mode for haploidentical HSCT: Cyclosporine A was administered at a dose of 3 mg/kg/day via continuous infusion over 24 h from day −1 to achieve a targeted therapeutic concentration ranging from 200 to 300 ng/mL; short-term methotrexate (MTX) was initiated at 15 mg/m^2/day on day +1 and 10 mg/m^2/day on days +3, +6, and +11; mycophenolate mofetil (MMF) was taken orally at 1.0 g twice daily from days +1 to +30, with a gradual tapering off until day +60 if no acute GVHD occurred, and rabbit antihuman thymocyte globulin (r-ATG, Genzyme Polyclonals S.A.S, France) was given at 2.5 mg/kg on days −5 and −2.

2.2 mNGS protocol

Blood samples were collected from patients following the requirements for mNGS testing and storage. Nucleic acid extraction from blood samples was fragmented to yield 150-bp to 200-bp fragments, and DNA fragments were constructed using an end-repair method. The MGISEQ-2000 platform was used for sequencing by BGI Patho-Genesis Pharmaceutical Technology Co. Ltd, China. The low-quality data and data less than 35 base pairs in length were removed to obtain high-quality sequencing results. The human nucleic acid sequence data were removed using Burrows–Wheeler Aligner (BWA) software alignment. The remaining data were compared with a dedicated microbial database downloaded from NCBI after removing low-complexity sequences. The sequenced data were then classified and arranged according to viruses, bacteria, fungi, and parasites.

3 Cases

3.1 Case 1

A 25-year-old man was diagnosed with AML with myelodysplasia-related changes. He was treated with cytarabine and daunorubicin before undergoing transplantation. Prior to transplantation, various tests, such as T-SPOT (The interferon gamma release assay), lung CT, and abdominal CT, were conducted to rule out evidence of tuberculosis infection. He received granulocyte colony-stimulating factor-mobilized peripheral blood stem cells (PBSCs) from his biological father after a myeloablative conditioning regimen, including CD34$^+$ cells at 4.8 × 10^6/kg and CD3$^+$ cells at 4.7 × 10^8/kg. The GVHD prophylaxis was administered as previously mentioned. Neutropenic fever was managed effectively with meropenem during the neutropenic period. Neutrophil and platelet engraftment were achieved on days +14 and +13, respectively. Subsequently, the patient experienced fever and abdominal pain from day +26. A lung CT showed only small nodules in both lungs and faint shadows in the lower lobe of the left lung. No typical imaging findings of tuberculosis were found. Isolated peritoneal multiple enlarged lymph nodes were identified through contrast abdominal CT scan and B-ultrasonography. The maximal size of lymph nodes was 1.57 cm × 1.08 cm, without the involvement of superficial lymph nodes. Potential causes of fever and lymphadenopathy, such as post-transplant lymphoproliferative disease, were ruled out, and routine examinations for MTB were negative. After unsuccessful empirical anti-infection therapies and the impracticality of performing a biopsy on peritoneal lymph nodes, mNGS was attempted. During episodes of fever, 5 mL of blood was collected and analyzed for the presence of MTB DNA fragments. Subsequently, experimental anti-MTB treatment with isoniazid, rifampin, and pyrazinamide was initiated, resulting in the resolution

of fever and abdominal pain after 2 weeks. Shrunken lymph nodes were noticed on a CT scan during a later follow-up. A tentative diagnosis of MTB was confirmed. Cyclosporine A was gradually tapered on day +120 and discontinued by day +180 after allogeneic HSCT. The patient experienced mild and localized chronic GVHD post-HSCT without systemic administration of corticosteroids. Anti-MTB therapies were continued until 1 year after HSCT. Presently, over 3 years have passed, and the patient has resumed normal activities without any further complications or recurrence of MTB.

3.2 Case 2

A 27-year-old man has been diagnosed with classical Hodgkin's lymphoma IIA (IPSS). He received ABVD, ICE, DECP, GDP regimens, and autologous transplantation. However, the disease recurred 5 months after autologous transplantation and recurred again after achieving remission with PD-1 inhibitor treatment. Later, he was treated with decitabine in combination with sindilizumab, a CD30 monoclonal antibody combined with bendamustine, and bendamustine as monotherapy. He had a negative T-SPOT result before transplantation. Ultimately, he underwent haploidentical HSCT following a reduced dose conditioning regimen BFM upon achieving complete remission with CD30 monoclonal antibody and bendamustine, with consolidation using the same regimen until the washout period of the PD1 inhibitor reached 90 days. The G-CSF-mobilized PBSCs from his biological father were infused with $CD34^+$ cells at 3.7×10^6/kg and $CD3^+$ cells at 5.7×10^8/kg. The GVHD prophylaxis was intensified with a reduced dose of cyclophosphamide at 14.5 mg/kg/day on days +3 and +4 post-transplant, in addition to cyclosporine A, MTX, MMF, and ATG, as reported by Wang (7). Neutrophil engraftment was achieved on day +15, but the platelet graft failed. On day +30, he developed a fever and cough. A lung CT scan revealed a local opacity in the upper lobe of the left lung, which was different from the appearance observed in the pretransplant lung CT scan (Figures 1–3). Empirical anti-infection therapies were immediately initiated, including antibiotics, while screening was done for bacteria, fungi, viruses, and parasites to identify the underlying cause. Consequently, due to the lack of positive results from the laboratory, poor response to the treatment, infeasibility of bronchoalveolar lavage (BAL) due to poor condition, and low platelet count, we conducted mNGS again to scan for pathogens in the blood samples. A DNA fragment of MTB was identified on day +45 and subsequently examined for its presence in sputum samples. Finally, MTB was successfully isolated on day +50.

Since the probable diagnosis of pulmonary tuberculosis (TB) was established, anti-MTB therapy was initiated with isoniazid, rifampin, and pyrazinamide. As a result, the body temperature dropped. Unfortunately, on day +46, the patient developed transplant-associated thrombotic microangiopathy (TA-TMA), characterized by the presence of protein in the urine, hypertension, heavy reliance on red blood cell (RBC) and platelet transfusions, elevated blood LDH levels, and the presence of schistocytes. Discontinuation of cyclosporine A, initiation of eculizumab (an antibody against complement C5), and plasma exchange therapy were all attempted, but the patient succumbed to multiorgan failure.

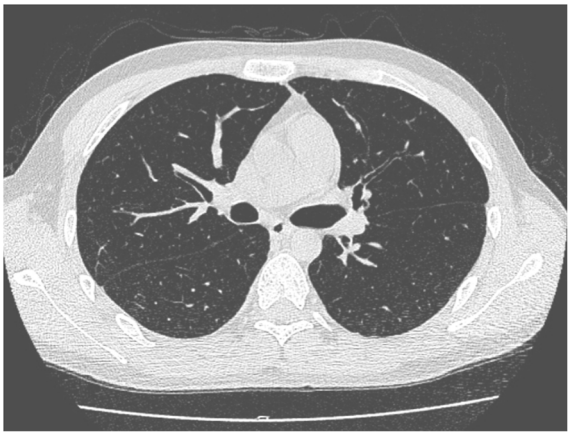

FIGURE 1
Case 2 lung CT on day –18.

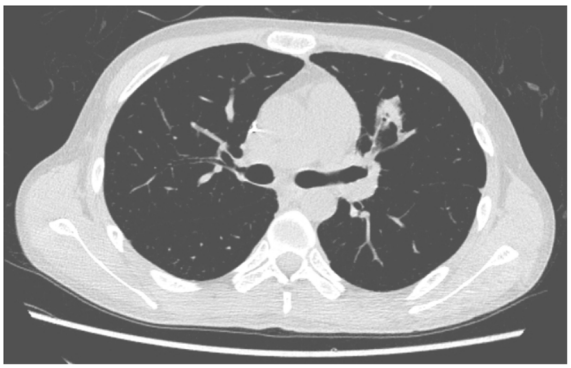

FIGURE 2
Case 2 lung CT on day +31.

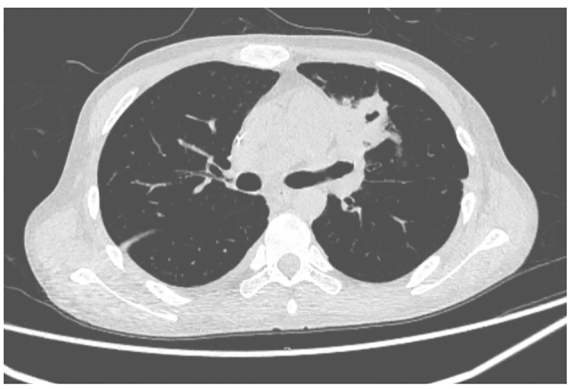

FIGURE 3
Case 2 lung CT on day +48.

4 Discussion

Research has indicated that changes in Th1 cell response in hematological diseases, either due to the diseases themselves, anti-hematologic tumor treatments, or hematopoietic stem cell transplantation (often involving the use of high doses of corticosteroids), may result in compromised immune function. This compromised immunity is a significant factor in the progression from latent TB infection to active TB (8). After undergoing allogeneic HSCT, individuals with persistent cellular immunodeficiency are susceptible to various pathogens, such as bacteria, fungi, viruses, and parasites. In this particular case study, two instances of MTB infection were diagnosed using mNGS after conventional screenings failed to detect MTB infection, underscoring the diagnostic utility of mNGS in complex scenarios post-allogeneic HSCT. So far, no similar reports have been documented.

The identification of active MTB infection after transplantation remains a complex task (1). One primary challenge is the reduced specificity of diagnosis due to exposure to broad-spectrum antibiotics aimed at preventing or managing common bacterial infections. Additionally, complications may arise if the individual is coinfected with other microorganisms after HSCT. Another significant hurdle is the limited availability of sensitive and specific diagnostic tools for TB, which are crucial for accurate diagnosis. While TB culture is considered the gold standard, its sensitivity is relatively low, and the process is time-consuming (Table 1). Immunological methods are often unsuitable for HSCT patients undergoing immunosuppressive therapy. Targeted polymerase chain reaction (PCR) methods have been developed to adapt to the evolving nature of the disease, including its epidemiology and global resistance patterns (11, 16). Notably, advanced diagnostic tools such as X-pert MTB/RIF and the highly sensitive but less popular Xpert MTB/RIF Ultra, recommended by the World Health Organization (WHO), were not accessible to the patients in this study. Furthermore, the risk of bleeding or poor performance after HSCT can impede the feasibility of conducting biopsies. Consequently, delays in diagnosing clinically active TB infections are common, leading to unfavorable outcomes and increased mortality rates (20).

Currently, there is an urgent demand for more sensitive and reliable diagnostic tools. Metagenomic next-generation sequencing is a comprehensive method that involves sequencing entire microbial nucleic acid fragments in suspected samples and analyzing and comparing them with a microbiome database to detect potential microbial species. This method offers several advantages and disadvantages (6, 21). It retrieves all DNA without bias and is a sensitive, specific, and rapid method for detecting pathogens present in clinical samples without the need for *in vitro* culture or amplification. It reveals the true status of all copathogens in suspected samples without any data loss, particularly for slowly and poorly growing pathogens *in vitro*. It can recognize both known and unknown pathogens without requiring specific conditions, like particular primers for PCR. It can detect uncommon pathogens and microbes within human cells, such as MTB, and contributes as a supplementary tool in diagnosis by providing a clue to providing a definitive diagnosis. In comparison with Xpert MTB/RIF, mNGS exhibits higher sensitivity in detecting pulmonary and extra-pulmonary samples, particularly in cases of MTB meningitis (18, 19). For complex infections caused by multiple pathogens, mNGS could identify all pathogens simultaneously, preventing the oversight of other causative microbes subsequent to the identification of MTB with Xpert MTB/RIF. However, the disadvantages of mNGS include background noise from the human DNA genome, interference from noncausative pathogens, the absence of uniform standards for the entire procedure, and the standardization of the bioinformatics analysis process. Therefore, combined with the

TABLE 1 The advantages and limitations of typical diagnostic methods for *Mycobacterium tuberculosis*.

Detections	Advantages	Limitations
Microscopy smear	Low cost	Hard to distinguish between *Mycobacterium tuberculosis* and nontuberculous mycobacteria (9)
	Rapidity (10)	Low sensitivity and poor positive rate (11)
Culturing of mycobacteria	Widely used	Time-consuming (12)
	Low cost	Low sensitivity and poor positive rate
	Gold standard	Production of harmful aerosols (13)
Xpert MTB/RIF	High cost	Analysis limited to specific mutations for few antibiotics (14, 15)
	Rapidity (10)	Lack of detection of heteroresistance (16)
	Drug resistance detection (17)	
	High sensitivity and specificity (14)	
mNGS	Detection of numerous mutations for a large panel of antibiotics	Expensive
	Detection of heteroresistance (16)	Time-consuming
	High sensitivity in pulmonary and extra-pulmonary samples, especially in MTB meningitis (18, 19)	Sequencing certain parts of genome (16)
	Identifying all pathogens	Interference of noncausative pathogens
WGS	Detection of all putative mutations for all antibiotics	Expensive
	Sequencing the entire genome	Time-consuming

MTB culture and Xpert MTB/RIF, it has the potential to significantly enhance diagnostic efficacy.

The concentration of MTB in blood samples is lower compared to sputum samples for pulmonary MTB. Despite this, blood samples are preferred over sputum samples for mNGS due to reduced microbial background interference and to avoid using unqualified sputum samples. Moreover, mNGS with high sensitivity could compensate for the low numbers of DNA copies in the blood samples (18). Certainly, it is imperative to meticulously analyze the positive outcomes to ascertain their relevance to the clinical context. For instance, in case 2, initial attempts to isolate MTB from sputum yielded negative results. After persistent efforts, we finally achieved the target of detecting MTB in blood using mNGS. In case 1, diagnosing isolated lymph node tuberculosis proved challenging due to the patient's poor post-allo-HSCT condition, which did not allow for safe invasive and histological procedures. Metagenomic next-generation sequencing of blood samples finally identified MTB DNA, validated by the treatment outcome and clinical matches. Studies have shown that mNGS is more suitable when the patient presents with unexplained manifestations beyond traditional assays or atypical symptoms, such as fever, dyspnea, and elevated inflammatory markers. It is also recommended when there is a strong suspicion of a multipathogen infection, in cases where the patient is in critical condition, and when timely and comprehensive detection results are crucially needed (22).

Various innovative diagnostic techniques for tuberculosis have been introduced. For instance, researchers are exploring the potential use of tongue swabs as an alternative to collecting sputum for diagnosing TB. The authors argue that while molecular diagnostics for TB are highly sensitive, their feasibility is constrained in resource-limited settings due to expensive equipment and inadequate infrastructure. Additionally, collecting sputum for TB diagnosis presents challenges and risks associated with the production of harmful aerosols. The study provides evidence supporting the possibility of detecting TB from a tongue swab without the requirement for DNA extraction or purification processes (13). Whole-genome sequencing (WGS) is widely recognized as the global benchmark for characterizing MTB isolates (23–25). WGS demonstrates exceptional discriminatory capability and offers a comprehensive approach to anticipating antibiotic resistance based on genotype. Nevertheless, additional clinical validation is necessary for these methods.

MTB infection after allo-HSCT is relatively less common than in solid organ transplantation (1, 2). This disparity may be attributed in part to the administration of antibiotics during the neutropenic phase of transplantation, especially fluoroquinolone, which is routinely used as prophylaxis for bacterial infection and actually has potential ability against MTB (2, 26, 27). However, neither of the two cases in our report received fluoroquinolones for various reasons. The diagnosis of MTB infection in our report was established on days +30 and +50, respectively, which is shorter than the timelines reported in most reports (2, 3). The reason is probably related to the endogenous reactivation of MTB (2), and there is no infection prophylaxis with fluoroquinolone during neutropenia. The high sensitivity of mNGS may provide an early indication for the prompt confirmation of MTB diagnosis. However, this case report is still limited due to the small number of cases, and it would be preferable to have a larger sample size to validate this technique in order to demonstrate that the presence of positive DNA in the blood truly reflects active infection rather than latent infection.

5 Conclusions

In conclusion, the diagnosis of MTB post-HSCT is still difficult, and mNGS might be an important technique for complicated infections, supplying important clues to the final diagnosis.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ZL: Writing – original draft. DC: Writing – review & editing. NS: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Hematopoietic stem cell transplantation: an Italian monocentric experience on the health assessment and eligibility of adult-related donors

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Introduction: Indications for HSCT are increasing worldwide, paralleled by a growing demand for donors of therapeutic cells.

Methods: Herein, we report our real-world experience of adult HPC donor assessment during a 5-year study period (2018–2023): we have retrospectively revised data of 455 potential related stem cell donors, consecutively evaluated at our center. Donor medical history was assessed by a questionnaire and an interview with a trained physician experienced in donation procedures to evaluate donor fitness and medical history. Pre-existing health disorders were fully investigated. Behavioral risk factors for communicable infectious diseases were also routinely explored.

Results and discussion: Overall, 351 donors were finally assessed as eligible for HPC donation, and 233 underwent stem cell collection, 158 through apheresis from mobilized peripheral blood, and 75 through bone marrow harvest. Among them, 27 donors were selected despite the presence of pre-existing health conditions, which would be potential exclusion criteria for unrelated donors: 16 suffered from well-controlled cardiovascular diseases (CVD) and 11 from allergic diathesis. Most of the selected donors with pre-existing disorders were candidates for apheresis HPC collection (21, 77.8%), while only six (22.2%) underwent BM harvest. We then analyzed the data relative to the corresponding 233 allogeneic HSCT to explore if the presence of pre-existing diseases in the donors could show any association with transplant characteristics. Transplants from CVD and allergy donors showed no significant disparities in comparison with those from healthy donors. A significant difference emerged regarding the disease severity, with a higher proportion of patients with high/very high disease risk index (DRI) among those receiving grafts from CVD donors (68.7% in transplants from CVD donors versus 36.0% in transplants from healthy donors, p=0.005). Multivariate analysis confirmed that high/very high DRI patients had an increased probability of receiving donations from CVD donors (OR, 4.89; 95%CI, 1.15–20.86; p=0.031). Among donors with well-controlled pre-existing conditions, no adverse events were recorded during stem cell

collection or at follow-up. Our results suggest that in patients at high risk for relapse requiring a prompt allogeneic transplant, a familiar donor might be accepted for HPC apheresis donation on less strict criteria than unrelated donors, without risk for both donor and patient.

KEYWORDS

related donor, donor assessment, eligibility criteria, hematopoietic stem cell transplantation, engraftment

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an established treatment for a wide range of acquired or congenital disorders (1–4). At present, available stem cell sources include bone marrow (BM), mobilized peripheral blood (PB), and cord blood. Indications for HSCT are increasing worldwide, paralleled by a growing demand for donors of therapeutic cells. The practice of haploidentical HSCT, together with the advances in transplant technique, supportive care, and conditioning regimens, allows the treatment of older patients with elderly familial donors or donors with comorbidities, imposing different challenges to hematologists (5, 6). Pretransplant hemopoietic progenitor cells (HPC) donor assessment and testing are critical processes that affect the quality and safety of donation. Many issues on donor safety have been addressed in recent years, but most data are collected from unrelated donors, while consistent information from related donors is sparse (7). For unrelated donors, detailed recommendations for the health assessment have been published (8, 9), allowing HPC donations only if they are in good health, without any medical conditions. The donors must have a performance status that permits safe apheretic HPC collection or be able to tolerate anesthesia during BM harvest, with adequate cardiac, pulmonary, hepatic, and renal function. Eligibility criteria for related donors are less rigorous and may vary between centers. In 2015, the Worldwide Network for Blood and Marrow Transplantation (WBMT) Standing Committee developed a consensus document with recommendations for donor workup and final clearance of family donors who were not eligible as unrelated donors because of their age or pre-existing diseases (10). The document has been recently updated (11). Despite that specific diagnosis and/or disease severity directly imply the donor exclusion, the presence of other well-controlled conditions may be overcome and does not prevent per se the donation.

Herein, we report our real-world experience of HPC donor assessment during a 5-year study period (January 2018–October 2023); we have retrospectively revised anamnestic data of potential related stem cell donors, consecutively evaluated at our center. The study aims to explore if the presence of one or more pre-existing health disorders in donors deemed eligible according to the recent WBMT recommendations (11) may have an impact on transplant outcomes.

Methods

Study population

We conducted a retrospective observational study, including potential related donors consecutively evaluated at the Transfusion Medicine Department of Fondazione Policlinico A. Gemelli IRCCS of Rome (Italy) and allo-HSCT consecutively performed from selected related donors at the Transplant Unit of the same hospital between 1 January 2018 and 31 October 2023. Transplants with BM grafts (HPC Marrow, HPC-M) and PB apheresis collections (HPC Apheresis, HPC-A) were included, while transplants with cord blood units were excluded from the study.

The study followed the tenets of the Declaration of Helsinki and received approval from the Ethics Committee of Fondazione Policlinico Universitario A. Gemelli IRCCS (Prot. 0030921/20).

Donor assessment

All donors were qualified according to JACIE standards (12) and Italian National regulation for transfusion activities (13, 14).

Donor medical history was assessed by a questionnaire and an interview with a trained physician experienced in donation procedures, to evaluate donor fitness, medical history, and willingness to donate before HLA-typing. Pre-existing health disorders were explored to exclude inherited or genetic coexisting diseases and behavioral risk factors for communicable infectious diseases. Donors characteristics that resulted in deferral from HPC donation were grouped into 11 categories according to WBMT standards (11): 1) infectious disease, 2) autoimmune disorders (AID), 3) low weight (defined as a weight lower than 50 kg), 4) abuse of alcohol or drugs, 5) CVD), 6) promiscuous sexual activity or cohabitation with hepatitis carriers, 7) allergic diathesis, including drug allergies, 8) lack of proper venous access, 9) history of cancer, 10) recent history of major surgery, and 11) other conditions. CVD specifically comprise arterial hypertension, hypotension, coronary heart disease, disturbance of heart rate and rhythm, congestive heart failure, cardiomyopathy, valvular heart disease, pericarditis, myocarditis, atherosclerotic peripheral vascular disease, aortic aneurism, and cardiac surgery for congenital heart disease.

According to the updated WBMT standards (11), donors affected by CVD are eligible for HPC apheresis collection if the American Society of Anesthesiology Physical Status (ASA-PS) classification (15) are ≤2, according to the European Society of Anaesthesiology (ESA) (16) and American College of Cardiology/American Heart Association guidelines (17). Among the autoimmune disorders, diseases with systemic multiorgan involvement are investigated such as ankylosing spondylitis, polymyositis, arteritis, dermatomyositis, polymyalgia rheumatic, arteritis, antiphospholipid antibody syndrome, multiple sclerosis/optic neuritis, systemic lupus erythematosus, scleroderma, Sjögren's syndrome, vasculitis syndromes, and Behçet's (11). Among single-organ autoimmune diseases, Hashimoto thyroiditis, Graves' disease, pernicious anemia, psoriasis, alopecia areata, and vitiligo are included (11).

Laboratory tests were performed on HPC donors deemed potentially eligible according to their medical history and after collecting a medical interview. These tests included complete peripheral blood count, serum creatinine, electrolyte and liver function studies, coagulation test, thrombophilia screening, microbiological screening for communicable infections (serologic studies for cytomegalovirus, herpes viruses, syphilis, anti-HIV antibodies HIV RNA, hepatitis B and C viruses, including nucleic acid amplification testing) blood typing and red cell antibody screening, human leukocyte antigen (HLA) typing, chest X-ray, electrocardiography, and abdominal ultrasound.

All donors eligible for BM harvest underwent a preventive anesthesiological assessment, while for HPC-A donors, an evaluation of peripheral vascular access was requested.

Mobilization protocol and apheresis procedures

Allogeneic peripheral blood stem cell (PBSC) donation was performed with subcutaneous (sc) administration of granulocyte colony-stimulating factor (G-CSF for days +1 to +4), followed by leukapheresis on day +5. G-CSF was administered at a standard dose of G-CSF 12 μg/kg sc daily. Prophylaxis with paracetamol was administered to prevent potential side effects of G-CSF. All collection procedures were performed at the Apheresis Unit using the COBE Spectra or Spectra Optia continuous flow cell separators (Terumo BCT, Shinagawa, Tokyo) with the mononuclear cell collection program, and a ratio anticoagulant: blood of 1:12. Anticoagulant always consisted of sodium citrate solution (Fresenius Kabi, Bad Homburg, Germany). In all patients, 2.5–3 total blood volumes (TBV, defined as the processing blood volume divided by the patient's blood volume) were processed. The apheresis procedures aimed to achieve a CD34+ cell dose of $4.0x10^6$ per kg of the recipient's body weight. If the required number of CD34+ cells/kg was not accomplished, G-CSF administration was continued, and a second collection procedure was performed on day +6. According to institutional procedures, in donors with circulating CD34+ cells <20/μL on day +5 or estimated collection harvest $<1\times10^6$/kg of the recipient's body weight, sc plerixafor at the dose of 240 μg/kg/day was planned in the consecutive night, from 4 to 6 h before leukapheresis. Red blood cell depletion in major and bidirectional AB0 mismatched transplants, and plasma removal in minor AB0 mismatched transplants, or transplants with transfused donors or female donors with previous pregnancies, were performed as previously reported (18). From March 2020 onward, all HPC products were cryopreserved. This procedure was introduced due to the COVID-19 pandemic and is still in place (19).

Bone marrow collection

BM harvest and processing were managed as previously reported (18, 20–22). The perioperative autologous donation practice was discontinued in April 2020, replaced by iron (ferric carboxymaltose 500 mg intravenous), and B12 vitamin supplementation (1 mg sc) 1 week before BM collection (22). BM was harvested from posterior iliac crests in the operating room under general anesthesia, with the goal to collect 20–22 ml/kg of the donor weight. After harvesting, donors were admitted to the Hematology Department and observed for the following 24–48 h or more, as necessary.

Donor follow-up

All donors were followed for 1 year after the donation. Hematological and biochemical tests were routinely performed at 1 week, 6 months, and 12 months after donation.

Donor, patient, and graft data

Donor variables included gender, age, weight, HLA match (HLA-identical, haploidentical, and 7/8 mismatch), and ABO match. Laboratory data included WBC and, for apheresis donors, CD34+ cell count in peripheral blood on the day of collection. Apheresis data included blood volume processed, content of total nucleated cells (TNC), and content of CD34+ cells in the apheresis product. Patient variables included basic demographics; diagnosis; date of transplant; disease status (complete remission or not), disease risk index (DRI) (23); hematopoietic cell transplantation comorbidity index (HCT-CI) (24); dates of neutrophil, platelet, and erythrocyte engraftment; the incidence of acute and chronic graft versus host disease (aGVHD and cGVHD, respectively) (25–27); relapse; and status at the last follow-up. Graft variables included source (BM or PBSC), TNC content, CD34+ cell content, and CD3+ cell content. Cell contents were expressed as cell dose (i.e., the number of cells per kilogram of the recipient's body weight) and were obtained as previously reported (28).

Study outcomes and definitions

We investigated the association of pre-donation health disorders with recipient features and transplant characteristics and outcomes, including patient's age, HCT-CI, and DRI;

conditioning regimens; neutrophil, platelet, and erythrocyte engraftment; all grade aGVHD and cGVHD; relapse; and recipient status at the last follow-up (alive or death). Neutrophil and platelet engraftments were defined as the achievement of an absolute neutrophil count (ANC) ≥ 0.5×10^9/L and a PLT count ≥ 20×10^9/L unsupported by transfusion, respectively; erythrocyte engraftment was defined as a reticulocyte count ≥ 2%. HCT-CI was defined according to Sorror et al. (24) DRI was defined according to Armand et al. (23) Diagnosis and grading of aGVHD and cGVHD were made according to standard criteria (25–27). Regimens were classified as myeloablative conditioning (MAC) or non-myeloablative (NMA) conditioning, including reduced-intensity conditioning (RIC) (18). In particular, MAC regimens consisted of fludarabine and total body irradiation (FLU-TBI; fludarabine 120 mg/m^2, followed by 9–12 Gy TBI) or thiotepa, busulfan, fludarabine (TBF; thiotepa 5 mg/kg on day −6 and −5 total; intravenous busulfan 3.2 mg/kg on day −4, −3, and −2; fludarabine 50 mg/m^2 on day −4, −3, and −2). Reduced and NMA regimens consisted of busulfan or fludarabine/TBI 2 Gy-based regimens.

Statistical analysis

Continuous variables were expressed as median with relative interquartile range (IQR) and categorical variables as n (%). Univariate analysis of continuous variables was performed by the Mann–Whitney U test or the Wilcoxon rank test, as appropriate. For categorical variables, Fisher's exact test or the χ^2 test was used, as appropriate. The association between donor status (fully eligible or eligible despite pre-existing diseases) and patients or transplant characteristics was assessed by multivariate logistic regression analysis incorporating the donor status as the dependent variable and recipients and transplant variables as covariates. The results were expressed as odds ratio (OR) with the relative 95% CI. All tests were two-sided, and a p-value <0.05 was considered statistically significant. Missing data were always <5% and were not considered. Analyses were performed using the IBM SPSS Statistics 25.0 and NCSS 10 v 10.0.19.

Results

Donor eligibility evaluation

Overall, during the study period, we examined 455 potential HSC donors (ratio M/F 240/215), accounting for a median number of 1 donor for the patient (range, 1–7). The median age at first donation screening was 39 years (IQR, 30–51). Table 1 summarizes the main characteristics of all evaluated donors.

At donor assessment, one or more pre-existing health disorders were identified (Table 1). Among 455 donors, 16 (3.6%) were excluded for previous hepatitis B and C infection, 15 (4.7%) for promiscuous sexual activities or cohabitation with hepatitis carriers, eight (1.8%) for oncological diseases, six (1.3%) for a recent history

TABLE 1 Characteristics of 455 potential HPC-related donors.

	N (%)
Median screened donors/patient	1 (1–2)
Age, years	39 (30–51)
Males/Females	240 (52.7)/215 (47.3)
Weight, kg	73 (62–84)
Previous pregnancy/abortion	121 (56.3)*
ABO/Rh typing	
O pos/neg	129 (28.4)/19 (4.2)
A pos/neg	121 (26.6)/16 (3.5)
B pos/neg	44 (9.7)/6 (1.3)
AB pos/neg	11 (2.4)/3 (0.6)
Not performed	106 (23.3)
Medical history	
Cardiovascular diseases	44 (9.7)
hypertension	24 (54.5)
arrythmia	9 (20.5)
congenital atrial septal defect	3 (6.8)
pericarditis/myocarditis/endocarditis	3 (6.8)
aortic aneurysm/ectasia	2 (4.5)
hypotension	1 (2.3)
carotid stenosis	1 (2.3)
previous myocardial infarction	1 (2.3)
Autoimmune disorders	31 (7.0)
thyroiditis	22 (71.0)
nonspecific antibodies positivity	3 (9.5)
psoriasis	2 (6.5)
coeliac disease	2 (6.5)
rheumatoid arthritis	2 (6.5)
Allergic diathesis	24 (5.3)
drugs	10 (41.7)
seasonal allergy	8 (33.3)
perennial allergy	4 (16.7)
nickel	2 (8.3)
Infectious diseases	16 (3.5)
HBV/HCV	4 (25.0)
HPV	3 (18.8)
EBV	3 (18.8)
viral pericarditis/myocarditis	2 (12.5)
tubercolosis	1 (6.3)
syphilis	1 (6.3)
malaria	1 (6.3)
prion disease risk	1 (6.3)
Oncological diseases	8 (1.8)
thyroid	2 (25)
skin	2 (25)
colon	1 (12.5)
breast	1 (12.5)
lung	1 (12.5)
uterus	1 (12.5)
Low weight	5 (1.1)
Abuse of alcohol or drugs	6 (1.3)
Promiscuous sexual activity or cohabitation with hepatitis carriers	23 (5.1)
Lack of proper venous access	14 (3.1)
Recent history of major surgery	6 (1.3)

(Continued)

TABLE 1 Continued

	N (%)
Others	25 (5.5)
medical investigations ongoing	5 (20.0)
not allergic asthma	2 (8.0)
diabetes mellitus II	1 (4.0)
benign prostatic hypertrophy	1 (4.0)
drugs	6 (24.0)
recent pregnancy	2 (8.0)
recent minor surgery/tattoo	6 (24.0)
microcytic anemia	1 (4.0)
underage	1 (4.0)
Eligible donors	351 (77.1)

*Percentage calculated on female donors.
Continuous variables are given as median (interquartile range). Categorical variables are given as a number (%).

of major surgery, and six (1.3%) for a previous history of alcohol or drug abuse. In addition, 14 donors (3.1%) were deferred from donation because of lack of peripheral venous access and five (1.1%) for a low body weight (< 50 kg). Overall, 31 donors (7% of the total), mainly female (26 F/5 M, 84% vs. 16%), were affected by one or more AID. Finally, 25 potential donors (5.5%) had several miscellaneous conditions that precluded HPC donation (Table 1).

Following our policy, we allowed HPC donation in donors with CVD if classified as ASA <3, in diabetes mellitus type 2 with no organ damage, or with allergic diathesis including drug allergies to a known pharmacological agent and nickel allergy. Accordingly, among 44 identified donors (9.7%) with CVD, 28 (63.6%) were definitively deferred from HPC donations, while 16 (36.3%) who were in well-controlled clinical conditions were deemed eligible for donation. Moreover, among 24 donors (5.3%) with allergic diathesis, 11 with allergies due to known pharmacological agents (9) or nickel allergy (2) were deemed eligible for donating.

Finally, after medical evaluation, 351 out of 455 donors were finally considered eligible for HPC donation and 233 underwent stem cell collection: 158 underwent apheresis and 75 bone marrow harvest. In total, among 233 selected donors, 27 had pre-existing well-controlled diseases, which would have prevented donation in the setting of unrelated HPC donors. Table 2 details the main features of this group of related donors. Pre-existing CVDs were equally distributed in both female and male donors, while allergic diathesis was more frequent in women. CVD donors were more frequently aged >60 years, and they more frequently were HLA-identical siblings. Conversely, drug allergies were mostly reported in the haploidentical setting. Most part of selected donors with pre-existing disorders were candidates to apheresis HPC collection (21, 77.8%), while only six (22.2%) underwent BM harvest, and they were considered suitable to be exposed to general anesthesia (Table 2).

TABLE 2 Characteristics of 27 related donors with pre-existing well-controlled clinical conditions and 206 healthy ones.

	Healthy donors N=206 (%)	CVD donors N=16* (%)		Allergy donors N=11 (%)	
Age, years	56 (45–63)	56 (46.75–58.75)		37 (32–47)	
> 60 years	11 (5.4)	3 (18.7)		1 (9)	
Male/female	130/76 (63.1/36.9)	9/7 (56.5/43.8)		4/7 (36.4/63.6)	
Weight, kg	72 (62–83.3)	82.5 (68.5–94)		62 (55–91)	
Type of disorder	–	Hypertension	10 (62.5)	Drug allergy	9 (81.8)
	–	Hypotension	1 (6.3)	Nickel allergy	2 (18.2)
	–	Arythmia	1 (6.3)		
	–	Carotid stenosis	1 (6.3)		
	–	Atrial septal defect	1 (6.3)	–	–
	–	Aortic aneurysm	2 (12.3)	–	–
Previous pregnancy/ abortion	40 (52.6)**	5 (71.4)**		6 (85.7)**	
ABO major/ bidirectional	51 (24.8)	3 (18.8)		0	
HLA match					
HLA-identical sibling	75 (36.4)	10 (62.5)		4 (36.4)	
Haploidentical sibling	130 (63.1)	6 (37.5)		7 (63.6)	
7/8	1 (0.5)	0		0	
Stem cell source *PBSC* *BM*	 137 (66.5) 69 (33.5)	 14 (87.7) 2 (12.3)		 7 (63.6) 4 (36.4)	

*Including one donor with diabetes mellitus type II.
**Percentage calculated on female donors.
CVD, cardiovascular diseases; HLA, human leukocyte antigen; PBSC, peripheral blood stem cell; BM, bone marrow. Continuous variables are given as median (interquartile range). Categorical variables are given as number (%).

