



Long Term Outcome and Immune Function After Hematopoietic Stem Cell Transplantation for Primary Immunodeficiency

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Transplantation techniques for patients with primary immunodeficiencies have improved so that survival from the procedure in many cases is >80%. However, long term complications may arise due to the use or not of conditioning agents. This may result in variable immune reconstitution, the long term effects of chemotherapy, particularly on fertility, and complications relating to the genetic disorder, unresolved by transplantation. For patients with severe combined immunodeficiency (SCID), long term T- and B-lymphocyte immune reconstitution is best achieved after pre-transplant chemotherapy. For patients who receive an unconditioned infusion of donor stem cells, the quality of immune reconstitution depends on the SCID genotype. Long term effects include chemotherapy-induced impaired fertility, and sequelae specific to the genotype. For patients with other primary immunodeficiencies, conditioning is required—sequelae related to direct effects of chemotherapy may be observed. Additional long term effects may be observed due to partial donor chimerism resulting in incomplete eradication of disease, and other geno-specific effects.

Keywords: SCID, thymopoiesis, Artemis, antibody-based conditioning, papillomavirus-associated warts, WAS, CGD

INTRODUCTION

Incremental improvements in the approach to transplantation have ensured that survival following allogeneic hematopoietic stem cell transplantation (HSCT) for primary immunodeficiency (PID) is now generally >80% (1–4). More accurate matching at HLA loci using molecular DNA techniques, pre-emptive treatment of viremia, adoption of less toxic condition regimens and pharmacokinetic monitoring (5–8), development of more effective T-lymphocyte depletion methods (9, 10), and more effective treatment of transplant-related complications (11–13) now mean that the majority of patients undergoing HSCT for PID can expect to survive the procedure. As a consequence of this increase survival rate, more emphasis is being put on the quality of long term outcome. An overview on both specific immuno-hematological as well as overall quality of health perspectives is discussed below.

SEVERE COMBINED IMMUNODEFICIENCY

Long Term Immune Function

The issue regarding long-term outcome is probably most complex but also best studied in patients with severe combined immunodeficiency (SCID). Severe combined immunodeficiencies are a heterogeneous group of inherited primary immunodeficiencies characterized by absent thymopoiesis due to lack of T-lymphocyte progenitors available to enter or to develop within the thymus, failure of T-lymphocyte maturation and function, and thus severally impaired cellular and humoral acquired immunity. Depending on the genetic defect, recipient B-lymphocytes, and/or Natural Killer cells may be present. The lack of T-lymphocytes, often accompanied by significant infection, and end-organ damage resulted in many patients receiving a stem cell infusion without preparative chemotherapy to empty osteo-medullary and thymic niches. Immune-reconstitution was reported to be variable, and it is now clear that the outcome depends on the specific SCID genotype and thereby the stage in which thymopoiesis is arrested. Mature donor stem cell-derived T-lymphocytes, transferred in the inoculum, populate the periphery, and expand to confer medium-term but finite immune protection, with a restricted T-lymphocyte receptor repertoire. Effective long-term thymopoiesis with T-lymphocyte immune reconstitution requires donor stem cell-derived T-lymphocyte progenitors to enter the thymus and undergo proliferation during the thymocyte double negative (DN) 1 and 2 stages, before DN3, when thymocytes undergo rearrangement of the T-lymphocyte receptor. The lack of recipient T-lymphocytes to facilitate rejection and the concept of host osteo-medullary and thymic environments which are either permissive or non-permissive to engraftment following infusion (14, 15) long provoked debate over approach to treatment. The debate centers around whether infusion of donor stem cells, without administering immunosuppressive and myeloablative pre-transplant chemotherapy conditioning, is equally effective and less toxic/more safe in realizing a long-term cure than transplantation of donor stem cells following administration of myeloablative chemotherapy conditioning. With careful analysis of immune reconstitution in single (16–21), and multi-center cohorts (1, 22, 23), there is emerging clarification about which molecular diagnoses permit adequate long-term thymopoiesis after graft infusion without conditioning, and which genotypes of SCID likely require conditioning for best long-term results.

