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Effectiveness of biosimilar pegfilgrastim in patients with lymphoma after high-dose chemotherapy and autologous stem cell transplantation: a real-life study

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Objectives: To evaluate the efficacy of biosimilar (BIO) pegfilgrastim (PEG) in lymphoma patients after autologous stem cell transplantation (ASCT).

Methods: 86 consecutive lymphoma patients who received BIO/PEG after ASCT were assessed. The primary endpoints of this study were the incidence of febrile neutropenia (FN) and time to neutrophil engraftment.

Results: Most patients were males (67.4%) with a median age of 48 years. FN occurred in 66 patients (76.7%), and most of the fever was grade 1-2. The median time to neutrophil engraftment was 9 days. The incidence of FN differs based on lymphoma type (p-value <0.01) and was higher in non-Hodgkin lymphoma (NHL) than in Hodgkin Lymphoma (HL). No statistical difference was found between NHL and HL regarding the time to reach the neutrophil engraftment. Hospitalization lasted from a minimum of 9 to a maximum of 34 days. The restricted mean time to discharge was 15.9 days (95%CI 14-16), without differences based on lymphoma type.

Conclusion: Although the study has the significant limitation of not being randomized and not having a control arm, it highlights the efficacy and safety of a BIO-PEG formulation in patients with Lymphoma and undergoing ASCT.

KEYWORDS

lymphoma, biosimilar pegfilgrastim, autologous stem cell transplantation, chemotherapy, BIO-PEG

1 Introduction

High-dose chemotherapy (HDC) and autologous stem cell transplantation (ASTC) remains a therapeutic option in patients with Hodgkin Lymphoma (HL) and Non-Hodgkin Lymphoma (NHL) who are refractory (R) or relapsed (R) after first-line therapy and who are responsive to salvage therapy (1–5). The BEAM (carmustine -BCNU-, etoposide, aracytin, and melphalan) has been widely used since 1990 as a standard conditioning regimen before ASCT in this setting (4).

Although advances in supportive care have dramatically improved the safety of ASCT, with expected rates of treatment-related mortality below 2%–3% (6), febrile neutropenia (FN) is a potentially fatal toxicity of many HDC regimens (7). The development of FN affects the cost and length of hospitalization (8), resulting in worse outcomes and high mortality (9, 10). Several studies show that the incidence of FN correlates with post-chemotherapy white blood cell recovery (11–13), so, early neutrophil engraftment post-transplantation is a goal to be pursued.

A strategy to reduce the risk of FN is the prophylactic use of granulocyte colony-stimulating factor (G-CSF) (14–17). The use of G-CSF has been associated with faster neutrophil engraftment, lower incidences of mortality rate due to infection, lower use of broad-spectrum antibiotics, a reduction of days of hospitalization, and a lower treatment cost (18, 19), and, in general, with an improvement in clinical outcomes (9, 20). Two types of G-CSF are available for reducing the duration of neutropenia: short-acting (SA) (e.g., lenograstim and filgrastim) (21–24) and long-acting (LA) (e.g., pegfilgrastim and lipegfilgrastim) (25–27). SA G-CSFs are administered as a daily subcutaneous injection (for a recommended ≥10 days per cycle), while LA G-CSFs are given as one shoot subcutaneous injection.

Biosimilars (BIO) are biological products that are highly like approved originator products with only minor differences in clinically inactive components and no clinically meaningful differences in efficacy and safety (28). BIO-PEG has been approved for prophylaxis of severe neutropenia duration and febrile neutropenia in cancer patients, including those affected by hematologic malignancies. However, poor data have been so far published among patients with Lymphoma undergoing ASCT.

This real-life study aimed to evaluate the efficacy and the safety of BIO-PEG when used in patients with Lymphoma undergoing ASCT.

2 Methods

2.1 Patients

This is a single-arm, longitudinal, real-life study investigating BIO-PEG's effectiveness in a cohort of patients who received this drug.

The study included autologous transplantation-eligible lymphoma patients who were aged 18–65 years. The clinical criteria for ASCT eligibility were: 1) HL; 2) diffuse large B-cell Lymphoma (DLBCL) in first chemo-sensitive relapse or refractory to first-line therapy but sensitive to salvage therapy; 3) follicular lymphoma (FL) in first or subsequent relapse; 4) mantle-cell lymphoma (MCL) in first or second-line treatment; 5) peripheral T-cell lymphomas in first response and the relapse setting. Patients were excluded if they met any of the following criteria: a World Health Organization performance status >2; New York Heart Association class II–IV heart failure; abnormal pulmonary function findings; history of active malignancy during the past 5 years (excluding basal cell carcinoma or stage 0 cervical cancer); absolute neutrophil count (ANC) of ≤ 1.0 × 109/L; platelet count of ≤ 75 × 109/L; a creatinine clearance of ≤ 60 mL/min.