Graft collection

No adverse events were observed during mobilization or collection. Among 158 HPC-A donors, 141 (89.2%) underwent one single collection procedure, while in 17 cases (10.8%), a second collection procedure was performed to achieve the required CD34+ cell dose (Table 3). Moreover, two HPC-A donors received plerixafor the night between day+5 and day +6 after starting of G-CSF. Five donors (3.2%) received a low prophylactic dose of enoxaparin the evening before stem cell apheresis because of hereditary thrombophilia without a personal medical history of venous thromboembolism (two heterozygous factor V Leiden, two protein S deficiency, and one antithrombin III deficiency). Neither thrombotic nor hemorrhagic complications were subsequently observed. Regarding donors with pre-existing well-controlled medical conditions, only one apheresis donor with CVD

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TABLE 3 Characteristics of stem cell collections grouped according to the medical history of HPC-related donors.

	Healthy donors N=206 (%)			CVD donors N=16 (%)			Allergy donors N=11 (%)		
	BM 69 (33.5)	PBSC 137 (66.5)		BM 2 (12.3)	PBSC 14 (87.7)		BM 4 (36.4)	PBSC 7 (63.6)	
Total blood volume harvested (mL)	1,629.0 (13,821.5–1,749)	–		1,556.0 (1,516–1,597)	–		1,430.0 (1,207–1,639)	–	
Volume (mL/kg)*	20.5 (17.5–21.9)	–		21.8 (20.8–22.8)	–		21.3 (18.3–24.3)	–	
Two-day collection	–	16		–	1		–	0	
Inherited thrombophilia**	–	5		–	0		–	0	
Apheresis procedure	–	1st day collection	2nd day collection	–	1st day collection	2nd day collection	–	1st day collection	2nd day collection
TBV (L)	–	13.0 (11.0–14.0)	12.0 (10.3–13.0)	–	13.7 (11.7–14.3)	14.0	–	13.0 (11.0–14.0)	–
TBV (mL/kg)*	–	169.7 (143.3–200.0)	177.0 (15.2–216.7)	–	158.1 (141.1–200.0)	218.1	–	169.7 (143.3–200.0)	–
WBC ($\times 10^9$/L) pre apheresis	–	46.90 (40.01–55.15)	50.62 (42.67–55.43)	–	48.99 (36.15–58.06)	54.24	–	46.88 (40.01–55.15)	–
CD34+ cells/μL pre apheresis	–	78.0 (54.2–103.0)	39.5 (31.0–59.8)	–	69.0 (54.5–94)	20.0	–	78.0 (54.2–103.0)	–

*Donor's body weight.
**Heterozygous factor V Leiden (2), protein S deficiency (2), and antithrombin III deficiency (1).
CVD, cardiovascular diseases; PBSC, peripheral blood stem cell; BM, bone marrow; TBV, total blood volume processed; WBC, white blood count. Continuous variables are given as median (interquartile range). Categorical variables are given as a number (%).

experienced a second-day collection, while none received plerixafor or anticoagulant prophylaxis (Table 3). Similarly, no adverse events were recorded among BM donors.

Donor follow-up

At follow-up, one healthy donor reported a hospital admission for cholecystectomy due to gallstones; the surgery occurred 3 months after the stem cell collection. No further adverse events were recorded among healthy donors or donors with pre-existing diseases.

Recipients and transplants

Overall, 233 allo-HSCT were performed in 227 patients (male/female, 140/87). Six patients received a second HSCT due to graft failure in four cases and relapse in additional two cases. Diagnoses were acute myeloid leukemia and myelodysplastic syndromes (118 transplants), acute lymphoid leukemia (29 transplants), primary or post-myeloproliferative neoplasm myelofibrosis (45 transplants), Hodgkin's and non-Hodgkin's lymphomas, chronic lymphocytic leukemia, and multiple myeloma (34 transplants), and severe aplastic anemia (seven transplants).

Table 4 illustrates the characteristics of recipients and transplants grouped according to the donor status (healthy donors, CVD donors, and allergy donors).

Regarding transplants from CVD donors, no significant disparities were observed for baseline characteristics (patients' age, diagnosis, conditioning type, donor type, graft type, and cell content). A significant difference emerged regarding the disease severity, with a higher proportion of patients with DRI > 2 among those receiving grafts from CVD donors (68.7% in transplants from CVD donors in comparison with 36.0% in transplants from healthy donors, p=0.005). There was no difference in the transplant cell doses, including TNC, CD34+ cells, and CD3+ cells (Table 4). Regarding transplants from allergy donors, no differences were found in comparison with transplants from healthy donors.

Outcomes

Regarding engraftment, the median time to obtain neutrophils, platelet, and erythrocyte engraftment was similar in all patients, independently from the donor type (Table 4). However, a trend for

TABLE 4 Characteristics of 233 allogeneic stem cell transplantations, and results of univariate analysis comparing transplants from healthy donors with those from HPC-related donors with pre-existing medical conditions.

	Transplants from healthy donors N=206	Transplants from donors with CVD N=16	p-value*	Transplants from donors with allergy N=11	p-value**
Age, years	56 (45–63)	56 (46.7–58.7)	0.459	52 (40–62)	0.830
> 60 years	73 (35.4)	4 (25.0)	0.586	5 (45.4)	0.529
Male/female	130/76 (63.1/36.9)	8 (50.0)/8 (50.0)	0.600	7 (63.6)/4 (36.4)	0.109
Weight, kg	75 (65–85)	76 (61–85)	0.717	65 (60–75)	0.166
Diagnosis					
Acute myeloid leukemia/MDS	104 (50.5)	6 (37.5)	0.300	8 (72.7)	0.321
Myeloproliferative neoplasms++	39 (18.9)	6 (37.5)		0 (0.0)	
Lympoproliferative disorder+	32 (15.5)	1 (6.3)		1 (9.1)	
Acute lymphoid leukemia	25 (12.1)	3 (18.7)		1 (9.1)	
Severe aplastic anemia	6 (2.9)	0 (0.0)		1 (9.1)	
HCT-CI score > 2	116 (56.9)	9 (56.3)	0.794	8 (72.7)	0.362
DRI high/very high	71 (36.0)	11 (68.7)	0.005	5 (45.5)	0.503
Complete remission	98 (47.6)	8 (50.0)	1.000	5 (45.5)	1.000
ABO mismatch major/bidirectional	51 (24.7)	3 (18.7)	0.766	0 (0.0)	0.071
MA conditioning regimen *NMA conditioning regimen*	46 (22.3) 160 (77.7)	6 (37.5) 10 (62.5)	0.216	3 (27.3) 8 (72.7)	0.714
Female donor to male	42 (20.4)	2 (12.5)	0.744	3 (27.3)	0.701
PBSC graft BM graft	137 (66.5) 69 (33.5)	14 (87.5) 2 (12.5)	0.099	7 (63.6) 4 (36.4)	1.000
HLA match *7/8* *HLA-identical sibling* *Haploidentical sibling*	1 (0.5) 75 (36.4) 130 (63.1)	0 10 (62.5) 6 (37.5)	0.116	0 4 (36.4) 7 (63.6)	0.973
TNC × 10^8/kg§	6.4 (4.5–8.6)	8 (6.0–9.4)	0.069	6.8 (4.8–7.7)	0.964
CD34+ cells × 10^6/kg§	5.7 (3.8–7.5)	6.4 (2.8–7.8)	0.841	6.8 (3.9–8.3)	0.539
CD3+ cells × 10^6/kg§	180.7 (43.6–266.1)	160.2 (80.0–252.5)	0.798	202.5 (39.3–247.6)	0.981
Neutrophil engraftment (days)	21 (17–25)	17 (17–22)	0.327	17 (16.75–21.75)	0.154
Platelet engraftment (days)	21 (15–29)	20 (16–33)	0.897	19 (14–24)	0.238
Erythrocyte engraftment (days)	30 (22–36)	23 (18–33.5)	0.265	25.5 (18.75–29.25)	0.197
Day +30 neutrophil engraftment	172 (83.9)	10 (62.5)	0.042	10 (90.9)	1.000
Day +30 platelet engraftment	138 (67.3)	8 (50.0)	0.176	9 (81.8)	0.508
Day +30 erythrocyte engraftment	90 (43.9)	6 (37.5)	0.794	7 (73.6)	0.227
aGVHD	42 (20.6)	2 (12.5)	0.744	1 (9.1)	0.697

(Continued)

TABLE 4 Continued

	Transplants from healthy donors N=206	Transplants from donors with CVD N=16	p-value*	Transplants from donors with allergy N=11	p-value**
cGVHD	37 (18.4)	1 (6.3)	0.694	1 (9.1)	0.693
Relapse	40 (19.4)	6 (37.5)	0.107	2 (18.2)	1.000
Death	69 (33.5)	9 (56.3)	0.099	3 (27.3)	1.000

MDS, myelodysplastic syndromes; + lymphoprolipherative disorders include Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukemia, and plasmacellular discrasias; ++ myeloproliferative neoplasms include idiopathic or post-myeloproliferative neoplasm myelofibrosis and myeloid chronic leukemia.
p* and p** indicate difference in comparison with other donations; § recipient's body weight. Continuous variables are given as median (interquartile range). Categorical variables are given as number (%). Significant p-values are highlighted in bold.
CVD, cardiovascular diseases; HLA, human leukocyte antigen; PBSC, peripheral blood stem cell transplant; BM, bone marrow; HCT-CI, Hematopoietic Cell Transplantation-Comorbidity Index; DRI, Disease Risk Index; MA, myeloablative regimen; NMA, non-myeloablative regimen; TNC, total nucleated cells; MNC, mononucleated cells; aGVHD, acute graft versus host disease; cGVHD, chronic graft versus host disease. Continuous variables are given as median (interquartile range). Categorical variables are given as a number (%). Significant values are in bold type.

a lower proportion of recipients with day-30 neutrophil engraftment was observed among transplants from CVD donors (62.5% in transplants from CVD donors in comparison with 83.9% in transplants from healthy donors, p=0.042) (Table 4). Moreover, similar proportions of patients in the three transplant groups developed aGVHD, cGVHD, or relapsed or died (Table 4).

Considering that the significant findings emerged only relative to transplants from CVD donors, we further evaluated in a multivariate regression logistic model the association between the CVD donor status and several recipient or transplant variables. We considered the CVD donor status as the dependent variable and included among covariates stem cell source, the CD34+ cell, and TNC graft content; HCT-CI>2; high/very high DRI; day-30 neutrophil; platelet and erythrocyte engraftment; and incidence of acute and chronic GVHD. We found that high/very high DRI patients had an increased probability of receiving donations from CVD donors (OR, 4.89; 95% CI, 1.15–20.86; p=0.031; Table 5).

Discussion

This study reported our monocentric experience in the health assessment of HPC-related donors and investigated for the first time the impact of pre-existing medical conditions in donors considered eligible on transplant outcomes. Our data showed that HPC collection can be safely performed in related donors suffering from some pre-existing diseases such as well-controlled cardiovascular disorders. In our setting, this situation occurred most for the transplant of patients at the highest risk for relapse, in whom allo-HSCT could not be postponed. Moreover, the presence of medical conditions that would have deferred donation in the unrelated setting, did not affect engraftment or was associated with an increased rate of acute or chronic GVHD.

The safety and welfare of the donor are recognized as major concerns for the transplantation community. Historically, HLA-matched sibling donors, available for 30% of patients, have been considered the best choice for both practical and biological reasons (29–31). Transplantation techniques have evolved over the past two decades. The practice of haploidentical HSCT, together with the advances in transplant technique, supportive care, and reduced-intensity conditioning regimens, allows the treatment of older patients with elderly familial donors or donors with comorbidities, imposing different challenges to hematologists. As a result of such substantial changes in the donation process, the best accessible graft for many patients may be from an older donor such as HLA identical-sibling or haploidentical relative, highlighting the importance of understanding if any characteristic of donors may negatively influence recipient outcomes. There are an increasing number of studies that have evaluated the risk associated with HPC collection in related donors (32–34), but no report has been published evaluating the impact of benign medical conditions of donors on transplant outcome.

Donor assessment and the final decision on donor clearance are under the responsibility of the collection center's physicians. The

TABLE 5 Multivariate analysis of the association of pre-existing well-controlled cardiovascular disorders in HPC donors' medical history on patient conditions, graft cellular doses, and transplant outcomes.

	OR	95% CI	p-value
HCT-CI >2	0.57	0.14–2.38	0.444
DRI high/ very high	4.89	1.15–20.86	0.031
Bone marrow source	0.49	0.04–6.09	0.581
CD34+ cells × 10^6/kg§	1.18	0.87–1.59	0.284
TNC × 10^8/kg§	1.05	0.83–1.32	0.704
Day-30 neutrophil engraftment	1.53	0.13–17.89	0.736
Day-30 platelet engraftment	0.85	0.16–4.63	0.850
Day-30 erythrocyte engraftment	1.03	0.24–4.43	0.964
aGVHD	1.13	0.20–6.48	0.888
cGVHD	0.33	0.03–3.29	0.347

§ Recipient's body weight.
HCT-CI, Hematopoietic Cell Transplantation-Comorbidity Index; DRI, Disease Risk Index; TNC, total nucleated cells; aGVHD, acute graft versus host disease; cGVHD, chronic graft versus host disease. Significant p-values are highlighted in bold.

evaluation of related and unrelated donors followed the same procedure based on the currently valid quality standards and recommendations [WMDA (35, 36), FACT-JACIE (37)]. Compared with the strict recommendations on the suitability of unrelated donors, criteria for related donors allow for more discretion. In 2015, the donor outcome committee of WBMT proposed consensus recommendations of suitability criteria for pediatric and adult-related donors, which have been recently updated (10, 11). The WBMT standards allow related donors with pre-existing health conditions that would have been deferred as unrelated donors might still undergo donation if these medical conditions are not expected to lead to a significant reduction in donor safety.

We excluded all potential donors with medical conditions or lifestyles that would have represented a serious risk for both the donor and the recipient. In our experience, 23% of related HPC donors would not fit the eligibility criteria of an unrelated donor registry because of pre-existing conditions, and medical history of autoimmune diseases, primarily thyroid affections, represented the main reason for non-eligibility. CVDs were the second cause of medical contraindications to HPC donation, mainly severe acute heart issues, uncontrolled hypertension, and tachyarrhythmias. Donors with ongoing malignancies or a history of a malignant condition other than minor skin cancers such as basal cell carcinomas were excluded from further consideration. As for eligible HPC donors, 12% would have been deferred according to WBMT standards (11), mainly because of hypertension. Of note, four of them were over 60 years of age. Similar results are reported from a Dutch study evaluating short- and long-term adverse reactions in 268 related donors who underwent PBSC mobilization (32). The 15% of donors would have been deferred based on NMDP criteria for unrelated donors due to age (older than 60 years), BMI (at least >40 kg/m^2), and hypertension (higher than 160/95 mmHg); other medical contraindications to HPC collection included clotting issues, diabetes, or severe heart issues. Of note, the authors detailed the follow-up of donors that would not have been eligible due to NMDP criteria, not reporting an increase in cardiovascular events, autoimmune diseases, or malignancy post-PBSC collection (32). Likewise, in the subsequent follow-up of related donors, we did not report the onset of additional medical conditions in the group of HPC donors with pre-existing benign medical conditions.

WBMT standards (11) recommend that in case of an active cardiac disorder, detailed evaluation by a cardiologist is required, and cardiac risk stratification should be performed by a specialist. Among CVD reported in our study population study, the most frequent pre-existing medical conditions were hypertension. All related donors were classified as ASA-PS <3. In addition, if a donor were considered suitable, we planned an in-depth cardiological evaluation with final approval for apheresis and extracorporeal circulation during the leukapheresis procedure, and an additionally fully anesthesiologic assessment in HPC-M donors, with continuous monitoring of the donor's vital parameters during and immediately after the collection procedure. Among CVD donors, stem cell collection was performed mainly through apheresis, while only two donors were subjected to BM harvesting; in none of them, we recorded severe adverse events. At the same time, donors suffering from allergic diathesis did not experience side effects during HPC collection, nor patients who received grafts from donors with drug allergies develop an allergy after HSCT.

The WBMT board agreed that HPC donation is typically to be disregarded in donors with systemic multiorgan involvement related to AID; on the other hand, among donors affected by single-organ autoimmune diseases such as Hashimoto thyroiditis, Graves' disease, pernicious anemia, psoriasis, alopecia areata, or vitiligo, the experts recommended that donation must be deferred only for candidate donors receiving systemic treatment (11). In our institution, all donors with AID were deferred from HPC donations, and a medical history of autoimmune diseases represented the main reason for non-eligibility. The impact on the recipient's immune reconstitution is not yet known. However, it is widely acknowledged that the pathogenesis of autoimmune disorders is multifactorial, with genetic and environmental factors combining to determine disease onset and evolution. For many autoimmune disorders, adoptive transfer of diseases from the donor to the recipient during allogeneic HSCT has been documented. They include thyroid diseases, type 1 diabetes, immune thrombocytopenia, vitiligo, and psoriasis (38–42).

Large registry-based studies have shown that younger donor age is the most important secondary donor characteristic after HLA matching and has been associated with improved overall and disease-free survival, with a 3% improvement in 2-year survival when a donor 10 years younger is selected (43–45). We did not find a significant correlation between the age of related donors and transplant outcome; the median donor age of our population was 40 years old (range, 16–75), which is usually used as a cutoff for younger versus older donors. Notably, 15 donors were older than 60 years, and three of them also suffered from CVD, in agreement with the increasing prevalence of conditions such as atherosclerotic cardiovascular disorders with aging. Aging is marked by the acquisition of somatic mutations in hematopoietic stem cells due to cumulative genomic DNA damage: this condition is commonly referred to as clonal hematopoiesis of indeterminate potential (CHIP) (46). The proportion of CHIP carriers increases exponentially with age even if mutations within genes including DNMT3A or TET2 can be detected for up to 95% of healthy individuals, with a mean age of 50 years old (47). CHIP is associated with a 0.5%–1% risk per year of leukemia (47). Remarkably, it confers a twofold increase in cardiovascular risk independent of traditional risk factors (46). In fact, CHIP is associated with a pro-inflammatory state that has been linked to coronary artery disease, myocardial infarction, and venous thromboembolic disease (48, 49). In the context of HSCT, the potential transfer of CHIP from donor to patient may bring up concerning implications. An early report first described the transfer of CHIP-mutated hematopoietic stem cells to recipients through HSCT (50). Indeed, these data imply precaution in selecting aging relatives suffering from CVD for donation and suggest that the CHIP screening could be worthwhile in these cases.

Our study exhibits some limitations. First, the short length of the follow-up of the study population requires caution in the interpretation of data. Second, the retrospective design does not allow to reach definite evidence. Finally, recipients were affected by different types of diseases, and the effect of various immunosuppressive regimens was not considered on the GVHD outcome.

Nevertheless, our results provide insights into the related donor selection and suggest that relatives may be accepted for safe HPC donation based on less strict criteria than unrelated donors, offering a lifesaving opportunity for patients whose allogeneic transplants cannot be postponed. Further multicenter studies on larger donor populations are worthy to compare donor selection policies and come to definite conclusions.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by The Ethics Committee of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Largo Agostino Gemelli, 8, 00168, Rome, Italy. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the patients for their anonymized information to be published in this article.

Author contributions

CGV: Writing – original draft, Writing – review & editing. SC: Writing – original draft. FF: Writing – original draft. EM: Writing – original draft. CP: Writing – original draft. PC: Writing – review & editing. SS: Writing – review & editing. LT: Writing – original draft, Writing – review & editing.

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Publisher's note

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Allogeneic stem cell transplantation in multiple myeloma: is there still a place?

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The introduction of novel agents dramatically improved response and outcomes of multiple myeloma (MM) and led to a sharp decline in the use of allogeneic hematopoietic stem-cell transplantation (allo-HSCT). Thus, recent guidelines do not recommend anymore allo-HSCT as consolidation in the first-line treatment of newly diagnosed MM, even in high-risk patients. In a relapsed/refractory setting, allo-HSCT is not routinely recommended but should only be performed within clinical trials in young and high-risk patients. Nonetheless, allo-HSCT still represents a potential curative approach that has been used for decades in the treatment of MM and plasma cell neoplasms with favorable results and may still represent a treatment option for carefully selected patients. Despite that promising results were obtained with CAR T-cell therapies and bispecific antibodies in triple- and penta-exposed/refractory MM, these patients will inevitably relapse. To date, less is known about outcomes of allo-HSCT in patients exposed to novel immunotherapeutic drugs. Therefore, allo-HSCT could represent a reasonable treatment choice for younger and high-risk patients who have relapsed after CAR T-cell therapies and bispecific antibodies as well as an alternative for patients not eligible to these treatments and in those countries where immunotherapies are not yet available. In the choice of conditioning, reduced intensity conditioning regimens are currently recommended for the lower toxicity and mortality. Moreover, the use of alternative donors, particularly haploidentical, has progressively increased in last years with results comparable to full matched donors. Finally, post-transplantation maintenance strategies are encouraged whenever feasible.

KEYWORDS

allogeneic transplantation, multiple myeloma, immunotherapy, relapsed refractory multiple myeloma, alternative donor

1 Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) still represents a curative treatment option for many hematological malignancies. Although its use has largely remained unchanged or increased in acute leukemia and myeloid neoplasms, recent years saw a sharp decline of allo-HSCT in multiple myeloma. (1–3) Since the introduction of novel agents such as proteasome inhibitors (PI), immunomodulating agents (IMIDs), monoclonal antibodies (MoAbs), and, ultimately, bispecific antibodies (BiAbs) and CAR-T cell therapies, response and outcomes of patients with MM have dramatically improved, thus leaving less and less room for allo-HSCT. (4) Nonetheless, allo-HSCT has been used for decades in the treatment of MM and plasma cell neoplasms with favorable results and may still represent a treatment option for individual patients.

2 Graft versus myeloma effect

The rationale for allo-HSCT in MM relies on both the cytotoxic effect of conditioning regimen and the long-term immunological control of the donor's T lymphocytes against tumor-associated antigens (TAA). Although less intense than in other hematological malignancies, a Graft versus Tumor effect was also reported in MM. Actually, the donor's CD8+ T cells proved able to recognize surface TAA on neoplastic plasma cells, thus granting significantly lower relapse incidence and longer survival. (5) Moreover, the occurrence of GvHD post allo-HSCT correlated in many trials with better outcome as an indirect evidence of Graft versus Myeloma effect (GvM). (6, 7) In the phase III BMT CNT 0102 trial, those patients with chronic GvHD had a significantly lower cumulative incidence of relapse. (8) Finally, in patients with MM persistent or relapsed after allo-HSCT, the administration of donor lymphocyte infusions (DLI) at escalating doses resulted in deeper response and longer survivals. (9–11) A multicenter retrospective study showed that among 61 patients with MM post allo-HSCT, the administration of prophylactic DLI deepened response rates up to minimal residual disease negativity in 26% of patients, with limited GvHD and mortality related to procedures (12).

3 Conditioning regimen

Conditioning regimens initially used in multiple myeloma were myeloablative (MAC). Although effective against MM, MAC regimens were burdened by severe toxicity, with 2-year TRM rates up to 50%. (13, 14) The improvement of supportive therapies and, above all, the introduction in recent years of reduced-intensity conditioning (RIC) regimens led to a significant reduction in TRM and made allo-HSCT possible for many more patients with MM. In a retrospective study on behalf of EBMT among patients with MM receiving RIC regimens mainly based on fludarabine, TRM at 100 days and 2 years were 10% and 26%, respectively. GvHD prophylaxis relied on either antithymocyte globulin (ATG) or alemtuzumab, the latter still determining a slightly higher TRM due to infectious mortality in the early post transplantation period. Nonetheless, in the whole cohort, 3-year progression-free survival (PFS) and overall survival (OS) were 21% and 41%, respectively. Notably, chronic GvHD was associated with longer OS and PFS, whereas chemoresistant and heavily pretreated patients benefited less from allo-HSCT. (7) A favorable TRM rate less than 20% after RIC allo-HSCT was reported in subsequent prospective trials. (15) Despite that the rationale of RIC allo-HSCT mainly relies on GvM, the cytotoxic effect of chemotherapy can be retained by the sequential approach of tandem autologous/allogeneic stem-cell transplantation as reported in several clinical trials. (16–20) Moreover, the alkylating agent treosulfan was included in RIC regimens for MM with the aim to further reduce toxicities. (21, 22) In a retrospective analysis comparing treosulfan-based RIC to "standard" RIC and MAC regimens in patients undergoing first allo-HSCT, treosulfan showed high engraftment rates and a favorable safety profile: non-relapse mortality (NRM) at 5 years was 17% overall and 9% when considering upfront allo-HSCT. Both treosulfan-based and "standard" RIC showed significantly higher OS when compared to MAC, although the benefit of treosulfan-based RIC was greater in the upfront setting. No differences emerged in terms of OS and PFS between conditioning regimens in patients with relapsed/refractory multiple myeloma (RRMM) (23).

Further attempts were made to improve efficacy of RIC regimens through the introduction of novel agents.

Proteasome inhibitors (PI) are key drugs in the treatment of MM. In addition to strong anti-myeloma effect, the first-in-class PI bortezomib showed immunomodulating properties and inhibitory effects on alloreactive T cells in murine models of allo-HSCT. (24) Notably, bortezomib showed a dual effect depending on the timing of administration. While an early administration together with conditioning chemotherapy resulted in increased disease control, the prolonged administration of bortezomib after allo-HSCT led to a harmful increase in acute GvHD, especially gastrointestinal and dependent on increased levels of TNFα and INFγ. (25) Two prospective clinical trials assessed bortezomib combined with a fludarabine and melphalan-based RIC in high-risk MM, followed by bortezomib maintenance starting at least after 50 days from allo-HSCT. At 1 year, the incidence of grade III–IV acute GvHD ranged between 10% and 25% and NRM approached 25%. OS and PFS at 2 years were 64% and 31%, respectively. Bortezomib both enhanced RIC efficacy and improved GvHD prophylaxis with limited toxicities. (26, 27) As long-term disease control was still suboptimal, a subsequent phase II trial tested maintenance with bortezomib and lenalidomide to decrease the risk of relapse. Despite that relapse rate was lower than previous studies (28.5% at 2 years), a limited number of patients actually proceeded to and completed maintenance due to the greater toxicity of lenalidomide post transplantation (28).

The radiosensitivity of neoplastic plasma cells favored the inclusion of radioimmunotherapy in RIC regimens. A phase I trial combined the anti-CD45 radio-labeled drug 90Y-DOTA-BC8 to fludarabine and low-dose total body irradiation (TBI) followed by allo-HSCT in patients with MM and high-risk features. Despite

the relatively low expression of CD45 antigen on plasma cells, 90Y-DOTA-BC8 exerts a crossfire effect by targeting adjacent hematopoietic cells in bone marrow. Among 14 treated patients, the incorporation of 90Y-DOTA-BC8 to RIC was well tolerated, with manageable non-hematological toxicities and TRM of 0% at 100 days. Radioimmunotherapy also prolonged disease response. After a median follow-up of 5 years, PFS was 41% and OS was 71%. (29) Another strategy of indirect bone marrow irradiation is based on rhenium-188-labeled antibody targeting CD66 antigen (re-188-antiCD66) preferentially expressed on myeloid cells. There were 30 patients with heavily pretreated MM who received re-188-antiCD66 coupled with fludarabine-based RIC prior to allo-HSCT. At 2 years, PFS and OS were 43% and 55%, respectively, whereas 2-year NRM was 17%. Grade III–IV acute GvHD and severe chronic GvHD were reported in 26% and 17% of patients, respectively. In addition to expected mucositis and hematological toxicity, renal toxicity was the most frequent adverse event (7% grade III–IV acute renal failure and 10% grade III–IV chronic renal failure) due to dissociation of rhenium-188 from monoclonal antibody in kidneys (30).

4 Allogeneic HSCT in newly diagnosed multiple myeloma

Before the introduction of novel agents, allo-HSCT has been used for a long time as consolidation therapy after induction treatment in newly diagnosed multiple myeloma (NDMM). Several prospective trials compared allo-HSCT to ASCT in this setting. An Italian study enrolled 162 patients with NDMM to receive either RIC allo-HSCT or ASCT as consolidation treatment after a chemotherapy-based induction and first ASCT. Patients were assigned between two arms depending on the availability of an HLA-identical sibling. (16) Any difference emerged in terms of TRM between allo-HSCT and ASCT, but disease-related mortality was higher in tandem-ASCT cohort (43% vs 7%, $p < 0.001$). After a median follow-up of 7 years, both median OS and PFS were significantly longer among patients with HLA-identical sibling vs those without a suitable donor (not reached vs 4.25 years, $p = 0.001$; and 2.8 vs 2.4 years, $p = 0.02$; respectively) as well as among patients who actually received allo-HSCT vs those treated with tandem-ASCT (not reached vs 5.3 years, $p = 0.02$; and 39 vs 33 months, $p = 0.02$; respectively). Notably, 53% of patients in complete remission after allo-HSCT compared with 19% after tandem-ASCT maintained response at last follow-up. (17) Similarly, a PETHEMA study enrolled patients with NDMM and incomplete response after a first ASCT to receive either a second ASCT (n = 85) or a RIC allo-HSCT (n = 25), depending on the availability of an HLA–identical sibling donor. The study showed higher CR rates (40% vs 11%, $p = 0.001$) and a trend toward longer median PFS (not reached vs 31 months, $p = 0.08$) in the allo-HSCT cohort, whereas no difference emerged in TRM and OS. (31) In a prospective trial on behalf of EBMT, ASCT followed by RIC allo-HSCT (n = 108) was compared with single (n = 145) or tandem-ASCT (n = 104) in NDMM. After a median follow-up of 61 months, 5-year PFS and OS were significantly longer in the allo-HSCT cohort compared with patients treated with ASCT (35% vs 18%, $p = 0.001$, and 65% vs 58%, $p = 0.006$, respectively), as was the incidence of disease relapse (49% vs 78%, $p = 0.003$). (18) As opposite, two different prospective trials failed to show a survival benefit in favor of allo-HSCT. After a median follow-up of 77 months, the HOVON-50 study showed comparable response rates and survivals between 138 patients without an HLA-identical sibling donor and 122 patients with a donor. A trend toward longer PFS emerged among the 99 patients who actually received allo-HSCT compared with 112 patients treated with single ASCT and thalidomide maintenance, whereas NRM at 6 years was 16% after allo-HSCT vs. 3% after ASCT ($p < 0.001$). (32) The prospective multicenter phase III BMT CNT 0102 trial also reported similar 3-year OS (77% vs. 80%) and PFS (43% vs. 46%) between patients diagnosed with standard-risk NDMM and treated with allo-HSCT vs. tandem-ASCT, in both intention-to-treat and as-treated population. (8) Results have been confirmed in a long-term analysis with over 10 years of follow-up. (33) A large retrospective Japanese registry study confirmed no survival advantage between the two transplantation approaches. (20) More recently, Kröger et al. reported results of a German multicenter phase II trial comparing allo-HSCT vs. tandem ASCT in NDMM on the basis of donor availability and evaluating the role of thalidomide maintenance and DLI post transplantation. (34) Among 217 enrolled patients, 65% received a bortezomib-based induction regimens. At 4 years, patients in the allo-HSCT cohort experienced higher NRM (13% vs. 2%; $p = 0.044$) but a lower relapse rate (40% vs. 63%; $p = 0.04$). Nonetheless, the lower incidence of disease relapse did not translate into longer PFS and OS at both 4 years (47% vs. 35%, $p = 0.26$, and 66% vs. 66%, $p = 0.91$, respectively) and 8 years (43% vs. 21%, $p = 0.1$, and 52% vs. 50%, $p = 0.87$, respectively). Prophylactic DLIs at escalating doses were given in 58 patients (50.4%) in the allo-HSCT cohort, but without improvement in PFS compared with those patients who did not receive DLI. Incidence of grade III–IV acute GvHD and chronic GvHD at 4 years was 6% in 61%, respectively. No increase in GvHD was observed following DLI and thalidomide maintenance. Although the relapse rate was lower in the allo-HSCT cohort and no relapse was observed after 5 years from transplantation, the trial failed to show improved survival with allo-HSCT. The deeper response rates observed after the bortezomib-based induction, the addition of thalidomide maintenance, and the greater proportion of patients who received allo-HSCT due to improved availability of matched unrelated donors (MUD) might have contributed to mitigating differences between arms and lowering the statistical power of the study. (34) Importantly, what emerges from these reported trials is that allo-HSCT is characterized by greater early TRM but lower risk of long-term disease relapses. Therefore, an appropriate follow-up of at least 5 years is needed to see the real benefit of allo-HSCT. For this purpose, a pooled analysis of 1,338 patients data provided an extended follow-up of the four major prospective trials. After a median follow-up of 118.5 months, NRM at 10 years was confirmed to be higher in the allo-HSCT group (19.7% vs. 8.3%, $p < 0.001$), but 10-year OS and PFS were significantly longer in patients who received allo-HSCT compared with ASCT (44.1% vs. 36.4%, $p = 0.01$; and 18.7% vs. 14.4%, $p = 0.06$). Moreover, survival of patients relapsed after allo-HSCT was

significantly longer than after ASCT (62.3 months vs. 41.5 months, p <0.001), probably due to a better immunological fitness and enduring GvM effect in subsequent lines of treatment. (15) Results of prospective and retrospective studies on allo-HSCT in NDMM are summarized in Table 1.

Patients with high-risk NDMM by either chromosomal abnormalities or clinical characteristics have dismal outcomes with standard treatment. Therefore, in this setting, allo-HSCT has been employed in the attempt to improve survival. Initial retrospective studies reported similar survival rates in high-risk NDMM who underwent allo-HSCT compared with standard-risk patients treated with conventional treatments. (35–37) A meta-analysis including 8,698 patients from 61 clinical trials showed similar OS and PFS between high-risk patients who received allo-HSCT and patients with standard-risk disease treated with ASCT, suggesting that GvM might in part overcome the poor prognostic features. (38) Few prospective trials selectively explored the role of allo-HSCT in high-risk NDMM. The Intergroupe Francophone du Myelome (IFM) evaluated in two parallel prospective studies the allogeneic transplantation approach (IFM99–03) versus consolidation with tandem ASCT (IFM99–04) after a chemotherapy-based induction in high-risk NDMM defined as elevated beta2-microglobulin and chromosome 13 deletion. At a median of follow-up of 24 months, both median OS and EFS were comparable (35 months vs. 41 months, p = 0.27, and 25 months vs. 30 months, p = 0.56, respectively) between 65 patients in the IFM99–03 trial and 219 patients in the IFM99–04 trial. A trend for longer OS emerged in tandem ASCT cohort (47.2 vs. 35 months; p = 0.07). (39) An extended follow-up analysis did not confirm the superiority of RIC allo-HSCT compared with tandem ASCT, in part explained by the conditioning regimen before allo-HSCT based on busulfan, fludarabine, and high-dose ATG that might have reduced the GvM. (40) Similarly, the BMT CNT 0102 trial and the HOVON-50 trial failed to show an advantage in terms of OS and PFS of allo-HSCT over tandem ASCT consolidation in the high-risk population. (32, 33) Remission status at transplant also appeared to significantly correlate with long-term survival in high-risk NDMM undergoing allogeneic transplantation. (41, 42) Recently, a retrospective registry analysis included NDMM with del(17p) and/or t(4;14) undergoing either single ASCT (n = 446), tandem ASCT (n = 105), or ASCT/RIC allo-HSCT (n = 72). Donors were MRD in 54% and MUD in 46% of cases. Notably, the majority of patients (n = 431, 69.2%) already received an induction regimen containing bortezomib. The OS at 5 years for single ASCT, tandem ASCT, and ASCT/RIC allo-HSCT were 51%, 60%, and 67%, respectively (p = 0.187). Similarly, 5-year PFS were 17%, 33%, and 34%, respectively (p = 0.048), and 5-year NRM were 1%, 4%, and 10%, respectively. In multivariate analysis, in patients harboring t(4;14), both tandem ASCT and ASCT/RIC allo-HSCT granted longer PFS compared with single ASCT, whereas only tandem ASCT was associated with longer OS. Conversely, the poor prognostic impact of del(17p) was partly mitigated by ASCT/RIC allo-HSCT in terms of PFS (HR, 0.65; p = 0.097), but no significant difference in OS emerged between groups (43).

