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ISCT Committee Paper

Transplant for non-malignant disorders: an International Society for Cell & Gene Therapy Stem Cell Engineering Committee report on the role of alternative donors, stem cell sources and graft engineering

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ABSTRACT

Hematopoietic stem cell transplantation (HSCT) is curative for many non-malignant disorders. As HSCT and supportive care technologies improve, this life-saving treatment may be offered to more and more patients. With the development of new preparative regimens, expanded alternative donor availability, and graft manipulation techniques, there are many options when choosing the best regimen for patients. Herein the authors review transplant considerations, transplant goals, conditioning regimens, donor choice, and graft manipulation strategies for patients with non-malignant disorders undergoing HSCT.

Introduction

Hematopoietic stem cell transplantation (HSCT) is curative for many non-malignant disorders, including primary immunodeficiency disorders (PIDDs), primary immune regulatory disorders (PIRDs), hemoglobinopathies, acquired and inherited bone marrow failure syndromes (BMFSs), and metabolic disorders, with overall survival reports of 90–100% after HSCT in most non-malignant diseases in the contemporary era [1–5]. Many non-malignant disorders are not imminently life-threatening, and the risk–benefit analysis of whether to transplant a patient is different than when considering transplant for an aggressive malignancy. At the same time, different non-malignant disorders present unique challenges to successful HSCT. There is a need to ensure adequate engraftment to achieve long-term disease control while minimizing infectious complications and exacerbation of organ dysfunction related to the underlying disease. Unlike the malignant setting, where there is a benefit to graft-versus-tumor—which has been nearly impossible to separate from graft-versus-host disease (GVHD)—there is no potential advantage of GVHD for patients with non-malignant disorders. Thus, minimizing the risk of acute and chronic GVHD remains essential in optimizing transplant for these patients. Although HSCT from a matched related donor has generally been considered the best choice in transplant for malignancies, a matched related donor may not always be the first choice for inherited genetic diseases, as family members who could be potential donors may themselves be affected or be carriers of the

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genetic mutation, thereby limiting their use as donors in certain disease settings. Additionally, only 25–30% of children in need of a transplant have a matched sibling donor [6]. Historically, the use of alternative donors, including mismatched family members, matched unrelated donors (MUDs), mismatched unrelated donors (MMUDs), and unrelated umbilical cord blood (UCB), has led to unacceptable rates of morbidity and mortality, with mortality of up to 10%, particularly when using full-intensity myeloablation in certain non-malignant disease settings [7–11]. Many patients have pre-existing comorbidities and poor organ function due to organ involvement related to the underlying disease, chronic inflammation, chronic infection, and associated treatment and/or iron overload, further increasing the morbidity of stem cell transplant. Furthermore, in heavily transfused patients, such as those with hemoglobinopathies or BMFSs, donor-specific antibodies frequently develop, leading to an additional barrier to engraftment. Better understanding and selection of elements of the conditioning regimen as well as graft characteristics and manipulation have the potential to improve outcomes for patients with non-malignant disorders undergoing HSCT across different platforms and donor options. As the morbidity and mortality of transplant are lessened with improved supportive care, transplant has become safer and better tolerated. Therefore, there is a vital need to expand the donor pool while preserving high rates of engraftment to offer this lifesaving therapy to more patients with non-malignant disorders. This goal has been accomplished by several different approaches, which the authors will review herein.

Pre-Transplant Considerations

Newborn screening has been critical in identifying patients with sickle cell disease (SCD), the most severe forms of PIDDs, and a growing number of metabolic disorders before they develop disease manifestations. Infants identified in this way can benefit from anticipatory guidance as well as disease-specific prophylaxis and/or treatment. For example, infants identified as having adrenoleukodystrophy undergo routine screening by magnetic resonance imaging, and those identified as having severe combined immunodeficiency (SCID) are typically placed in protective isolation and started on antimicrobial prophylaxis. Although this approach has improved outcomes of HSCT for SCID, it has not uniformly eradicated the risk of pre-HSCT infections, and management is variable at different centers [12].