2.2 Treatment

Patients received a conditioning BEAM regimen consisting of BCNU (300 mg/m2 i.e., day − 7), etoposide (200 mg/m2 days − 6 to − 3), cytarabine (400 mg/m2 days − 6 to − 3), and melphalan (140 mg/m2 day −2). The minimum target dose of CD34+ cells required to support HDC safely was 2×10^6/kg. Twenty-four hours after stem cell infusion, patients received a single subcutaneous BIO/PEG (PEG-bmez) injection (6 mg). Antibiotic prophylaxis was not used. All patients received oral acyclovir 800 mg twice daily from day 3 until approximately day 90 post-ASCT. Pneumocystis jirovecii pneumonia prophylaxis was administered with trimethoprim/sulfamethoxazole (1 double-strength tablet; 2–3 times weekly) and initiated post-hematologic recovery for 3 months. Red blood cell (RBC) and platelet transfusions (PT) were administered to maintain hemoglobin levels of ≥ 8 mg/dL and platelet counts of ≥ 10×10^9/L or in patients with symptomatic anemia/minimal mucocutaneous hemorrhagic syndrome. Intravenous hydration and electrolyte support were also provided. Where FN occurred following a long period of neutropenia

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(ANC < 0.5×10^9/L or ANC of 1×10^9/L with a predicted decline to < 0.5×10^9/L over the subsequent 48 h) blood and catheter-drawn cultures were ordered, and intravenous Piperacillin/tazobactam was promptly started.

2.3 Endpoints

The primary endpoints of this study were the incidence of FN and time to neutrophil engraftment. FN was defined as a temperature of ≥ 38.2°C on at least two consecutive occasions or a persistent temperature of ≥ 38.0°C for at least 1 h, accompanied by an ANC of < 0.5×10^9/L in the absence of any documented infectious cause (e.g., transfusion reaction or administration of cytotoxic drugs). Time to neutrophil engraftment was defined as three consecutive days where the patient had an ANC of ≥ 0.5×10^9/L.

Secondary endpoints included platelet engraftment (platelet count ≥ 20×10^9/L, not requiring a platelets transfusion in the preceding 7 days), the incidence of diarrhea, and mucositis. An additional analysis evaluated the difference between HL and NLH subtypes. The safety endpoint of the study was the incidence of study drug-related adverse events.

Complete blood counts were collected using samples before chemotherapy and daily during the aplastic phase until hospital discharge.

2.4 Statistical analysis

Descriptive statistics presented data, including median, interquartile range (IQR), and percentage values. Univariate Kaplan-Meier analyses assessed the relationship between time to neutrophil engraftment and other patient variables. As the proportional hazard assumption was violated, the restricted mean survival time (RMST) was adopted to estimate the treatment effect. RMST, defined as the area under the survival function curve up to a specific time (t*), shows the mean survival time or, in our case, the mean time in which there was no neutrophil engraftment. Univariate logistic regression analysis evaluated the relationship between FN and other patient variables; identified covariates were used for multiple logistic regression analysis. For the logistic models, data were expressed as odds ratio (OR), 95% confidence intervals (CI), and p-values. All analyses were adjusted by patient sex and age, irrespective of the association with the outcome (significant/not significant).

3 Results

From January 2021 to June 2022, 86 consecutive lymphoma patients underwent ASCT and administration of PEG-bmez. Table 1 summarizes patient characteristics at the time of ASCT. The majority were males (n 44, 67.4%) with a median age of 48. Most patients (94.2%) had a complete response. The median basal CD34+ infusion was $6.2x10^6$/kg (IQ 5.2-7.1), and for only five patients, the basal infusion was $<4\times10^6$/kg. Mild bone pain was observed in approximately 20% of PEG patients (n = 24/86). Bone pain occurred primarily on days of neutrophil engraftment. In most patients, pain symptoms were controlled by the administration of paracetamol. No cardiac, neurological, renal, or pulmonary complications were reported, and no patients died in the first 100 days post-transplantation. Twenty-nine patients were affected by HL (33.7%) and 57 by NHL (66.3% - 32 DLBCL (56.1%), 16 MCL (28.1%), one FL (1.8%) and 8 PTCL-NOS). HL and NHL patients differed for gender, age at transplant.