Major limits of the reported experiences on allo-HSCT in NDMM are the heterogeneity of disease and patients' characteristics, the variability in the identification of high-risk features and staging systems, the diversity of induction regimens given before allo-HSCT, the short follow-up, and, above all, the lack of novel agents that currently represent the milestone in the treatment of NDMM. Therefore, upfront RIC allo-HSCT is not recommended in first-line treatment of standard-risk and high-risk NDMM. It may be considered in patients with very high-risk MM, only in the context of clinical trials (44–46).

5 Allogeneic HSCT in relapsed/refractory multiple myeloma

In patients with RRMM after first-line treatment, allo-HSCT has been use as a salvage treatment. To date, large prospective trials are lacking in this setting and the majority of evidence is based on retrospective studies. A report from EBMT actually showed between 1990 and 2012 a steady increase in the use of allo-HSCT for treatment of RRMM parallel to a progressive decline of upfront allo-HSCT. Among 3,405 patients who underwent salvage allo-HSCT, 5-year OS was 32%. (47) In the attempt to identify prognostic factors, another EMBT registry study analyzed outcomes of 413 patients with RRMM who received RIC allo-HSCT from MRD or MUD. Overall, 44.6% of patients had received at least two prior ASCT. Median OS and PFS were 24.7 and 9.6 months, respectively, whereas 1-year NRM was 21.5%. In multivariate analysis, CMV negative status in both donor and recipients and less than two prior ASCT significantly correlated with better outcomes. (48) In patients exposed to PI (bortezomib 100%) and IMIDs (lenalidomide 61.5%) and after a median of three prior lines of therapy, a Japanese study reported 3-year PFS and OS of 18.8% and 47.2%, respectively, whereas 3-year NRM was 23.4%. In multivariate analysis, older age (≥50 years) and incomplete response before allo-HSCT independently predicted worse PFS and OS. Although allo-HSCT appeared as a reasonable treatment option in heavily pretreated patients with RRMM, better results are obtained mainly in young patients with chemo-sensitive disease and in good response before transplantation. (49) Similarly, in a cohort of heavily pretreated patients with high-risk RRMM (57% have at least one abnormality among t(4:14), t(14:16), del17p or gain1q), salvage allo-HSCT showed 5-year OS and PFS of 66% and 48%, respectively. TRM at 5 years was low (9%), whereas incidence of grade II–IV acute and chronic GvHD accounted for 21% and 58%, respectively. Notably, in this cohort, the development of chronic GvHD predicted longer survival. (50) Conversely, the efficacy of allo-HSCT is limited in patients who have active disease at transplantation (median PFS and OS of 6 months and 23 months, respectively) as well as in those patients with early relapse (<12 months) after first-line treatment. (51–53) Compared with non-transplantation approaches, an Italian retrospective study showed a potential benefit for allo-HSCT in RRMM. Patients with MM in first relapse after ASCT received either allo-HSCT (n = 72) or salvage treatment with PI and IMIDs (n = 90) depending on donor availability. After a median follow-up of 110 months, PFS and OS at 7 years were significantly longer in the allo-HSCT group compared

TABLE 1 Prospective and retrospective studies on allogeneic HSCT in newly diagnosed multiple myeloma.

Study	Type of study	Pts (n)	Median age (years)	Induction regimen	Prior ASCT	Conditioning regimen	MRD MUD	ORR CR	TRM	Median follow up	OS	PFS	Acute GvHD	Chronic GvHD	Advantage of allo-HSCT over ASCT
Bruno (17)	Prosp	80	54	VAD	Yes	RIC 100%	100% 0%	86% 55%	16%	7 years	NR	33.6 months	43%	32%	Yes
Rosiñol (31)	Prosp	25	52	VBMCP/ VBAD	Yes	RIC 100%	100% 0%	- 40%	16%	5 years	NR	NR	32%	66%	Yes
Björkstrand (18)	Prosp	108	54	VAD	Yes	RIC 100%	100% 0%	93% 50%	16%	5 years	65% at 5 years	35% at 5 years	31%	54%	Yes
Lokhorst (32)	Prosp	122	54	VAD/ TAD	Yes	RIC 100%	100% 0%	- -	16%	6 years	55% at 6 years	28% at 6 years	48%	64%	No
Giralt (33)	Prosp	189	53	VAD/ T/B	Yes	RIC 100%	100% 0%	- 58%	20%	10 years	59% at 6 years	22% at 6 years	26%	54%	No
Kawamura (20)	Retro	89	49	–	Yes	MAC 12% RIC 88%	59% 24%	–	–	–	54% at 6 years	–	–	–	No
Kröger (34)	Prosp	132	51	B	Yes	RIC 100%	60% 40%	92% 71%	13%	10 years	52% at 8 years	43% at 6 years	38%	61%	No
Costa (15)	Retro	439	53	–	Yes	RIC 100%	100% 0%	–	19.7%	10 years	44% at 10 years	18% at 10 years	–	–	Yes

ASCT, autologous stem-cell transplantation; MRD, matched related donor; MUD, matched unrelated donor; ORR, overall response rate; CR, complete remission; OS, overall survival; PFS, progression-free survival; GvHD, graft-versus-host disease; allo-HSCT, allogeneic stem-cell transplantation; VAD, vincristine, adriamycin, dexamethasone; T, thalidomide-based induction; B, bortezomib-based induction; RIC, reduced intensity conditioning regimen; MAC, myeloablative conditioning regimen; NR, not reached; VBMCP, vincristine, carmustine, melphalan, cyclophosphamide, prednisone; VBAD, vincristine, carmustine, adriamycin, dexamethasone (VBAD).

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with the non-transplantation group (18% vs. 0%, p < 0.0001; and 31% vs. 9%, p < 0.0001; respectively). (54, 55) Interestingly, the benefit of allo-HSCT seems to persist in subsequent lines of treatments, possibly due to the lower immunological exhaustion of the donor's immune system granting better response to further therapies. Indeed, a registry analysis by CIBMT reported longer post-relapse survival (44% vs. 35% at 6 years, p = 0.05) in patients with RRMM treated with ASCT/RIC allo-HSCT compared with tandem ASCT. (56) Although uncommon, a second allo-HSCT was also attempted in past years. The EBMT Chronic Malignancies Working Party retrospectively analyzed data of 215 patients who underwent a second allo-HSCT either for relapse (n = 159) or for graft failure (n = 56). In the relapse group, OS at 2 years and 5 years were 38% and 25%, respectively. The majority of patients (83%) received the second allo-HSCT from the same MRD. Despite a higher incidence of grade II–IV acute GvHD in those patients who received second transplantation from the same donor (50% vs. 22%, p = 0.03), the use of the same MRD conferred better outcomes in multivariate analysis (5-year OS 35% vs. 9%; p < 0.001). The interval between transplantations also influenced outcomes. Patients who received second allo-HSCT within 2 years from the first procedure had shorter survival compared with late relapses. (57) Results of retrospective studies on allo-HSCT in RRMM are summarized in Table 2.

Similarly to the first-line setting, the introduction of novel agents in recent years has significantly improved the prognosis of RRMM; therefore, the indication for allo-HSCT is significantly reduced in this setting. Allo-HSCT might represent a possible treatment option in carefully selected RRMM who have exhausted other therapeutic alternatives, especially in case of chemo-sensitive disease and late relapses from previous ASCT. Then, allo-HSCT is not routinely recommended for RRMM and it should possibly be performed in the context of a clinical trial (44–46, 59).

6 Alternative donors

The studies reported so far in the treatment of both NDMM and RRMM have mainly included allo-HSCT from MRD and, to a lesser extent, MUD. However, approximately one-third of candidates to allo-HSCT do not have a full matched donor. Therefore, over the years there was a progressive increase in the use of alternative donors such as mismatched unrelated donors (MMUD), haploidentical donors (haplo), and cord blood units (CBU). (2, 3) A German multicenter prospective study reported on 49 patients with RRMM after prior ASCT and treated with RIC regimen based on fludarabine and melphalan followed by allo-HSCT from either MUD or MMUD. Overall, OS and PFS at 4 years were 26% and 20%, respectively, and were significantly longer for patients with persistent CR at day +100 (41% vs. 7%, p = 0.04; and 56% vs. 16%, p = 0.02). The incidence rates of acute and chronic GvHD were 25% and 25%, respectively, and compared favorably with those previously reported with MRD. However, 1-year TRM was significantly higher for MMUD than MUD (53% vs. 10%, p = 0.001). (60) A subsequent retrospective study confirmed favorable long-term outcomes but with limited TRM rates of 12%, similar

TABLE 2 Retrospective studies on allogeneic HSCT in relapsed/refractory multiple myeloma.

Study	Type of study	Pts (n)	Median age (years)	Median LOT (n)	Prior ASCT	Conditioning regimen	MRD MUD	ORR CR	TRM	Median follow-up	OS	PFS	Acute GvHD	Chronic GvHD
Sobh (47)	Retro	3,405	54	–	Yes	MAC 25% RIC 75%	46% 14%	–	29%	3 years	33% at 5 years	15% at 5 years	–	–
Auner (48)	Retro	413	54	–	Yes	–	58% 39%	–	28%	–	24.7 months	9.6 months	49%	47%
Kawamura (49)	Retro	65	49	3	Yes	MAC 26% RIC 74%	40% 60%	51% 27%	23%	–	47% at 3 years	18% at 3 years	45%	44%
Jurgensen-Rauch (50)	Retro	37	52	2	Yes	RIC 100%	59% 41%	–	9%	4.6 years	66% at 5 years	48% at 5 years	21%	58%
Patriarca (55)	Retro	72	53	–	Yes	RIC 100%	35% 65%	–	27%	9 years	31% at 7 years	18% at 7 years	33%	65%
Strassl (58)	Retro	38	55	7	Yes	MAC 55% RIC 45%	26% 34%	89% 68%	16%	3 years	51.4 months	13.6 months	42%	12%

ASCT, autologous stem-cell transplantation; MRD, matched related donor; MUD, matched unrelated donor; ORR, overall response rate; CR, complete remission; OS, overall survival; PFS, progression-free survival; GvHD, graft-versus-host disease; allo-HSCT, allogeneic stem-cell transplantation; RIC, reduced intensity conditioning regimen; MAC, myeloablative conditioning regimen.

between donor's types. (61) Then, a large retrospective study by EBMT included 570 patients with MM early relapsed after single or tandem ASCT. Patients received RIC allo-HSCT from MUD (n = 419), MMUD (n = 93), and CBU (n = 58). No significant difference emerged in terms of OS, PFS, and TRM according to type of donors (5-year OS was 33%, 39%, and 25%, respectively; 5-year PFS was 14%, 27%, and 4%, respectively; TRM was 22%, 33%, and 27%, respectively). Notably, a trend for better long-term survivals emerged within the MMUD cohort compared with MUD possibly related to a stronger GvM, whereas allo-HSCT from CBU was burdened by greater toxicities (62).

The cord blood unit has the advantage of being a readily available graft source but is burdened by technical difficulties in transplantation and greater complications compared with allo-HSCT from other donors that limit its wide application. Two registry analyses on behalf of the Eurocord and the Japan Society for Hematopoietic Cell Transplantation including over 180 patients with RRMM allografted with CBU showed high TRM ranging 29%–39% but favorable rates of PFS and OS ranging 14%–25% and 31%–40% at 3 years, respectively (63, 64).

Haploidentical donors are the source of alternative donors with the greatest increase in use for allo-HSCT in the last decades, considering the wide availability of familiar donors as well as the relative ease of execution. In the setting of multiple myeloma, a collaborative retrospective study from EBMT and CIBMTR identified 96 patients with RRMM treated with allo-HSCT from haplo. Among pretreated patients mainly relapsed post ASCT, NRM was 21% at 1 years, whereas 2-year OS and PFS were 48% and 17%, respectively. Following a GvHD prophylaxis based on post-transplantation cyclophosphamide (PTCy), the cumulative incidence of grade II–IV acute GvHD was 39% at 100 days, whereas chronic GvHD occurred in 46% of patients. (65) Similar results were also reported by a smaller retrospective Italian study. (66) Notably, the GvHD prophylaxis based on PTCy was initially developed for haploidentical allo-HSCT but has been subsequently applied also to other graft sources. Among 295 patients with RRMM undergoing allo-HSCT from different grafts (MRD, n = 67; MUD, n = 72; MMUD, n = 27; haplo, n = 129), PTCy was used as GvHD prophylaxis in combination with calcineurin inhibitors (n = 239, 81%) and/or mycophenolate mofetil (n = 184, 77%). In this different setting of patients, incidence of grade II–IV acute GvHD was 30% at day +100 whereas chronic GvHD occurred in 27% of cases. Notably, no differences were observed according to donor type neither in GvHD incidence nor in outcomes. In multivariate analysis, the use of MRD conferred better OS compared with haplo, whereas only a trend was reported for MUD. Therefore, PTCy appeared as a wide applicable platform for GvHD prevention granting for favorable outcomes even in non-haplo settings (67).

7 The role of maintenance

Proteasome inhibitors such as bortezomib have been widely given as maintenance treatment after ASCT in MM. Considering both anti-myeloma and immunologic properties, bortezomib has been used after allo-HSCT in the attempt to maintain response and prolong survival. (68–70) In a prospective phase II trial, 39 patients with high-risk NDMM received a bortezomib-based induction followed by tandem ASCT/RIC allo-HSCT and then maintenance with bortezomib. Treatment was well tolerated (NRM 12%), with limited toxicities and incidence of grade II–IV acute GvHD and chronic GvHD of 26% and 57%, respectively. The 5-year PFS was 41% and 5-year OS was 80%. In a multivariate analysis, minimal residual disease positivity both prior to allo-HSCT ($p = 0.037$) and after 3 months from transplantation ($p = 0.001$) strongly predicted disease relapse. (71) A recent retrospective study by the same group selectively analyzed the role of bortezomib in reducing the incidence and severity of GvHD post allogeneic transplantation in a cohort of 46 NDMM patients compared with 61 patients who did not received maintenance. According to NIH 2014 criteria, patients in the bortezomib group had lower incidence of both overall and moderate/severe chronic GvHD than the control group (61.2% vs. 83.6%, $p = 0.001$; 44.5% vs. 77.0%, $p = 0.001$, respectively). Moreover, bortezomib favored a lower use of systemic steroids (45.1% vs. 76.4%, $p < 0.001$) and allowed a greater number of patients to discontinue immunosuppression (77% vs. 56%, $p = 0.046$). (72) As in the autologous transplantation setting, maintenance with the second-generation PI ixazomib has been tested in high-risk NDMM after allo-HSCT. Although incidence rates of acute and chronic GvHD were limited, a phase II double-blind trial did not show a survival advantage compared with the placebo group. (73) Thus, further studies are needed to explore the effective role of ixazomib in the allogeneic setting.

The other cornerstone in the treatment of MM is represented by IMIDs. The first-in-class thalidomide proved feasible and effective as maintenance post allo-HSCT as previously reported. (34) Lenalidomide is currently approved for post ASCT maintenance. (74) In the post allogeneic transplantation setting, lenalidomide promotes immune-mediated GvM by enhancement of NK cell activation as well as induction of a strong anti-myeloma activity, as well as an increase in the release of IFN-γ by CD4+ and CD8+ T cells and late expansion of regulatory T cells. (75) The prospective HOVON-76 study reported promising results (2-year OS 93%, 2-year PFS 60%) in high-risk NDMM receiving lenalidomide 10 mg on days 1 to 21 of a 28-day cycle after allo-HSCT, but maintenance was burdened by relevant acute and chronic GvHD incidence (53%) and toxicities that led to premature discontinuation of lenalidomide in 47% of participants. (76) Similar results were reported by other prospective studies. (77–79) Then, lowering doses of lenalidomide to 5 mg daily showed better tolerability without negatively impacting survival outcomes (PFS and OS 61% and 79% at 2 years, respectively) (75).

The combination of novel agents such as PI or IMIDs together with DLI has been explored as post-transplantation immunotherapy in those patients failing to achieve CR after allo-HSCT. Among 32 enrolled patients, approximately 60% achieved CR with acceptable rates of both grade II–IV acute and chronic GvHD (33% and 17%, respectively). Notably, deepening the response up to CR significantly predicted for longer 5-year PFS and OS (53% vs. 35%, $p = 0.03$; and 90% vs. 62%; $p = 0.06$, respectively), thus highlighting the importance of achieving and maintaining deeper response even in the post allogeneic transplantation setting (11).

8 Allogeneic HSCT in the era of novel drugs

The introduction in the last decade of novel agents such as PI, IMIDs, and anti-CD38 MoAbs alone or in combination has dramatically improved outcomes for both NDMM and RRMM. (4) Nonetheless, multiple myeloma eventually relapses. Currently, these patients represent an unmet clinical need with dismal outcome: median OS is approximately 12 months in triple-exposed/refractory patients but reaches less than 6 months in those penta-exposed/refractory. (80, 81) Unfortunately, data on allo-HSCT in this setting are very scarce. A recent single-center retrospective experience by Strassl et al. reported on 38 patients with heavily pretreated RRMM who consecutively received allo-HSCT between 2013 and 2022. The median number of previous lines of therapy was 7 (range, 4–13); 74% was triple-class exposed, whereas 24% was triple-class refractory. The conditioning regimen was MAC in 55% of patients whereas 45% of them received RIC mainly based on TBI. The source of donor was heterogenous: MRD 26%, MUD 34%, MMUD 8%, and haplo 34%. The overall response rates (at least PR) to bridging therapy were 87% and 23% achieved CR/sCR. Notably, allo-HSCT was able to deepen response only in those patients who initially responded to bridging therapy, whereas the proportion of refractory patients remained almost unchanged before and after allo-HSCT (13% vs. 11%). After transplantation, only 26% of patients could receive maintenance considering previous drug exposure and expected toxicities whereas 37% of them received DLI. Overall, NRM was 16% and allo-HSCT appeared as a feasible choice in advanced-stage MM. After a median follow-up of 37.5 months for survivals, median PFS and OS were 13.6 months and 51.4 months, respectively. In multivariate analysis, remission status before allo-HSCT (VGPR or better) as well as the absence of high-risk cytogenetic abnormalities by FISH significantly predicted longer survivals. Nonetheless, 58% of patients relapsed after allo-HSCT and the majority of them could receive at least one further treatment. As expected, prognosis was dismal, with an estimated OS of 22.6 months. Among 41 different treatment regimens, five patients received belantamab mafodotin (23%), seven patients were treated with teclistamab (32%), and one patient subsequently also received talquetamab. Notably, all these novel agents proved feasible when used after allo-HSCT, without unexpected severe toxicity or GvHD flares (58).

Novel therapies such as CAR-T and BiAbs have shown promising results in triple- and penta-exposed/refractory MM. (82–85) However, despite high response rates, patients still eventually relapse and few data are available on salvage treatments in this setting. In a recent retrospective analysis, Van Oekelen et al. reported on 79 patients with multiple myeloma relapsed following treatment with BCMA-directed CAR T. After a median follow-up of 21.3 months, median OS from relapse was 17.9 months. In multivariate analysis, penta-drug refractoriness was associated with worse outcomes (median OS 13.9 vs. 29.9 months, $p = 0.018$), whereas achievement of at least a partial response to salvage regimen predicted longer OS compared with non-responding patients (29.9 vs. 14.6 months, $p = 0.028$). In absence of a standard of care, patients received more than 200 different salvage regimens. The most common were CAR T and BiAbs (35 patients, 44.3%) both BCMA-directed and non–BCMA- directed, with overall response rates (ORR) of 91.4% and median OS not reached at data cutoff. Notably, seven patients received allo-HSCT as salvage therapy, obtaining high response rates (ORR 100%) and favorable outcomes (median OS 23.2 months). (86) Similar results (ORR 42%, median OS 18 months) were reported in another single-center analysis of 68 patients relapsed after commercially available CAR-T. (87) Thus, although additional T-cell–engaging therapies showed clinical activity in case of MM relapsed after CAR T, allo-HSCT also appears as a reasonable treatment option in this setting and, moreover, in all that countries where CAR T and BiAbs are not yet available and for those patients who are not eligible to receive these treatments.

9 Conclusion

The use of allogeneic transplantation in multiple myeloma has dramatically dropped in recent years following the introduction of novel agents. Thus, the role of allo-HSCT as consolidation in the first-line treatment of NDMM has disappeared, even in high-risk patients. In RRMM, allogeneic transplantation is not routinely recommended and should only be performed in carefully selected high-risk patients within clinical trials. Less is known about allo-HSCT in patients exposed to new drugs which currently represent the majority of relapsed patients. Therefore, specific studies are encouraged in triple- and penta-exposed/refractory population. Although promising results are reported with CAR T and BiAbs in this setting, patients still eventually relapse. Then, allogeneic transplantation could represent a reasonable treatment choice for younger and high-risk patients who have relapsed after CAR T and BiAbs as well as for those patients not eligible to CAR T and BiAbs and in those countries where these treatments are not yet available. In the choice of conditioning, RIC regimens are widely recommended for the lower TRM. The use of alternative donors, particularly haploidentical, has demonstrated favorable results compared with full matched donors. Finally, post-transplantation maintenance strategies are encouraged whenever feasible.

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Myelofibrosis and allogeneic transplantation: critical points and challenges

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New available drugs allow better control of systemic symptoms associated with myelofibrosis (MF) and splenomegaly but they do not modify the natural history of progressive and poor prognosis disease. Thus, hematopoietic stem cell transplantation (HSCT) is still considered the only available curative treatment for patients with MF. Despite the increasing number of procedures worldwide in recent years, HSCT for MF patients remains challenging. An increasingly complex network of the patient, disease, and transplant-related factors should be considered to understand the need for and the benefits of the procedure. Unfortunately, prospective trials are often lacking in this setting, making an evidence-based decision process particularly arduous. In the present review, we will analyze the main controversial points of allogeneic transplantation in MF, that is, the development of more sophisticated models for the identification of eligible patients; the need for tools offering a more precise definition of expected outcomes combining comorbidity assessment and factors related to the procedure; the decision-making process about the best transplantation time; the evaluation of the most appropriate platform for curative treatment; the impact of splenomegaly; and splenectomy on outcomes.

KEYWORDS

myelofibrosis, bone marrow transplantation, JAK inhibitors, scoring algorithm, splenomegaly

1 Introduction

Myelofibrosis (MF) includes primary myelofibrosis (PMF) and secondary myelofibrosis (SMF). The latter includes post-essential thrombocythemia (PET) and post-polycythemia vera (PPV) myelofibrosis. PET and PPV are associated with inferior overall survival (OS) rates compared to PMF, often due to its higher risk of leukemic transformation (LT). According to WHO and International Consensus Classification of Myeloid Meoplasms and Acute Leukemias (ICC's) current diagnostic criteria, PMF may present two different

clinical pictures: prefibrotic or early myelofibrosis (pre-PMF) and overt myelofibrosis, differing from each other essentially in the bone marrow grade of fibrosis (1–3).

MF treatment options are still limited. The treatment of low-risk MF is generally related to symptom severity. The treatment of high-risk diseases includes JAK inhibitors (JAKi) and allogeneic hematopoietic stem cell transplantation (HSCT). HSCT remains the only chance of a definitive cure for patients with both primary and secondary myelofibrosis (4). After a failure of conventional treatments, in MF patients ineligible for HSCT, enrollment in clinical trials represents an alternative option, when available.

Guidelines recommend upfront allogeneic bone marrow transplantation in patients with high-risk disease, following data from a retrospective study showing patients with intermediate-2 or high-risk score in the Dynamic International Prognostic Scoring System (DIPSS) who benefited the most from transplant than conventional therapy only (5–8).

Thus, an accurate assessment of MF-related risk should be provided by clinicians to promptly identify patients with < 5 years of expected survival, potentially candidates for hematopoietic cell transplantation. Information about transplant-related morbidity and mortality, the expected post-HSCT outcome, as well as MF-related risk, should be adequately shared with patients and their families. Such an integrated evaluation may allow proper counseling about global post-transplant prognosis. Finally, the decision has to be always taken on an individual basis (9).

Moreover, novel strategies for patient and donor selection, conditioning regimens, and post-transplant care in the last years allowed the reduction of disease relapse incidence, 5-year non-relapse mortality and survival in related and unrelated donor transplants in patients with myeloproliferative neoplasms (10), thus, justifying allo-HSCT as a curative option in younger patients of all risk categories and not just in high-risk diseases (11, 12) or in carriers of high-risk non-driver mutations (EZH2, ASXL1, IDH1/2, and SRSF2), predictive of inferior OS and disease-free survival (DFS) (13).

HSCT for MF patients remains challenging, particularly in older age patients or in those with cytopenias, splenomegaly, and severe bone marrow fibrosis (14).

Certainly, the global number of HSCTs in MF rose recently, signifying the increased interest in the only available curative treatment for the disease.

In the present review, we will analyze the main controversial points concerning allogeneic bone marrow transplantation in myelofibrosis.

2 Age at transplant

Older patients are often carriers of metabolic or systemic comorbidities making them more vulnerable to toxicity associated with treatment (10, 15). In studies with a long follow-up, the recipient's age was shown to have an impact on overall survival (OS) and on the risk of treatment failure (16). In a single-center retrospective study on patients with MF who underwent a reduced intensity conditioned (RIC) HSCT, older male patients reported an increased incidence of poor graft function (P = 0.05). This phenomenon was not associated with an increased risk of relapse/progression and did not impact OS (17).

Accordingly, age has been considered the most important factor adversely impacting transplant outcomes in myeloproliferative neoplasms (MPN) (17, 18) and clinicians have been traditionally reluctant to offer the procedure to older patients.

The age of 70 represented the upper limit established in European Society for Blood and Marrow Transplantation (EBMT)/Europena Leukemia Net (ELN) recommendations to proceed with allogeneic transplantation in subjects with intermediate-2 or high-risk disease (19).

Recently, encouraging results were shown in studies involving older patients (>70) undergoing HSCT for MF (20). Engraftment, rates of graft-vs. -host disease (GvHD), progression-free survival (PFS), and OS comparable to those reported in younger patients were shown in selected patients with primary or secondary myelofibrosis aged 60 to 78 years old who received HSCT from Human Leukocyte Antigen (HLA)-identical siblings or unrelated donors (21). Thus, age should not represent an absolute contraindication to allo-HSCT, in case of absent or well-controlled comorbidities (6).

The use of RIC regimens allow more favorable survival in older patients aged > 65 years old with no or minimal comorbidities (22). EBMT/ELN recommendations suggest considering the possibility of HSCT case by case, taking into account patients' and disease variables and also the recipient's preferences (6).

3 Selection of patients

3.1 Stratification of the risk associated with MF

Traditional prognostic models include the International Prognostic Scoring System or IPSS (only applicable to newly diagnosed patients) (23); the dynamic IPSS or DIPSS (24) (applicable at any time point after diagnosis); and the DIPSS plus (25). They all include clinical parameters only (age, anemia, leukocytosis, circulating blasts, and constitutional symptoms), each independently predicting inferior survival. DIPSS plus also includes thrombocytopenia (platelets $<100 \times 10^9$/L), unfavorable karyotyping (traditionally established), and the need for transfusion support (26).

In the pre-ruxolitinib era, only high-risk patients seemed to gain the greatest survival advantage from transplantation. A retrospective multicenter study including 438 patients with primary or PET and PPV myelofibrosis aged less than 65 years clearly showed a significantly lower risk of death after HSCT in comparison with subjects treated with conventional therapies only in case of DIPSS intermediate-2 and high-risk patients (respectively, p: 0.005 and 0.0007 vs. conventional therapies) (5).

Scoring systems including more prognostic parameters, mainly molecular data, were later introduced (Table 1). Among driver mutations, it has become clear that CALR, particularly type I mutation, is associated with a more indolent course, thus its

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TABLE 1 Variables included in prognostic scores applied in myelofibrosis and identification of patients with poor OS.

	Dynamic International Prognostic Scoring System (DIPSS)	Dynamic International Prognostic Scoring System (DIPSS-Plus)	Genetically Inspired Prognostic Scoring System (GIPSS)	Mutation-Enhanced International Prognostic Scoring System Plus Karyotype (MIPSS70 + 2.0)
Age	✔	✔	✖	✖
Constitutional symptoms	✔	✔	✖	✔
Blood count values	✔	✔	✖	✔
Blasts in peripheral blood	✔	✔	✖	✔
Karyotype	✖	✔	✔	✔
Driver mutations	✖	✖	✔	✔
Non-driver mutations	✖	✖	✔	✔
Expected overall survival for each class of risk *	• **LR→ not reached** • **Int-1→14.2 years** • **Int-2→4 years** • **HR→1.5 years**	• **LR→185 months** • **Int-1→78 months** • **Int-2→35 months** • **HR →16 months**	• **LR →26.4 years** • **Int-1→10.3 years** • **Int-2→ 4.6 years** • **HR→2.6 years**	• **VLR→ not reached** • **LR→7 years** • **HR →3.5 years** • **VHR →1.8 years**

*Expected overall survival for each class of risk according to a single stratification risk system: for DIPSS, DIPSS plus, and GIPSS: LR, low risk; Int-1, intermediate 1; Int-2, intermediate 2; HR, high risk. For MIPSS70 + 2.0: VLR, very low risk; LR, low risk; HR, high risk; and VHR, very high risk.

✔, variable included; ✖, variable not included.

protective function against progressive disease has been recognized and with better post-transplant outcome [higher 4-year OS and lower 4-year non-relapse mortality (NRM) after allo-HSCT] (27–29). On the opposite, the worst prognosis is associated with the JAK2/CALR/MPL triple-negative profile (30) (31).

Among non-driver mutations, ASXL1, EZH2, IDH1/2, and SRSF2 were identified as mutations associated with a poor prognosis, defining the group of "high molecular risk (HMR) mutations," linked with poorer prognosis (31–33). The Mutation Enhanced International Prognostic Score Systems (MIPSS) were designed for HSCT decision-making in patients aged ≤70 years.

MIPSS70 identifies as significant risk factors for OS both clinical factors (anemia, leukocytosis, thrombocytopenia, constitutional symptoms, and circulating blasts ≥2%) and nonclinical conditions, not included in the previous traditional models, such as bone marrow fibrosis grade ≥2, absence of CALR type-1 mutation, presence of high-molecular risk mutation (ASXL1, EZH2, SRSF2, and IDH1/2), and the number of two or more high-molecular risk mutations.

The MIPSS70-plus is enriched with cytogenetic information (34), adding a more refined definition of cytogenetic risk, thus providing three risk categories. MIPSS70-plus version 2.0 represents a more complex system including more non-driver mutations (U2AF1) and also considering the number of high-risk mutations and a three-tiered cytogenetic risk classification as independent prognostic factors (34–37). New prognostic thresholds considering severity and sex-adjusted values for hemoglobin levels were also integrated (38).

Genetically inspired prognostic scoring system for primary myelofibrosis (GIPSS) focuses only on genetic and molecular factors, particularly on a limited number of non-driver lesions, without considering clinical parameters at all (39).

Patients may be identified for the HSCT path also according to the best response obtained to pharmacological therapy used as "bridge to transplant," usually JAKi. Lower rates of responses to ruxolitinib have been shown in cytopenic vs. non-cytopenic MF, making cytopenic patients more often considered for earlier HSCT (40).

Moreover, in a recent retrospective study, a positive correlation has been found between peripheral blood CD34 cells and spleen length in both PMF and SMF, thus identifying a possible tool facilitating the assessment of spleen response more objectively than deep palpation of the abdomen (41).

Discrepancies emerged from the application of standard prognostic scores in patients with secondary MF (42). MYelofibrosis SECondary to PV and ET prognostic Model (MYSEC-PM) was validated as the only specific prognostic tool suitable for patients with MF secondary to PV and ET including both clinical and molecular data (43).

Disagreement between modern prognostic scores and traditional scores based on only clinical parameters have been observed (34, 44). GIPSS and clinical-only scores may differ quite frequently as they do not share any variable. That is why at the same risk class, an inferior OS and a worse leukemia-free survival (LFS) were shown in genomically vs. clinically established higher-risk patients ($p = 0.08$ and $p = 0.04$, respectively) (44).

To ensure the most complete evaluation of disease-associated risk, a simultaneous assessment of as many scores as possible could be facilitated by a PMF-specific calculator (45). However, recent EBMT/ELN recommendations indicate allogeneic HSCT based exclusively on DIPSS, MIPSS70, and MIPSS70 plus scores (6).

Many other disease-specific factors have an impact on the outcome as increased circulating CD34+ cells, increased bone marrow or circulating blasts (46, 47), TP53, CBL, N/KRAS mutations (48), triple negativity (31), cytopenic PMF (49). The latter is associated with both higher rates of leukemic transformation and worse survival, and generally, it pairs up with JAK2 V617F allele burden, less prominent splenomegaly, greater genomic complexity and increased risk for infections and bleeding (50).

Splenomegaly itself is not included among the relevant parameters of the prognostic scores used for myelofibrosis despite the fact that larger baseline spleen volume correlates with an increased risk of death in the COntrolled MyeloFibrosis study with ORal jak inhibitor Treatment (COMFORT) studies (51).

Studying a large cohort of patients with MPN (n = 2,035), not necessarily with MF, Grinfeld et al. identified distinct subgroups of MF patients with distinct clinical, cytogenetic, and mutational features, thus developing a personalized MPN risk calculator predicting survival and leukemic transformation, and demonstrating for the first time, the detrimental effect of mutated TP53 on survival in MF patients (52).

3.2 Prediction of post-HSCT outcomes

The role of current prognostic systems in predicting outcomes after HSCT is still uncertain (12, 53–55). DIPSS and DIPSS plus have been shown as predictive tools also for survival following HSCT despite not including the evaluation of transplant-specific variables (5, 53, 56). In SMF, MYSEC was predictive also for survival after allogeneic HSCT, as shown in a recent study (57).

A recent retrospective study published this year by Polverelli et al. on behalf of the Chronic Malignancies Working Party of EBMT confirmed the relevant and negative impact of comorbidities on HSCT outcomes for patients with MF, underlining the need to integrate such an information in the selection process (58).

The hematopoietic cell transplantation-specific comorbidity index, better known as Sorror index provides a reliable scoring of pretransplant comorbidities to more precisely define both non-relapse mortality (NRM) and survival (OS), showing a better prediction power than the Charlson Comorbidity Index (CCI). It is usually applied to all hematological diagnoses, MF included, despite having patients diagnosed with MF who were not included in the validation cohort (59).

Undoubtedly, patient- and transplant-specific risk factors like the intensity of the conditioning regimen, recipient age, cytomegalovirus serostatus, performance status or HLA matching of the donor, influence the patient's post-HSCT outcome (19, 60).

"Myelofibrosis transplant scoring system" or MTSS, a four-level clinical-molecular score including clinical data, donor type, and mutation status for ASXL1/CALR/MPL, has been validated as a specific prognostic tool for an objective evaluation of the risk/benefit ratio of HSCT in the counseling phase, before transplantation (61).