Infusion without chemo-conditioning of replete marrow from HLA-matched sibling or matched unrelated donors or T-lymphocyte-depleted haplo-identical stem cells from parental donors facilitates thymopoiesis and T-lymphocyte immune reconstitution. This is particularly the case in patients with IL-2 receptor gamma chain (IL-2R γ -), janus-associated kinase 3 (JAK3)-, or adenosine deaminase-(ADA) deficient SCID, and leads to good survival (1, 15, 20, 21, 24, 25). Pre-thymic and early intrathymic stromal niches are vacant with no competition between donor progenitors and endogenous, immature, DN thymocytes, which are absent in these SCID conditions. Thymic

niches are thus available for donor T-lymphocyte precursor engraftment, leading to sustained donor-derived thymopoiesis in the absence of myelopoiesis (26), which nevertheless may be of finite durability (21). Donor B-lymphocyte engraftment usually fails to occur because the osteo-medullary niche is occupied by recipient B lineage pre-cursors and mature cells. In IL-2R γ - and JAK3-deficient SCID, recipient B-lymphocytes are functionally impaired (27), and infused patients usually require long-term immunoglobulin replacement. IL-7R α -deficient patients usually develop B-lymphocyte function, as recipient B-lymphocytes have intact intrinsic function, and produce immunoglobulin in the presence of functioning donor T-lymphocytes. Patients with ADA-deficient SCID often develop cellular and humoral immune reconstitution in the absence of conditioning, possibly because the local toxic effects of ADA deficiency on the marrow act as “auto-conditioning” combined with a selective growth advantage and permit donor stem cell engraftment in the absence of chemotherapy. Rare patients with a CID-phenotype due to ADA deficiency require chemo-conditioning to achieve engraftment.

Thymopoiesis and humoral immunity is infrequently observed in unconditioned patients with NK+ SCID due to defects in recombination activating genes 1 and 2- (*RAG1/2*) and *DCLRE1C* (Artemis). In these patients, early T-lymphocyte development is arrested at later stages of committed T-lymphocyte differentiation creating a non-permissive thymic environment occupied with high numbers of DN2/DN3 cells competing with donor T-lymphocyte progenitors for thymic niches. As a consequence SCID patients with these genetic defects are refractory to thymic and B lineage reconstitution following transplantation without conditioning because of competition for thymic and osteo-medullary niches. Following infusion of donor cells without conditioning, immune reconstitution is poor; T-lymphocyte engraftment relies on post-thymic peripheral T-lymphocyte expansion, with a failure of thymopoiesis, and a restricted T-lymphocyte receptor repertoire (17, 18, 28).

Together, in the long-term, in unconditioned transplants, superior thymopoiesis is observed in IL-2R γ -, JAK3-, IL-7 receptor alpha- (IL-7R α), or ADA- deficient SCID compared with recombination activating genes 1 and 2- (*RAG1/2*) and *DCLRE1C* (Artemis) -deficient SCID. However, in the absence of pre-conditioning chemotherapy, donor B-lymphocyte, and myeloid chimerism is generally absent in either group (14), with the exception of ADA- deficient SCID (24).

As there is no survival difference between those patients receiving chemotherapy conditioning and those receiving either immunosuppression only, or no preparative regimen (1, 23), at present, a chemotherapy conditioning preparation is preferred to achieve donor stem cell engraftment and thus durable immune reconstitution if the physical condition of the patient will allow this. Durable T-lymphocyte reconstitution is associated with better survival (29), good T-lymphocyte reconstitution at 1 to 2 years post-HSCT is associated with better T-lymphocyte long-term immune reconstitution (18), and high T-lymphocyte receptor excision (TREC) circle counts, markers of thymopoiesis, at 6 months associate with robust long-term T-lymphocyte reconstitution (1, 16, 17, 20, 21).