TABLE 1 Patient characteristics at the time of ASCT.

	Overall population (n 86)	HL (n 29)	NHL (n 57)	p value
Demographic characteristics				
Males (%)	58 (67.4)	12 (41.4)	46 (80.7)	<0.001
Median age (IQR)	47.5 (33-61)	32 (24-40)	55 (44-65)	<0.001
Disease status at transplant				
CR n (%)	81 (94.2)	26 (89.7)	55 (96.5)	0.20
PR n (%)	5 (5.8)	3 (10.3)	2 (3.5)	
CD34+ infused				
Median (IQR)	6.2 (5.2-7.1)	6.7 (5.5-7.6)	6 (5-6.8)	0.08
CD34<4 n (%)	5 (5.8)	1 (3.4)	4 (7.0)	0.50
CD34>=4 n (%)	81 (94.2)	28 (96.6)	53 (93.0)	
Number previous lines of therapies				
1 n (%)	16 (18.6)	0 (0%)	16 (28.1%)	<0.001
2 n (%)	63 (73.3)	23 (79.3%)	40 (70.2%)	
3 n (%)	7 (8.1)	6 (20.7%)	1 (1.8%)	

ASCT, autologous stem cell transplantation; HL, Hodgkin Lymphoma; NHL, Non-Hodgkin Lymphoma; CR, complete remission; PR, partial remission; N, number.

Outcome measurements are summarized in Table 2. FN occurred in 66 patients (76.7%). Grade 2-3 mucositis occurred in about 20% of patients, and grade 2-3 diarrhea in 19 cases. The median time to neutrophil and platelet engraftment was 9 days (range, 9-10) and 13 days (range, 11-15), respectively. The time to reach neutrophil engraftment was further investigated using a Kaplan–Meier analysis (Figure 1). Cumulative median and mean survival-free time of neutrophil engraftment was 9 days (95% CI 8.7-9.3) and 9.8 days (95% CI 9.4-10.1), respectively. HL and NHL patients differed for the incidence of febrile neutropenia, request for platelet support and number of platelet bags infused.

Univariate logistic analyses show a significant association between FN and NHL in univariable and multivariable logistic analyses, although with large confidence intervals due to a relatively low sample size (Table 3).

No statistical difference was found between HL and NHL regarding the time to reach the neutrophil engraftment. Figure 2 shows the same pattern of time to engraftment in HL and NHL patients. The restricted

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TABLE 2 Outcome measurements for overall population and by lymphoma type.

	Overall population (n 86)	HD (n 29)	NHL (n 57)	p value
Patients who required RBC transfusions (%)	42 (48.8)	16 (55.2)	26 (45.6)	0.400
No. of RBC transfusions, median (IQR)	2 (1-3)	1.5 (1-2.5)	2 (2-3)	0.140
Patients who required PLT transfusions (%)	62 (72.1)	25 (86.2)	37 (64.9)	0.040
No. of PLT transfusions, median (IQR)*	2 (2-3)	2 (1-2)	3 (2-4)	0.001
Median (IQR) days to reach platelet count ≥20 x 109/L*	13 (11-15)	12 (11-14)	13 (11-15)	0.240
Median (IQR) days to neutrophil engraftment (ANC ≥0.5 x 109/L)	9 (9-10)	9 (9-10)	9 (9-10)	
Febrile neutropenia, no. patients (%)	66 (76.7)	17 (58.6)	49 (86)	0.005
Fever grade**				
WHO grade 1, n (%)	38 (44.2)	11 (37.9)	27 (47.4)	0.380
WHO grade 2, n (%)	23 (26.7)	6 (20.7)	17 (29.8)	
WHO grade 3, n (%)	5 (5.8)	0 (0)	5 (8.8)	
Fever origin**				
FUO, n (%)	56 (65.1)	17 (58.6)	39 (68.4)	0.053
Microbiologically documented, n (%)	10 (11.6)	0 (0)	10 (17.5)	
Mucositis				
WHO grade 0, n (%)	6 (7)	2 (6.9)	4 (7)	0.522
WHO grade 1, n (%)	63 (73.3)	19 (65.5)	44 (77.2)	
WHO grade 2, n (%)	10 (11.6)	4 (13.8)	6 (10.5)	
WHO grade 3, n (%)	7 (8.1)	4 (13.8)	3 (5.3)	
Diarrhea				
WHO grade 0, n (%)	4 (4.7)	2 (6.9)	2 (3.5)	0.195
WHO grade 1, n (%)	66 (76.7)	20 (69)	46 (80.7)	
WHO grade 2, n (%)	13 (15.1)	7 (24.1)	6 (10.5)	
WHO grade 3, n (%)	3 (3.5)	0 (0)	3 (5.3)	