MTSS identified independent risk factors for poor survival after transplant (pretransplantation thrombocytopenia, leukocytosis, older age, poor performance according to Karnofsky performance status, a non-CALR/MPL driver mutation genotype, ASXL1-mutation and transplantation from an HLA-mismatched unrelated donor). It should be noted that it does not include significant risk factors (from existing scoring systems) like anemia and transfusion dependency, constitutional symptoms, cytogenetic risk stratification, or the presence of two or more HMR mutations (61).

Unfortunately, the MTSS scoring system did not maintain its predictive role in other series of cases (62). Another limitation on the use of MTSS is the lack of information about comorbidities. Therefore, the application of MTSS does not disregard the need for a comorbidity index evaluation as well.

Outside the MTSS score, other variables such as spleen size, transfusion history, donor type (11), JAKV617F status, age, and constitutional symptoms are predictive of 5-year OS (55).

Recently, a detrimental effect on transplant outcome was shown in carriers of TP53 mutations of a large multicenter cohort. In particular, higher mortality was demonstrated as a consequence of higher rates of early leukemic transformation, almost a case of "*multi-hit constellation*" (63).

3.3 Final decision about HSCT

In conclusion, there is experts' consensus on the eligibility to transplant for intermediate-2/high-risk DIPSS patients, high-risk MIPSS70 or MIPSS70-plus, high-risk or intermediate-2 MYSEC-PM who, at the same time, present a low to intermediate-risk profile according to MTSS.

Allogeneic HSCT should also be offered to DIPSS intermediate 1 risk patients and to MIPSS70 or MIPSS intermediate patients who present a low-risk profile with MTSS, taking into great consideration patients' preferences, response to treatment, and other issues such as availability of clinical trial or additive data (6).

Traditionally, variables to consider in non-high-risk patients with MF, suggesting eligibility for transplant are represented by (1) transfusion-dependent anemia, (2) a percentage of blasts in peripheral blood > 2%, (3) adverse cytogenetics, and (4) high-risk mutations (64).

4 Splenomegaly and splenectomy

Splenomegaly is a hallmark of both primary and PET and PPV myelofibrosis, as it represents the malignant clone expanding outside the bone marrow. The real impact of spleen size and eventual splenectomy on HSCT outcomes in myelofibrosis is still debated.

Several studies have shown that splenomegaly can adversely impact transplant outcomes, as it may promote the sequestration of hematopoietic progenitors (65, 66).

In a retrospective study involving a limited number of patients with myelofibrosis, the authors considered massive splenomegaly as one of the variables adversely affecting the outcome of HSCT. This variable was included in a scoring tool used for decision-making,

alongside other variables such as a transfusion history of > 20 red blood cell units before transplantation and the type of alternative donor (11).

The effect of a huge spleen on OS and relapse after allo-HSCT is not completely clear, as conflicting data emerged from other works (60, 67, 68).

Furthermore, splenomegaly was associated with a higher risk of relapse after transplantation in recent studies (69, 70).

Potentially, splenectomy before HSCT could be useful for disease debulking and also to favor a faster hematopoietic recovery (66, 71) but some other data, in contrast, did not confirm it (12, 72).

A retrospective EBMT study on 1,000 cases of MF splenectomized in comparison with non-splenectomized patients, did not report a different OS (P = 0.274) rate, but the results seemed associated with a lower rate of NRM (P = 0.018) and increased risk of relapse (P = 0.042). However, in a subanalysis considering splenectomy in different subgroups of patients, an improved outcome was reported with splenectomy in subjects with a palpable spleen length ≥ 15 cm (better OS, significant reduction in NRM, not significantly increased relapse risk, P <.001, P <.001, and P = .147 for each phenomenon) (73).

How splenectomy affects the risk of disease relapse and survival after HSCT is still unclear, thus, making it mandatory for future more prospective randomized trials.

Moreover, data available from retrospective studies on GvHD in previously splenectomized patients are quite conflicting (65, 67, 74).

The course of splenectomy can be complicated by thrombosis, bleeding, infections in up to 30% of patients, disease transformation, and death (peri-operative mortality is in the range of 5%–10%) (75). All complications eventually preclude or simply delay allo-HSCT (72, 76–78).

A multicenter retrospective study on 530 patients with a diagnosis of myelofibrosis from the French bone marrow transplantation registry (RFGM) who underwent splenectomy in the period 2008–2017 showed reassuring results, as pretransplant splenectomy did not preclude allo-HSCT; in particular, splenectomized patients had a higher rate of transplantation in the first 4 months after splenectomy [HR (95% CI) = 7.2 (5.1–10.3)] but not after this time point (79).

As spleen size in patients with MF sensitively benefit from JAKi (80–82), the need for splenectomy has to be discussed rarely nowadays.

Despite not being routinely performed or recommended, splenectomy remains useful in patients who did not benefit from therapy with JAKi, with residual massive splenomegaly.

Splenic irradiation represents a further alternative to splenectomy to reduce spleen size and alleviate splenic discomfort, although the results of such therapy are generally short-lasting and associated with the risk of severe cytopenias, eventually difficult to manage (83).In contrast, the results of a recent retrospective study on HSCT for MF preceded by splenic irradiation are encouraging, showing a reduced relapse after HSCT, without association between total irradiation dose and efficacy (84).

Therefore, it may be considered for patients not eligible for surgery or who were no longer responsive to JAKi (85, 86).

The impact of splenic radiotherapy in leukemic transformation (LT) is still unclear; conversely, similar engraftment rates and GvHD incidence have been described in patients who underwent splenic irradiation or not (74).

5 JAKi and timing

The option of upfront HSCT is still recommended for patients stratified as intermediate 2 and high-risk DIPSS, with an expected survival of fewer than 5 years (6), as it provides the best gain in life expectancy. This indication was reinforced by a decision analysis recently published (87).

In the case of a patient with intermediate-risk disease, the decision about HSCT requires a more tailored approach, and generally, the procedure can be delayed; usually, in this setting, more prognostic factors, even outside traditional scores, have to be considered, identifying those patients less likely to have lasting response from non-transplant therapy (6, 88).

The best timing of HSCT has become a more controversial point in the era of JAKi as these drugs produce a better action on spleen size, constitutional symptoms, and also on survival outcomes.

Studies showed better response in patients treated earlier during the disease course with both HSCT (56) and JAKi, thus, decision-making about transplant becomes even more complex. It should be underlined that JAKi are not curative (89, 90), and they do not prevent the progression to blast phase or leukemic transformation, the main determinant of death in MF (23, 91, 92).

Furthermore, despite the success with ruxolitinib in the frontline setting, discontinuation of JAKi therapy may occur because of intolerance or refractoriness, events associated with a poor OS according to retrospective studies (93, 94).

Comparative studies testing the results of upfront HSCT approaches with non-transplant therapies of the JAKi era are still lacking, thus leading to a wide variability of conducts on the use of HSCT in MF. In 2024, upfront JAKi therapy was compared with upfront HSCT strategy in MF patients not older than 70 years old in a large, multicenter and retrospective study; in patients treated with upfront HSCT, an earlier mortality was observed and in general, they do not report significative benefit (95).

Thus, one can imagine that in the "JAKi era," HSCT is limited to cases of cytopenic myelofibrosis, not manageable with cytoreductive or JAKi therapy; could be delayed until response to JAKi is lost, and that delaying time could become even longer as more than one JAKi has become available (21). In fact, according to some recent data, fedratinib or other JAKi may improve upon the poor prognosis associated with ruxolitinib discontinuation (96, 97).

Advanced-stage disease, increasing age, or leukemic transformation, often associated with the emergence of acquired unfavorable mutations, could represent the dramatic consequences of delaying the HSCT procedure, as impactful disease-modifying therapy other than HSCT still does not exist.

For this reason, many authors underline that patients whose therapeutic goal is cure should still undergo HSCT even if responding to JAKi (98).

The possibility to rapidly obtain a spleen response with JAKi represents an attractive option for clinicians looking for a "bridge to transplant strategy," thus eventually making engraftment time more rapid (99, 100). The use of JAKi as pre-HSCT strategy is increasing and offers encouraging results. With this approach, eligible patients should undergo HSCT at the time of the best response to JAKi (100).

In non-randomized and retrospective studies, the treatment of patients with ruxolitinib in the phase preceding HSCT is well-tolerated and associated with better post-transplant outcomes and survival (101, 102). The prospective phase-2 trial JAK ALLO study showed that a short course of ruxolitinib administered before HSCT and stopped progressively or abruptly before the conditioning regimen is safe and associated with a high probability of HSCT for those with a donor and no increased risk of disease progression (103).

The initiation of ruxolitinib is recommended ≥2 months before HSCT, careful weaning 5–7 days before conditioning, and complete withdrawal on the day before conditioning according to the European guidelines for primary MF (19). Adverse events happened in patients who stopped JAK inhibitor ≥ 6 days before conditioning therapy (104), while they were infrequent in those treated with JAK inhibitor until HSCT conditioning therapy was started (105).

Future studies will clarify the hypothesis that JAKi treatment in candidates for HSCT may reduce the incidence of poor graft function (17).

It should be noted that in MF patients pre-treated with ruxolitinib for 6 months before HSCT, different outcomes were shown according to the type of donor. In particular, poorer mortality and GvHD outcomes were associated with patients receiving HSCT from an unrelated donor compared to those with a matched sibling donor in JAK ALLO phase-2 trial. These results could be explained by many factors such as advanced disease, loss of response to ruxolitinb at the time of HSCT or insufficient period of treatment, thus not showing a direct impact of ruxolitinib on post-HSCT outcomes (103).

In a multicenter German study reporting the experience of ruxolitinib pretreatment in 159 MF patients who underwent RIC HSCT between 2000 and 2015 from different types of donors, ruxolitinib did not negatively impact HSCT outcomes, as similar outcomes were shown in non-ruxolitinib pre-treated patients. Similar OS, DFS, and GvHD were reported among ruxolitinib responders and those who failed to respond or were no longer responsive to JAKi (106).

Following JAKi failure (93, 107), HSCT should be considered in any patient (108), according to little data from retrospective studies showing improved survival with HSCT in this setting (109).

The treatment landscape has become more intricate with the availability of fedratinib and novel combination strategies involving ruxolitinib within clinical trials. Nevertheless, HSCT remains a viable option for eligible candidates. Despite the efficacy of fedratinib on splenomegaly, there is still lack of information on the use of this agent or other novel agents, as an alternative to ruxolitinib, before HSCT (6).

Thus, response to ruxolitinib should be systematically assessed 6 months after initiating therapy (6), as recently recommended by EBMT/ELN.

The model, named Response to Ruxolitinib After 6 Months (RR6), was validated as a prognostic model allowing the identification of MF patients who have already been treated with ruxolitinib for 6 months and in need of second-line treatment strategies, HSCT included. The predictive role of such a prognostic tool, evaluating three variables (drug dose, spleen response, and transfusion requirement) and thus stratifying the risk into three categories (low, intermediate, and high) overcomes conventional risk stratification in MF treated with ruxolitinib (110). According to the RR6 model, high-risk patients need a prompt evaluation for HSCT (6).

6 Identification of stem cells donors

Donor type is an important predictor of outcome for MF transplanted patients, with HLA-matched sibling donors (MSD) being preferred over matched unrelated donors (MUD) and mismatched unrelated donors (mMUD). Gupta et al. reported HSCT outcomes of 233 MF patients for CIMBTR. In multivariate analysis, donor type was the sole independent factor associated with survival (5-year OS was 56%, 48%, and 34% for MSD, MUD, and mMUD, respectively) (111).

Alternative donor options in MF expand the donor pool in patients who do not have a suitable sibling or unrelated donor. Unrelated cord blood units are rarely used in MF patients, with graft failure remaining a major concern. A retrospective study from the EBMT registry evaluated 35 patients who received cord blood HSCT reporting 2 years of OS and EFS rates being 44% and 30%, respectively (112).

The haploidentical setting is still under investigation with improving results over time. Bregante et al. evaluated the outcome of 95 patients with myelofibrosis who were allografted between 2001 and 2014. The 3-year HSCT-related mortality (TRM), relapse rate, and overall survival were 16% vs. 32%, 16% vs. 40%, and 70% vs. 39%, respectively, in the 2011 to 2014 period versus the 2000 to 2010 period. Improved survival was most pronounced in alternative donors (69% vs. 21%), compared with MSD (72% vs. 45%) (113).

Kunte et al. reported the results from a multicenter retrospective study of 69 patients who underwent haploidentical HSCT with post-procedural cyclophosphamide (PTCy) with 3-year OS being 72%, 3-year relapse-free survival of 44%, and non-relapse mortality of 23% (69).

7 Primary graft failure and poor graft function

Primary graft failure and poor graft function are two difficult challenges after HSCT.

Primary graft failure is defined according to the EBMT criteria by an ANC < 0.5×10^9/L by day +28 following stem cell infusion, Hb <8.0 g/L, and platelets <20×10^9 (114).

In a retrospective EBMT study involving 2,916 MF patients who underwent allo-HSCT from an HLA-identical sibling or unrelated donor between 2000 and 2016, the 5-year survival rate in patients who developed graft failure was 14% (115).

Recognized risk factors for transplanted patients are related to donor, conditioning, cell dose, and HLA sensitization if the recipient is heavily transfused (116).

No consensus is available about therapeutic options for patients with graft failure, second allo-HSCT using either the same or alternative stem cell donor is warranted (116).

Recently, a retrospective study from the Francophone Society of Bone Marrow Transplantation and Cellular Therapy demonstrated the rescuable potential of salvage haplo-HSCT with PTCy for graft failure. The median time to neutrophil engraftment was 18 days and the cumulative incidence of neutrophil engraftment at day 30 was 79%. One-year overall survival (OS) was 56% and HSCT complications accounted for 80% of causes of death, with multiple organ failure as the leading cause (117).

According to the EBMT criteria, poor graft function (PGF) is defined by the presence of bi- or tri-lineage cytopenia lasting for more than 2 weeks, after day +28 in the presence of donor chimerism >5% (114).

Moreover, PGF is also defined by the presence of mild/moderate cytopenias in at least two hematopoietic lines (ANC < 1.5×10^9/L, platelet count < 30×10^9/L, Hb < 8.5 g/dL) lasting for more than 2 consecutive weeks following engraftment beyond day +14. This definition was recently introduced by an expert panel of the EBMT Chronic Malignancies Working Party, because it is easier to apply in clinical practice than the former one (116).

In a cohort of 100 patients with primary MF or post-ET/PV MF who received a reduced-intensity HSCT, the cumulative incidence of poor graft function was 17% and all cases occurred before day 100 after HSCT at a median of 49 days (range: 24–99 days). In univariate analysis, recipients of older age and splenomegaly at day 30 after HSCT showed an increased cumulative incidence of poor graft function (17).

An expert panel from the EBMT/ELN International Working Group recommends the use of growth factors for anemia (erythropoietin) or neutropenia (granulocyte colony-stimulating factor), whereas data on the use of thrombopoietin analogs in patients with myelofibrosis who underwent allogeneic HSCT are scarce. The most definitive treatment for poor graft function is a CD34+ stem-cell boost from the original donor, either fresh or cryopreserved, without further conditioning in patients without active GvHD (6).

In the Hamburg cohort, CD34+ selected stem cell boost infusion in patients with PGF achieved similar outcomes at 3 years when compared to patients who did not have PGF (17).

Management of persistent splenomegaly in patients with PGF after HSCT is challenging. Splenectomy was reported to be an option in selected patients (17) but it is not without risks. JAK2 inhibitors have not been tested for the indication of post-procedural poor graft function. In majority of the patients, tri-lineage hematologic recovery can be achieved, but will require several months.

8 Relapse after HSCT

Unfortunately, 10%–30% of transplanted patients experience MF relapse after a median of 7 months after HSCT with a median overall survival from the time of relapse of 2 years (116, 118).

Ataganduz et al. also described a late relapse in 14% of patients later than 5 years after HSCT at a median of 7.1 years (119) (Table 2).

TABLE 2 Transplant outcomes in MF patients.

Type of study/ Reference	Patients/ Follow-up	Outcomes	TRM/ NRM
Retrospective multicenter Maze D et al., BMT 2024 (95)	302 patients: 89 upfront HSCT vs. 213 JAKi Median follow-up: 49 months	OS@ 36 months: prior JAKi 69%, upfront HSCT 42%	TRM @ 12 months: 27% HSCT group vs. 3% JAKi group
Retrospective multicenter Hernandez-Boluda et al., BMT 2024 (120)	346 CALR-mutated patients Median follow-up: 40 months	OS @ 1, 3, and 5 years: 81%, 71%, and 63%	TRM @ 1, 3, and 5 years: 16%, 22%, and 26%
Retrospective multicenter Kunte et al., Leukemia 2022 (69)	69 patients, haplo donors with PTCy GvHD prophylaxis Median follow-up: 23 months	OS @ 3 years 72%, @ 1 year 74% RFS @ 3 years 44%	TRM @ 1 year 21%, @ 3 years 23%
Retrospective multicenter Hernandez-Boluda et al., American J Hematol 2021 (20)	556 patients aged ≥65 years Median follow-up: 3.4 years	OS @ 5 years 40% Relapse @ 5 years 25%	NRM @ 5 years 37%
Retrospective multicenter Kroger et al., Leukemia 2021 (121)	551 patients: 277 JAKi pre HSCT, 274 no JAKi	EFS @ 2 years: 68.9% for JAKi pre HSCT vs. 53.7% no JAKi	NRM @ 1 year 22%
Retrospective multicenter McLornan et al., BMT 2021 (122)	4142 patients Median follow-up: 48 months	OS @ 3 years 58% Relapse @ 36 months 22%	NRM @ 36 months 23%
Prospective multicenter Robin M et al., BMT 2021 (103)	64 patients Median follow-up: 31 months	OS @ 12 months 68%, @ 24 months 55% DFS @ 12 months 52%, @ 24 months 46%	NRM @ 12 months 42%, @ 24 months 46%
Retrospective multicenter Lwin Y et al., BBMT 2020 (123)	142 patients Median follow-up: 51.8 months	OS @ 1 year 67%, @ 5 years 57%	NRM @ 100 days 16%, @ 1 year 25%

HSCT, hematopoietic stem cell transplantation; OS, overall survival; JAKi, JAK inhibitors; TRM, transplant related mortality; PTCy, post-transplant cyclophosphamide; GvHD, graft versus host disease; RFS, relapse-free survival; NRM, non-relapse mortality; EFS, event-free survival; and DFS, disease-free survival.

The EBMT Chronic Malignancies Working Party defined MF relapses after HSCT as molecular relapse only, cytogenetic relapse only (rarely reported), molecular and cytogenetic relapse only, and morphological/clinical relapse (116).

The expert panel from the EBMT/ELN International Working Group recommends molecular monitoring by sensitive PCR for one of the driver mutations (JAK2, CALR, or MPL) or highly sensitive chimerism for triple-negative MF after HSCT at 1 month and at 3-month intervals thereafter, for up to 1 year and annual testing thereafter (6).

In case of detection of a molecular relapse, early intervention with the aim of reduction of immunosuppressive therapy and use of adoptive immunotherapy with donor lymphocyte infusions (DLI) can achieve molecular remission avoiding progression to overt hematological relapse in responders (116, 124, 125).

Moreover, Gaglemann et al. showed higher rates of complete molecular remission after DLI for molecular relapse comparing hematological relapse (88% and 60%, respectively) (125).

Second HSCT is a valid option to rescue selected fit patients. Nabergoj et al. for the Chronic Malignancies Working Party of EBMT analyzed 216 patients undergoing a second allo-HSCT for either relapse (56%) or graft failure (31%), achieving 42% 3-year overall survival and 39% relapse-free survival (RFS) (126).

Date are insufficient to recommend the use of JAKi after HSCT as maintenance therapy to prevent relapse and in molecular relapse to prevent overt hematological relapse (6, 116). In patients experiencing hematological relapse after HSCT JAKi represent a valid option to reduce constitutional symptoms and/or splenomegaly (127).

Results of transplant outcomes in MF are showed in Table 2 (20, 69, 95, 103, 120–123).

9 Conclusions

HSCT remains a challenging and controversial procedure in MF; the assessment of the opportunity and modality of HSCT is usually carried out taking into account specific disease variables but also the recipient's conditions and preferences, case by case.

As the number of HSCT rises rapidly, the best approach to patient and donor selection, splenomegaly management, and timing of HSCT in the era of new drugs need to be clarified. Further studies are required and will test, last but not the least, how to improve HSCT outcomes in this setting. The most appropriate transplant platforms, GvHD prophylaxis, infections management, and thrombosis prophylaxis need to be addressed undoubtedly, as soon as possible.

Author contributions

PR: Writing – original draft, Writing – review & editing. AN: Writing – original draft, Writing – review & editing. FG: Writing – original draft. SS: Writing – review & editing. CC: Writing – review & editing. GL: Writing – review & editing. MD: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Sorafenib maintenance in FLT3-ITD mutated AML after allogeneic HCT: a real-world, single-center experience

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Despite allogeneic hematopoietic stem cell transplant (allo-HCT) and the development of novel FLT3 inhibitors in both induction (midostaurin) and in the relapsed/refractory setting (gilteritinib), FLT3-ITD mutated leukemia (FLT3-ITD+ AML) still represents a challenge for modern hematology. Sorafenib is, to this date, the only inhibitor that demonstrated efficacy in improving both progression-free and overall survival as post-HCT maintenance therapy, even if its use in this setting has not been approved so far by regulatory agencies. The aim of our study was to evaluate the feasibility, safety, and efficacy of sorafenib maintenance in preventing early relapse in FLT3-ITD+ AML after HCT in a single-center experience. We analyzed 26 consecutive patients who received post-HCT 2-year maintenance with sorafenib at our center between 2017 and 2023. The median time from HCT to sorafenib start was 130 days, and the median dosage was 200 mg per day. Two (8%) and three (12%) patients discontinued maintenance due to toxicity and disease relapse, respectively. Eight (31%) patients terminated the 2-year maintenance and stopped sorafenib, while 13 patients are still under treatment. Overall, 21/26 patients (81%) are alive and in stable complete remission as outlined by a 2-year disease-free survival of 83.61%. No major long-term toxicity was reported at the last follow-up. Our real-world experience supports the use of sorafenib as a feasible and effective therapeutic option in post-HCT maintenance for FLT3-ITD+ AML.

KEYWORDS

sorafenib, maintenance, allogeneic stem cell transplantation, FLT3 ITD, acute myeloid leukemia

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Introduction

Acute myeloid leukemia (AML) with the Internal Tandem Duplication (ITD) mutation of the FMS-like tyrosine kinase 3 gene (FLT3-ITD) remains, to this day, one of the greatest challenges of modern hematology due to poor prognosis despite allogeneic hematopoietic stem cell transplantation (allo-HCT). FLT3 inhibitors have proven their efficacy in induction and salvage treatment, both in combination and in monotherapy. Three FLT3 inhibitors (FLT3-i) are currently approved by the FDA and EMA. Midostaurin and quizartinib have been approved by both the FDA and the EMA for induction therapy in combination with the "7 + 3" multi-chemotherapy regimen and for subsequent maintenance monotherapy based on the results of phase 3 trials RATIFY (1) and QuANTUM-First (2), respectively. Gilteritinib is a second-generation FLT3 inhibitor approved by the FDA in 2018 and by the EMA in 2019 as a monotherapy for patients with relapsed/refractory FLT3 mutated AML based on the results of the phase 3 ADMIRAL trial (3). However, none of these drugs have been approved as post allo-HCT maintenance. The use of sorafenib, a multi-targeted tyrosine kinase inhibitor, has been successfully explored in this setting in the phase 2 trial SORMAIN (4). Similarly a randomized, phase 3 trial showed long-lasting improved overall survival (OS) and leukemia-free survival (LFS—5-year follow up) in patients receiving sorafenib as post-HCT maintenance (5), confirming the results highlighted in a meta-analysis (6) evaluating 12 studies and more than 2,000 patients with a clear benefit on OS and LFS from post-transplant FLT3-i maintenance. Based on the increased relapse-free survival and good tolerability provided by sorafenib as post-HCT maintenance for FLT3 mutated AML, its use was recommended by the Acute Leukemia Working Party (ALWP)–European Society for Blood and Marrow Transplantation (EBMT) to optimize long-term disease control (7). It is worth noting that its use in maintenance after allo-HCT has not been approved so far by regulatory agencies. The aim of our study was to evaluate the feasibility, safety and efficacy of sorafenib maintenance in preventing early relapse in FLT3-ITD+ AML after allo-HCT in a single center experience.

Methods

Study design and participants

At our center, we performed allo-HCT in 297 AML patients between January 2017 and September 2023. Overall, 73 patients harbored a FLT-ITD mutation; of these, 47 patients (64%) could not receive maintenance due to various conditions (Figure 1), while 26 (36%) received sorafenib after allo-HCT. Considering this last cohort of patients, transplant was performed from all donor types, in particular, matched related, matched unrelated, haploidentical donor, and cord blood unit in 11 (42%), six (23%), six (23%), and three (12%) cases, respectively. According to center guidelines, a treosulfan-based conditioning regimen was adopted (8) in all cases, including all degrees of transplant conditioning intensities (9) (high n =15, 58%; intermediate n = 7, 27%; low n = 4, 15%). GvHD prophylaxis consisted of post-transplant cyclophosphamide (PtCy), sirolimus, and mycofenolate mofetil (MMF). Patients receiving matched related donors did not receive MMF, while patients receiving a cord blood unit did not receive PtCy. The inclusion criteria for sorafenib maintenance were as follows: (a) complete hematologic reconstitution (hemoglobin >10 g/dL, platelets >100,000/μL, and neutrophils >1,000/μL), (b) discontinuation of letermovir prophylaxis (day 100), (c) tapering of immunosuppressive therapy, and (d) absence of graft-*versus*-host disease (GvHD) requiring systemic treatment.

Disease status was re-evaluated at days +45 and +90 from transplant. In case of complete remission (CR), off label sorafenib was initiated at day +100 as recommended by the ALWP (5), after provision of an informed signed consent. Disease was evaluated at different timepoints (45 days from transplant, 3 and 6 months, 1 year, 1.5 years, 2 years, and then yearly until the 5th year). Patients with concomitant nucleophosmin1 (NPM1) mutation were monitored for the presence of the transcript by real-time quantitative polymerase chain reaction (RT-PCR) on peripheral blood and bone marrow at every disease re-evaluation time-point, and MRD negativity was defined as the ratio NPM1mut/ABL × 100 transcript <0.01%. For patients with unmutated NPM1 mutation, complete response was defined as morphological remission (marrow blasts <5%) associated with full donor chimerism.

Statistical analysis

Overall survival (OS) was defined as the time from transplant to death from any cause or date of the last follow-up. The events for disease-free survival (DFS) were relapse or death. GRFS (GvHD/relapse-free survival) events were defined as the first event among grades III to IV acute GvHD, moderate to severe chronic GvHD, leukemia relapse, and death from any cause after allo-HCT. The OS, DFS, and GRFS rates were calculated using the Kaplan–Meier method and compared using log-rank test. A p-value lower than 0.05 was interpreted as significant.

Patient-, disease-, and transplant-related characteristics were compared using the χ^2 or Fisher's exact test for categorical variables and the Mann–Whitney U-test for continuous variables.

Results

Patient-, disease-, and transplant-related features are reported in Table 1. It is worth noting that, among the two groups of patients (patients treated with sorafenib and patients that did not receive sorafenib maintenance), no evidence of significant differences in terms of disease status at transplant, conditioning intensity, donor source, or post-transplant MRD positivity were observed.

Among patients in the sorafenib cohort, the median age at allo-HCT was 51 years (range, 34–75). The cohort included 13 male and 13 female patients. A total of 16 patients (62%) had concomitant NPM1 mutation, allowing for measurable residual disease (MRD) monitoring. Moreover, 21 patients were in CR at the time of transplantation (81%), three of which were with MRD positivity

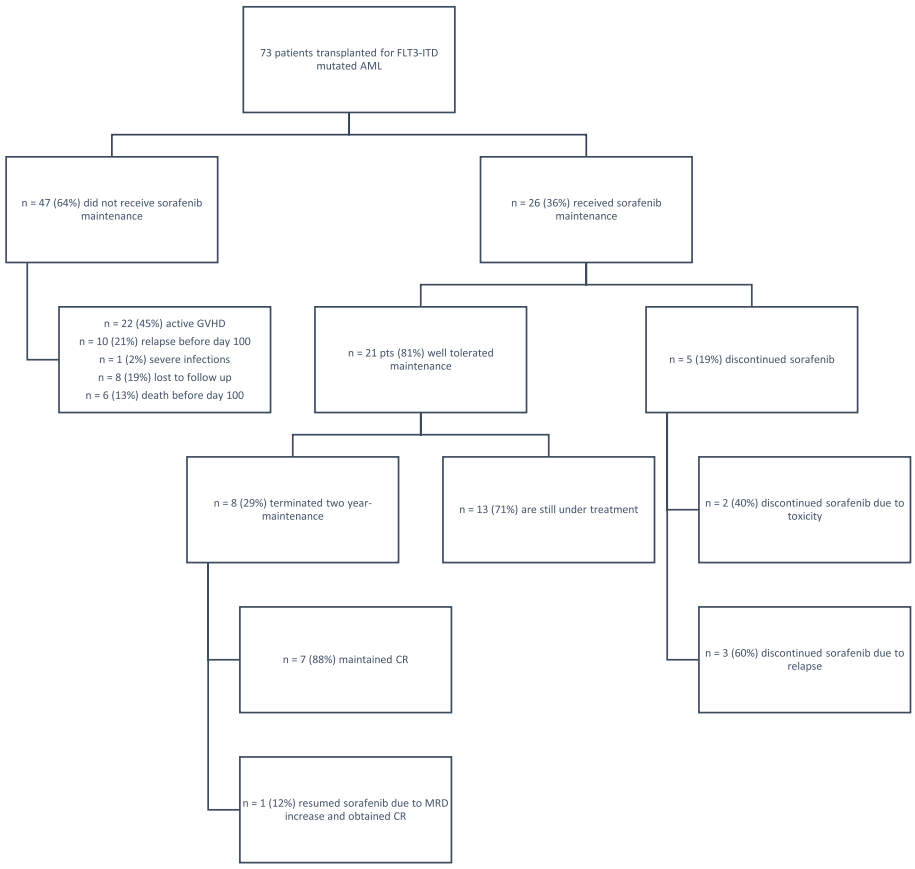

FIGURE 1
Eligibility and follow-up of patients. AML, acute myeloid leukemia; CR, complete remission; GvHD, graft-*versus*-host disease. A total of 79 patients with FLT3-ITD AML underwent transplantation; of these, 47 patients did not receive sorafenib due to various reasons— GvHD, early relapse, or severe infections; eight patients were lost to follow-up. The study group included 26 patients who received sorafenib; five patients discontinued maintenance for toxicity or relapse, while 21 patients tolerated the treatment well. Of these patients, 13 are still under treatment.

(11%) and five had active disease (19%). All patients were in complete morphological remission at the time of sorafenib initiation. Out of the NPM-positive patients, seven patients were MRD-positive at the time of sorafenib initiation. Interestingly, 21 patients had already received FLT3 inhibitors prior to allo-HCT, either in induction together with cytotoxic chemotherapy or at relapse: 18 patients had received prior midostaurin (69%), two had gilteritinib (8%) for relapsed/refractory disease, two had sorafenib (8%), and one patient had been included in a randomized trial with novel FLT3 inhibitors.

The median time from allo-HCT to start of sorafenib was 130 days (range, 49–1,026). Sorafenib was introduced at a minimum dosage of 200 mg every other day to reduce the drug–drug interaction with concomitant therapies (sirolimus, azoles, etc.), and it was progressively increased to 200 mg twice daily after immunosuppressive therapy discontinuation, with a median dosage of 200 mg daily. Two patients whose MRD was increasing were able to tolerate the maximum dosage of 400 mg twice daily without toxicities as well.

Sorafenib was overall well tolerated, with only two (8%) patients permanently discontinuing it for grade 3 – CTC AE toxicity (one gastro-intestinal and one cardiac toxicity). Six patients required a reduction to 200 mg every other day to mitigate the side effects, mainly gastro-intestinal discomfort. Other observed toxicities included hand–foot syndrome (n = 2, 8%; CTC AE G1), liver enzyme alteration (n = 2, 8%; CTC AE G2), and neutropenia (n = 1, 4%; CTC AE G3).

Eight patients completed the 2-year maintenance with sorafenib, and 13 patients are currently under treatment. At a median follow up of 34 months after sorafenib discontinuation, seven out of the eight patients that completed the 2-year maintenance (88%) maintained a continuous complete response. A single patient needed to restart sorafenib 96 days after maintenance completion due to early re-appearance of MRD positivity, which was confirmed at two subsequent controls. After resumption of sorafenib, MRD negativity was achieved soon after, and the patient is still alive and in CR, under sorafenib treatment. Overall, 21/26 patients (81%) with FLT3-ITD+ AML maintained stable CR, with no major long-term toxicity.

With regard to GvHD, 22 of the 73 patients transplanted for FLT3-ITD AML could not receive maintenance due to concomitant severe GvHD requiring high-dose steroids and drugs with possible interactions with sorafenib. In the cohort of patients receiving sorafenib, 8/26 patients (30%) previously had aGvHD, while 9/26

TABLE 1 Patients' features.

	Entire population 73 patients	Control group 47 patients	Sorafenib group 26 patients	*p*-value
Sex (M/F)	37/36 (50%/50%)	24/23 (51%/49%)	13/13 (50%/50%)	1
Median age at HCT, years (range)	52.5 (24–75)	53 (24–71)	51.5 (34–75)	0.73
Mutational status at diagnosis				0.34
NPM1+/FLT3+	39 (53%)	23 (49%)	16 (62%)	
FLT3+	34 (47%)	24 (51%)	10 (38%)	
Disease status at transplant				0.52
CR1	36 (50%)	22 (47%)	14 (54%)	
CR2	14 (19%)	10 (21%)	4 (15%)	
CR MRD+	5 (6%)	2 (4%)	3 (12%)	
Active disease	18 (25%)	13 (28%)	5 (19%)	
TCI				0.49
Low (1 to 2)	9 (12%)	5 (11%)	4 (15%)	
Intermediate (2.5–3.5)	26 (36%)	19 (40%)	7 (27%)	
High (4–6)	38 (52%)	23 (49%)	15 (58%)	
GvHD prophylaxis				0.69
PTCy based + rapamycin	66 (90%)	43 (91%)	23 (88%)	
Rapamycin + MMF	7 (10%)	4 (9%)	3 (12%)	
Donor				0.41
Matched related donor	14 (19%)	8 (17%)	6 (23%)	
Mismatched related donor	26 (36%)	20 (42%)	6 (23%)	
Matched unrelated donor	25 (34%)	14 (30%)	11 (42%)	
Cord blood unit	8 (11%)	5 (11%)	3 (12%)	
NPM1-positive patients (*n*)	39/73	23/47	16/26	
MRD status post-HSCT				1
Negative	21 (54%)	12 (52%)	9 (56%)	
Positive	18 (46%)	11 (48%)	7 (44%)	

HCT, hematopoietic stem cell transplantation; CR, complete remission (with MRD negativity for NPM1-mutated patients); MRD, minimal residual disease —for NPM1-mutated patients; TCI, transplant conditioning intensity; GvHD, graft-versus-host disease; MMF, mycophenolate mofetil.

(35%) developed moderate to severe GvHD which did not require sorafenib discontinuation. At 2 years, GRFS was 53.57% in the cohort treated with sorafenib and 25.95% in the cohort that did not receive sorafenib [$p = 0.0451$, hazard ratio (HR): 1.82, 95% CI: 1.01–3.27] (Figure 2A).