The advantageous effect of conditioning on long term graft and immune function also raises new challenges in the context of the observation that infants treated in the 1st months of life, before the onset of infection, have the most favorable outcome, with a survival of >90%, and fewer long-term infectious, and immune-related complications (22, 30). This is particularly relevant given the ongoing implementation of SCID newborn screening (NBS) programs in many countries worldwide (*refer to chapters on SCID/NBS*). Whilst there is unease in the transplant community about administering chemotherapy to young infants to optimize engraftment and reconstitution, it is not clear what the long term effects of such administration are, or at what age these effects are likely to be less significant. One study using treosulfan and fludarabine in infants <5 months of age showed good survival and no significant early toxicity, although long term effects will need to be evaluated (6). The routine adoption of pharmacokinetic studies during chemotherapy delivery may help answer some of the questions.

Although we may now have a better understanding of how to avoid poor graft function, there are many surviving patients living with the effects of poor immunity or sequelae of post-transplant complications, such as graft-vs. -host disease. There are few published data on this—one single center cohort study of 90 patients describes chronic graft-vs. -host disease in 10% of patients (31). Additionally, patients were described with autoimmune and inflammatory conditions, and significant infections. Within this cohort, about one third of patients did require any form of long-term treatment (31). In another large cohort study of 124 patients, over half of whom had IL-2R γ - and JAK3-deficient SCID, 86% of 111 survivors with follow up were considered healthy by the physicians, although 53% required long-term immunoglobulin replacement indicative for incomplete immune correction. Other long-term complications reported included autoimmunity, hypothyroidism, malignancy, and developmental delay (30).

Long Term Sequelae in SCID Patients

In transplanted SCID patients several long-term sequelae are directly related to the underlying genetic defect as part of their syndromal disease, and occur independent of the immune-hematological defect, and reconstitution characteristics after stem cell therapy. Patients with radiosensitive SCID due to mutations in *DCLRE1C* experience significant long-term sequelae including growth, endocrine and dental abnormalities, pancreatic insufficiency, pulmonary fibrosis, as well as increased mortality, if conditioning regimens contain alkylating agents (1, 32). On the other hand, unconditioned transplants result in poor immune reconstitution (*vide supra*), and the best approach to treating these patients has yet to be determined. For Artemis deficient SCID, but also similar vulnerable patients, innovative targeted therapy directed toward the stem cell niches on marrow, and thymus using antibody-based conditioning (33–35) may achieve some myeloid engraftment without the chemo-conditioning associated toxicities.

Patients with ADA-deficiency, a systemic metabolic disease in which HSCT only corrects the immune defect, cognitive, behavioral, or other neurological outcomes appear not to be

affected by transplantation, although it is not possible to know if there is some amelioration (36–38). Similarly, SCID variants caused by DNA ligase IV and Cernunnos are associated with an intrinsic defect associated with long term neurological impairment which will not be corrected by HSCT. Many patients with reticular dysgenesis have an associated sensorineural deafness, related to the defect in adenylate kinase 2, which is not corrected by HSCT but may be ameliorated by cochlear implants (39, 40).

Patients with IL-2R γ - and JAK3-deficient SCID are at risk of developing extensive cutaneous human papillomavirus-associated warts which are recalcitrant to treatment, and not clearly associated with degree of donor chimerism and the level of T-lymphocyte reconstitution (41, 42) but also seen with low numbers of NK cells. Although the pathophysiologic mechanism is not completely understood, evidence has been provided that lack of the common γ chain function in non-hematologic cells, i.e., keratinocytes may impair the secretion of chemokines that may guide the influx of protective immune cells. A canine model of IL-2R γ -deficient SCID demonstrates a similar problem, in which malignant transformation has been demonstrated (43)—patients will require careful long-term follow up.

Non-SCID Immunodeficiencies

Data on long-term follow up and immune function in non-SCID primary immunodeficiencies are more scarce than for SCID. Non-SCID patients usually require full or reduced intensity chemotherapy conditioning to achieve donor stem cell engraftment and myeloid chimerism for cure of their immune disorder. In contrast to SCID where mixed or split chimerism as a result of the selective growth advantage of donor T- and B lymphocytes may already be curative this does not necessarily apply for non-SCID immunodeficiencies. In a number of these disease categories described hereafter, mixed donor/recipient stem cell chimerism may result in only partial correction of the immune disorder and thus occurrence or persistence of concomitant long term complications.