For some non-malignant diseases potentially cured by HSCT, good control of the underlying disease and disease-related comorbidities prior to transplant is associated with better outcomes after allogeneic HSCT. In patients who are chronically transfused, such as those with hemoglobinopathies or BMFSs, the pre-HSCT iron status is critical, and consideration should be given to iron chelation prior to HSCT in patients with evidence of iron overload [13]. In hemophagocytic lymphohistiocytosis and other PIRDs, patients with normalized laboratory markers of inflammation and clinical symptoms have better engraftment and lower rates of complications [14]. A thorough pre-HSCT infectious evaluation should be undertaken, especially in patients with PIDDs, and infections should be well treated and under control at the time of transplant. In some children with metabolic disorders, enzyme replacement therapy with normal measured enzyme levels can avoid organ dysfunction prior to and during the HSCT period [15].

Although pre-transplant infectious screening is universal, the need for more thorough screening is essential in PIDD/PIRD patients. If available, patients with chronic granulomatous disease should be routinely screened with positron emission tomography/computed tomography scan or magnetic resonance imaging prior to transplant and any identified active lesions biopsied to detect any active infection at the time of transplant in order to provide pre-HSCT treatment and to inform peri- and post-HSCT antimicrobial regimens [16]. Additional imaging should be considered in other patients with PIDDs/PIRDs depending on their prior infectious history. The development of cytomegalovirus organ disease prior to HSCT leads to high rates of morbidity and mortality during transplant [17]. Consideration can be given to using virus-specific cytotoxic T lymphocytes—which are available as off-the-shelf multivalent cytotoxic T lymphocytes both commercially and in phase 1/2 clinical trials—prior to HSCT to provide control of viral infections [18]. In developing countries, the use of bacillus Calmette–Guérin is the most significant contributor to the infectious morbidity and mortality of HSCT [19].

Statement

Early identification of diseases curable by HSCT can improve outcomes by optimizing pre-HSCT management and the timing of HSCT.

Transplant Goals

For non-malignant diseases, the goal of HSCT is to establish robust engraftment of healthy donor hematopoietic stem cells (HSCs). The level of donor engraftment needed to achieve this goal varies based on the underlying condition. In many autosomal recessive disorders, carrier status does not cause any disease manifestations. Therefore, in these conditions, 50% donor chimerism in the affected lineage may be adequate to cure the underlying disease—or even as low as 20–25% in certain disease settings, such as SCD [20,21]—and patients can remain mixed chimeras with disease cured for life as long as the level of donor chimerism remains stable. There are a few caveats to this statement: (i) there is a growing understanding that some carriers may actually be symptomatic; (ii) the long-term stability of incomplete donor chimerism can be difficult to predict, leading to late graft failure; and (iii) residual hematopoiesis from the host stem cells may lead to clonal proliferation, as was elegantly demonstrated in two patients with SCD who had graft rejection and then developed myelodysplastic syndrome/acute myeloid leukemia (the myeloid clone was host-derived from a *TP53* mutation existing pre-SCT) [22]. Conversely, in many immune regulatory and metabolic disorders, mixed chimerism is not adequate to cure the underlying disease. Overall, conditioning intensity can be decreased in many but not all of these diseases (see later discussion) in order to reduce treatment related mortality (TRM) and decrease the risk of GVHD while providing adequate donor chimerism for disease cure.

Statement

The goal of HSCT in the non-malignant setting is to cure the underlying disorder by providing adequate and durable donor chimerism while limiting short- and long-term toxicity.

Conditioning Regimen

The earliest successes in the field of HSCT for non-malignant disorders depended on myeloablative regimens with either total body irradiation [23] or busulfan [24]. Since that time, busulfan has been the conditioning agent of choice for patients with non-malignant disorders. However, like any chemotherapy agent, it has significant short- and long-term toxicities, and can be associated with a high burden of TRM. More recently, targeting busulfan exposure based on pharmacokinetic monitoring to achieve targeted myeloablation or non-myeloablation dosing has demonstrated that optimal exposure is associated with predictability of engraftment and minimization of toxicity in HSCT for non-malignant disorders [25,26]. Similarly, for HSCT recipients receiving anti-thymocyte globulin (ATG) as part of the conditioning regimen, recent dosing algorithms have been associated with improved outcomes and predictable immune reconstitution [27,28]. Many additional non-busulfan-based conditioning regimens have been developed [29], but further pharmacokinetics