Only three patients experienced disease progression during sorafenib therapy: the first one had positive MRD at the time of transplant, which increased steadily thereafter until overt hematological relapse. Due to a FLT3-ITD-positive relapse, an off-label treatment consisting of gilteritinib in combination with the bcl-2 inhibitor venetoclax was administered, but the patient died from disease progression. The second patient also had detectable MRD at the time of transplant, with transient MRD reduction after sorafenib initiation. Due to progressive MRD increase with initial FLT3-ITD positivity, the patient initiated gilteritinib therapy with consequent MRD clearance; the patient is still alive and in CR at 13 months from allo-HCT. The third patient had been included in a randomized clinical trial with novel FLT3-inhibitors; due to initial MRD positivity, without hematological relapse, the patient was switched to sorafenib maintenance and nevertheless later needed rescue with a second HCT.

With a median follow-up for the entire cohort (sorafenib group + control group) of 3 years, the sorafenib cohort reported a medium follow-up of 624 days (range, 139–2,499 days) and a median treatment exposure of 547 days (range, 3–1,686 days). We observed only one death due to disease progression. The 2-year

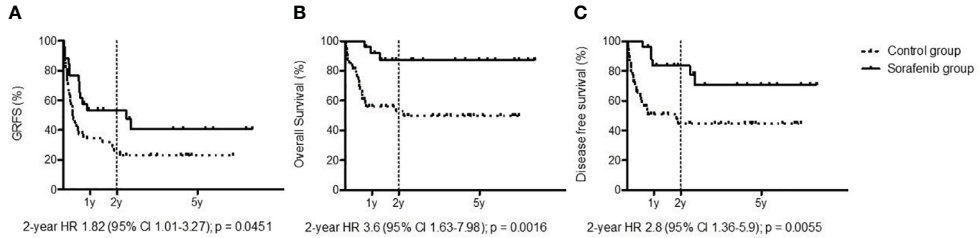

FIGURE 2
Outcomes: graft-*versus*-host disease/relapse-free survival **(A)**, overall survival **(B)**, and disease-free survival **(C)** among patients treated with sorafenib (black line) and patients untreated with sorafenib as post-allo-HCT maintenance (dotted line).

OS for the cohort treated with sorafenib was 87.13%, while in the cohort that did not received sorafenib it was 52.82% (p = 0.0016, HR: 3.6, 95% CI: 1.63–7.98) (Figure 2B). The 2-year DFS for the cohort treated with sorafenib was 83.61%, while in the cohort that did not receive sorafenib it was 44.52% (p = 0.0055, HR: 2.8, 95% CI: 1.36–5.90) (Figure 2C).

Discussion

Our real-world analysis confirms that sorafenib maintenance therapy is feasible, highlighting that the majority of candidate patients can start and complete the planned 2-year maintenance treatment. It is worth noting that, despite the limit of a retrospective study, the cohort of patients treated with sorafenib obtained a better outcome in terms of OS and DFS, which can be considered a direct measure of clinical benefit, outweighing (outlined as well by the significantly better GRFS) the possible toxicities exerted by sorafenib. Furthermore, the improvement of GRFS clarifies the conditional benefit of sorafenib capturing clinically meaningful events that impact the quantity and quality of survival after allo-HCT.

As reported by the two randomized trials (4, 5) and other groups (10, 11), sorafenib dosing can be individualized in the post-transplant setting according to patient tolerability. Sorafenib was well tolerated in our practice: drug-related toxicities and drug–drug interactions proved to be manageable through a customized approach, reducing the percentage of patients that permanently discontinued the maintenance. In fact, only 8% of patients discontinued sorafenib treatment in our study *versus* 22% of patients in the SORMAIN trial (4) and in contrast with other experiences (12).

Furthermore, preliminary results on the discontinuation of maintenance after 2 years of treatment confirm both the persistence of long-term remission and possibility to revert MRD positivity through resumption of the drug: sorafenib contributes to sustained long-lasting remissions of FLT3-ITD+ AML after allogeneic HCT.

Our real-world experience supports the use of sorafenib as a feasible and effective therapeutic option in post-HCT maintenance for FLT3-ITD+ AML across different donor sources.

Data availability statement

The datasets generated for this study are available on request to the corresponding author. Requests to access these datasets should be directed to diral.elisa@hsr.it.

Ethics statement

All patients were treated according to current Institutional programs upon written informed consent for transplant procedures, use of medical records and immunological studies for patients undergoing allogeneic HSCT within the non-interventional ALMON study, approved by San Raffaele Institutional Ethical Committee in date 19/10/2007. Sorafenib was given off-label after provision of an informed signed consent.

Author contributions

ED: Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. GF: Data curation, Validation, Writing – original draft. AB: Validation, Writing – review & editing. RG: Validation, Writing – review & editing. DC: Validation, Writing – review & editing, Formal analysis. SMar: Validation, Writing – review & editing. FF: Validation, Writing – review & editing. SMas: Validation, Writing – review & editing. LV: Validation, Writing – review & editing. SP: Validation, Writing – review & editing. JP: Validation, Writing – review & editing. CC: Validation, Writing – review & editing. MB: Validation, Writing – review & editing. FC: Validation, Writing – review & editing. ML-S: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Publisher's note

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Pure red cell aplasia among ABO mismatched hematopoietic stem cell transplant recipients: a 13-years retrospective study and literature review

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Background: Pure red cell aplasia (PRCA) is a possible complication after allogeneic hematopoietic stem cell transplantation (HSCT) with major ABO incompatibility. Patients experience delayed engraftment of the erythroid series, with prolonged transfusion-dependent anemia and iron overload.

Methods: We performed a revision of the most recent literature about post-HSCT PRCA treatment procedures. Moreover, we conducted a retrospective study, over the last 13-years, which included all consecutive major ABO mismatched HSCT performed in our unit, with the aim to assess PRCA incidence, risk factors, and response to different treatments. Overall, 194 patients received a major ABO mismatched transplant from 2010 to 2022. For each patient, data about demographic and transplant characteristics, engraftment, blood transfusion, and possible treatment received were collected.

Results: The literature review returned 23 eligible papers on PRCA treatment, with high success rate using plasma-exchange (PEX) and immunoadsorption procedures, daratumumab, and eltrombopag. Our study identified a total of 24 cases of PRCA. Among risk factors for PRCA development, we have found older recipient age ($p=0.01$), high pre-HSCT IgG and IgM IHA titer ($p<0.0001$), major rather than bidirectional ABO incompatibility ($p=0.02$), low T CD8 lymphocyte count in the graft ($p=0.006$), relative donor ($p=0.02$) and bone marrow as stem cell source ($p=0.002$). However, multivariate analysis confirmed only pre-HSCT IgG IHA titer as the unique risk factor for PRCA occurrence. The optimal cut-off value of pre-HSCT IgG IHA for PRCA development, resulted to be 1/64, with a 100% sensitivity and 68.8% specificity ($p<0.0001$). All patients with PRCA had received rhEPO and transfusion support and 20 patients received additional treatments like PEX, rituximab, and more recently daratumumab. Comprehensively, PEX and rituximab

obtained a response in half of the cases, at a variable time, while the few cases of patients we treated with daratumumab suggest promising results. The overall response rate in our cohort was 75%, with significantly better survival (94.4% vs. 16.7%) and lower transplant-related mortality (6.3% vs. 80%) for PRCA responders.

Conclusions: Standardized guidelines on when and how to treat PRCA are necessary because the current treatment is controversial among centers.

KEYWORDS

PRCA, HSCT, plasma-exchange, isohemagglutinins, rituximab, daratumumab, AB0

Scope statement

We have performed a retrospective analysis of the Pure Red Cell aplasia cases we diagnosed in the last 13 years at our Transplant Unit. The scope of the analysis was to identify which risk factors might favor PRCA development among recipients of AB0 mismatched allogeneic stem cell transplantation. The second scope was to evaluate the efficacy of different treatments performed for PRCA management to determine which ones would be the most useful. For this purpose, we also reviewed the literature of the last recent 7 years to highlight the principal treatments mainly used for PRCA management with the relative results in terms of efficacy in PRCA resolution. Currently, a shared algorithm on when and how to treat PRCA patients does not exist, therefore the management of PRCA still remains controversial.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative option for many malignant diseases (1). An indispensable element in transplant planning is the selection of a suitable donor in terms of human leukocyte antigen (HLA) match, while ABO compatibility is not mandatory (2). However, the ABO mismatch between recipient and donor must be taken into account as it may lead to acquired pure red cell aplasia (PRCA) (3, 4), with prolonged transfusion requirement and the risk of iron overload. Up to 50% of HSCTs are performed across ABO incompatibility but the influence of this condition on post-transplant outcomes remains controversial (3–5). The incidence of PRCA after AB0 mismatched transplant varies from 10 to 29% of cases (3, 4, 6, 7), and it is observed after major or bi-directional AB0 mismatch. In major AB0 mismatch, accounting for 20–25% of transplants, the recipient showed anti-donor AB0 antibodies, as for a group 0 patient receiving cells from a group A or B donor. In bidirectional AB0 mismatch, which accounts for 5% of transplants, both donor and recipient have antibodies directed against AB0 group antigens of each other, as for group A patient receiving a group B donor or vice versa (4). A picture of PRCA is likely in the presence of persistent anemia and reticulocytopenia for more than 60 days post-HSCT and hypoplasia/aplasia of erythroid precursors in otherwise normal bone marrow (8). The occurrence of PRCA was attributed to the activity of residual recipient plasma cells that continue to produce isohemagglutinins (IHA), albeit in most recipients anti-donor IHA disappeared within 120 days (9, 10).

In this paper, we conducted a retrospective analysis of PRCA cases that occurred after AB0 mismatched HSCT at our Transplant Centre in the last 13 years and we reviewed the recent literature on current treatments of PRCA.

Methods

Retrospective study

We conducted a retrospective observational study at the Transplant Unit of Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome. All the patients had given written informed consent to use their data for research purposes. The study was conducted according to the Declaration of Helsinki and was approved by the ethics committee of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome as part of the TOHP (Transplant Outcome in Hematological Patients) study (protocol number 0030921/20).

Patients, data collection, definitions, and endpoints

All patients who had received a first stem cell transplant, from January 2010 to December 2022, in the context of major or bidirectional AB0 incompatibility were included. As per institutional guidelines, haematopoietic bone marrow product were treated for red blood cells (RBCs) depletion <1 ml/Kg of the recipient. Among patients with anemia requiring packed red blood cell transfusions at day +60 from HSCT, PRCA was diagnosed when all the following criteria were fulfilled: persistent normochromic and normocytic anemia, reticulocytopenia (absolute count <10*10^9/L

and percentage <1%), isolated erythroid aplasia in the bone marrow (11), negative direct antiglobulin test, full leukocyte donor chimerism, normal leukocyte and megakaryocyte hemopoiesis. Anemia cases due to poor graft function, graft failure (12), or early relapsed hematological disease were excluded. Patient's data were extracted through review of medical records. We collected the following data: recipient and donor age, sex, and AB0 blood group, recipient hematological disease, disease response at transplant, transplant date, hematopoietic cell transplant comorbidity index (HCT-CI) (13), conditioning regimen used, graft-versus-host disease (GvHD) prophylaxis used, donor relationship with recipient, HLA match between donor and recipient, stem cell source, graft composition (CD34, total nucleated cells (TNCs), total mononucleated cells (MNCs), CD3+, CD4+ and CD8+ T lymphocytes count, CD19+ B lymphocytes count), number of packed red blood cell transfusions required from transplant to reticulocyte engraftment, neutrophil, platelet and reticulocyte engraftment, acute GVHD (aGVHD) occurrence and time to aGvHD onset, donor and recipient Cytomegalovirus (CMV) serostatus, CMV DNAemia after transplant, relapse occurrence and time to relapse, death and time to death, cause of death, time to last follow-up. If available, the pre-transplant IHA titers were collected. In patients with PRCA pre- and post-treatment IHA titers were recorded together with treatment performed. PRCA resolution was defined as a stable level of hemoglobin without transfusion requirement and with a stable reticulocyte percentage above 2%. The IHA titers were determined serologically using patient whole blood collected in ethylenediaminetetraacetic acid (EDTA), as previously described (14). Natural IHA (anti-A IgG and IgM, anti-B IgG and IgM) were determined by incubating a 0.8% standard A and B erythrocyte suspension (Diacell AB0 kit, Bio-Rad, California USA) in saline with twofold serial dilutions of plasma, followed by centrifugation. Titers were scored using an anti-human globulin test card (ID-Card Coombs Anti-IgG and ID-Card NaCl, DiaMed, Bio-Rad, California USA). The end point for titration was the highest dilution giving a 1+ reaction. In this paper, we aimed to assess PRCA incidence among patients who had received AB0 mismatched HSCT, with particular interest in risk factors for developing PRCA. Moreover, we looked for possible differences between patients who spontaneously recovered and those who required treatment. Finally, we inquired if different treatments determined different responses.

Treatments

One of the main treatments used in our center was plasma-exchange (PEX) either before or after HSCT. Pre-HSCT PEX protocol includes two every other day procedures: replacement of 1 to 1.5 plasma volumes per procedure with 5% albumin was performed to reduce IHA levels before transplantation (15). Post-HSCT PEX protocol includes six every other-day procedures in addition to a double dose (80.000 U) of recombinant human erythropoietin (rhEPO) after the third and the sixth procedures. Other treatments were rhEPO (40.000 IU per week), steroids (1 mg/Kg), antiCD20 monoclonal antibody (rituximab 375 mg/m2/week for 4 weeks), thrombopoietin receptor agonist (eltrombopag 50 to 150 mg per day), and more recently antiCD38 monoclonal antibody (daratumumab 1800 mg subcutaneously weekly for 2 to 8 weeks).

Statistical analysis

The cumulative incidence of PRCA was estimated using cumulative incidence analysis, considering death as competing event. The cumulative incidence of aGVHD was estimated using cumulative incidence analysis considering relapse occurrence as competing event. Transplant-related mortality (TRM) was assessed with cumulative incidence analysis, considering relapse occurrence and death for other causes as competing events. Cumulative incidence between groups was compared by applying Fine and Gray's model. Overall survival (OS) and disease-free survival (DFS) were determined using Kaplan Meier method and log-rank for comparing curves. All patient, graft, and transplant variables were tested for PRCA occurrence using the logistic regression method: recipient and donor age, sex and AB0 incompatibility, IHA titre, underlying hematological disease type and status at transplant, conditioning regimen intensity, GvHD prophylaxis, aGvHD occurrence before day +60 after transplant, graft composition, donor type, HLA match, stem cell source. Only significant variables in univariate analysis were included in multivariate analysis. Patients were divided into two groups according to PRCA status. All patient, graft, and transplant variables were compared between groups using the Mann-Whitney U test for numerical variables and the chi-square tests (Fisher's exact test was used when the conditions for a chi-square test were not reached) for categorical variables. For IHA titer, Receiving Operator characteristic curves (ROC) were applied to determine the threshold for predicting PRCA occurrence. The statistical analysis was performed with NCSS 10 software. A statistical significance was attributed to a p-value <0.05.

Literature review

We reviewed published literature on the treatment of PRCA after HSCT with AB0 mismatch in the adult population. The research was performed using PubMed Central (PMC) database, available at the following link https://pubmed.ncbi.nlm.nih.gov/. The keywords used in the research were: PRCA, Pure red cell aplasia, AB0, stem cell transplant, and treatment. The research involved papers published in the last seven years, from 2017 to 2023. Only papers with available full text, case reports or regular articles were considered. Papers on Pediatric patients were excluded.

Observational study results

We evaluated 194 patients who had received AB0 mismatched HSCT from January 2010 to December 2022. Median follow-up at the observation time fixed in June 2023 was 778 days (95% CI 591–1055). At the observation time, 100 patients (51.5%) were alive after a median of 1723 days (95% CI 1501–2060), and 94 patients (48.5%)

died at a median of 406 days after transplant (95% CI 180–318). The cause of death was relapse/progression in 38 cases, secondary neoplasia in one case and transplant-related in 55 cases (intracranial bleeding n=4, myocardial ischemia n=1, heart failure n=2, acute renal failure n=1, pulmonary failure n=3, multi-organ failure n=13, graft failure n=1, GVHD n=5, encephalitis n=3, pneumonia n=5, and sepsis n=17). One- and two-year OS was 68% (95% CI 61.5–74.6) and 57.2% (95% CI 50.1–64.2), respectively. Patients and transplant characteristics are reported in Table 1. Recipient/Donor blood groups were as follows: 0/A in 104 couples (53.6%), 0/AB in 7 couples (3.6%), 0/B in 32 couples (16.5%), A/AB in 3 couples (1.6%), A/B in 25 couples (12.9%), B/A in 22 couples (11.3%) and B/AB in one couple (0.5%). At day 30 after transplant neutrophil engraftment (>0.5*10^9/L) was achieved by 88.2% of patients (95% CI 83.7–93) and platelet engraftment was achieved by 71% of patients (95% CI 64.8–77.8). At day 100 after transplant, the cumulative incidence of aGVHD was 39% (95% CI 32.4–46.9) (n=69), graded as follows: 35 grade I (50.7%), 24 grade II (34.8%), 8 grade III (11.6%), and 2 grade IV (2.9%). A total of 59 patients (30.4%) experienced a relapse of the underlying hematological disease with a 1-year and 2-ys DFS of 58.2% (95% CI 51.3–65.2) and 50.6% (95% CI 43.5–57.7), respectively. Finally, 1-year and 2-ys cumulative incidence of TRM was 28.5% (95% CI 22–36.9) and 35.9% (95% CI 28.8–44.7), respectively.

PRCA diagnosis and characteristics

At day +60 after HSCT, the cumulative incidence of PRCA was 13.4% (95% CI 9.2–19.5). Twenty-four cases of PRCA were identified in our cohort. In one case the recipient was group B with a group A donor (4.2%). All the other recipients were group 0 with a group A donor in 16 cases (66.6%), a group AB donor in one case (4.2%), and a B group donor in 6 cases (25%). In Table 1 we reported the comparison of the variables between PRCA group and no PRCA group. Patients of the PRCA group were older compared with no PRCA group (59.5 vs. 53 years, p=0.01). Pre-transplant IHA titers were higher for PRCA group compared with no PRCA group: 1/256 vs. 1/16 for IgG (p<0.0001) and 1/128 vs. 1/12 for IgM (p<0.0001). AB0 incompatibility was mainly major in PRCA group (95.8% vs. 73.5%, p=0.02). Comparing graft composition among groups, patients in the PRCA group had received a low T CD8 lymphocyte amount compared with patients in the no PRCA group (18.8 vs. 57*10^6/Kg, p=0.006). In the PRCA group, the donor was more frequently a relative one (66.7% vs. 40%, p=0.02) and the graft stem cell source was mainly bone marrow (50% vs. 18.2%) or peripheral blood (50% vs. 75.9%) (p=0.002). As expected, the median number of red blood cell transfusions needed until reticulocyte engraftment in the PRCA group was significantly higher compared to no PRCA group (31.5 vs. 6.5, p<0.0001). A trend was identified according to HLA match, with a prevalence of PRCA among HLA haploidentical transplants (41.7% vs. 21.2%) and a minor prevalence among HLA mismatched transplants (8.3% vs. 22.3%) (p=0.05). No differences between the groups were seen when accounting for sex, underlying hematological disease, disease status at transplant, HCT-CI, CD34+, TNC, MNC, T CD3+, T CD8+, and B CD19+ count in the graft, conditioning regimes, GVHD prophylaxis, ATG use, donor age, aGvHD occurrence before day 60, and CMV DNAemia before day 60.

Univariate logistic regression model for PRCA occurrence identify recipient age (OR 1.05, 95% CI 1.01–1.09, p=0.02), major AB0 incompatibility (OR 8.28, 95% CI 1.09–63.10, p=0.04), IgG IHA titer (OR 1.00, 95% CI 1.00–1.00, p=0.04), low CD8+ lymphocytes count in the graft (OR 0.97–0.99, p=0.01), bone marrow stem cell source (OR 4.48, 95% CI 1.84–10.92, p=0.0009) and relative donor (OR 3.0, 95% CI 1.22–7.40, p=0.02) as independent variables. The multivariate logistic regression model confirmed IgG IHA titer as the only significant variable for PRCA occurrence (OR 1.00, 95% CI 1.00–1.00, p=0.02), while a trend returned for recipient age (OR 1.05, 95% CI 0.99–1.11, p=0.05). Using the ROC curve, the pre-transplant IgG IHA cut-off value predictive for PRCA occurrence was 1/64, with 68.8% specificity, 100% sensitivity, 34.5% PPV, and 100% NPV (AUC 0.889, 95% CI 0.821–0.932, p<0.0001; Figure 1).

PRCA treatment, response, and outcome

Ten patients (41.7%) with a high pre-HSCT IHA titer had received 2 pre-HSCT PEX. Nine of them developed PRCA and required further treatment after transplant. All patients received rhEPO started approximately 20 days after HSCT. RhEPO was maintained throughout any specific treatment adopted, until PRCA response. Patients with high level of ferritin had received oral deferasirox 10–20 mg/Kg/day or deferoxamine 20–40 mg/Kg 1–3 times a week, according to initial ferritin level, patients ability to swallow tablets, allergies or renal function. Four patients (16.6%) had not received specific treatment after HSCT for PRCA. Reticulocyte engraftment with transfusion avoidance was achieved at a median of 150 days from transplant (range, 110 to 293) in 3 patients, whereas the last died before obtaining a response. Twenty patients had received a first treatment at a median time of 100 days after transplant (95% CI 75–120): steroids in one case (4.2%), a combination of steroids and rituximab in 7 cases (29.2%), rituximab alone in 6 cases (25%), post-HSCT PEX (6 procedures) with double rhEPO in 5 cases (20.8%), and daratumumab in one case (4.2%). Four patients (20%) had also received eltrombopag (4.2%). Ten patients obtained a response at a median time of 200 days (range, 120 to 282) after HSCT. Two patients died before obtaining a response and the remaining 8 patients needed a second line of treatment started at a median time of 150 days after HSCT (range, 128 to 250): post-HSCT PEX (6 procedures) with double rhEPO in 6 cases (75%), daratumumab in one case (12.5%), and rituximab in one case (12.5%). Three patients obtained a response at a median time of 210 days after HSCT (range, 204 to 308). Two patients died before obtaining a response and the other three patients needed a third line of therapy at a median of 180 days after HSCT (range, 180 to 300): daratumumab in one case, post-HSCT PEX (6 procedures) with double rhEPO in one case, and rituximab in the last case. Two patients obtained a response at 210 and 330 days after HSCT, respectively, whereas the last patient died before obtaining a response. Overall, among 24 patients with PRCA, 8 patients

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TABLE 1 Characteristics of patients and comparison between groups with or without PRCA.

Variables	All patients (n=194) n (%) or median (95% CI)	PRCA (n=24) n (%) or median (95% CI)	No PRCA (n=170) n (%) or median (95% CI)	P value
Rec age, ys	55 (51–56)	59.5 (55–62)	53 (50–55)	**0.01**
Rec sex F/M	85 (56.2)/109 (43.8)	9 (37.5)/15 (62.5)	76 (44.7)/94 (55.3)	0.5
Diagnosis				
AML/ALL MDS/MPD LPD/PCD	104 (53.6) 62 (32) 28 (14.4)	15 (62.5) 7 (29.2) 2 (8.3	89 (52.3) 55 (32.4) 26 (15.3)	0.6
Status at HSCT				
CR/No CR	88 (45.4)/106 (54.6)	11 (45.8)/13 (54.2)	77 (45.3)/93 (54.7)	1
HLA				
Matched Mismatched Haplo	108 (55.7) 40 (20.6) 46 (23.7)	12 (50) 2 (8.3) 10 (41.7)	96 (56.5) 38 (22.3) 36 (21.2)	0.05
HCT-CI	3 (2–3)	2.5 (2–3)	3 (2–3)	0.8
IHA titre at HSCT				
IgG IgM	1/32 (1/16–1-/32) 1/16 (1/8–1/32)	1/256 (1/128–1/1024) 1/128 (1/32–1/512)	1/16 (1/8–1/32) 1/12 (1/8–1/16)	**<0.0001** **<0.0001**
AB0 incompatibility				
Major Bidirectional	148 (72.3) 46 (23.7)	23 (95.8) 1 (4.2)	125 (73.5) 45 (26.5)	0.02
Graft composition				
CD34*10^9/Kg TNC*10^8/Kg MCN*10^8/Kg CD3*10^6/Kg CD4*10^6/Kg CD8*10^6/Kg CD19*10^6/Kg	5.7 (5.2–6) 6.6 (6.1–7.4) 4.9 (4.7–5.4) 202.6 (165.4–219.1) 125.8 (104.4–132) 52.1 (40.7–65) 44.1 (38–50.1)	5.1 (3.3–6.3) 5.8 (3.2–7.5) 3 (1.6–5.8) 99.5 (28.7–210.9) 58.4 (18–170.5) 18.8 (11.1–38.3) 26.3 (11.8–50.2)	5.8 (5.3–6.1) 6.7 (6.2–7.5) 4.9 (4.8–5.4) 207.4 (170.8–227.2) 128.4 (113.2–141.1) 57 (48.3–67) 44.9 (39–51)	0.2 0.2 0.1 0.05 0.09 **0.006** 0.08
Conditioning				
RIC/MAC	111 (57.2)/83 (42.8)	15 (62.5)/9 (37.5)	96 (56.5)/74 (43.5)	0.6
GvHD prophylaxis				
CsA+MTX CsA+MFA CsA+MFA+PTCy	55 (28.4) 13 (6.7) 126 (64.9)	7 (29.2) 0 (0) 17 (70.8)	48 (28) 13 (8) 109 (64)	0.3
ATG	61 (31.4)	7 (29.2)	54 (31.8)	0.8
Stem cell source				
PB BM CB	141 (72.7) 43 (22.2) 10 (5.1)	12 (50) 12 (50) 0 (0)	129 (75.9) 31 (18.2) 10 (5.9)	**0.002**
Donor				
REL/UD	84 (43.3)/110 (56.7)	16 (66.7)/8 (33.3)	68 (40)/102 (60)	**0.02**
Don sex F/M	64 (33)/130 (67)	7 (29)/17 (71)	57 (34)/113 (66)	0.6
Don age, ys	33 (30–36)	38 (27–47)	33 (3.-36)	0.2

(Continued)

TABLE 1 Continued

Variables	All patients (n=194) n (%) or median (95% CI)	PRCA (n=24) n (%) or median (95% CI)	No PRCA (n=170) n (%) or median (95% CI)	P value
Others				
aGvHD until day +60	61 (31)	7 (29)	54 (32)	0.8
CMV until day +60	62 (32)	8 (33)	54 (32)	0.9
RBC transfusion ¥	8 (6–9)	31.5 (25–40)	6.5 (5–8)	**<0.0001**

Rec, recipient; F, female; M, male; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplatic syndrome; MPD, myeloproliferative disease; LPD, lymphoproliferative disease; PCD, plasma cell disease; CR, complete remission; HSCT, hematopoietic stem cell transplantatio; HCT-CI, hematopoietic cell transplant comorbidity index; IHA, isohemagglutinins titre; CD34, stem cells; TNC, total nucleated cells; MNC, mononucleated cells; CD3, CD3 positive t lymphocytes; CD4, CD4 positive T lymphocytes; CD8, CD8 positive t lymphocytes; CD19, CD19 positive B lymphocytes; RIC, reduced intensity conditioning; MAC, myeloablative conditioning; CsA, cyclosporine A; MTX, methotrexate; MFA, mycofenolic acid; PTCy, post-transplant Cyclophosphamide; ATG, anti-thymocyte globulins; PB, peripheral blood; BM, bone marrow; CB, cord blood; REL, relative; UD, unrelated; ¥, RBC transfusion received until reticulocytes engraftment of death.
Bold values are those with statistical significance (p<0.05).

needed two lines of therapy and 3 required three lines of therapy for PRCA. Eighteen patients (75%) obtained a response with reticulocyte engraftment and transfusion avoidance at a median of 207 days after HSCT (95% CI 150–230). Data about PRCA treatment and response are reported in Table 2. No predictive variables for response were identified. No treatment-related complications were documented. None of the patients who achieved a response experienced a relapse of PRCA. Comparing outcome variables between PRCA and no PRCA groups, no differences were found in terms of aGVHD occurrence at day 100 (33% vs. 40%, p=0.5), 1-year OS (75 vs. 67%, p=0.9), 1-yr DFS (75% vs. 56%, p=0.4), and 1-year TRM (28 vs. 29%, p=0.8). Considering only the PRCA group, 1-year OS was 94.4% (95% CI 83.9–100) for responders as compared with 16.7% (95% CI 0–46.5) for non-responders (Figure 2A). Accordingly, 1-year TRM was 6.3% (95% CI 1–42) for responders and 80% (95% CI 52–100) for non-responders (p<0.0001, Figure 2B).

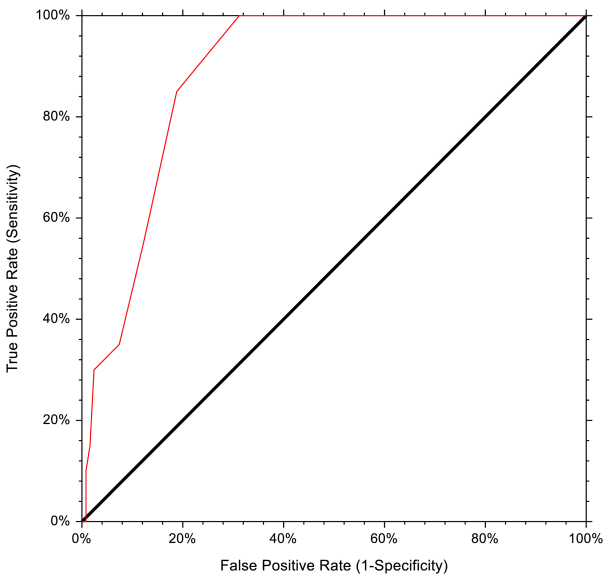

FIGURE 1
Receiver operating characteristics curve of pre-HSCT IHA titer for PRCA development.

Results from literature review

Our initial research produced 37 articles (Figure 3). Upon first revision of titles and abstracts, 7 articles were excluded: 2 were guidelines and 5 were not related to the treatment of post-HSCT AB0-induced PRCA. During full-text revision, an additional 7 articles were excluded because they were not pertinent within the context of our research. Finally, we analyzed 23 articles. Table 3 provides a comprehensive summary of therapeutic modalities and their corresponding efficacy parameters across all reviewed cases. A total of 130 cases were identified, all of which exhibited successful resolution, defined as either achieving transfusion independence or an increase in reticulocyte count. Twenty-two patients (17% of cases) required three or more therapeutic lines to achieve a clinical response, while 31% experienced spontaneous remission or recovery without targeted therapeutic intervention. The rest of the patients only required 1 or 2 treatment lines. Some studies included in this review did not provide precise details regarding response times. An analysis of available data revealed variations in the average response times for distinct therapeutic interventions. Three primary modalities for the management of PRCA were used: Daratumumab, Eltrombopag, and apheresis-based therapy like plasma exchange (PEX) and immunoadsorption (IA). These therapeutic interventions were utilized either as monotherapy or as precursors to additional measures. Specifically, from the beginning of the mentioned treatments, patients treated with Daratumumab exhibited an average response time of 26.4 days, while those who had received Eltrombopag therapy demonstrated an average response time of 60 days. PEX and IA exhibited distinct average response times, 28.5 days and 36 days, respectively. Daratumumab, a humanized IgG1-kappa monoclonal antibody targeting CD38, emerges as a focused intervention influencing delayed erythroid engraftment in the context of PRCA. Recent literature underscores the efficacy of Daratumumab in treating nine cases of PRCA (16, 22, 25, 26, 29, 30, 33, 34). Responses were evident following the initial and second doses in three patients (16, 26, 33). Six patients had a prolonged course of PRCA and had undergone extensive previous treatment. Within this cohort, three patients received Daratumumab monotherapy at 205, 270, and 60 days post-HSCT, achieving transfusion independence at 14 days for one patient and 28 days

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TABLE 2 PRCA cases: treatment and response.

Patient	Donor	Source	Treatment *(starting day, +d)*	Response Y/N
# 1	MRD	PB	Pre-HSCT PEX (-3, -1 d), rhEPO (+21 d)	N
# 2	MUD	PB	rhEPO (+21 d)	Y
# 3	MUD	PB	rhEPO (+21 d)	Y
# 4	Haplo	BM	Pre-HSCT PEX (-3, -1 d), rhEPO (+20 d)	Y
# 5	MRD	PB	Rh EPO (+20 d), rhEPO + PDN (+30 d)	N
# 6	MUD	PB	rhEPO (+21 d), rhEPO + PEX x 6 + PDN (+110 d)	Y
# 7	Haplo	BM	Pre-HSCT PEX (-3, -1 d), rhEPO (+20 d), rhEPO + PEX x 6 (+90d)	Y
# 8	Haplo	BM	Pre-HSCT PEX (-3, -1 d), rhEPO (+20 d), rhEPO + PEX x 6 + Eltrombopag	Y
# 9	Haplo	BM	rhEPO (+20 d), rh EPO + RTX x 4 (+92 d), rhEPO + PEX x 3 (+150 d)	N
# 10	MRD	PB	rhEPO (+21 d), rhEPO + RTX x 4 + PDN (+110 d), rhEPO + PEX x 12 (+145 d)	N
# 11	MUD	PB	Pre-HSCT PEX (-3, -1 d), rhEPO (+20 d),rhEPO +RTX x 4 (+120 d), rhEPO + PEX x 6 (+150d)	Y
# 12	Haplo	BM	Pre-HSCT PEX (-3, -1 d), rhEPO (+21 d), rhEPO + RTX x 4 (+210 d), rhEPO + PEX x 6 + PDN (+250 d)	Y
# 13	MMUD	PB	Pre-HSCT PEX (-3, -1 d), rhEPO (+20 d), rhEPO + RTX x 4 (+88 d), rh EPO + PEX x 6 (+128 d), rh EPO + Daratumumab x 8 (+180 d)	Y
# 14	Haplo	BM	rhEPO (+20 d), rhEPO + PEX x 6 (+110 d), rhEPO + RTX x 4 (+180 d)	Y
# 15	Haplo	BM	rhEPO (+19 d), rhEPO + RTX x 4 (+94 d)	Y
# 16	MUD	PB	rhEPO (+19 d), rhEPO + RTX x 4 (+120 d)	Y
# 17	Haplo	BM	rhEPO (+20 d), rhEPO + RTX x 4 (+75 d)	Y
# 18	Haplo	BM	Pre-HSCT PEX (-3, -1 d), rhEPO (+21 d), rhEPO + RTX x 4 (+100 d)	Y
# 19	Haplo	BM	rhEPO (+21 d), rhEPO + RTX x 4 + PDN (+120 d)	Y
# 20	MRD	PB	rhEPO (+21 d), rhEPO + RTX x 4 + PDN (+93 d)	N
# 21	MRD	PB	rhEPO (+19 d), rhEPO + RTX x 4 + PDN (+110 d)	Y
# 22	MUD	BM	rhEPO (+21 d), rhEPO + PEX x 6 (+90 d, +165), rhEPO + RTX x 4 + PDN (+300 d)	Y
# 23	MRD	PB	Pre-HSCT PEX (-3, -1 d), rhEPO (+19 d), rhEPO + RTX x 4 (+91 d), rhEPO + Daratumumab x 6 (+130 d)	N
# 24	MMUD	BM	Pre-HSCT PEX (-3, -1 d), rhEPO (+21 d), rhEPO + Daratumumab x 2 (+100 d)	Y

MUD, Matched unrelated donor; MMUD, Mismatched unrelated donor; MRD, Matched related donor; Haplo, haploidentical donor; HSCT, Hematopoietic stem-cell transplantation; BM, bone marrow; PB, peripheral blood stem cell; PDN, prednisone; RTX, Rituximab; DLI, rhEPO, erythropoietin; PEX, plasma exchange; d, the day of first administration; m, month of first administration; n, number of patients.

for the remaining two (33, 34). The other patients obtained a response after a median of 33 days (range, 28 to 60) (22, 25, 29, 30). The review included 5 PRCA patients successfully treated with Eltrombopag, an oral thrombopoietin receptor agonist (17, 27, 31). All patients were resistant to multiple lines of treatment, including Rituximab (RTX), Bortezomib, and PEX. In three of these patients, transfusion independence was achieved after 60, 30, and 90 days of treatment (17, 27). No data are available in the remaining patients regarding the exact time of initiation of treatment with Eltrombopag and response. The realm of apheresis therapy presents various procedures, including IA and PEX, designed to eliminate anti-donor IHA. Some authors advocate for IHA reduction through PEX as a preemptive measure before HSCT to prevent the occurrence of PRCA (28, 29). Four patients exclusively subjected to IA using Glycosorb® and an additional two individuals treated with a sequential regimen of IA Glycosorb® followed by PEX and prednisone, on day +159, demonstrated a significant reduction in IHA titer and transfusion independence, achieved within a mean duration of 28.5 days (24). The use of PEX as a therapeutic modality, often in conjunction with other interventions, has been prevalent; however, its efficacy in the context of PRCA treatment varies across reported cases (17–19, 24, 25, 27, 31, 36). In this review, three articles are described in which patients have shown a response following the use of PEX (17, 31, 36). In the first article, two patients developed PRCA refractory to various therapies, leading to the implementation of 10 and 5 series of PEX over 3 and 2 weeks, respectively (36). The second article reports two patients showing a prompt erythroid response after 3 and 5 cycles of PEX, respectively, with one case involving EPO (16). The third article does not specify the number of sessions conducted (31).