The possibly unfavorable impact of mixed chimerism on correction of the immune disorder has been reported in Wiskott Aldrich syndrome, a syndromal combined immune deficiency due to defects in the *WASP* gene which plays a pivotal role in actin cytoskeleton. There is no selective advantage to cells harboring the wild type gene, and so partial donor stem cell chimerism results in a mixed recipient/donor population of antigen presenting cells, and lymphocytes. The presence of mixed donor and recipient chimerism has been reported to be associated with late onset autoimmunity in these patients (44, 45). Although the exact pathophysiologic mechanism for this autoimmunity remains to be defined it seems best to aim to achieve high-level or complete donor chimerism.

In the X-linked form of chronic granulomatous disease recent data suggest that, because of random lyonisation, female carriers of X-linked chronic granulomatous disease are at significant risk of experiencing autoimmunity, fatigue, anxiety and depression, likely because of inflammation caused by the genetically faulty phagocytes (46–48). Neutrophil function of <10% was highly associated with an increased risk of infection

(47). Although to date, there are no reported similar symptoms in transplanted patients with mixed donor chimerism, nevertheless, these findings suggest that high or complete donor chimerism is desirable, and ideally X-linked disease carriers are not used as donors if other suitable donors are available.

A growing group of primary immune disorders that may benefit from allogeneic stem cell therapy and may be even gene therapy is represented by patients with monogenic diseases associated with autoimmunity and inflammatory symptoms. Whilst the numbers of patients reported are few, data are emerging to suggest that residual dysfunctional host immunity in these immune dysregulation diseases may cause persistent autoimmunity and inflammation and therefore high or complete donor chimerism may be required to abolish disease symptoms, especially in those diseases where the genetic defect results on an activated (gain-of-function) instead of a non-functional gene product. Diseases thus described include Activated PI3K Delta Syndrome (49), CTLA4 deficiency (50), LRBA deficiency (51), and STAT1 gain-of-function disease (52). The degree of donor chimerism required to cure these different disease entities is yet to be determined. However, based on the pathophysiologic mechanism of some of these diseases, full donor chimerism may be required to avoid disease manifestations due to residual recipient immunity.

Complications in SCID and Non-SCID Infertility and Other Endocrine Complications

Similar as for many other HSCT indications requiring chemotherapy-based conditioning, a significant concern is that of fertility. There are few data regarding this issue specifically in patients transplanted for PID, partly because a long follow up is required before the reproductive capability of patients transplanted as young children is known, should the patient even wish to have children. Furthermore, conditioning regimens evolve over time, and the fertility of patients now under investigation often reflects historic conditioning regimens. Finally, there may be differences in fertility outcomes depending on whether chemotherapy was given to a young infant or an adolescent. In one study of patients, including 68 patients transplanted for non-malignant disease, spontaneous puberty was achieved in all males, and 90% of females who received a reduced intensity conditioning regimen containing fludarabine and melphalan, compared with 56% of females, and 89% of males who received a myeloablative regimen containing busulfan, and cyclophosphamide (53). In a recent study documenting transplant outcomes of 55 children and adolescents undergoing stem cell transplantation for chronic granulomatous disease from a single center, 6 of 11 survivors older than 21 years at the time of the study had experienced successful unassisted pregnancy themselves or with their partner, of whom 4 had received busulfan and cyclophosphamide, 1 received busulfan and fludarabine, and 1 received fludarabine and melphalan (54). Two adults transplanted for chronic granulomatous disease were reported as fathering children after receiving a targeted dose regimen of busulfan with fludarabine (5). A recent study of the European Society for Blood and Marrow Transplantation

suggests that gonadal damage may be less following treosulfan-based conditioning compared to busulfan-based conditioning, although the number of patients receiving treosulfan was much smaller (55). Although these data are few, they suggest that infertility is not inevitable following conditioned HSCT for PID, and that the outlook may be considerably better than previously feared. There may be differences between conditioning regimens, and careful long term follow up should be continued.