and pharmacodynamics are needed for these regimens. Supportive care for transplant-related toxicities has improved over the past four decades, including the development of new anti-infectious agents, new prophylaxis and monitoring strategies, the development of defibrotide to treat sinusoidal obstruction syndrome [30,31] and etanercept to treat idiopathic pneumonia syndrome [32], such that myeloablation has become a safer procedure. However, even in the contemporary era, there is still about a 10% risk of TRM associated with myeloablation [33–36]. Cytoreduction prior to HSCT for non-malignant disorders must balance the higher risk of graft failure in chemotherapy-naive patients with the risk of TRM due to pre-transplant organ dysfunction and chronic or latent infections. The late effects of the conditioning regimen also need to be considered—particularly with regard to full-dose total body irradiation and alkylating agents—including effects on fertility and cognition and the risk of secondary malignancy. In certain non-malignant disorders with cancer predispositions, consideration should be given to a non-busulfan-based conditioning regimen.

In some PIDDs, conventional or T-cell-depleted HSCT from matched or mismatched related donors is associated with adequate engraftment, such that truly non-myeloablative conditioning can be considered [37]. For other conditions, including hemoglobinopathies and PIRDs, the risk of graft failure is high, and conditioning regimens to reduce toxicity/intensity have been associated with varying degrees of success [3,38,39]. In a large Center for International Blood and Marrow Transplant Research analysis comparing myeloablative (busulfan/cyclophosphamide) and reduced toxicity (busulfan/fludarabine) regimens in patients transplanted from matched related donors or 7/8 or 8/8 HLA-MUDs/MMUDs for a variety of non-malignant disorders, transplant related toxicities (including GVHD, sinusoidal obstruction syndrome, and hemorrhagic cystitis) were decreased in the reduced toxicity group, but overall survival was the same in both groups [40]. Similarly, in alternative donor transplantation, reduced intensity and non-myeloablative preparatory regimens are associated with decreased TRM but increased primary and secondary graft failure [38]. One approach for preventing rejection is to prolong administration of post-HSCT immunosuppression [41–43], though this increases the risk of infection and immunosuppression-associated toxicity. Alternatively, pre-conditioning with pre-transplant immunosuppressive therapy, such as azathioprine and hydroxyurea or low-dose fludarabine and dexamethasone, in HSCT recipients with hemoglobinopathies has contributed to successful engraftment [44,45], including in haploidentical T-cell-depleted grafts [46]. Overall, there is a need to develop reduced toxicity regimens with adequate immune ablation to prevent rejection by a sensitized recipient immune system and to quiesce underlying inflammation to promote robust engraftment of donor HSCs without high rates of GVHD.

Treosulfan-based conditioning regimens have been successfully used for many non-malignant disorders as a result of the lower toxicity profile and adequate myeloablation in comparison with busulfan. A European Society for Blood and Marrow Transplantation (EBMT) retrospective analysis of 316 children with non-malignant disorders transplanted using treosulfan showed high rates of engraftment and low rates of toxicity independent of age, dose of treosulfan, other agents used in combination with treosulfan, donor type, stem cell source, or second or subsequent transplant [47]. Treosulfan is widely used in Europe for non-malignant disorders [48,49] but has not yet been approved by the US Food and Drug Administration and therefore has limited availability except in the setting of an emergency investigational new drug. However, with targeted busulfan dosing, the two chemotherapy backbones have been shown to be equally efficacious in some non-malignant disease settings, albeit with small numbers [50,51]. In a larger EBMT study in Wiskott–Aldrich syndrome, patients who underwent treosulfan-based conditioning had higher rates of graft failure and mixed chimerism compared with busulfan-based conditioning regimens [2]. Larger prospective randomized studies are necessary to compare toxicities and immune reconstitution between the two regimens. Prospective studies on treosulfan may be needed to determine optimal exposure for adequate myeloablation in patients with non-malignant disease [52].

A novel approach for conditioning prior to transplant is to use antibodies or antibody–drug conjugates targeting HSCs specifically or hematopoietic elements more broadly. Two classes of antibodies have been evaluated in clinical trials: JSP191, a targeted monoclonal antibody against CD117 (c-Kit), has been evaluated in patients with SCID [53]; and YTH 24 and YTH 54, CD45-targeting antibodies, have been evaluated in Fanconi anemia, metabolic disorders, and PIDDs [54]. This promising therapy has the potential to revolutionize the field by providing adequate myeloablation without the genotoxicity of chemotherapy and could be broadened to other disease types soon.