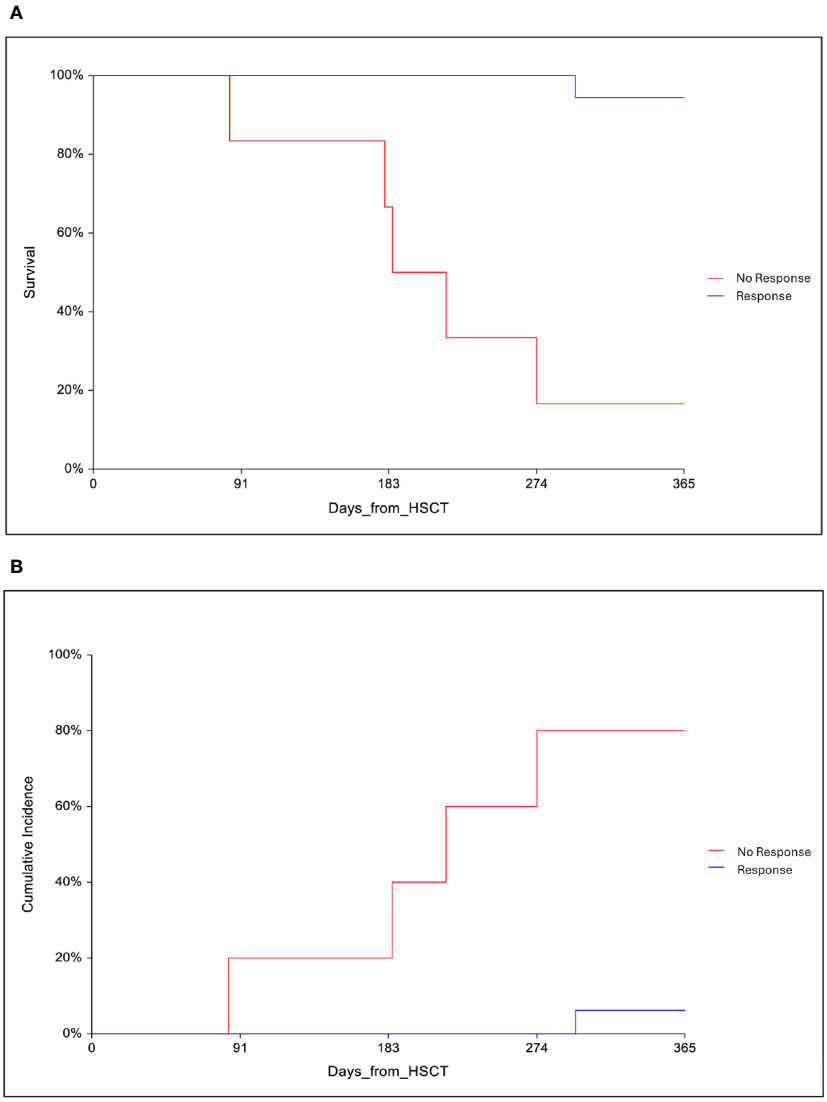

FIGURE 2
(A) One-year overall survival (OS) in responders and non-responders patients with PRCA. **(B)** One-year cumulative incidence of transplant-related mortality in responders and non-responders patients with PRCA.

Discussion

In this paper, we aimed to study PRCA cases that occurred in our transplant unit in the last thirteen years. The purpose of this retrospective analysis was to identify possible risk factors for PRCA occurrence among patients transplanted across AB0 mismatch and to analyze different treatments applied to PRCA cases with relative responses. The incidence of PRCA at day 60 in our cohort was 13.4%, in line with other reports (3, 4, 6, 7). The sole variable resulting from multivariate analysis as predictive for PRCA developed was pre-HSCT IgG IHA, with an optical cut-off value of 1/64 (100% sensitivity and 68.8% specificity). The second point that emerged from our analysis was that pre-HSCT PEX was not found to be an effective procedure to prevent PRCA since it failed in 9 out of 10 cases. The main treatments used at our center for PRCA treatment were post-HSCT PEX, rituximab, and, more recently, daratumumab. Comprehensively, post-HSCT PEX and rituximab had guaranteed a response in half of the cases, at a variable time, while the few cases in which we used daratumumab suggested promising results. The overall response rate in our cohort was 75%, with significantly better survival (94.4% vs. 16.7%) and lower TRM (6.3% vs. 80%) for responders. However, the higher mortality in non-responders may be affected by those patients who died from HSCT-related complications before responding who were assigned to the non-responders group. Nevertheless, it cannot be denied that prolonged immunosuppressive therapy with rituximab, steroids, or daratumumab may increase transplant-related mortality due to a higher risk of infectious complications.

Although the exact pathogenesis of PRCA after HSCT is not fully understood, the hypothesis is that the persistence of host B lymphocytes and plasma cells producing anti-donor IHA is responsible for delayed erythroid engraftment (9). PRCA is more frequently reported after a transplant from a group A donor to a group 0 recipient (4, 38). Other factors reported to increase PRCA

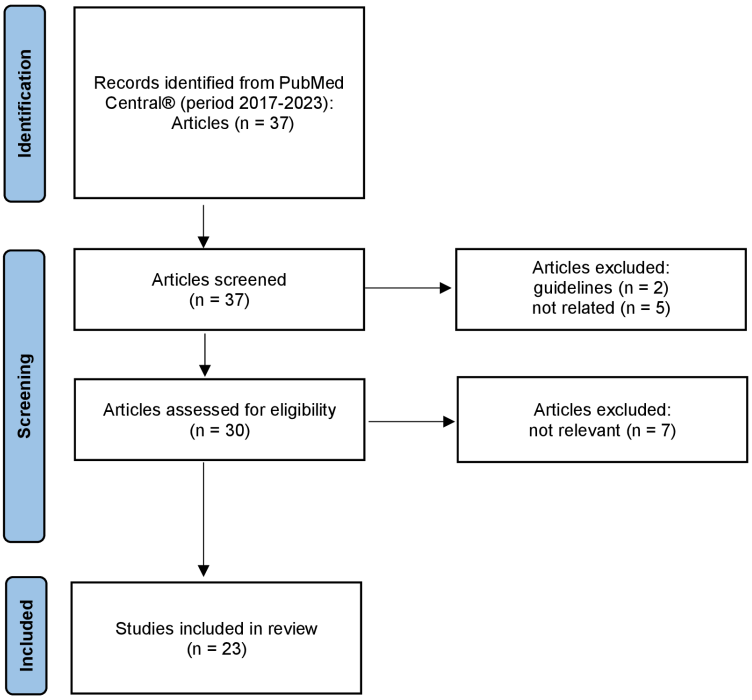

FIGURE 3
PRISMA flow diagram for the literature review.

risk are reduced intensity conditioning (14), sibling donor (39), and high anti-A IHA titer (40, 41). Regarding the conditioning regimen, it was reported that PRCA occurred more frequently after fludarabine-busulfan conditioning regardless of intensity (42) and less frequently after myeloablative conditioning including cyclophosphamide and total body irradiation (14). In our cohort, no differences in terms of PRCA incidence were observed according to the conditioning regimen. According to donor type, it was reported that a matched related donor is associated with a high risk for PRCA and prolonged persistence of anti-donor IHA when compared to an unrelated donor or a haploidentical one (5, 31, 43–45). In our study, a relative donor, regardless of HLA match, was associated with high PRCA incidence as was for bone marrow source. According to stem cell source, no difference in terms of PRCA was reported between peripheral blood and bone marrow, albeit delayed engraftment was seen after bone marrow HSCT from AB0 mismatched donor (46). Bone marrow hematopoietic cell products contain a high amount of RBCs (25–35% of the total volume) which can cause acute hemolysis during infusion as well as subsequent PRCA. RBC depletion of bone marrow graft is usually performed to reduce donor RBCs infusion to 10–40 ml (15). On the other hand, no cases of PRCA were usually described after cord blood transplant as was in our cohort (6, 23, 47), albeit the low number of cord blood grafts in our cohort (n=10). Although the exact reason for this is still unknown it has been thought that the low expression of A and B antigens on the red blood cells of infants determines a minor hemolysis induced by recipient IHA against donor blood group (23, 48, 49). Moving to the pre-HSCT IHA titer, a recent paper by Lemaire and colleagues (50) analyzed the trend of the IHA titer in a group of patients submitted to HSCT with AB0 incompatibility. Anti-A IHA disappeared spontaneously after a median of 28 days in 82% of the cases. Anti-B IHA spontaneously disappeared after a median of 16 days in 96% of cases. This faster disappearance of anti-B IHA compared with anti-A IHA is also reported elsewhere (40, 51). The prolonged persistence of anti-A IHA together with high anti-A titer might justify the higher incidence of PRCA reported for group 0 recipients of a group A donor (40, 45).

A high titer of IHA before HSCT is associated to an increased risk for PRCA development. In our cohort, the threshold of 1/64 has the best combination of sensitivity and specificity, as previously described by the group of Longval (6). This observation explains why some centers use pre-HSCT PEX or IA to reduce the risk of PRCA, however, results are controversial, and an agreement on the IHA title to be considered high is lacking. Stussi and colleagues reported pre-HSCT PEX alone or combined with red blood cell transfusion according to the donor group as a reliable procedure to reduce the occurrence of PRCA (44). Curley and collaborators reported the results of pre-HSCT PEX combined with donor group secretor plasma infusion after PEX and before stem cell infusion on day 0. In this case, residual IHA titer would be significantly reduced via antigen-antibody binding, and the use of secretor plasma would eliminate the risk of hemolysis that might occur using donor group red blood cell infusion (7). On the contrary, Damodar and

TABLE 3 Summary of PRCA in ABO-mismatched allogeneic hematopoietic stem cell transplantation reported in the literature from 2017 to 2023.

Author (year)	*n*	Source	HSCT	Treatment *(n) (+d/+m)*	Response
Chapuy CI (16)	1	PB	MUD	Taper tacrolimus (+105 d), HDG (+209 d), RTX (+235 d), Darbepoetin (+263 d), Daratumumab (+390 d)	TI (+404 d)
Busca A (17)	8	PB	MUD	PEX (1) PEX + EPO (1) EPO (3) PEX+ EPO, RTX (1) EPO (+47 d), PEX (+124 d), RTX (+234 d), Eltrombopag (+365 d) EPO (+47 d), PEX (+112 d), RTX+ EPO (+5 m), Bortezomib (+11 m), Eltrombopag (+16 m)	TI (+425 d, +17 m)
Varela Gómez R (18)	1	BM	MRD	Pre-HSCT IA anti-A (+1 d), Taper CsA, EPO (+1 m), RTX (+10 m), Bortezomib (+18 m), HDG (+22 m)	TI (+24 m)
Tomac G (19)	1	BM	MUD	Pre-HSCT PEX, Prednisone (+470 d) + IVIg (+500 d)	TI (+624 d)
Okamoto K (20)	1	BM	MRD	Conservatively manage, only red blood cell transfusion	TI (+ 2 m)
Nakamura N (21)	1	PB	MRD	Taper CsA (+60 d) → Failure. IL-6 secreted during an infection may have stimulated erythropoiesis (+236 d)	TI (+244 d)
Bathini S (22)	1	PB	MUD	Taper tacrolimus (+68 d) + HDG, RTX (+103 d), Bortezomib (+152 d), Daratumumab (+411 d)	TI (+439 d)
Wada S (23)	5	PB BM	N/A	Resolved spontaneously (3) Withdrawal of tacrolimus (2)	TI (+261 d)
Handisurya A (24)	6	PB	MUD	Darbepoetin alfa/epoetin theta (+55 d) Tapering of IS (+90 d) per-protocol. Antigen-Specific IA with the Glycosorb® only (4) (+159 d) Antigen-Specific IA with the Glycosorb® + PEX + prednisone (2) (+159 d)	IR (+28.5 d after IA)
Salas MQ (25)	1	PB	MRD	RTX (+18 m), HDG (+20 m), PE (+21 m), Bortezomib (+22 m), Daratumumab (+31 m)	TI (+33 m)
Rautenberg C (26)	1	PB	MUD	Taper tacrolimus (+ 63 d), RTX (+77 d), Daratumumab (+206 d)	TI (+216 d)
Gao Y (27)	1	PB	MRD	Taper CsA (+34 d), Prednisone (+34 d), Testosterone (+34 d), EPO (+34 d), PEX (+43 d, +63 d, +119 d and +132 d), DLI (+77 d and +112 d), Eltrombopag (+111 d)	TI (+201 d)
Crysandt M (28)	7	PB	MUD MRD Haplo	Low IHA titre group: Transfusion (1) High-IHA titre group: Transfusion (2) High-IHA titre group: Other methods than selective ABO IA before transplant including PEX (3) High-IHA titre group: Pre-HSCT Selective ABO IA, Rituximab (1)	TI
Henig I (29)	1	PB	MRD	PEX (-3 d), Rituximab (+88 d), Taper until complete discontinuation CsA (+98 d), Bortezomib (+210 d), Daratumumab (+320 d)	TI (+355 d)
Longval T (6)	66	PB BM	MRD/ other	Untreated 44 (16 only rhEPO), Specific treatment 22: rhEPO (6) + specific treatment (+70 d) RTX (10) RTX, DLI (5) DLI (2) (+431 d, +236 d) Prednisone (1) (+100 d) Prednisone, RTX (1) (+78 d, +92 d) Romiplostim, RTX (1) (+56 d, +588 d) Boost CD34+ (1) (+326 d) 2nd HSCT (1) (+153 d)	TI
Jeyaraman P (30)	1	PB	MRD	Taper tacrolimus (+60 d), HDG (+74 d), IVIg (+109 d), Bortezomib (+151 d), Daratumumab (+163).	TI (+184 d)
Zhu, P (31)	13	PB	MRD Haplo MUD	Transfusion (4) IVIg + transfusion (3) PEX + transfusion (2) PEX + IVIg + transfusion (2)	TI

(Continued)

TABLE 3 Continued

Author (year)	*n*	Source	HSCT	Treatment *(n) (+d/+m)*	Response
				PEX + RTX + Eltrombopag + Transfusion (1) PEX + DLI + Eltrombopag + Transfusion (1)	
Arslan, S (32)	5	PB	MRD MUD	IS withdrawal + prednisone + RTX + ibrutinib (1) IS withdrawal + prednisone + RTX + bortezomib (1) IS withdrawal + prednisone + DLI + RTX + bortezomib + danazole + ibrutinib (1) IS withdrawal + dexamethasone + IVIg + RTX + ibrutinib (1) IS withdrawal + RTX + darbepoetin + ibrutinib (1)	TI
Martino R (33)	2	N/A	N/A	Daratumumab (+205 d, +270 d)	IR (+219 d, 298 d)
Dovern E (34)	1	PB	MRD	Daratumumab (+60 d)	TI (+88 d)
Tavakoli F (35)	1	N/A	MRD	Taper CsA (+50 d), rhEPO (+53 d)	TI (+170 d)
Vivero A (36)	2	PB BM	MRD	LDI (+6 m), RTX (+10 m, +4 m), Daratumumab (+11 m, +5 m), PEX (+12 m, +5,6 m)	TI (+14 m, +6 m)
Jiménez-Ochoa, M (37)	3	N/A	N/A	RTX	RCE (+120 d, +248 d, N/A)

MUD, Matched unrelated donor; MRD, Matched related donor; Haplo, haploidentical donor; HSCT, Hematopoietic stem-cell transplantation; BM, bone marrow; PB, peripheral blood stem cell; HDG, High dose glucocorticoids; IVIg, intravenous immunoglobulins; CsA cyclosporine A; RTX, Rituximab; DLI, Donor lymphocyte infusion; IS, immunosuppression; IHA, isohemagglutinins; rhEPO, erythropoietin; PEX, plasma exchange; IA, immunoadsorption; IL-6, Interleukin 6; TI, Transfusion independence, IR, Increase of reticulocyte; RCE, Red cell engraftment; N/A, not available; d, the day of first administration; m, month of first administration; n, number of patients.

colleagues did not find any difference in PRCA occurrence according to pre-HSCT IHA titer, as well as for patients who received PEX with donor plasma group for reducing pre-HSCT IHA titer in bone marrow recipients (52). Also in our cohort, pre-HSCT PEX did not prevent PRCA in patients with high pre-HSCT IHA titer. Finally, opposite to other authors (6, 39), we had not reported an association between early aGVHD occurrence and PRCA development. Mielcarek reported a close relationship between aGVHD occurrence and IHA disappearance after matched related donor HSCT. He postulated that anti-recipient donor T cells would eliminate antibody-producing recipient cells leading to IgG and IgM IHA disappearance. However, they cannot exclude that immunosuppressive therapy against GVHD rather than GVHD itself might contribute to rapid IHA titer abatement (39). To date, a clear correlation between AB0 incompatibility and GVHD is not stated, as is for a correlation between AB0 incompatibility and DFS or TRM (31).

The revision of the literature cases of PRCA who had received a specific therapy reported varying results for the different treatments administered. A comment is due about time to response that favors daratumumab, followed by PEX and IA, and finally eltrombopag.

The main point that needs to be assessed is which patients with PRCA need to be treated, given the possibility of spontaneous recovery within a few months. It is undeniable that patients with prolonged and heavy transfusion needs, at risk of iron overload, and unresponsive to rhEPO could benefit from a specific treatment. EPO-agonist, although widely used for transfusion-dependent anemia, appeared to be not enough to achieve red cell engraftment in patients with erythroid precursor aplasia (6, 17). The role of PEX or IA alone can be useful to rapidly reduce the IHA titer, although the effect might be transient and unable to reverse red cell aplasia (17, 24, 25, 31, 32). The reduction of immunosuppression can be considered as a possible option, enhancing donor T cell activity against donor residual plasma cells, but it should be carefully weighted given the risk of GVHD flare and the variability of responses (16, 21–23, 26, 27, 30, 32). Another option is represented by monoclonal antibodies rituximab and daratumumab. Rituximab is used to remove residual recipient B lymphocytes and the results for rituximab alone or combined with other therapy were frequently satisfying (6, 17, 32, 37). The last entry is daratumumab, targeting host plasma cells sustaining delayed erythroid engraftment guarantees a response even in patients who have previously received more lines of treatment (16, 18, 22, 25, 26, 29, 30, 33, 34, 36).

In conclusion, among patients who developed PRCA, treatment should be considered for those patients who do not spontaneously recover after 4 months. During the watch and wait phase, iron depletion methods together with rhEPO should be applied to avoid iron overload and to stimulate erythroid precursors. When PRCA is prolonged the choice of the most appropriate treatment should be made balancing carefully risks and benefits, with particular attention to infectious and GVHD risks.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: since the database contains sensitive patient data, the same could be shared under email request to the corresponding author and after anonymization of sensitive data. Requests to access these datasets should be directed to elisabetta.metafuni@policlinicogemelli.it.

Ethics statement

The studies involving humans were approved by ethics committee of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Largo Agostino Gemelli, 8, 00168, Rome, Italy. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

EM: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. MBu: Conceptualization, Writing – original draft, Writing – review & editing. CV: Data curation, Writing – review & editing. SG: Data curation, Writing – review & editing. ML: Writing – review & editing. FS: Writing – review & editing. MBi: Writing – review & editing. GM: Writing – review & editing. NP: Writing – review & editing. RP: Writing – review & editing. FF: Data curation, Writing – review & editing. AB: Writing – review & editing. LT: Writing – review & editing. PC: Writing – review & editing. SS: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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Efficacy and survival outcome of allogeneic stem-cell transplantation in multiple myeloma: meta-analysis in the recent 10 years

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Introduction: Allogeneic hematopoietic cell transplantation (alloHCT) possessed direct cytotoxicity and graft-versus-multiple myeloma effect (GvMM). Growing trials have shown survival benefits of performing alloHCT in both newly diagnosed and relapsed MM.

Methods: We aimed to provide a comprehensive analysis in the recent 10 years to verify the efficacy and survival outcome of alloHCT in MM patients. A total of 61 studies which provide data between 14/04/2013 and 14/04/2023 and a total of 15,294 data from MM patients who had undergone alloSCT were included in our study. The best response rates (CR, VGPR, PR) and survival outcomes (1-, 2-, 3-,5-, and 10-year OS, PFS, NRM) were assessed. We further conducted meta-analysis in the NDMM/frontline setting and RRMM/salvage setting independently.

Results: The pooled estimate CR, VGPR, and PR rates were 0.45, 0.21, and 0.24, respectively. The pooled estimates of 1-, 2-, 3-, 5-, and 10-year OS were 0.69, 0.57, 0.45, 0.45, and 0.36, respectively; the pooled estimates of 1-, 2-, 3-, 5-, and 10-year PFS were 0.47, 0.35, 0.24, 0.25, and 0.28, respectively; and the pooled estimates of 1-, 2-, 3-, 5-, and 10-year NRM were 0.16, 0.21, 0.16, 0.20, and 0.15, respectively. In the NDMM/upfront setting, the pooled estimate CR rate was 0.54, and those for 5-year OS, PFS, and NRM were 0.69, 0.40, and 0.11, respectively. In a relapsed setting, the pooled estimate CR rate was 0.31, and those for 5-year OS, PFS, and NRM were 0.24, 0.10, and 0.15, respectively.

Discussion: Our results showed constant OS, PFS, and NRM from the third year onwards till the 10th year, suggesting that alloSCT has sustained survival benefits. Good response rate and promising survival outcome were observed in the NDMM/ frontline setting.

Conclusion: Although comparing with other treatments, alloSCT had a lower response rate and poorer short-term survival outcome, long-term follow-up could reveal survival benefits of alloSCT in MM patients.

KEYWORDS

multiple myeloma, allogeneic stem cell transplantation, response rate, survival outcome, OS, PFS

Introduction

Multiple myeloma (MM), the second most common hematological malignancy, is a monoclonal tumor characterized by the expansion of malignant plasma cells in the bone marrow (BM) (1). Uncontrolled expansion interferes with osteogenesis in BM, leading to lytic bone disease (2). Moreover, progression of the disease may lead to acute kidney injury, anemia, and hypercalcemia (3).

Drug resistance arises due to the intratumor high heterogeneity nature of MM (2). Recently, the standard treatment for transplant eligible MM patients is a combination of induction therapy (injectable proteasome inhibitor, oral immunomodulatory agent, and dexamethasone) and autologous hematopoietic stem cell transplantation (autoSCT) followed by lenalidomide maintenance therapy (3).

Allogeneic hematopoietic cell transplantation (alloHCT) possesses direct cytotoxicity and graft-versus-multiple myeloma effect (GvMM) (4). It remains controversial due to the high occurrence of graft-versus-host disease (GVHD), treatment-related mortality (TRM), and relapse rate. Recent data showed the crucial role of GVHD in the GVMM effect, specifically chronic GVHD (5). In research comparing survival between auto-auto and auto-allo after induction therapy, results showed higher overall survival (OS) and progression-free survival (PFS) in the auto-allo group. Moreover, there was a higher non-relapsed mortality (NRM) and lower risk of disease progression in the auto-allo group, verifying the continuous GVMM effect on disease control (6).

In a phase 3 trial comparing auto-auto versus auto-alloSCT in newly diagnosed MM (NDMM) patients with high-risk cytogenetic abnormalities (del13q, del17p), patients undergoing auto-alloSCT had a much higher median PFS and OS, showing the effectiveness of prolonged GVMM effect in improving survival in high-risk NDMM patients (7). The BMT CTN 0102 trial with long-term follow-up over 10 years showed a reduction in relapse, better PFS, and similar OS among high-risk NDMM patients treated with auto-allo. This trial further revealed the potential of alloSCT in overcoming the deleterious effect brought by high-risk cytogenetic chromosomal abnormalities in NDMM patients (8). Furthermore, there are evidence showing the effectiveness of alloSCT in overcoming translocation t(4;14) (9), del(17p13) (10), and del(13) abnormalities (11).

In addition, multivariate analysis of several research showed age as an influencing factor for survival outcome in alloSCT. In a study from the Japanese Society of Myeloma, age ≥50 years would adversely affect PFS (12). Another research showed both reduction in PFS and OS in patients >55 years (13).

All in all, there are growing evidence verifying the positive effect of alloSCT in newly diagnosed and young MM patients. Our meta-analysis aimed to provide a more comprehensive and reliable analysis to verify the efficacy and survival outcome of alloHCT in MM patients, patients in NDMM/frontline, and patients in an RRMM/salvage setting.

Methods

Search strategy

We conducted our search on 14/04/2023 in PubMed, Embase, Cochrane Library, and Web of Science with "(Allogenic) AND (myeloma)" as our searching term. We aimed to analyze research published in the past 10 years; thus, the publication date was limited to 14/04/2013 in all databases. All results were then downloaded to EndNote 20, and duplicated studies were removed. Studies were further filtered by their title and abstract. Full text of the remaining studies was downloaded for the final screen. In addition, studies that do not provide sufficient data were identified and removed after data extraction.

Search criteria

The following are the inclusion criteria: (1) studies concerning patients diagnosed as multiple myeloma and have no other reported hematological disease; (2) studies that have a reported response rate and survival after allogenic transplantation (studies that did not regard allo-transplantation as their main intervention but have reported that the above data were also included in our analysis); (3) studies reported in English; (4) studies with full text.

The following are the exclusion criteria: (1) cord blood as the stem cell source; (2) insufficient reported data; (3) studies concerning pediatric cases; (4) sample size <5.

We further conducted meta-analysis in an NDMM/frontline setting and an RRMM/salvage setting independently. The study design of each study was carefully read, and studies which did not clarify research population or treatment setting were excluded.

Statistical method

The following data were extracted: number of participants, age range, median follow-up, best response to allo-transplantation (complete remission (CR), very good partial remission (VGPR), and partial remission (PR)), and survival (1-, 2-, 3-, 5-, and 10-year OS, PFS, NRM). Our main outcome was best response rate and survival after allotransplantation in MM patients. Our secondary outcome was best response rate and survival after allotransplantation in the NDMM/frontline setting and RRMM/salvage setting.

Data were first collected in Excel, and all analyses were performed using STATA 15.1. This is a single-arm research; a random-effect model was adopted, and the results were presented in forest plot. The P value of Cochrane's Q test <0.1 indicated the existence of heterogeneity. I^2 statistic was used in the assessment of heterogeneity. Sensitivity analysis was then conducted. High heterogeneity (I^2 statistic >50) was commonly observed in a single-armed study; thus, the change in I^2 statistic after removal of a certain study was used to verify the extent of interference cause by the particular study. Sensitivity analysis could further confirm the stability of our study. Publication bias was assessed by funnel plots and was further confirmed by Begg's and Egger's tests. The P value in Begg's and Egger's tests >0.05 could confirm the absence of publication bias in our study.

Results

A total of 1,709 studies were yielded from the primary search, and 210 duplicated studies were removed. Based on title and abstract, 88 studies were selected for full-text screening. After full-text screening, 66 studies remained. After data extraction, six studies were further removed as there were insufficient data provided. Additionally, we have included a study which analyzed RRMM patients who underwent alloSCT between 2013 and 2022 published in July 2023 as to enhance the veracity of the analysis. Finally, 61 studies were included in our meta-analysis (7 (11, 14–19) in 2013, 5 (5, 20–23) in 2014, 3 (24–26) in 2015, 3 (27–29) in 2016, 6 (30–35) in 2017, 4 (12, 36–38) in 2018, 7 (7, 39–44) in 2019, 12 (8, 45–55) in 2020, 7 (56–62) in 2021, 3 (63–65) in 2022, 4 (66–69) in 2023) (Figure 1). The overall result is summarized in Table 1.

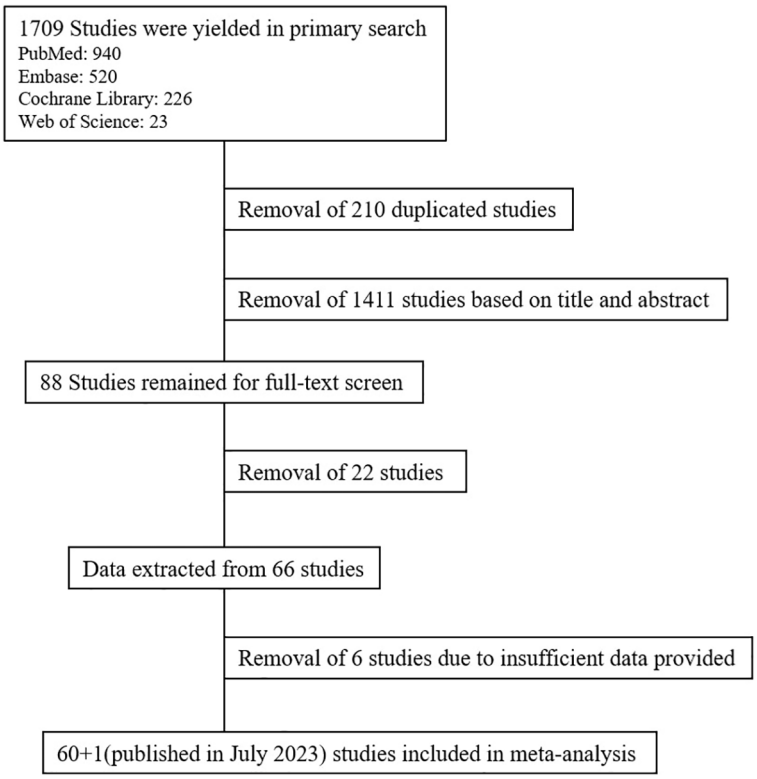

FIGURE 1
Flow diagram of the study selection.

TABLE 1 Summary table of meta-analysis results.

	Overall	NDMM/ upfront	RRMM/ salvage
Response rate			
CR	0.45 (95% CI 0.44,0.47)	0.54 (95% CI 0.48,0.61)	0.31 (95% CI 0.24,0.38)
VGPR	0.21 (95% CI 0.19,0.24)	–	0.21 (95% CI 0.14,0.29)
PR	0.24 (95% CI 0.22,0.26)	0.22 (95% CI 0.16,0.28)	0.12 (95% CI 0.07,0.18)
Survival OS			
ly	0.69 (95% CI 0.66,0.72)	–	–
2y	0.57 (95% CI 0.54,0.59)	–	–
3y	0.45 (95% CI 0.42,0.48)	–	0.30 (95% CI 0.24,0.36)
5y	0.45 (95% CI 0.43,0.47)	0.69 (95% CI 0.65,0.73)	0.24 (95% CI 0.21,0.28)
10y	0.36 (95% CI 0.33,0.39)	–	0.06 (95% CI 0.03,0.11)
PFS			
ly	0.47 (95% CI 0.44,0.50)	–	–
2y	0.35 (95% CI 0.32,0.38)	0.61 (95% CI 0.49,0.73)	–
3y	0.24 (95% CI 0.22,0.27)	–	–
5y	0.25 (95% CI 0.23,0.27)	0.40 (95% CI 0.35,0.44)	0.10 (95% CI 0.07,0.13)
10y	0.28 (95% CI 0.25,0.31)	0.32 (95% CI 0.27,0.38)	–
NRM			
ly	0.16 (95% CI 0.14,0.18)	–	–
2y	0.21 (95% CI 0.19,0.23)	–	0.20 (95% CI 0.17,0.23)
3y	0.16 (95% CI 0.14,0.19)	–	–
5y	0.20 (95% CI 0.18,0.21)	0.11 (95% CI 0.08,0.15)	0.15 (95% CI 0.11,0.20)
10y	0.15 (95% CI 0.13,0.18)	–	–

Response rate

Among the studies included, 31 studies (5, 7, 11, 12, 14–21, 23, 25, 26, 29, 34, 38–41, 44, 47, 48, 54, 56, 59, 60, 64, 68, 69) have reported the CR rate, 19 studies (5, 12, 14–16, 19, 21, 23, 25, 29, 34, 39, 40, 56, 59, 60, 64, 68, 69) have reported the VGPR rate, and 23 studies (5, 7, 11, 14, 16, 18–21, 23, 25, 26, 29, 34, 39, 40, 47, 54, 59, 60, 64, 68, 69) have reported the PR rate. Based on the random-effect model, the pooled estimate CR, VGPR, and PR rates were 0.45 (95% CI 0.44, 0.47), 0.21 (95% CI 0.19, 0.24), and 0.24 (95% CI 0.22, 0.26), respectively (Figure 2).

Survival

OS

Based on the random-effect model, the pooled estimates of 1-, 2-, 3-, 5-, and 10-year OS were 0.69 (10 studies (12, 22, 28, 29, 35, 42, 44, 55, 58, 60), 95% CI 0.66, 0.72), 0.57 (12 studies (15, 19, 26, 32, 33, 51, 52, 54, 55, 58, 61, 64), 95% CI 0.54, 0.59), 0.45 (11 studies (12, 18, 22, 28–31, 39, 44, 55, 69), 95% CI 0.42, 0.48), 0.45 (21 studies (5, 11, 17, 20, 22, 25, 26, 34, 40, 43, 48, 50, 56, 57, 59–63, 66, 68), 95% CI 0.43, 0.47), and 0.36 (11 studies (8, 17, 20, 34, 40, 43, 46, 59, 60, 63, 68), 95% CI 0.33, 0.39), respectively (Figure 3).

PFS

Based on the random-effect model, the pooled estimates of 1-, 2-, 3-, 5-, 10-year PFS were 0.47 (10 studies (12, 22, 28, 29, 35, 42, 44, 55, 58, 60), 95% CI 0.44, 0.50), 0.35 (13 studies (7, 15, 19, 26, 32, 33, 41, 51, 52, 55, 58, 61, 65), 95% CI 0.32, 0.38), 0.24 (9 studies (12, 22, 28–30, 39, 44, 55, 69), 95% CI 0.22, 0.27), 0.25 (19 studies (5, 11, 17, 20, 25, 26, 40, 41, 43, 50, 54, 56, 57, 59–62, 66, 68), 95% CI 0.23, 0.27), and 0.28 (9 studies (8, 17, 20, 40, 43, 46, 59, 60, 68), 95% CI 0.25, 0.31), respectively (Figure 4).