*among transfused; **among patients with fever. RBC, red blood cells; PLT, platelets; No, Number; IQR, interquartile range.

mean survival time analysis (RMST) confirms that over 17 days of follow-up, neutrophil engraftment occurred, on average, 9.9 days after the transplant (95% CI 9.2-10.5) in HL and 9.7 days (95% CI 9.3-10.1) in NHL (ΔRMST HD-NHL, -0.16 days; 95% CI -0.91–0.59, p 0.67) without any significant difference. Age and sex-adjusted analyses also confirmed these results.

Hospitalization lasted from a minimum of 9 to a maximum of 34 days (Figure 3). The restricted mean time to discharge was 15.9 days (95%CI 14-16), without differences by lymphoma type (HL 16.2, 95% CI 14.4-18.0; NHL 15.8, 95%CI 14.6-17.0).

4 Discussion

BEAM regimen followed by ASCT causes myelosuppression, which can result in FN and potentially lead to severe infections. The risk of neutropenia and its complications can be reduced with ST G-CSF administration. ST G-CSF is safe and effective, cleared rapidly from the body, with a half-life of approximately 3.5 hours, and requires daily administration for up to 14 days. The alternative to ST G-CSF is an LT G-CSF, such as PEG. PEG is a pegylated form of G-CSF with similar indications and adverse events, although because of its longer half-life, it requires a one-shoot of 6 mg for a single HDC (29, 30). This dosage is sufficient in adult patients, regardless of body weight, making PEG a simple, effective, and well-tolerated option for managing HDC-induced neutropenia.

Although few studies compare the two drugs after HDC and ASCT, clinical trials have shown that a single, subcutaneous dose of PEG is as safe and effective as daily ST G-CSF.

Wannesson et al. (31) showed that neutrophil engraftment was reduced with PEG in multiple myeloma (MM) and lymphoma

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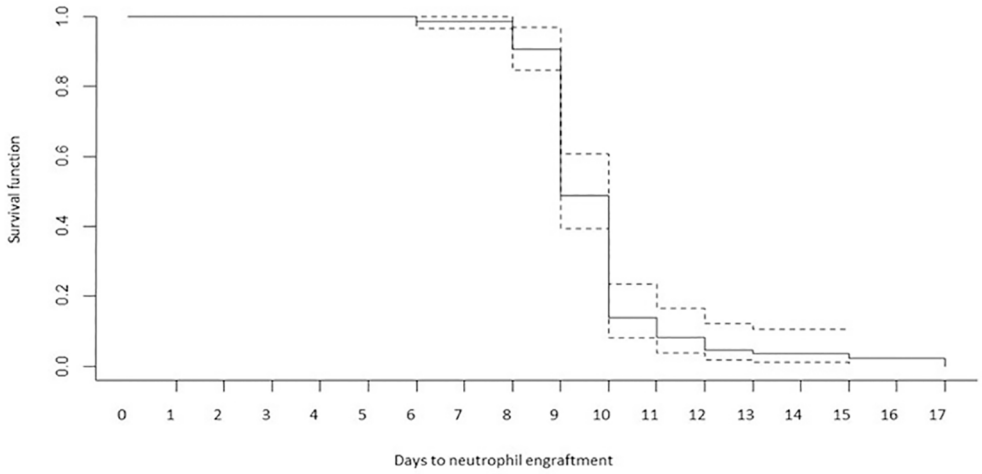

FIGURE 1
Time to reach neutrophil engraftment (Kaplan–Meier analysis). Cumulative median and mean survival-free time of neutrophil engraftment was 9 days (95% CI 8.7-9.3) and 9.8 days (95% CI 9.4-10.1).

patients. Some authors reported that PEG had similar efficacy and safety profiles compared with SA G-CSF after ASCT (32), with a lower incidence of FN in the PEG group (33). Wang et al. showed in a retrospective analysis that PEG prophylaxis was more effective than SA G-CSF for FN prophylaxis in patients post-ASCT, especially for MM patients (34). Other studies characterized by heterogeneity in trial design, conditioning regimen and initiation of post-transplant drug administration, compared PEG versus G-CSF, demonstrated substantial equivalence in terms of days to engraftment, incidence of febrile neutropenia, antibiotic use and length of hospitalization (35–37). However, the efficacy of neutropenia prophylaxis may differ for G-CSF derivatives and different diseases (38, 39).