Statement

The conditioning regimen should be designed to minimize graft failure while avoiding organ toxicity. A targeted busulfan-based conditioning regimen could be considered equivalent to a treosulfan-based regimen. Monoclonal antibody-based conditioning regimens may lead to future successes, abrogating genotoxicity.

Donor Choice

Transplantation from an unaffected matched sibling remains the standard of care in HSCT for non-malignant disorders. However, donor availability for patients with non-malignant diseases is limited because family members may also be affected or may be carriers of the same mutation. This situation has led to broadened use of unrelated donors in these disease settings.

One advantage of HSCT in the treatment of non-malignant disorders is that, with some exceptions, there is not the same urgency as in the setting of high-risk malignancy. Therefore, there is usually time to perform an unrelated donor search and plan for unrelated donor HSCT. However, there are select patients in whom the 2–3 months it takes to find an unrelated donor may lead to additional disease or infectious complications and/or further organ damage, potentially making them ineligible for transplant or putting them at higher risk of transplant-related complications. Therefore, even a MUD who is well matched may not always be optimal.

Currently, several groups have reported the same rate of engraftment and TRM using either a 10/10 HLA-MUD or a matched sibling donor [17,55,56]. However, based on their ethnicity, only 20–50% of children in need of HSCT have a MUD [6,57]. Among patients of white European descent, 75% will have an 8/8 HLA-MUD, but this number is as low as 18–19% in patients with an African or African American background, and 16% in patients with a black South or Central American background [6]. A 9/10 HLA-MMUD can also be used in this setting, with similarly reported rates of engraftment and mortality [58].

For unrelated donors, both bone marrow and peripheral blood stem cells (PBSCs) have been successfully used as a stem cell source. Bone marrow is traditionally the preferred source because of associated lower rates of GVHD [59] compared with PBSCs, though this has not been clearly borne out in the pediatric setting [60]. Occasionally, unrelated donors are unwilling to donate the stem cell source requested, so it is useful that the other stem cell source can be utilized as a backup, particularly in patients who do not have other donor options. The use of MUDs and MMUDs has been further expanded with the recent Food and Drug Administration approval of abatacept for GVHD prophylaxis. In the hematologic malignancy setting, abatacept showed decreased rates of GVHD in 7/8 and 8/8 HLA-MUDs when added to the standard GVHD backbone, with a more enhanced benefit in the mismatched setting [61,62]. It has also

demonstrated benefit in some non-malignant settings, including SCD [63] and severe aplastic anemia [64], albeit with smaller patient numbers.

There are several limitations to the use of unrelated donors, most importantly the inability to control the cell dose. In the setting of non-malignant disorders, an adequate cell dose is crucial for promoting durable engraftment [65]. Because the graft is coming from an outside center, the stem cell dose can be unpredictable and may sometimes be inadequate for patients with higher body weight. Additionally, timing may be urgent in some settings, which could limit the use of unrelated donors. Finally, there is a significant cost to using an unrelated donor, particularly if transporting cells internationally, which may be prohibitive in many parts of the world.

Umbilical Cords

UCB transplantation has been used as an alternative donor source for many decades, including for patients with metabolic disorders (Hurler syndrome and other leukodystrophies) [66–69]. Although the chance of finding a 6/6 HLA-matched cord for patients of underrepresented minorities is still quite low, at 2% in African American patients and 5% in Hispanic patients, when expanding to 5/6 or 4/6 HLA-matched cords, the likelihood increases to a respective 24% and 81% for African American recipients and 43% and 90% for Hispanic recipients [6].

Historically, a major limitation of UCB transplantation has been delayed immune reconstitution compared with other stem cell sources [70], particularly with the inclusion of ATG in the preparative regimen [71]. Delayed hematopoietic and immunological recovery leads to a higher incidence of infections, and delayed neutrophil engraftment may also lead to prolonged hospitalization and increased TRM [72]. In many patients with non-malignant disorders, there is a clinical history of chronic infection, placing them at higher risk of infectious complications, and therefore rapid and robust immune reconstitution is of paramount importance. More recent data on UCB transplantation without the use of ATG or with low ATG exposure [73] show improved engraftment kinetics that are comparable to other stem cell sources [74,75]. The Parachute-Study demonstrated excellent immune reconstitution using individualized ATG dosing [76], and these advances have led to significant improvements in the infectious complications associated with UCB transplantation. Additionally, recent developments with regard to new preparative regimens in the field have shown promising results, with improved engraftment compared with older regimens in single-center experiences with novel preparative regimens [77].