NRM

Based on the random-effect model, the pooled estimates of 1-, 2-, 3-, 5-, 10-year NRM were 0.16 (15 studies (5, 12, 20, 22, 29, 35, 39, 42–44, 48, 53–55, 58), 95% CI 0.14, 0.18), 0.21 (11 studies (7, 15, 20, 26, 30, 32, 52, 55, 58, 61, 64), 95% CI 0.19, 0.23), 0.16 (10 studies (11, 12, 14, 18, 22, 39, 44, 53, 55, 66), 95% CI 0.14, 0.19), 0.20 (14 studies (20, 22, 26, 36, 38, 40, 43, 45, 53, 59, 61, 63, 66, 68), 95% CI 0.18, 0.21), and 0.15 (7 studies (8, 40, 43, 46, 59, 63, 68), 95% CI 0.13, 0.18), respectively (Figure 5).

Response rate and survival outcome in an NDMM/upfront setting

After screening, 13 studies (15, 17, 27, 33, 38, 43, 46, 57, 59, 62, 65, 66, 68) were included in the analysis. Due to insufficient data available, only CR, VGPR rate, 5-year OS, 2-, 5-, and 10-year PFS, and 5-year NRM could be analyzed in this section. In an NDMM/upfront setting, the pooled estimate CR rate and VGPR rate were 0.54 (4 studies (15, 38, 59, 68), 95% CI 0.48, 0.61) and 0.22 (3 studies (15, 59, 68), 95% CI 0.16, 0.28), respectively, whereas the pooled estimate of 5-year OS was 0.69 (7 studies (17, 43, 57, 59, 62, 66, 68), 95% CI 0.65, 0.73). The pooled estimates of 2-, 5-, and 10-year PFS were 0.61 (3 studies (15, 33, 65), 95% CI 0.49, 0.73), 0.40 (7 studies (17, 43, 57, 59, 62, 66, 68), 95% CI 0.35, 0.44), and 0.32 (3 studies (43, 46, 59), 95% CI 0.27, 0.38), respectively. The pooled estimate of 5-year NRM was 0.11 (4 studies (38, 59, 66, 68), 95% CI 0.08,0.15). (Figure 6).

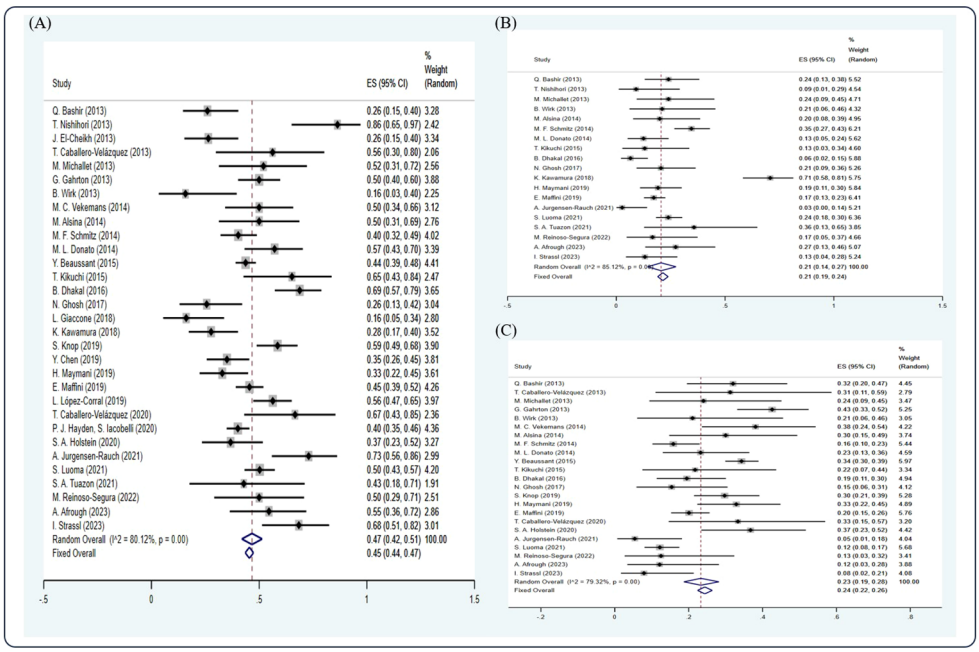

FIGURE 2
Forest plot of pooled weighted **(A)** CR, **(B)** VGPR, and **(C)** PR based on the random-effect model.

Response rate and survival outcome in an RRMM/salvage setting

After screening, 12 studies (14, 17, 22, 30–32, 43, 57, 59, 61, 63, 69) were included in the analysis. Due to insufficient data available, only CR, VGPR, PR rate, 5- and 10-year OS, 5-year PFS, and 2- and 5-year NRM could be analyzed in this section. In the RRMM/salvage setting, the pooled estimate CR, VGPR, and PR rates were 0.31 (5 studies (14, 31, 32, 59, 69), 95% CI 0.24, 0.38), 0.21 (3 studies (14, 59, 69), 95% CI 0.14, 0.29), and 0.12 (4 studies (14, 31, 59, 69), 95% CI 0.07, 0.18), respectively, whereas the pooled estimates of 3-, 5-, and 10-year OS were 0.30 (3 studies (22, 31, 69), 95% CI 0.24, 0.36), 0.24 (7 studies (17, 22, 43, 57, 59, 61, 63), 95% CI 0.21, 0.28), and 0.06 (3 studies (43, 59, 63), 95 CI% 0.03, 0.11), respectively. The

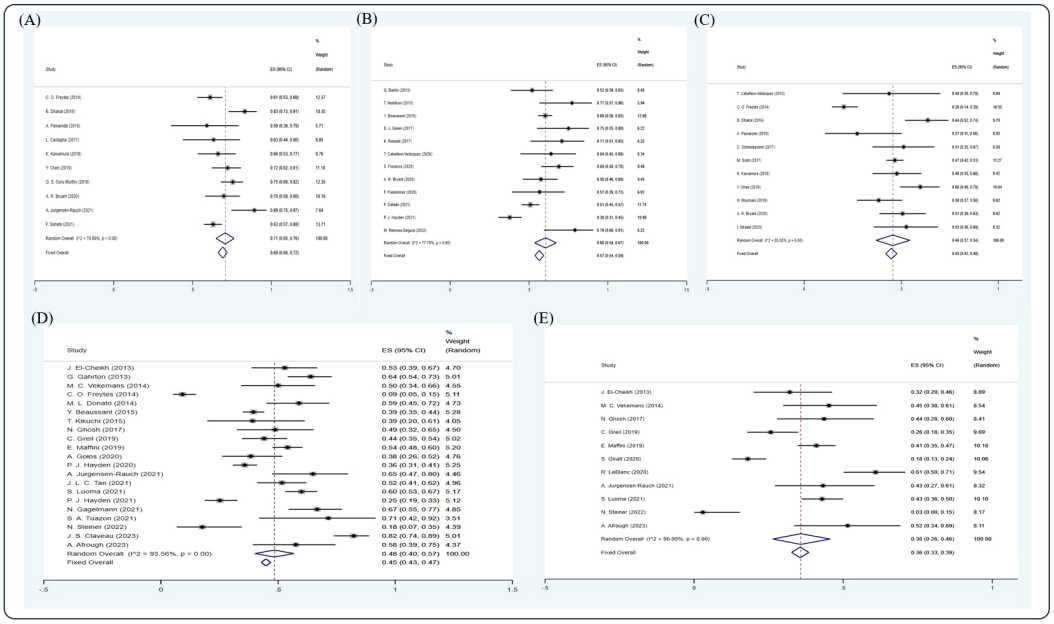

FIGURE 3
Forest plot of pooled weighted **(A)** 1-year, **(B)** 2-year, **(C)** 3-year, **(D)** 5-year, **(E)** 10-year OS based on the random-effect model.

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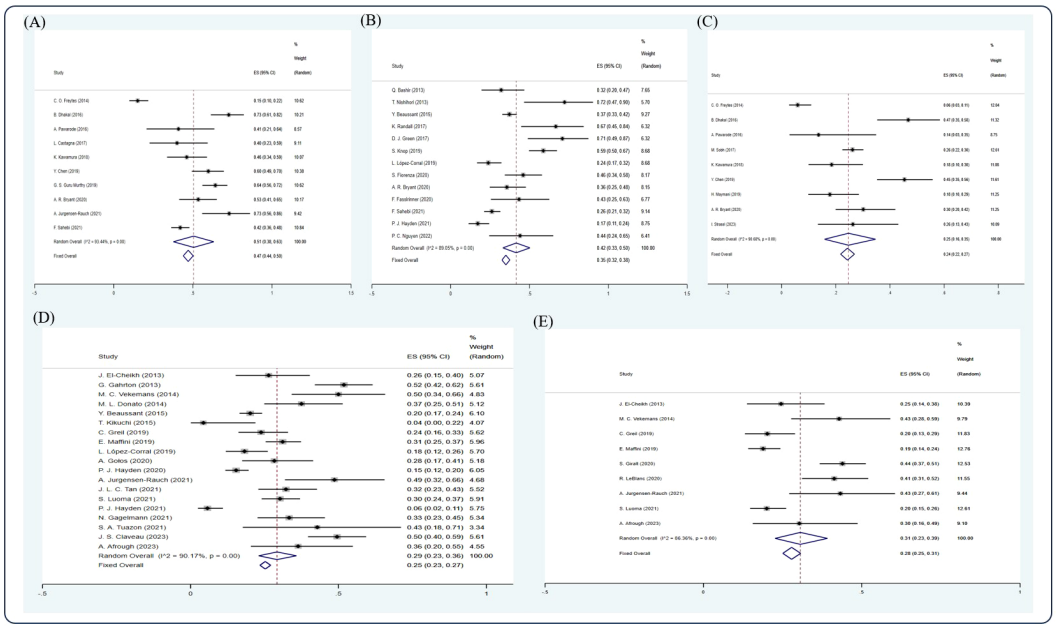

FIGURE 4
Forest plot of pooled weighted **(A)** 1-year, **(B)** 2-year, **(C)** 3-year, **(D)** 5-year, **(E)** 10-year PFS based on the random-effect model.

pooled estimate of 5-year PFS was 0.10 (5 studies (17, 22, 43, 57, 59, 61), 95% CI 0.07, 0.13), whereas the pooled estimates of 2- and 5-year NRM were 0.20 (4 studies (30, 32, 43, 61), 95% CI 0.17, 0.2) and 0.15 (3 studies (59, 61, 63), 95% CI 0.11, 0.20), respectively (Figures 7, 8).

Heterogeneity analyses and sensitivity analyses

I^2 statistic was >50% in all analyses, which indicates large heterogeneity between data sources. We failed to identify the

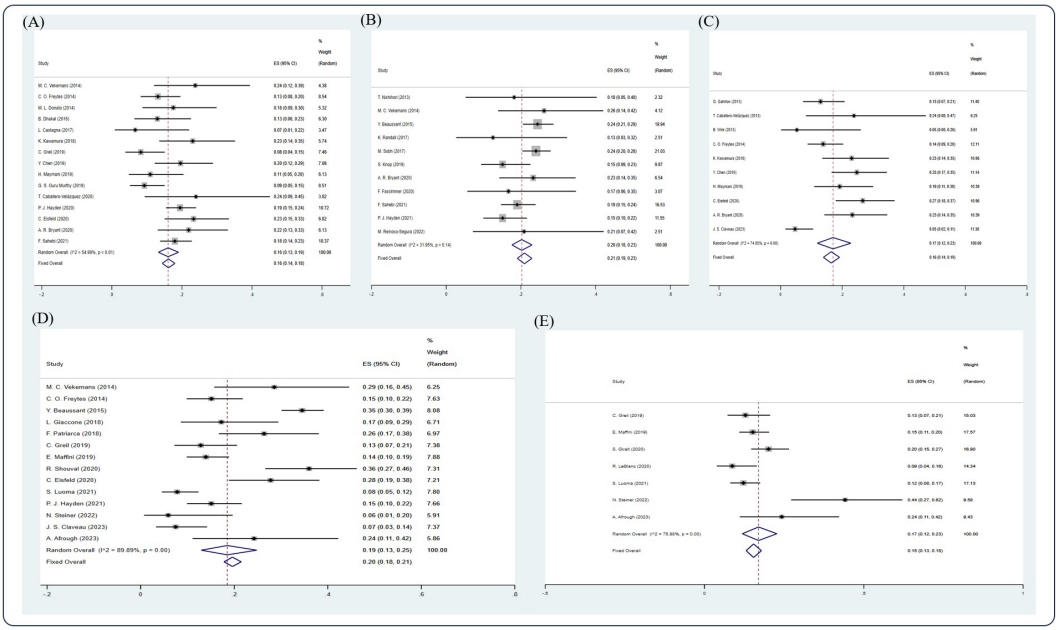

FIGURE 5
Forest plot of pooled weighted **(A)** 1-year, **(B)** 2-year, **(C)** 3-year, **(D)** 5-year, and **(E)** 10-year NRM based on the random-effect model.

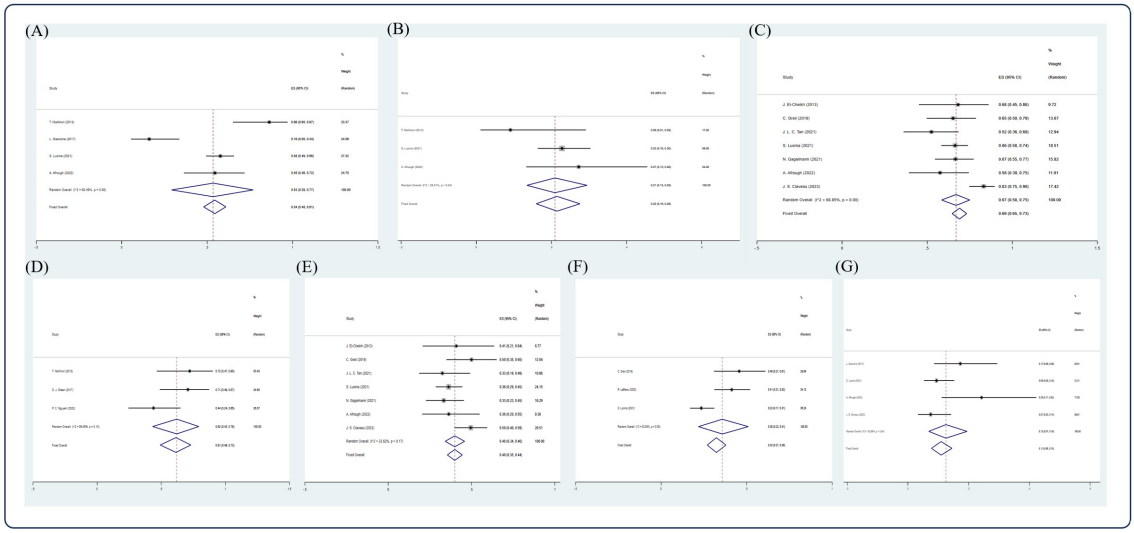

FIGURE 6
Forest plot of pooled weighted **(A)** CR, **(B)** PR, **(C)** 5-year OS, **(D)** 2-year PFS, **(E)** 5-year PFS, **(F)** 10-year PFS, **(G)** 5-year NRM in NDMM/frontline setting based on random effect model.

source of heterogeneity using sensitivity analysis. Sensitivity analysis showed good stability without obvious interference by particular study.

Publication bias

All funnel plots were visually symmetric. The P value in Begg's and Egger's tests of all analysis was >0.05, further confirming the symmetry of all funnel plots. No publication bias was found in our study.

Discussion

Having a history of 66 years since the first alloSCT held by Donnall Tomas in 1957 (70), there has been an accumulation of a certain number of studies with long-term follow-up. In the past 10 years, a simple search on engines could yield 1,709 studies related to alloSCT in MM patients. The IMWG group made consensus that allogeneic SCT or tandem auto-allo-SCT should be limited to clinical trials (71), alloSCT patient data were precious and scarce. Our meta was held to optimize the use of these limited data.

In our results, OS and PFS of alloSCT, both had a marked fall from first to second and second to third years and then remained constant till the 10th year. NRM increased from the first to the second year and then remained relatively stable. The response rate of alloSCT was comparatively low. The survival benefits from alloSCT sustained. Long-term follow-up could reflect a relatively better survival outcome in alloSCT. Due to insufficient data available, the analysis of relapse rate could not be performed. The gap between OS and PFS in both settings give a clue on the survival status of patients. Furthermore, good response rate and promising survival outcome were observed in the NDMM/frontline setting.

AlloSCT could be adapted in MM patients under different conditions, as mentioned; studies suggested that it was most effective in high-risk NDMM patients. Meanwhile, there is evidence showing the beneficial effect of using alloSCT in a

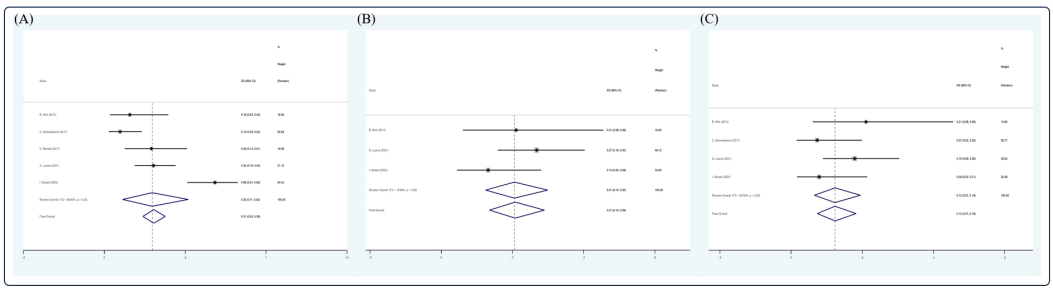

FIGURE 7
Forest plot of pooled weighted **(A)** CR, **(B)** VGPR, and **(C)** PR in RRMM/salvage setting based on the random-effect model.

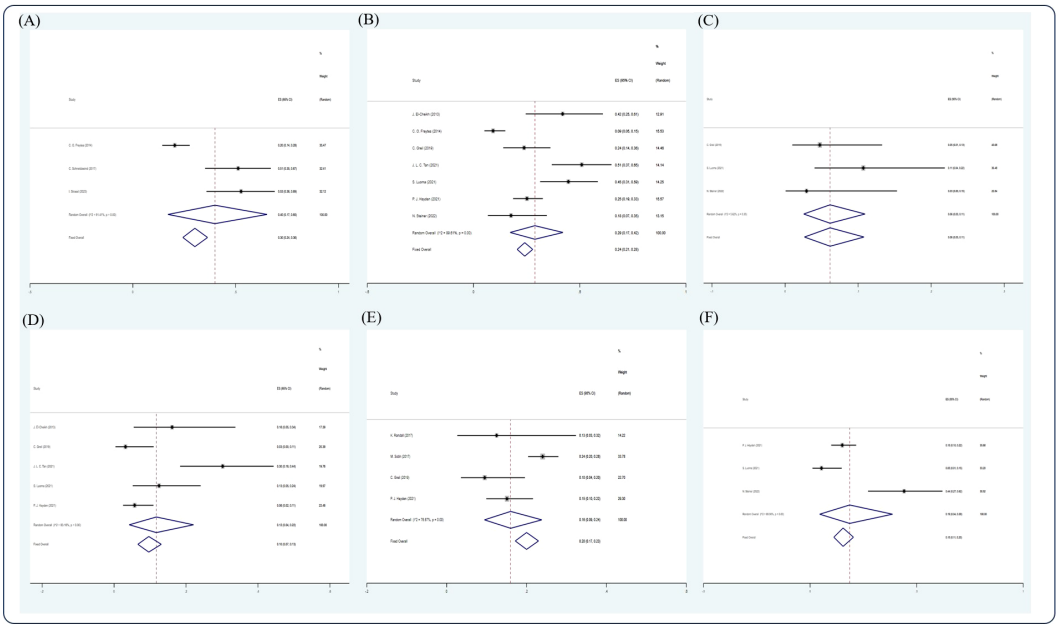

FIGURE 8
Forest plot of pooled weighted **(A)** 3-year OS, **(B)** 5-year OS, **(C)** 10-year OS, **(D)** 5-year PFS, **(E)** 2-year NRM, and **(F)** 5-year NRM in an RRMM/salvage setting based on the random-effect model.

relapse setting, especially in young relapse patients (72). A long-term follow-up trial comparing survival outcome of relapse patients using salvage treatment with bortezomib and/or immunomodulatory agents and salvage alloSCT showed a higher 7-year OS and PFS in the alloSCT group (36). However, there is contradicting research evidence. In research aiming to compare the outcome of alloSCT in NDMM or RRMM, results showed better patient outcome in the first-line setting, with a good CR rate of 48.3%, a median PFS of 30.2 months, and a 10-year OS of 51%. The median PFS was only 8 months in the relapse setting (73). The effectiveness of alloSCT in the relapse setting is inconsistent, and age might be a more important determinant influencing the outcome.

In our meta-analysis, the CR rate and survival outcome in the RRMM/relapsed setting was below the average of the overall result, with a low CR rate of 0.31, 5-year OS of 0.24, and 10-year OS of 0.06. Due to insufficient data on survival status before alloSCT, the improvement of survival outcome could not be assessed. Despite prognostic factors such as age and cytogenetic risk, conditioning therapy and consolidation regimen could cause great influence to the result.

Since the introduction of less ablative conditioning regimens reduced-intensity conditioning (RIC) and nonmyeloablative (NMA) in 1998, NRM and systemic toxicity greatly decreased while keeping promising GvMM effects (4). Traditional myeloablative conditioning regimens such as total body irradiation, cyclophosphamide, and busulfan were less used afterwards. The working party of the EBMT had held a retrospective study comparing outcomes of MM patients undergoing alloSCT after treosulfan-conditioning (Treo), non-Treo RIC or non-Treo MAC, higher 5-year OS (Treo: 62%, RIC: 57%, MAC: 47%), and lower NRM (Treo: 10%, RIC: 17%, MAC: 19%) were observed in the group using Treo-based conditioning (49).

The use of novel agents such as PI, IMID, and ADC as post-transplant consolidation regimens have shown promising results with acceptable toxicity. The use of DLI or in combination with PI and IMID in patients relapsing after alloSCT showed sustained GvMM effects in early studies. However, GVHD was commonly observed in patients treated with DLI after SCT (74). CD19 CAR "DLI" was developed and studied in patients relapsing after allo-HCT in B-cell malignancies. Studies have shown comparatively low incidence of GVHD with promising effects (75). Besides, a case report has shown relief of myelosuppression due to rapid proliferation of BCMA CAR-T cells using auto-SCT in MM patients (76). Small sample research has shown acceptable efficacy and safety of using CAR-T in post-alloSCT RRMM patients (77, 78). In addition, Liana Nikolaenko conducted a retrospective study to evaluate GVHD of using monoclonal antibody daratumumab in a post-alloSCT setting; 41% of the 34 RRMM patients included achieved PR or better, five developed acute GVHD, and none developed chronic GVHD (79). CAR-T, antibody, or immunoconjugate may have potential synergistic immunomodulatory effect with SCT; further studies are required to verify the effectiveness and safety of treatment.

There were only a few meta-analyses with regards to alloSCT. The data were hard to organize as the fundamental state of each patient varied and there were numerous preconditioning and maintenance regimens. Our meta could only provide a comprehensive but rough overview of the relative effectiveness and trend of survival of alloSCT over the years.

Conclusion

Our research gathered alloSCT MM data over the recent 10 years and provided a comprehensive analysis to verify the response rate and survival outcome of alloSCT in MM patients. AlloSCT has sustained OS, PFS, and NRM rates from the third year on. Long-term follow-up could reveal survival benefits of alloSCT in MM patients. Moreover, results have shown a promising effect of AlloSCT in an NDMM/upfront setting, whereas its effect in an RRMM/salvage setting is below average in our meta-analysis. Novel treatments such as CAR-T, antibody, or immunoconjugate may have potential synergistic immunomodulatory effects with SCT, whereas further studies were required to verify the effectiveness and safety of treatment.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

SL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft. KL: Formal analysis, Methodology, Software, Validation, Writing – review & editing. XZ: Conceptualization, Data curation, Validation, Writing – review & editing. JH: Project administration, Supervision, Validation, Writing – review & editing. TL: Project administration, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The impact of donor-specific antibodies' presence on the outcome post-allogeneic hematopoietic stem cell transplantation: a survey from a single center

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Introduction: Donor-specific antibodies (DSAs) correspond to anti-HLA antibodies of the recipient that are specifically directed to a mismatched antigen of the donor. In the setting of solid organ transplantation DSAs are associated with rejection. Their role is still debated in allogeneic cell transplantation. International guidelines recommend testing patients for DSA before transplant, and if possible, choosing a donor with negative screening.

Methods: We collected clinical data of 236 recipients of alloSCT, performed at our institution from March 2019 to October 2023, to evaluate their impact on engraftment. Serum from all patients was tested for DSA.

Results: 186 patients (79%) achieved sustained myeloid engraftment within day 30 post alloSCT. Thirty-two out 236 (13%) patients engrafted after day 30 post alloSCT. The median times to neutrophil engraftment and platelet engraftment were respectively 21 days (range 11-121 days) and 19 days (range 10-203 days). Fourteen out 236 patients (6%) experienced PrGF. .Twenty-nine patients (12 %) were DSA-positive. Among 29 patients with DSA positivity, 17 had a haploidentical donor and 12 had a UD donor. DSA positivity directly correlates respectively with neutrophil and platelets engraftment failure at 30 days after alloSCT (p=0.01 and p= 0.0004). Univariate Cox analysis showed that factors, including DSAs positivity, disease type, disease status, donor type, conditioning regimen, patient's age, and CD34+ were correlated with neutrophil and platelet engraftment failure at 30 days after alloSCT. Younger patients with DSA negativity, with acute leukemia, in complete response at the time of transplant, who received a higher dose of CD34+ cells from a sibling donor after a myeloablative conditioning regimen, have a reduced risk of neutrophil and platelet engraftment failure at day +30 post alloSCT.Multivariate analysis

confirmed the impact of the presence of DSA only for platelet engraftment, confirming the role of type and status disease, donor type, recipient age, and CD34+ cells infused on engraftment. DSA presence has no impact on TRM, DFS, and OS.

Discussion: PrGF has a multifactorial pathogenesis, where DSA is not the only player, but its impact could vary depending on the transplant platform. Thus patient screening may be helpful to choose the best donor and transplant strategy.

KEYWORDS

donor-specific antibodies, primary graft failure, neutrophil and platelets engraftment failure, anti HLA antibodies, allogeneic stem cell transplantation (allo-SCT)

Introduction

Anti-human leukocyte antigen antibodies (HLAs) are directed against class I (HLA-A, -B, -C) and or class II (HLA-DRB1, -DQB1, DP) HLA antigens, resulting from a previous exposure to non-self HLA antigens; risk factors for anti-HLA antibodies are represented by pregnancy, blood product transfusions (higher risk from receiving leukocyte and platelet transfusion rather than erythrocyte transfusions), prior organ transplantations, and gender, with a higher prevalence in female (86% vs 5%) (1).

Anti-HLA antibody detection has no clinical significance for a patient submitted to transplantation (2), while the donor-specific anti-HLA antibodies (DSAs), which are preformed antibodies of the recipient and specific for HLA antigens of the donor, are associated with an increasing risk of rejection in solid organ transplantation settings (3, 4); their role in HCST is still debated (5).

Rejection is a potentially fatal complication, which consists in primary graft failure (PrGF). PrGF is a lack of engraftment of donor stem cells, consisting of cytopenia associated with a lack of donor chimerism on the bone marrow (6). PrGF is different from poor graft function, where the inadequate function of engrafted donor stem cells produces cytopenia, despite full donor chimerism (7).

Probably DSAs can cause graft failure by cytotoxicity, mediated by both antibodies and by complement, but the exact mechanism is not fully understood (8).

Other common risk factors for primary graft failure are represented by the disease, the remission status at transplantation time, the conditioning regimen intensity, HLA-mismatched graft, stem cell dose, stem cell source, AB0 incompatibility, and T-cell depletion (9).

In recent years, ELISA-based methods, flow cytometry, and Luminex platform are the most used tests for DSA screening, because they are more sensitive than the complement-dependent cytotoxicity (CDC) assay (10). The introduction of flow cytometry crossmatching gives the possibility of detection and quantifying antibody specificities.

Materials and methods

The purpose of our study is to evaluate the impact of DSA presence on the outcome post-transplant, focusing our attention on engraftment. In this aim, in our retrospective study, we analyzed a heterogeneous population of 236 patients undergoing HCT. We tested DSA recipients of allogeneic SCT performed at our institution from March 2019 to October 2023. Patients' characteristics are summarized in Table 1. There were 97 female patients and 139 male patients.

The median age was 56 years (range 19–74). HCT was performed for acute leukemia and myelodysplastic syndrome in 148 patients (63%), chronic myeloproliferative disease (myelofibrosis or chronic myeloid leukemia) in 52 patients (22%), severe aplastic anemia in 12 patients (5%), and lymphoproliferative disorders in 24 patients (10%) (Table 1).

At the time of transplant, 114 patients (48%) were in complete remission, 97 (41%) were in stable disease, and 23 patients (10%) had a progressive disease; two (1%) patients underwent HSCT as frontline therapy.

There were 153 patients (64%) who underwent a myeloablative conditioning regimen with the association of thiotepa (5 mg/kg on days −6 and −5), fludarabine (50 mg/m^2 once a day iv on days −4, −3 and −2), and busulfan (0.8 mg/kg four times a day on days −4, −3, and −2) (TBF); a reduced intensity, a conditioning regimen with the Baltimore scheme, including cyclophosphamide 14.5 mg/kg on days −6 and −5 and fludarabine 50 mg/kg on days −6, −5, −4, −3, and −2, and total body irradiation with 2 Gray on day −1 (11) were performed in 83 patients (35%), and only cyclophosphamide (50 mg/kg for 4 days) was used in 4 patients (1%).

The main GvHD prophylaxis scheme consisted of cyclosporine (CSA), mycophenolic acid (MMF), and post-transplant cyclophosphamide (PTCY), used in 232 patients (98%). Only four patients (2%) received CSA, anti-thymocyte globulin, and methotrexate.

TABLE 1 Patients' characteristics.

Patients (n)	**236**
Median age (range)	56 years (range 19–74 years)
Gender	M/F = 139/97
Diagnosis – Acute leukemia/MDS – Lymphoproliferative disease – Chronic myeloproliferative disease – Aplasia	 – 148 (63%) – 24 (10%) – 52 (22%) – 12 (5%)
Disease status before HCT – Complete remission – Stable disease – Progressive disease – HCST frontline	 – 114 (48%) – 97 (41%) – 23 (10%) – 4 (1%)
Conditioning regimen – Myeloablative – Reduced intensity – CTX	 – 153 (64%) – 83 (35%) – 1 (4%)
Donor – MUD 7/8 – MUD 8/8 – SIB – HAPLO – CB	 – 41 (17%) – 86 (36%) – 38 (16%) – 68 (30%) – 3 (1%)
GvHD prophylaxis – CSA, CTX, MMF – CSA, CTX, MTX, ATG	 – 232 (98%) – 4 (2%)
CD34+ cell median (range)	5.9×10^6/kg (1.6–15)
Acute GvHD grade >/=2	57 (24%)
Chronic GvHD grade >/=2	23 (10%)
Presence of anti HLA antibodies	29 (12%)

CTX, cyclophosphamide; CSA, cyclosporine; MMF, mycophenolic acid; MTX, methotrexate; ATG, anti-thymocyte globulin.

There were 38 donors who were identical siblings (16%), 68 were haploidentical family donors (30%), 127 were unrelated donors (54%), 86 (68%) were matched unrelated donors (8/8), and 41 (32%) were mismatched unrelated donors (7/8).

Patients received a median dose of CD34+ stem cells of 5.9×10^6/kg (range 1.6×10^6/kg–15×10^6/kg). The stem cell source was predominantly peripheral blood (225 patients, 95%). Eight patients received bone marrow stem cells and three patients a cord blood unit.

All patients were screened for the presence of DSAs (class IgG and IgM) with a FlowPRA Screening Test and, only if tested positive, were quantitatively determined with Luminex Single Antigen Beads. The test is based on a series of polystyrene microspheres (beads). Every beads contain fluorochromes of differing intensity embedded within the bead, giving each group of beads with an HLA molecule or molecules derived from lymphoblastoid cell lines attached with a unique signal. The Luminex platform has a greater sensitivity than ELISA and nowadays represents the gold standard for DSA testing. A positive result was considered a median fluorescence intensity (MFI) cutoff >1,000 (10).

Primary graft failure (PrGF) represents the lack of blood count recovery by day +28, with donor chimerism <10%. All patients were tested for chimerism on bone marrow cells at day +30 after HCT, by PCR analysis of highly polymorphic short tandem repeats (STR). Comparing the STR expression profiles between recipient, donor, and post-transplant samples, we can obtain donor chimerism percentage, according to international guidelines (12).

Statistical analysis

Statistical analysis was performed using NCSS 19 Statistical Software–2016 (NCSS, LLC, Kaysville, Utah, USA; ncss.com/software/ncss). Data are shown as median and range for continuous variables and as number and proportion for categorical variables. The cumulative incidence of neutrophils, platelets, and reticulocyte engraftment was calculated at day 30 according to DSA presence. Comparison between curves was made using the Grey's test. Variables affecting the time-dependent outcome such as platelets, neutrophils, and reticulocyte engraftment were identified by the Cox regression method. Statistical significance was attributed for p-value <0.05. In multivariate analysis were included only variables with a p-value ≤0.05 in univariate analysis.

The Kaplan–Meier method was used for overall survival (OS), and comparison between curves was assessed with a log-rank test.

Results

Neutrophil engraftment (neutrophil count $\geq 0.5 \times 10^9$/L) within day +30 after HCT was reached in 186 patients (79%) at a median interval from the transplant of 21 days (range 11–121). The median time to platelet engraftment (platelet count $\geq 20 \times 10^9$/L) was 19 days (range 10–203 days).

Primary graft failure (PrGF) was seen in 14/236 patients (6%) with failure to recover a neutrophil count $\geq 0.5 \times 10^9$/L: it occurred in one patient after TBF3 (3 days of busulfan), three patients after TBF2 (two days of busulfan), seven patients after TBF1 (one day of busulfan), and three after the Baltimore conditioning regimen. We found 4 patients with PrGF in the group with DSA (13%) and 10 patients in the group with no DSA (4.8%) (p = 0.06).

There were 29 patients (12%) who were DSA-positive. A total of 15 patients had antibodies against HLA class I antigens, 10 patients had antibodies against HLA class II, and 4 patients had antibodies against classes I and II. Among 29 patients with DSA positivity, 17 patients received graft from a haploidentical donor, seven patients from an MUD, and five patients from an MMUD. Among patients who experienced PGF, the four patients with DSA received graft from a haploidentical donor.

Acute and chronic GVHDs were present respectively in 57/236 (24%) and 23/236 (10%) patients.

We found that DSA positivity directly correlates with neutrophil and platelet engraftment failure at 30 days after allogeneic SCT (p = 0.01; p = 0.0004). We found no correlation between DSA presence and reticulocyte engraftment.

Cumulative incidence of neutrophil engraftment at day +30 post alloSCT resulted in 58% in the DSA+ group versus 82% in the DSA− group (p = 0.08) (Figure 1A).

Cumulative incidence of platelet engraftment at day +30 post alloSCT resulted in 41% in the DSA+ group versus 74% in the DSA − group (p = 0.006) (Figure 1B).