The FDA has approved 6 biosimilars to PEG: PEG-apgf, PEG-bmez, PEG-cbqv, PEG-fpgk, PEG-jmdb, and PEG-pbbk (40–43). There were no significant differences between the BIO-PEGs and reference PEG in the rate of FN (44). To date, there are no studies on the use of BIO-PEG in patients with Lymphoma and undergoing ASCT. We conducted the first single-center real-life analysis of lymphoma patients undergoing PEG-bmez post-ASCT. Our study demonstrated that PEG-bez prophylaxis was safe and effective for neutrophil engraftment and FN prophylaxis. Single-arm, real-life studies complement traditional randomized controlled trials (RCTs) by providing valuable insights into how treatments work in real-world settings (45). While RCTs are considered the reference standard for evaluating interventions, they often have strict inclusion criteria and controlled environments that may not fully reflect the complexities of everyday clinical practice. Single-arm studies allow clinicians to assess interventions' effectiveness, safety, and tolerability in diverse patient populations under real-world conditions. They provide valuable data on how treatments work outside controlled clinical trials, capturing nuances such as comorbidities, concomitant medications, and patient adherence that can influence outcomes. These studies are particularly important for evaluating interventions in rare diseases, where recruiting sufficient participants for traditional RCTs may be challenging. Additionally, they offer insights into the long-term effects of treatments as they follow patients over extended periods, providing valuable information on real-world outcomes and helping clinicians make informed decisions about treatment strategies. Overall, single-arm, real-life studies complement RCTs by providing essential data on the effectiveness and safety of interventions in diverse patient populations, ultimately contributing to improved patient care and clinical decision-making. This type of study is of relevance when the evolution of the disease is well known and when there is no evidence of the placebo effect.

Our real-life study was not aimed at a cost analysis. It is crucial, however, to emphasize that the recent licensing of BIO-PEG-containing products offers the opportunity to deliver the additional advantages of long-term SA G-CSF at a reduced cost. For countries using reference PEG, evident cost savings are reported by switching to BIO-PEG (46–48). Recently, the introduction of SA G-CSF biosimilars favored their

TABLE 3 Univariate and multiple logistic regression on FN.

	Univariate				Multiple			
	OR	Inferiore	Superiore	p value	OR	Inferiore	Superiore	p value
F *vs* M	1.167	0.394	3.452	0.781	2.783	0.740	10.464	0.130
>47 *vs* <= 47yrs	1.694	0.613	4.682	0.310	0.822	0.222	3.038	0.768
NHL *vs* HL	4.324	1.511	12.368	0.006	7.645	1.764	31.582	0.006

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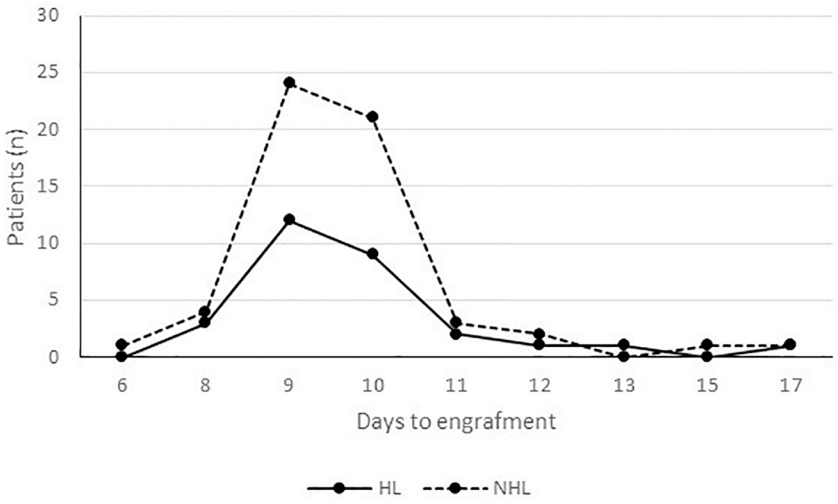

FIGURE 2
Time to engraftment by lymphoma type. Neutrophil engraftment occurred, on average, 9.9 days after the transplant (95% CI 9.2-10.5) in HL and 9.7 days (95% CI 9.3-10.1) in NHL (ΔRMST HD-NHL, -0.16 days; 95% CI -0.91–0.59, p 0.67).