A typical limitation of using UCB is the stem cell dose, which is often inadequate to support HSCT in adolescents and young adults. The low stem cell dose may contribute to the higher rates of graft failure seen when using UCB as the donor source in patients with non-malignant disorders [78,79]. Approaches for overcoming this limitation include *ex vivo* stem cell expansion and the use of two UCB units concurrently, though the latter approach has led to higher GVHD rates [80,81]. The two units can be infused without manipulation, or one unit can be selected for expansion of hematopoietic stem and progenitor cells. Newer innovations in cord blood expansion further broaden the use of this as a stem cell source option for patients, particularly larger adolescents and young adult patients. Several techniques, which will be reviewed later, have been developed to expand the umbilical cord unit *ex vivo* prior to infusion, increasing the infused CD34 and total cell dose and leading to more rapid engraftment. Additionally, there has been some success reported co-infusing haploidentical related bone marrow and unrelated cord blood (haploidentical cord transplantation) to speed neutrophil engraftment, which may enhance the kinetics of immune reconstitution [82]. Finally, an important consideration is cost, which—with a cost per unit ranging between $25,000 and $50,000—may make the use of cord blood units prohibitive in resource-poor settings [83,84].

Haploidentical Related Donors

Historically, HSCT from haploidentical related donors was associated with higher rates of graft failure and increased transplant-related complications in patients with non-malignant disorders [7,85–87]. This led to many centers preferentially using MMUDs or UCB donors over haploidentical related donors. However, more recent studies have demonstrated low rates of rejection and TRM with HSCT from haploidentical related donors compared with HSCT from other donor types [88–90], such that the use of haploidentical related donors as a stem cell source has become more common. Like cord blood, haploidentical related donors are readily available and usually can be flexible with timing. Over 95% of patients in need of HSCT have a haploidentical donor, and the average patient in the US has three potential haploidentical donors [91]. Furthermore, using a related haploidentical donor is significantly less expensive than using a cryopreserved cord blood unit. Another advantage of a related donor is that if an additional infusion of cells is needed because of graft failure or dwindling donor chimerism, haploidentical donors are almost always readily available and eager to donate. Haploidentical transplantation requires depletion of alloreactive T cells, and this can be accomplished by one of two extensively studied methods: *in vivo* post-transplant cyclophosphamide (PTCy) or *ex vivo* graft manipulation. See later discussion of graft manipulation strategies for further details and Table 1 for considerations specific to different diseases.

Statement

For patients without an unaffected matched sibling donor, the use of alternative donors (haploidentical, unrelated cord blood, or matched or mismatched unrelated) is safe and effective, and virtually all patients in need of a transplant now have an available donor.

Graft Engineering/Manipulation Approaches

Post-transplant cyclophosphamide

When administered at day +3 and day +4 after infusion of non-manipulated haploidentical HSCs, PTCy selectively depletes alloreactive T cells while preserving the stem cells necessary for engraftment and memory cells responsible for protection from infectious organisms. PTCy has been successfully used to treat patients with a variety of non-malignant disorders, with high rates of engraftment and overall survival, and low rates of GVHD and transplant-related toxicities [4,45,88,92–97]. Moreover, PTCy has been successfully used in coordination with other donor sources, including MUDs and MMUDs, with improved outcomes, especially in the setting of HLA-mismatched donors [98–100]. PTCy is associated with low rates of acute and chronic GVHD along with low rates of severe opportunistic infections, including Epstein–Barr virus lymphoproliferative disease [101]. The use of PTCy is associated with rapid immune reconstitution, which is comparable to the immune reconstitution observed with other GVHD prophylaxis regimens [102,103].

There are several benefits to using PTCy with haploidentical related donors. Cyclophosphamide is a commonly used chemotherapy agent and therefore readily available all over the world, including in resource-poor areas. No additional training is necessary. PTCy is the GVHD prophylaxis regimen of choice in most adult centers in the US performing haploidentical transplant, with over 90% of centers using PTCy [104]. The ability to use a haploidentical family member donor ensures that nearly all patients in need of a transplant will have a potential donor. PTCy has also been safely used with non-

Table 1
Special considerations by disease type.