Cumulative incidence of reticulocyte engraftment at day +30 post alloSCT resulted in 17% in the DSA+ group versus 34% in the DSA− group (p = 0.07).

The median MFI at transplant was 5,933 with a range value between 2,000 and 23,769, and we found a correlation between PrGF and degree of MFI intensity (p = 0.01). The four patients with

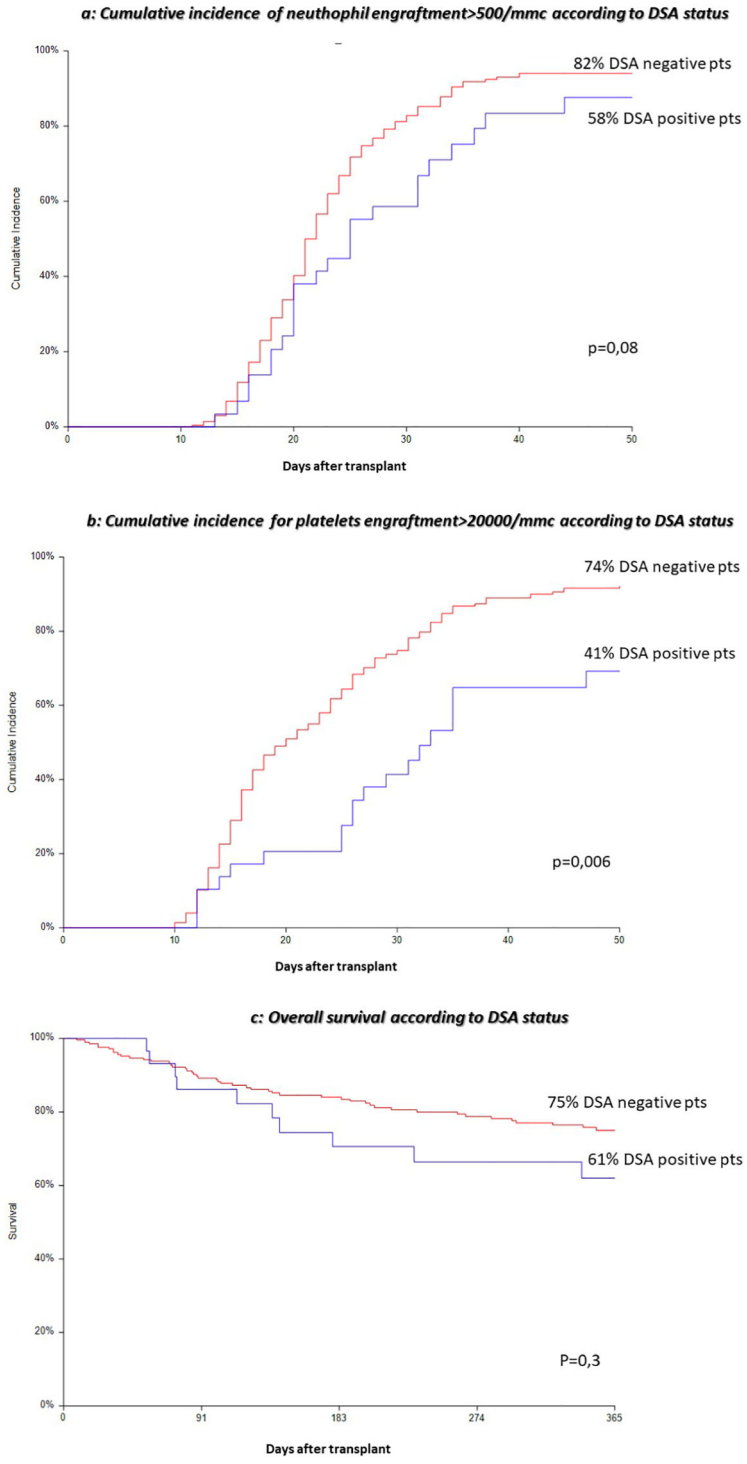

FIGURE 1
(A) Cumulative incidence of neutrophil engraftment>500/mmc according to DSA status. **(B)** Cumulative incidence for platelets engraftment>20000/mmc according to DSA status. **(C)** Overall survival according to DSA status.

DSA who experienced PrGF have a higher MFI with a median value of 11,547 (range 2,000–23,769), compared with patients with DSA without PrGF with a median value of 4,500 (range 2,000–21,530). We can suppose that patients with an MFI value greater than 10,000 could be at risk of PGF.

Univariate Cox analysis was performed to evaluate which factors could influence engraftment after allogeneic SCT. This analysis showed that factors, including DSA positivity ($p = 0.02$), disease type ($p = 0.0001$), disease status ($p < 0.0001$), donor type ($p = 0.0001$), conditioning regimen ($p = 0.04$), age at transplant ($p = 0.003$), and number of CD34+ cells infused ($p = 0.0003$) were correlated with neutrophil engraftment failure at 30 days after alloSCT (Table 2A). The same factors have the same impact on platelet engraftment, as reported in Table 2B.

Multivariate analysis confirmed a role for the presence of DSA only in the setting of platelet engraftment [HR 0.43 (95% CI 0.23–0.82), ($p = 0.01$)]. Age at transplant, disease type, disease status at transplant, donor type, and number of CD34+ cells infused remain strong factors affecting trilinear recovery after SCT (Tables 2A, B).

One-year overall survival was 70%. Causes of death were disease relapse in 35 patients, chronic Graft versus host disease (GVHD) in 10 patients, and transplant-related mortality (TRM) in 25 patients.

DSA presence has no impact on TRM, relapse, disease-free survival (DFS), and OS (Figure 1C).

Among the 14 patients who experienced PrGF, seven (50%) patients received a second transplant. In two patients, the donor was the same, and in the remaining five patients, the donor was different. The stem cell source was peripheral blood. The conditioning regimen was performed according to the Baltimore scheme, where the TBI was replaced with melphalan at a dosage of 30 mg/kg, due to the severe cytopenia of these patients, except for one patient, who was treated with a low dose of fludarabine and cyclophosphamide. Patients' characteristics are summarized in Tables 3A, B.

Two of these patients were also submitted to a desensitization treatment before second transplant, in order to reduce DSA titer, with plasmapheresis and donor platelet infusion. In this way, we reduced the median MFI title from 24,874 to 4,500. After the second transplant, five out seven patients are alive (71%), with one patient who died because of gut GVHD after engraftment and one patient because of sepsis.

Discussion

Donor-specific antibodies (DSAs) correspond to anti-HLA antibodies, which are specifically direct against a mismatched antigen of the donor (5). Healthy non-transplanted individuals can have DSA as a result of common exposures including pregnancy; on the other hand, patients can present DSA due to blood product transfusion, or as a result of previous organ transplantation (13). DSA presence at the time of transplant is correlated with graft rejection and decreased survival in solid organ transplantation (14–16). The American Society for Histocompatibility and Immunogenetics (ASHI) strongly recommends DSA tests as mandatory in solid organ transplants.

DSA seems to have an important role as a barrier against successful engraftment of donor cells, with a negative impact on survival, especially in the setting of haploidentical stem cell transplant. Their role appears to be more prevalent in this setting due to the degree of mismatch and to a higher likelihood of alloimmunization of multiparous females against offspring's HLA antigens (17).

Previous studies reported the association between DSA and PrGF in HSCT with unrelated HLA mismatched donors or CBU.

Takanashi et al. showed that the graft failure rate was significantly higher with a lower neutrophil recovery in the DSA-positive patients, compared with the negative ones, in unrelated cord blood transplantations (68% vs 17%) (18).

Cutler et al. reported similar data in the setting of double UCB HCT, with a graft failure rate of 57% in the DSA-positive patients vs. 6% in the DSA-negative patients, respectively (19).

Spellman et al. showed that 24% of patients with PrGF had performed DSA in the setting of unrelated donors (20). Similarly, Ciurea et al. found that the presence of DSA was the only factor associated with a significantly higher rate of graft failure, in the MUD transplant population (DSA+ 38% vs DSA– 3%) (21).

The same author in a largest study confirmed the same finding in the setting of haploidentical HCT: in a 122-patient population, the incidence of DSA was 18% and 32% of the patients with DSA experienced PrGF, while only 4% of patients without DSAs had PrGF ($p < 0.001$). DSAs' presence has a significant impact also on delayed engraftment (19 days vs. 18 days, $p = 0.004$) (22).

In another study on 79 patients submitting to haploidentical HCT, Yoshihara et al. found a significantly lower cumulative incidence of donor neutrophil (61.9% vs. 94.4%, $p = 0.026$) and platelet engraftment (28.6% vs. 79.6%, $p = 0.035$) in the DSA-positive group (23).

Moreover, Chang et al. showed that DSA positivity was associated with PrGF and delayed engraftment but also with poor graft function (5).

In our study on 236 patients, we focused our attention on the impact of DSA presence on the outcome post-transplant, in particular on engraftment. There were 29 patients (12%) who showed DSA positivity. We found that DSA positivity directly correlates with neutrophil and platelet engraftment failure at 30 days after allogeneic SCT ($p = 0.01$) ($p = 0.0004$), but we did not find a direct correlation with PrGF.

Univariate Cox analysis showed that younger patients with DSA negativity, with acute leukemia, who had an incomplete response at the time of transplant, and who received a higher dose of CD34+ from a sibling donor after a myeloablative conditioning regimen have a reduced risk of neutrophil and platelet engraftment failure at day +30 post alloSCT. In multivariate analysis, the presence of DSAs continued to be significantly associated only with platelet engraftment delay: [RR 0.43 (95% CI 0.23–0.82) ($p = 0.01$)]. Thus, we confirmed an association between DSA presence and a delay of engraftment, but not with PrGF. In our population, DSA's presence

TABLE 2A Univariate and multivariate Cox analyses: neutrophil engraftment at day 30 post-HCT.

Risk factors	Univariate		Multivariate	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
DSA pos vs neg	0.52 (0.28-0.95)	**0.02**	0.65 (0.37-1.13)	0.12
Disease *MFI vs AL*	0.36 (0.23-0.57)	**<0.0001**	0.48 (0.27-0.86)	**0.01**
Conditioning *RIC vs ABL*	0.73 (0.53-0.99)	**0.04**	0.87 (0.61-1.23)	0.44
Stem cell source *PBSC vs others*	0.7 (0.45-1.34)	0.3	–	–
Disease status at transplant *No CR vs CR*	0.44 (0.33-0.60)	**<0.0001**	0.47 (0.31-0.71)	**0.0004**
Donor *SIB vs UD* *SIB vs Haplo*	0.57 (0.39-0.85) 0.40 (0.25-0.62)	**0.005** **0.0001**	0.6 (0.39-0.90) 0.46 (0.28-0.75)	**0.01** **0.001**
CD34+ cell continuous	1.11 (1.04-1.17)	**0.0003**	1.12 (1.06-1.19)	**P<0.0001**
Age *continuous*	0.98 (0.97-0.99)	**0.003**	0.99 (0.97-1.00)	0.10
Recipient sex *Female vs male*	0.98 (0.62-1.39)	0.7	-	-
GvHD prophylaxis PTCY vs others	0.55 (0.20-1.34)	0.24	-	-

MFI, myelofibrosis; AL, acute leukemia; RIC, reduced intensity conditioning regimen; ABL, myeloablative conditioning regimen; PBSC, peripheral blood stem cells; SIB, sibling donor; UD, unrelated donor; HAPLO, haploidentical donor.
Risk factors affecting neutrophil engraftment failure at 30 days after HCT: DSA positivity (p = 0.02), disease type (p = 0.01), disease status (p < 0.0001), donor type (p= 0.0001), conditioning regimen (p = 0.04), age at transplant (p =0.003). Multivariate analysis confirmed the role of disease type (p <0.0001), disease status (p = 0.0004), donor type (p= 0.001), and number of CD34+ cells infused (p <0.0001).

TABLE 2B Univariate and multivariate Cox analyses: platelet engraftment at day 30 post-HCT.

Risk factors	Univariate		Multivariate	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
DSA pos vs neg	0.40 (0.22-0.72)	**0.02**	0.43 (0.23-0.82)	**0.01**
Disease MFI vs AL	0.52 (0.32-0.82)	**0.005**	0.62 (0.34-1.11)	0.11
Conditioning RIC vs ABL	0.7 (0.50-0.97)	**0.03**	0.89 (0.56-1.41)	0.6
Stem cell source PBSC vs others	0.52 (0.19-1.40)	0.19	–	–
Disease status at transplant no CR vs CR	0.52 (0.42-0.77)	**0.0004**	0.58 (0.38-0.90)	**0.01**
Donor SIB vs UD SIB vs Haplo	0.66 (0.38-1.17) 0.4 (0.27-0.71)	0.1 **0.0009**	1.10 (0.71-1.70) 0.70 (0.42-1.16)	0.65 0.17
CD34+ cell continuous	1.14 1.076-1.20)	**<0.0001**	1.17 (1.10-1.24)	**<0.0001**
Age continuous	0.9 (0.5-0.9)	**<0.0001**	0.97 (0.96-0.99)	**<0.0001**
Recipient sex Female vs male	0.93 (0.62-1.39)	0.7	-	-
GvHD prophylaxis PTCY vs others	0.78 (0.25-2.46)	0.67	-	-

MFI, myelofibrosis; AL, acute leukemia; RIC, reduced intensity conditioning regimen; ABL, myeloablative conditioning regimen; PBSC, peripheral blood stem cells; SIB, sibling donor; UD, unrelated donor; HAPLO, haploidentical donor.
Risk factors affecting platelets engraftment failure at 30 days after HCT: DSA positivity (p = 0.02), disease type (p =0.005), disease status (p=0.0004), donor type (p= 0.0009), conditioning regimen (p = 0.03), age at transplant (p <0.0001), and number of CD34+ cells infused (p < 0.0001). Multivariate analysis confirmed the role of DSA positivity (p=0.01), disease status (p=0.01) age (p < 0.0001) and number of CD34+ cells infused (p < 0.0001).

TABLE 3A Clinical characteristics of patients with primary graft failure at first alloSCT.

n	Patient gender	Age	DX	Disease status at 1 SCT	Conditioning regimen	Donor gender	Donor age	SC Source	CD34+ cell dose	DSA
1	F	64	AML	CR1	TBF2	M	38	BM	3.7	POS
2	M	69	AML	FRONTLINE	TBF1	M	41	BM	4.2	NEG
3	M	69	AML	FRONTLINE	TBF1	F	33	BM	6.8	POS
4	M	73	MFI	STABLE	TBF1	M	46	BM	3.8	NEG
5	F	60	MDS	CR1	TBF2	M	30	BM	7.5	POS
6	M	43	AML	CR1	TBF3	M	0	CBU	2.5	NEG
7	M	69	MDS	STABLE	TBF1	F	30	PBSC	5.8	POS

AML, acute myeloid leukemia; MFI, myelofibrosis; MDS, myelodysplastic syndrome; CR1, first complete remission; TBF3, 3 days of busulfan; TBF2, 2 days of busulfan; TBF1, 1 day of busulfan; BM, bone marrow; PBSC, peripheral blood stem cell; CBU, cord blood unit.

TABLE 3B Clinical data of seven patients at second alloSCT.

N	Donor 2^{nd} Tx	Cond 1^{st} 2^{nd}	Int-dd 2^{nd} Y/N	Engr	GvHD grade	Alive 1 year Y/N	Cause death
1	same	MEL	42	Y	III	N	GvHD
2	other	MEL	39	No	0	Y	–
3	other	Flu-CTX	48	Y	0	Y	–
4	other	MEL	53	Y	III	Y	–
5	same	MEL	32	Y	I	Y	–
6	other	MEL	30	No	0	N	Sepsis
7	other	MEL	58	Y	0	Y	–

Donor 2^{nd} Tx, donor of the second transplant; same, the same HAPLO donor as in the first transplant; other, other HAPLO family member; Int-dd 1^{st}–2^{nd}, interval in days between the first and second HAPLO transplants; Engr 2^{nd}, engraftment after a second HAPLO Yes/NO; aGvHD, acute GvHD grade.

has no impact on TRM, relapse, DFS, and OS. With the limit of a retrospective study, on a population of 236 patients, the incidence of DSA positivity is similar to that reported in literature, and, as previously described, DSA may have a role in the engraftment, but it is not the only potential risk factor and its impact may depend on the sum of the other factors.

Other studies found no correlation between DSA presence and impact on PrGF, as reported by Altared et al. in a population of 107 patients submitted to haploidentical transplant, after receiving a myeloablative conditioning regimen: there is no evidence of DSA in the three patients who experienced graft failure. On the other hand, engraftment was achieved in the 17 DSA-positive patients, similarly to 87 DSA-negative patients (24).

Moreover, DSA seems to have no role on PrGF, and neither in predicting engraftment after a second HAPLO graft, as reported in another study (25, 26).

The host immunologic reaction against donor cells is the principal cause of graft rejection. Graft rejection is due to cytolytic reaction mediated by T and/or NK cells of the recipient, who survived the conditioning regimen. The immunologic reaction is based on the genetic disparities between the donor and the recipient and the status of anti-donor alloreactivity of the recipient. This is more likely to happen in mismatched unrelated and haploidentical donors (13).

On the other hand, in more recent years, *in vitro* and *in vivo* studies have demonstrated that there is also an antibody-mediated graft rejection humoral, called humoral rejection (27).

The humoral rejection can occur by cytotoxicity mediated by antibodies and by complement. An MFI above 1,000 is indicative of a positive screening for DSA. As reported in several studies, the incidence of PGF appears to be directly correlated with MFI levels above 5,000 (22, 23). We confirmed these data also in our study, where we found a correlation between PrGF and degree of MFI intensity ($p = 0.01$). As reported by Ciurea et al., the risk of rejection rate for patients with DSA >5,000 MFI was significantly higher (54% vs 9%) (21). Furthermore, higher MFI levels (>5,000) also correlate with the complement-binding ability. It remains unclear whether this depends on the higher ability of some antibodies to bind complement or on the higher levels of antibodies, which are more likely to activate complement cascade and destroy targeted cells. On the other hand, Chen et al. found no correlation between MFI levels and the ability to fix complement (28). Due to these discrepant data, a uniform MFI cutoff cannot be used as a surrogate for clinical relevance.

As suggested by EBMT guidelines, all patients should be screened before transplant, to select donors with no DSA against, when possible, and desensitize patients with DSA before transplant (17).

There are four strategies to desensitize patients with DSA. The first one consisted in mechanical antibody removal by using plasmapheresis or immunoabsorption. The second one is based on the use of monoclonal antibodies against CD20+ B lymphocytes (rituximab), and proteasome inhibitors against plasma cells, to inhibit the antibody production. The third procedure is based on the antibody neutralization by infusion of intravenous immunoglobulin (IVIg), and platelet or buffy coat transfusions. Another strategy is the inhibition of complement cascade, by using anti C5 or C3 agents (17, 18).

Among the seven patients with PrGF, who were submitted to a second alloHCT, four patients resulted positive for DSA. Among these, two female patients resulted positive for DSA against their offspring donor, with a higher MFI. After the first transplant and before the second one, patients were submitted to desensitization therapy, which included plasmapheresis and platelet transfusion. In this way, we reduced the median MFI title from 24,874 to 4,500.

Conclusion

The increasing use of haploidentical and mismatched unrelated donors highlighted new interest in the field of DSA. Their role in the setting of alloSCT is still debated, with conflicting data from several studies. Probably different results depend on the multifactorial pathogenesis of PrGF, where DSA presence is a potential risk factor, where its weight varies according to several transplant settings.

EBMT consensus guidelines recommend testing DSAs in all patients. Donors with a negative DSA screen should be selected. If this is not possible, it is recommended to reduce the antibody levels prior to transplant, in order to favor a successful engraftment.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

SS: Writing – review & editing. EM: Methodology, Writing – review & editing. FF: Data curation, Writing – original draft. ML: Data curation, Writing – review & editing. EG: Data curation, Writing – review & editing. FS: Data curation, Writing – review & editing. AB: Data curation, Writing – review & editing. EP: Methodology, Writing – review & editing. MF: Methodology, Writing – review & editing. AM: Methodology, Writing – review & editing. PC: Data curation, Writing – review & editing. SG: Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing.

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Sorafenib maintenance after allogeneic stem cell transplantation in patients with FLT3+ AML receiving midostaurin during induction and consolidation: a retrospective analysis

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Introduction: Acute myeloid leukemia (AML) relapse is the main cause of death after allogeneic stem cell transplant (allo-SCT). In AML FLT3+, it was shown that Sorafenib used as maintenance therapy after allo-SCT, significantly reduces the risk of relapse and death.

Methods: We analyzed 29 adult patients with FLT3m AML and underwent allogeneic stem cell transplant from 2019 to 2023. All patients received midostaurin plus conventional CT during induction and consolidation. After transplantation, Sorafenib maintenance was administered in all patients independently from MRD status at transplantation.

Results: Sorafenib maintenance was applied in 18 patients out 29 patients (62%). Median time to start sorafenib was 100 days (range 37-225) and median duration of treatment was 775 days (range 140-1064). For the whole population (n=29), 2-year OS, LFS, and CIR was 76%, 68% and 28%, respectively. The median time to relapse was 137 days (range 49-246). For patients treated with sorafenib (n=18), the 2-year OS, LFS, and CIR were 94%, 84% and 11%, respectively. For the whole population, the 100-day NRM was 0% and 1-year NRM was 3%. Death was caused by transplant-associated thrombotic microangiopathy in 1 patient. For patients who were administered with Sorafenib, the 1-y NRM was 5%. Death was caused by transplant associated transplant-associated thrombotic microangiopathy.

Discussion: This retrospective study suggests that sorafenib maintenance seem to be effective even in patients pre-treated with midostaurin.

KEYWORDS

acute myeloid leukemia (AML), relapse, sorafenib, allogeneic stem cell transplantation (Allo-SCT), maintenance

1 Introduction

Acute myeloid leukemia (AML) is a complex and heterogeneous group of hematologic malignancies characterized by various genetic abnormalities. The FMS-like tyrosine kinase 3 mutation (FLT3m) is recognized to confer a poor prognosis due to a high relapse rate and low survival. FLT3 mutations are present in approximately 30% of newly diagnosed adult AML patients, with internal tandem duplication (ITD) in the juxtamembrane domain being the most common FLT3m. First-line conventional treatment with FLT3 inhibitors (FLT3i), such as midostaurin in association with standard chemotherapy, is considered the gold standard (1). Consolidation with allogeneic stem cell transplantation (allo-SCT) is frequently performed in FLT3m patients to reduce the risk of disease relapse (2). Despite the therapeutic advances with allo-SCT, the risk of disease relapse persists, prompting the exploration of additional treatment strategies. Sorafenib is a first-generation type II FLT3i that has been found to be effective in blocking multiple pathways. It has been shown to be effective in reducing the incidence of relapse after allo-SCT in various retrospective and randomized phase 2 and 3 trials (3–6). In these studies, most of the patients did not receive FLT3i during the induction and consolidation phases.

In our analysis, we have specifically focused on patients who were treated with midostaurin during the conventional treatment phase and subsequently received maintenance therapy with sorafenib following allo-SCT.

2 Materials and methods

In this retrospective study, we analyzed adult patients diagnosed with FLT3m AML who underwent allogeneic stem cell transplantation between 2019 and 2023. At diagnosis, Nucleophosmin (NPM1) and FLT3-ITD identification was performed by PCR amplification using gene-specific primers followed by capillary electrophoresis, according to Noguera et al. (7). All patients received midostaurin plus conventional chemotherapy (CT) during induction and consolidation. Pre-transplant conditioning regimens were carefully selected based on the individual needs of patients, ranging from myeloablative to reduced intensity, and in some cases, non-myeloablative. Graft-versus-host disease (GVHD) prophylaxis varied depending on donor type. Patients who received allografts from Human leucocyte antigen (HLA) identical sibling (SIB) or matched unrelated donor (MUD) also received prophylaxis with cyclosporine (CSA), methotrexate (MTX), and anti-thymocyte globulin (ATG), whereas those with haploidentical (HAPLO) and mismatched unrelated donors (mMUD) received a regimen of post-transplantation cyclophosphamide in combination with CSA and mycophenolate mofetil (MMF). Patients who did not receive frontline midostaurin as a part of induction were excluded from the study.

The patients' minimal residual disease (MRD) status was assessed before transplant through PCR amplification using NPM1 as a molecular marker, and in those without this molecular marker, MRD status was evaluated by multiparametric flow cytometry assay.

In our protocol, sorafenib was administered at a starting dose of 200 mg twice daily according to the SORMAIN trial (4). Sorafenib maintenance was administered in all patients independently from MRD status at the time of transplantation. The time to start sorafenib varied depending on engraftment, presence of acute GVHD, or infectious complications. Sorafenib maintenance was planned for up to 2 years after transplantation.

The primary endpoint was leukemia-free survival (LFS) at 2 years post-transplant. LFS is defined as the time to relapse and/or death. The secondary endpoints were cumulative incidence of relapse (CIR), overall survival (OS), and non-relapse mortality (NRM).

For LFS analysis, the Kaplan–Meier method and log-rank test were used. CIR and NRM were based on cumulative incidence estimates and gray tests. All data were recorded in an Excel data sheet, and analysis was performed using the NCSS 2019 software.

3 Results

This study identified 29 patients diagnosed with FLT3m AML who were treated with midostaurin and received allo-SCT. The median age was 55 years (range: 19–73). Patient characteristics are reported in Table 1. A total of 24 patients (82%) were in first

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TABLE 1 Patient, disease, and transplant characteristics.

	Overall (n = 29)	SOR (n = 18)
Age median (range)	54 years (19–73)	55 (31–73)
Mutational status: FLT3-ITD NPM1	 29 (100%) 18 (62%)	 18 (100%) 9 (56%)
Disease status at ALLO: CR1 CR2 Active	 24 (82%) 3 (10%) 2 (10%)	 17 (95%) / 1 (5%)
MRD status at ALLO (only CR): Negative (mol) Positive	 22 (81%) 5 (18%)	 16 (94%) 1 (6%)
Donor: SIB MUD mMUD HAPLO	 8 (28%) 10 (34%) 1 (3%) 10 (34%)	 4 (22%) 7 (39%) 1 (6%) 6 (34%)
Source: PBSC BM	 24 (83%) 5 (17%)	 14 (78%) 4 (22%)
Conditioning: MAC RIC	 26 (90%) 3 (10%)	 17 (95%) 1 (5%)

SOR, sorafenib; MRD, minimal residual disease; CR, complete remission; SIB, sibling; MUD, matched unrelated donor; mMUD, mismatched unrelated donor; HAPLO, haploidentical; PBSC, peripheral blood stem cells; BM, bone marrow; MAC, myeloablative conditioning; and RIC, reduced-intensity conditioning.

complete remission (CR1), three patients (10%) were in CR2, and two were not in CR. A total of 22 patients (76%) were MRD-negative for NPM1 or FLT3-ITD. Donor type was SIB for eight patients (28%), MUD/mMUD for 11 (37%), and HAPLO for 10 (34%). The median follow-up was 33 months (range: 5–52).

The median time to absolute neutrophil count (ANC) of more than 0.5/L and that of platelet count of more than 20/L was 17 days (range: 9–31) and 15 days (range: 9–33), respectively.

In the whole cohort, the cumulative incidence rates of acute GVHD (aGVHD) were 23% and 3% for grades 2–4 and grades 3–4, respectively. The median time to aGVHD was 43 days (range: 25–172). The chronic GVHD (cGVHD) all-grade incidence rate was 15%.

Sorafenib maintenance was administered in 18 out of 29 patients (62%). Reasons for not starting maintenance were as follows: lack of approval by authorities (n = 1, 3%), early relapse (n = 2, 6%), prior tyrosine kinase inhibitor (TKI) resistance (n = 2, 6%), acute GVHD (n = 3, 10%), poor performance status (n = 1, 3%), and other causes (n = 2, 6%). The median time to start sorafenib was 100 days (range: 37–225), and the median duration of treatment was 775 days (range: 140–1,064).

Sorafenib was withdrawn in 12/18 (67%) patients in seven because of the end of treatment, in two because of relapse on therapy, and in three because of complications such as transplant-associated thrombotic microangiopathy (one), idiopathic thrombocytopenic purpura (one), and pericarditis (one).

For the whole population (n = 29), 2-year OS, LFS, and CIR were 76%, 68%, and 28%, respectively. The median time to relapse was 137 days (range: 49–246). For patients treated with sorafenib (n = 18), the 2-year OS, LFS, and CIR were 94%, 84%, and 11%, respectively (Figure 1).

For the whole population, the 100-day NRM was 0%, and the 1-year NRM was 3%. Death was caused by transplant-associated thrombotic microangiopathy in one patient. For patients who were administered with sorafenib, the 1-year NRM was 5%. Death was caused by transplant-associated thrombotic microangiopathy.

In the no-sorafenib cohort (n = 10), there were no cases of toxic death; 1-year LFS and OS were 40% and 50%, respectively. Six

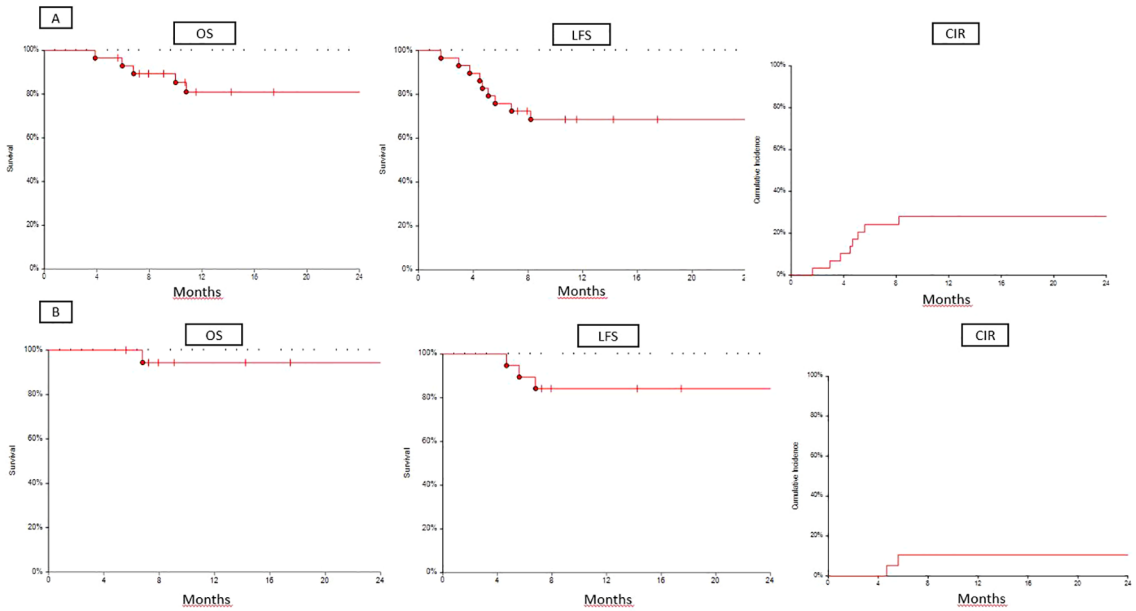

FIGURE 1
(A) OS, LFS, and CIR for whole cohort (n=29). **(B)** OS, LFS, and CIR for sorafenib cohort (n=18).

patients relapsed, and five of them died. Six of ten (60%) patients were CR1/CR2-MRD negative, 3/10 (30%) patients were CR1/CR2-MRD positive, and 1/10 (10%) patients had an active disease. Of the patients who relapsed, three were CR1/CR2-MRD negative, and three were CR1/CR2-MRD positive.

In the sorafenib cohort (n = 19), 16 (84%) patients were CR1-MRD negative, two (11%) patients were CR1-MRD positive, and one (5%) patient had an active disease.

For all patients in CR1 (n = 24), 2-year OS, LFS, CIR, and NRM were 81%, 71%, 25%, and 4%, respectively. The median time to relapse was 140 days (range: 49–204). For patients in CR1 treated with sorafenib (n = 18), the 2-year OS, LFS, CIR, and NRM were 94%, 83%, 11%, and 6%, respectively, and the median time to relapse was 168 (range: 140–204).

4 Discussion

Our retrospective analysis suggests that in patients with FLT3-ITD AML receiving midostaurin, sorafenib maintenance after allo-SCT still reduces the incidence of relapse, improving survival. Adding midostaurin to conventional chemotherapy improved the survival of patients with AML with FLT3 mutation (1) and is regularly being used in clinical practice. Not only midostaurin but also quizartinib plus conventional chemotherapy at diagnosis has recently been shown to improve survival in FLT3-ITD-positive patients in a randomized clinical trial (8).

Although allo-SCT is considered mandatory for FLT3-mutated AML in the first complete remission (9), relapse remains a cumbersome point. Several strategies can be used to reduce the risk of relapse, but targeted molecules may be preferred based on a good safety profile. In randomized clinical trials, sorafenib administered as maintenance after allo-SCT significantly improved survival because of the reduction of relapse (4, 5), even when the duration of maintenance was 2 years (5) and 6 months (4). Recently, Xuan et al. updated the results after a median follow-up of 60.4 months, confirming that all major endpoints were improved in the sorafenib arm compared to placebo (10). However, in both of these randomized studies, few patients received midostaurin or any other TKIs during the conventional phase of treatment. In Xuan's trial, 24% of patients received sorafenib during induction (4), and in the multivariate analysis, this did not impact survival or relapse (9). In the SORMAIN study, only nine patients were pre-treated with midostaurin (5). Based on this, we analyzed patients with FLT3-ITD AML who were treated with midostaurin during induction and consolidation, allo-SCT, and sorafenib as maintenance. Not all eligible patients received sorafenib (60%), primarily due to complications such as acute GVHD (10%). The median time to start maintenance was 100 days, longer than 30 days (median, range: 30–42) in the Chinese trial (4) and between 60 and 100 days in the SORMAIN study (5). Despite this, the results observed in this small cohort (n = 29) of patients were interesting (2-year OS was 75%, 2-year LFS was 70%, and 2-year CIR was 24%) and similar to those reported in randomized studies. Furthermore, considering only patients treated with sorafenib, as expected, OS and LFS were higher than those of the whole cohort (2-year OS and 2-year LFS were 93%, and CIR was 11%). These results strongly suggest that sorafenib is active in patients previously exposed to midostaurin.

Recently, the data from the MORPHO study were published showing that gilteritinib used as maintenance after allo-SCT did not improve relapse-free survival in the whole population but only in those patients who were MRD-positive before allo-SCT. In this trial, approximately 60% of patients received an FLT3 inhibitor during induction/consolidation, and gilteritinib seemed to be more effective in terms of relapse-free survival and OS when FLT3 inhibition was used previously (11).

5 Conclusions

This study had several limitations, such as its retrospective nature, small number of patients, time to start sorafenib being longer than that in randomized studies, and patient selection bias. The majority of our patients were in the CR1- and MRD-negative before allo-SCT. Nevertheless, the clinical results seem to be similar to those of other studies (4, 5).

In conclusion, prior exposure to TKIs does not reduce the protective activity of sorafenib administered after allo-SCT in patients with FLT3m AML.

Therefore, our results encourage the potential use of sorafenib as maintenance therapy in the post-transplant setting, offering a promising approach to improve survival and reduce relapse in this patient population.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comitato Etico Territoriale della Regione Siciliana. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

GS: Writing – original draft, Writing – review & editing. MC: Data curation, Writing – review & editing. ST: Writing – review & editing. RB: Writing – review & editing. CR: Writing – review &

editing. AM: Writing – review & editing. VC: Writing – review & editing. CP: Writing – review & editing. CA: Data curation, Writing – review & editing. VR: Data curation, Writing – review & editing. AS: Data curation, Writing – review & editing. DM: Data curation, Formal analysis, Writing – original draft. LC: Conceptualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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