adoption due to their cost-efficiency in reducing the incidence of FN in chemotherapy-treated patients than SA G-CSF originator and LA G-CSFs (48); hence, a similar pattern is expected for the LA GCSFs category. These results are consistent with a study's findings, which showed that the introduction of BIO-PEGs in place of SA G-CSF treatments has a substantial cost-saving potential for the Italian National Healthcare Service (49). The analysis highlighted the economic advantage of using BIO-PEGs in place of SA G-CSF treatments in the FN treatment setting, providing a substantial cumulative cost saving of € 59,650 and € 41,539, respectively, for a 1000 patients population with solid tumors and lymphomas over a 3-years' timeframe.

In conclusion, our study highlights the efficacy and safety of a BIO-PEG formulation in patients with Lymphoma and undergoing ASCT. Even though the study has the significant limitation of not being randomized and not having a control arm, it can be considered a preliminary assessment of effectiveness. Thus, these results can be helpful for the design of randomized Phase III studies. Compared with SA G-CSF, the development of randomized trials that can confirm the advantage of BIO-PEGs is desirable. Advantages may be related to overall cost (drug, reduced complications, and hospitalization), single and not daily administration, standardized dosing, and not related to patient weight.

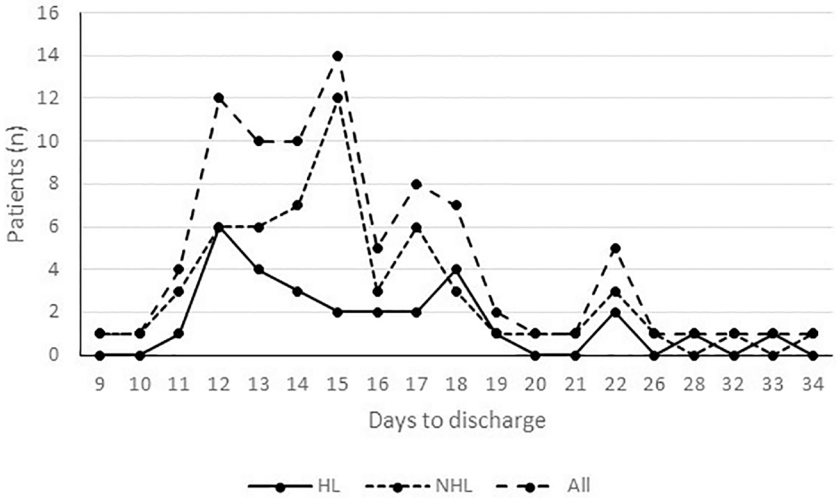

FIGURE 3
Time to discharge by lymphoma type. Hospitalization lasted from a minimum of 9 to a maximum of 34 days. The restricted mean time to discharge was 15.9 days (95%CI 14-16), without differences by lymphoma type (HL 16.2, 95%CI 14.4-18.0; NHL 15.8, 95%CI 14.6-17.0).

Data availability statement

Raw data were generated at the Institute of Clinical Physiology (IFC-CNR), Reggio Calabria, Italy. Derived data supporting the findings of this study are available from the corresponding author upon request.

Ethics statement

The studies involving humans were approved by Calabria region ethics committee. 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. All procedures performed in this study were in accordance with the ethical standards of the International Conference on Harmonization Guidelines for Good Clinical Practice and with the 1964 Helsinki Declaration and its later amendments.

Author contributions

BL: Conceptualization, Investigation, Writing – original draft. AP: Data curation, Formal Analysis, Writing – original draft. MP: Project administration, Writing – original draft, Writing – review & editing. CA: Investigation, Resources, Writing – original draft. GT: Data curation, Writing – original draft. MMi: Formal Analysis, Investigation, Writing – original draft. MP: Formal Analysis, Methodology, Writing – original draft. FC: Supervision, Writing – original draft. GaP: Formal Analysis, Methodology, Writing – original draft. GiP: Data curation, Writing – original draft. GU: Data curation, Writing – original draft. ID: Data curation, Writing – original draft. ASg: Data curation, Formal Analysis, Writing – original draft. ASc: Data curation, Writing – original draft. AI: Data curation, Writing – original draft. GL: Data curation, Writing – original draft. MA: Supervision, Writing – original draft. GD: Supervision, Validation, Writing – review & editing. MG: Resources, Supervision, Validation, Writing – original draft. MMa: 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.

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