Disease	Consideration	Gene therapy
Bone marrow failure syndromes	T-cell depletion to reduce risk of GVHD	NA
Fanconi anemia	Alkylator sensitivity	
Dyskeratosis congenita	Alkylator sensitivity	
Diamond–Blackfan anemia	High rates of antibody formation causing engraftment barrier in RIC setting	
Severe aplastic anemia	MSD is gold standard; if no MSD, haplo or MUD/MMUD versus immunosuppression	NA
PIDDs	History of infection; need increased peri- and post-transplant surveillance and more aggressive prophylaxis strategies	
ADA, X-linked, RAG deficiency, Artemis SCID	Radiation sensitivity[a]	x
Wiskott–Aldrich syndrome		x
X-linked CGD		x
CD40L/hyper-IgM		x
PIRDs		
With auto-inflammation	Increased risk of graft rejection; consider intensity of regimen	
With autoimmunity	May be engraftment barrier; consider plasmapheresis and/or rituximab	
IPEX syndrome		x
Hemoglobinopathies	Iron overload leading to increased VOD risk; consider pre-HSCT iron chelation	
SCD	ABO mismatch increases risk of erythrocyte lineage engraftment failure	x
Beta thalassemia	High rates of allosensitization causing engraftment barrier in RIC setting; consider desensitization protocols before HSCT	x
Metabolic disorders	Improved outcomes using cord blood; size/cell dose may be an issue	
Metachromatic leukodystrophy	HSCT before disease is symptomatic	
X-linked adrenoleukodystrophy		x
Krabbe disease		x
Hurler syndrome		

ADA, adenosine deaminase; CGD, chronic granulomatous disease; haplo, haploidentical; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; MSD, matched sibling donor; NA, not applicable; RIC, reduced intensity conditioning; VOD, veno-occlusive disease.
[a] Deficiencies of Artemis, DNA ligase IV, DNA-dependent protein kinase catalytic subunit, Cernunnos/XLF.

first-degree haploidentical relatives [105,106]; therefore, if a patient does not have a suitable first-degree haploidentical donor, the donor search can be broadened to second-degree relatives, further expanding the donor pool. One disadvantage of PTCy is the exposure of a patient with a non-malignant disorder to a toxic alkylating agent. Although many years of long-term follow-up have demonstrated that there is no increased risk of donor-derived malignancy in patients treated with PTCy [107], there are many well-described short- and long-term side effects of high-dose chemotherapy. Additionally, because of the increased toxicity, there are some disorders (Fanconi anemia, telomeropathies such as dyskeratosis congenita, and other DNA repair disorders) in which high-dose cyclophosphamide should be used with caution. Successful transplants have been performed using a reduced dose of PTCy in patients with Fanconi anemia and dyskeratosis congenita [88,108].

Ex vivo *graft manipulation*

The earliest experience with graft manipulation was T-cell depletion with soybean agglutinin and E-rosette depletion using haploidentical related donors in infants with SCID without any preparative regimen or additional GVHD prophylaxis [109,110]. Many patients with SCID were successfully cured using this method [7]. This approach is typically associated with mixed donor chimerism, which is tolerable and durable in the setting of SCID. However, when expanded to other PIDD/PIRD patients and non-malignant disorders, the graft failure rate was unacceptably high [5]. Subsequent CD34+ purification with antibody-coated paramagnetic beads from granulocyte colony-stimulating factor-mobilized PBSCs (so-called megadose CD34+) was also successfully used without additional post-transplant immunosuppression [111–114]. This approach has been used for HSCT in patients with SCID and Omenn syndrome [111] and has been successfully used with a reduced-intensity fludarabine-based regimen to treat Fanconi anemia patients [112,113]. However, this approach is complicated by very slow immune reconstitution [114], and therefore more refined graft manipulation strategies have been developed. In a small study of 10 children with PIDDs transplanted using CD3/CD19 depletion of haploidentical related donors, researchers noted rapid early engraftment and immune reconstitution and 100% overall survival [115]. Further refinement of the graft manipulation strategy led to development of a new method: depletion of alpha/beta T-cell receptors (TCRs) and CD19+ B cells without post-HSCT immunosuppression. This approach enriches for CD34+ cells as well as gamma/delta T cells and natural killer cells, which provides protection from infection and allows for more rapid immune reconstitution [90].