Thyroid dysfunction may occur as an immune-mediated manifestation of residual primary disease or due to chemotherapy related toxicity after HSCT and not related to the underlying immune disorder (56).

Secondary Malignancies

A survey by the European Society for Blood and Marrow Transplantation has estimated the incidence of myelodysplastic syndrome or acute myeloid leukemia to be 1.2:1,000 in transplants for malignancy, mostly occurring within 4 years of HSCT (57). However, these patients present with malignancy, usually receive more intense chemotherapy than that administered as preparative pre-conditioning, and often have irradiation as part of their treatment. The risk of a non-post-transplant lymphoproliferative malignancy post-transplantation in patients who were transplanted for PID is less well-understood. The presence of a PID is associated with an increased risk of malignancy, around 4–5 times greater than in age-matched controls (58). Risks of developing a malignancy post-transplantation may be related to the underlying genetic disease, the tissue distribution of genetic defect (confined to the hematopoietic compartment or more wide-spread), previous graft vs. host disease, viral infections, and the extent of donor chimerism, and quality of restored immune function. Three studies together found 21 of 3,340 (0.6%) patients developed a malignancy (59–61). Interestingly, in a large series of patients transplanted for systemic DNA double strand-breakage repair disorders, which predispose to malignancy, there were no reported cases of secondary tumors, although median follow up was only 35 months (62). Collectively, these data demonstrate that there is a small but real risk of malignancy developing in this post-transplant cohort and re-enforce the need for careful long term surveillance. This will be particularly important for patients in whom malignancy risk is a significant part of the immunodeficiency, such as those patients with systemic DNA double strand-breakage repair disorders, or cartilage hair hypoplasia.

Quality of Life

For many years, studies of patients receiving hematopoietic stem cell transplantation for PID have concentrated on survival, and more recently on the quality of immune reconstitution. Long-term quality of life is an important consideration for patients transplanted for SCID. There are few studies examining this, and whilst one found a diminished quality of life compared to normal controls (38), two others found that quality of life was related to requirement of on-going treatment, particularly

immunoglobulin replacement, with those patients who were on no medication reporting a normal life quality (20, 21). Both in SCID and non-SCID patients, patient reported outcome on quality of life is an important measure of treatment outcome, largely ignored in this field. There are no studies comparing quality of life before and after transplantation, and only one that compares transplanted, and non-transplanted age-matched pediatric cohorts in chronic granulomatous disease (63). This study showed a normal quality of life in patients who had been transplanted, compared with those receiving conventional therapy. In the last decade HSCT has become an increasingly safe therapeutic modality. In addition to the traditional severe immune deficiency syndromes in which survival is the primary goal, HSCT is more often considered in the broadening spectrum of patients with severe/profound but not-acute life threatening primary immune disorders. In these chronic disabling diseases HSCT primarily aims to improve quality of life and add value both from the patient and physician perspective. More studies performed in close collaboration between physicians and patients are required in the growing field of these rare primary immune disorders to measure the impact of stem cell transplantation and

alternative (e.g., biologicals/GT) on long term disease control as well as quality of life.

CONCLUSION

There is no doubt that hematopoietic stem cell transplantation has saved and transformed the lives of many patients with PID. However, although many patients are able to subsequently live normal lives, significant post-transplant sequelae reduce life expectancy, or impair the quality of life in a subgroup of patients. Given that many patients have extremely rare immunodeficiencies, the number of patients in follow up is small, with a short time period of post-transplant follow up. Continued careful observation and enhanced surveillance is required to learn more about the effects of our transplant techniques on these patients, and to improve long term outcomes.

AUTHOR CONTRIBUTIONS

AG and AL contributed to the inception and design of the review and wrote and edited it.

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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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