Alpha/beta TCR/CD19 depletion has many benefits specific to non-malignant disorders. The lack of post-transplant immunosuppression is ideal in this patient population—which often comes to transplant with chronic infections or dormant viruses—allowing for rapid immune reconstitution and clearance of infections. This platform has been associated with very low reported rates of acute and chronic GVHD and other transplant-related complications [90,116,117].

One major drawback of alpha/beta TCR/CD19 depletion is cost and availability. Thus far, the necessary equipment and expertise are available at only a handful of major medical centers, and the upfront cost of the cell manipulation is high compared with other GVHD prevention strategies. However, because there is rapid immune reconstitution and no post-transplant immunosuppression, the cost of post-transplant care is greatly reduced compared with other approaches. There have been no direct cost comparisons between transplant regimens, including the peri- and post-transplant periods, so a true understanding of the cost difference is unknown. Overall, alpha/beta TCR/CD19 depletion is a very appealing option and should be offered to patients who can travel to a specialized center for this therapy.

Expanded cord blood

The limitation of low total nucleated and CD34+ cell doses in UCB units has been overcome by the development of several *ex vivo* expansion methods. These methods use a variety of cytokine or small-molecule stimulators to exponentially enhance the stem and progenitor cells in the cord blood product, leading to faster neutrophil engraftment and altering the kinetics of immune reconstitution. The earliest method used was stimulation of one unit with Notch ligand, and co-infusion with another non-manipulated unit, led to

earlier neutrophil recovery supported by the manipulated unit and ultimate long-term engraftment from the non-manipulated cord blood unit [118]. A copper chelation technique using tetraethylenepentamine to expand one portion of the cord blood unit was also developed, and co-infusing the expanded and non-manipulated fractions led to improved overall survival and earlier platelet and neutrophil engraftment in a large multi-center trial in which historical double UCB transplant recipients were used as controls [119]. A more recent manipulated product developed is omidubicel (NiCord; Gamida Cell, Jerusalem, Israel), containing a CD133+ fraction stimulated with cytokines and nicotinamide, a vitamin B derivative that inhibits differentiation and enhances functionality of CD34+ stem and progenitor cells *in vivo*, and a non-manipulated CD133−/CD34− fraction. This product led to sustained myeloid engraftment in the first subset of patients [120], and a phase 1/2 study in patients transplanted for malignant disorders demonstrated earlier neutrophil and platelet engraftment and improved overall survival compared with standard double UCB transplant controls [121]. This treatment was expanded to SCD patients, in whom omidubicel and a myeloablative regimen were used either alone or in combination with a non-manipulated cord [122]. Additionally, stimulation with the pyrimidoindole derivative UM171, an HSC self-renewal agonist, showed success, with rapid early engraftment and low rates of GVHD in adult patients with hematologic malignancies [123].

Statement

The broadened use of both *ex vivo* and *in vivo* graft manipulation techniques has expanded the utilization of alternative donors for HSCT. Although some of these approaches are thus far available at only specialized centers in resource-rich regions, the use of alternative donors is anticipated to improve access to HSCT globally, especially with the broad availability of PTCy.

Unique Considerations for Disease Types

There are a wide range of non-malignant disorders for which HSCT is potentially curative, each with its own set of considerations. Moreover, within each disease category, there are nuances specific to each disease that need to be considered when planning a transplant. These include issues related to disease-specific considerations of ideal donor selection, stem cell dose, pre-transplant conditioning, required degree of immune ablation and myeloablation, post-transplant monitoring, and the consideration of disease manifestations not corrected by HSCT that may lead to increase toxicity. For example, patients with Fanconi anemia and dyskeratosis congenita have increased toxicity with radiation-containing regimens, and therefore radiation-free conditioning is preferred [124]. Patients with PIRDs and severe aplastic anemia have a higher risk of graft rejection (10–15%) [3,38,95]; therefore, T-cell-depleted approaches need to be carefully evaluated. Because of the presence of severe tissue inflammation at the time of HSCT, patients with PIRDs and PIDDs might experience a higher risk of severe GVHD [38,97], and thus ad hoc GVHD prophylaxis regimens should be considered.

Finally, for many monogenic disorders, gene therapy is either available or on the horizon. However, there are limitations related to the cost of and access to this novel therapy, degree of correction required for disease control, and potential clonal evolution of transfected cells. Additionally, most current approaches to *ex vivo* gene therapy still require myeloablation with busulfan, which has its own associated toxicities. See Table 1 for a list of unique considerations for each disease type.

Statement

When planning a transplant, there are many unique considerations that need to be assessed for specific diseases.

Discussion

A number of considerations are critical when planning HSCT for non-malignant disorders. First, the goal of HSCT in the non-malignant setting is to provide adequate donor chimerism that will cure the underlying disorder without excessive short- or long-term toxicity. In addition, specific considerations regarding underlying disease control and reductions in disease-related side effects going into HSCT are critical for transplant outcomes. The conditioning regimen should also be designed to minimize graft failure while avoiding organ toxicity: a pharmacokinetically targeted busulfan-based conditioning regimen could be considered equivalent to a treosulfan-based regimen; monoclonal antibody-based conditioning regimens may lead to future successes without genotoxicity; and individualized ATG dosing can lead to more predictable immune reconstitution, resulting in lower TRM. Moreover, for patients without an unaffected matched sibling donor, the use of alternative donors (haploidentical, unrelated cord blood, or matched or mismatched unrelated) is safe and effective, and virtually all patients in need of a transplant have an available donor. The broadened use of both *ex vivo* and *in vivo* graft manipulation techniques has expanded the utilization of alternative donors and made transplant accessible to patients globally. However, additional large prospective randomized clinical trials are needed to further our understanding of the best transplant design for specific diseases.

Conclusions

The many exciting developments in the field of transplant for non-malignant disorders have greatly broadened the applicability of this therapy. By reducing the toxicity of the preparative regimen, broadening the donor pool, and reducing post-transplant immunosuppression and thereby enhancing immune reconstitution, we can offer this therapy to many more patients with a wide variety of non-malignant disorders in need of transplant. The use of PTCy has revolutionized the field of transplant globally, especially for patients from minority backgrounds with no unrelated donor options, allowing haploidentical transplant to be offered to many more patients with non-malignant disorders. With regard to those regimens that are relatively new to the field, we do not yet know the full spectrum of late effects that might arise, and this will have to be closely monitored. Patients with mixed chimerism require ongoing monitoring for late graft failure, as has been reported by some groups [38,88]. Multi-center clinical trials for these rare disorders are essential and will allow us to refine the preparative regimens, graft manipulation techniques, and GVHD prophylaxis regimens, with the ultimate goal of improving stem cell transplant outcomes for patients with non-malignant disorders.

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Declaration of Competing Interest

AA served on the safety monitoring committee for Sangamo Therapeutics and has no financial interest in the development of gene therapies. AB serves as a consultant for Neovii, Sobi, Adicet Bio, and Cellevolve Bio. JJB serves as a consultant for AVROBIO, BlueRock Therapeutics, Race Oncology, Advanced Clinical, Omeros, Sanofi, Medexus Pharmaceuticals, Equillium, and Sobi. CB serves as a consultant for Zodiac Produtos Farmacêuticos, Amgen, and Novartis. SC serves as a consultant for, owns shares in, and receives royalties from ExCellThera. ORK serves as a consultant for Sobi. SP receives support for the conduct of clinical trials through Memorial Sloan Kettering Cancer Center from AlloVir, Atara Biotherapeutics, and Jasper Therapeutics,

and is an inventor of intellectual property related to the development of a third-party virus-specific T-cell program, with all rights assigned to Memorial Sloan Kettering Cancer Center. DP's institution (Fiona Stanley Hospital) has received honoraria from Novartis, Gilead Sciences, Bristol Myers Squibb/Celgene, and Jazz Pharmaceuticals. AS has served as a consultant for Spotlight Therapeutics (2020), Medexus Pharmaceuticals (2021), and Vertex Pharmaceuticals (2021), and received research funding from CRISPR Therapeutics (2021–2022) and honoraria from Vindico Medical Education (2020). AS has also collaborated on research with Magenta Therapeutics (2021–Present) and served as clinical trial principal investigator for CRISPR Therapeutics (2018–Present), Vertex Pharmaceuticals (2018–Present), Novartis (2019–Present), and Magenta Therapeutics (2021–Present).

Author Contributions

Conception and design of the study: All co-authors. Drafting or revising the manuscript: All co-authors. All authors have approved the final article.

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