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Advances in unrelated and alternative donor hematopoietic cell transplantation for non-malignant disorders

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Abstract

Purpose of review—The role of hematopoietic stem cell transplantation (HCT) in non-malignant disorders (NMD) has increased exponentially with the recognition that multiple diseases can be controlled or cured of engrafted donor derived cells. This review provides an overview of advances made in alternative donor transplants for NMD.

Recent findings—Stem cell sources, novel transplant methods, and sophisticated supportive care have simultaneously made giant strides toward improving safety and efficacy of HCT. This has led to the utilization of marrow, cord, peripheral blood stem cell and haploidentical stem cells sources, and novel reduced toxicity or reduced intensity conditioning regimens to transplant NMD groups such as immune disorders, marrow failure syndromes, metabolic disorders and hemoglobinopathies. HCT complications such as graft rejection, infections, and graft versus host disease are better combated in this modern era of transplant, with decreased late effects and better survival. These aspects of HCT for NMD are discussed.

Summary—This review presents progress made in the realm of HCT for NMD. It advocates for consideration of alternative donor transplants in the absence of HLA matched siblings when indicated by disease severity. The ultimate goal is to provide curative transplant options for more patients with NMD that can benefit from this intervention, prior to detrimental outcomes.

Keywords

Nonmalignant disorders; hematopoietic stem cell transplant; alternative donors

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Conflicts of interest

Both authors have no conflicts of interest.

Introduction

Allogeneic hematopoietic cell transplantation (HCT) has become the “standard-of-care” treatment for a variety of non-malignant disorders (NMD) disorders such as immunodeficiencies, bone-marrow failure syndromes, inborn errors of metabolism (IEM) and hemoglobinopathies (1-4). The majority of hereditary disorders need HCT intervention in the pediatric age group prior to the development of complications. Over the last decades HCT has become safer and better tolerated, resulting in higher disease free survival. In addition, unrelated and alternative donor sources have made HCT more available to patients in the absence of suitable HLA matched siblings. In this mini-review we provide an overview on the advances made in the use of unrelated and alternative donors for HCT and its implications and future perspectives for the treatment of NMD.

Primary Immune-deficiencies (PID)

PID diseases arise from genetic defects that lead to abnormalities in immune cell development or functions. Replacement of the defective lineage by HCT from healthy allogeneic donors remains the curative approach for most patients. Other management options including enzyme replacement therapy and gene transfer into autologous hematopoietic stem cells may provide an alternative approach to HSCT in specific immune deficiencies.

PID may be broadly divided into severe combined immunodeficiencies (SCID) and non-SCID, including hemophagocytic syndromes and autoimmune and immunoregulatory disorders (Table 1). Guidelines for HCT for (non-)SCID including detailed protocols have been produced by the European Society for Blood and Marrow Transplantation (EBMT) Inborn Errors Working Party (5).

Currently, the outcomes after matched sibling donor (MSD)-HCT exceeds 90% (1, 6). Sibling donor bone marrow (BM) may be infused into SCID recipients without the requirement for conditioning or graft versus host disease (GVHD) prophylaxis. This leads to the rapid development of T- and B-cell function post-HCT, although usually only T-cells of donor origin develop, and myeloid and erythroid cells remain of recipient origin. The majority of patients achieve humoral reconstitution despite lack of donor B-cells, although this is dependent on the type of SCID (1, 6). In non-SCID diseases conditioning is always required for all donor sources. In addition to MSDs, mismatched related (e.g. haploidentical) as well as unrelated donors can be used as alternative donors. In comparison to MSD, these donors have a trend to reduced overall survival (1, 6, 7). As the risk of rejection/GVHD is too high for a simple infusion, conditioning and GVHD prophylaxis is recommended. A variety of conditioning regimens have been used and current recommendations include the use of intravenous busulfan/fludarabine or treosulfan/fludarabine based protocols (5). A special consideration needs to be made for radio-sensitive SCID. Although this does not impact donor choice it has an impact on the choice of conditioning regimen.

The advantage of haploidentical donors is that virtually all children have a haploidentical parental donor that is readily available. However, HLA-disparity necessitates deep T-cell

depletion in order to avoid GVHD. With the introduction of peripheral blood stem cells (PBSCs), centers that prefer haploidentical donors over an unrelated cord blood (CB) donor employ CD34⁺ cell selection or large scale CD3/CD19 negative depletion. More recently, α/β -TCR-depletion methods have been employed to a threshold of $1-5 \times 10^4/\text{kg}$ CD3⁺-cells, below which GVHD prophylaxis is not required (8). Some centers perform such haploidentical HCT without any conditioning. The best results are seen in those transplanted at <3.5 months of age and in those with a T⁺B⁺ phenotype SCID. A major drawback is that B-cell function is only restored in ~20%; others require life-long immunoglobulin supplementation (1). With conditioning, immune-reconstitution is generally better; the clinical condition (including co-morbidities) is of importance to take into consideration when deciding.

Unrelated CB is regarded as another readily available alternative donor source. Over 600,000 cord blood units are stored worldwide. Theoretical advantages using CB as donor source in SCID patients are rapid availability, no requirement for T-cell depletion (resulting in faster immune-reconstitution), lower risk of GVHD compared to adult unrelated donors, and a greater proliferative life span which might be particularly important in such young recipients. Disadvantages are: (historically) slower engraftment (depending on cell dose infused) and lack of availability of the donor for a boost HCT. In cell source comparison studies CB showed similar outcomes compared to other alternative donors (1, 9). In a recent Eurocord/EBMT haploidentical vs. CB HCT comparison, survival was similar, but the probability of getting off immunoglobulin supplementation was higher in CB recipients (9). In this comparison study the haploidentical transplants were performed at 4 specialized haplo-centers in contrast to over 30 transplant centers proficient in CBT, suggesting that CBT may be more generally applicable.

Over the last decade alternative cell therapies have been developed for PIDs, gene-therapy being the greatest advancement. The first human condition for which gene-therapy has shown unequivocal benefit is X-linked severe combined immunodeficiency (SCID-X1) using retroviral mediated transfer of the IL-2RG gene into autologous CD34⁺ cells (10). Nowadays a variety of PID gene-therapy protocols are open; e.g. WAS, X-CGD, ADA and a few more which are in the pipeline will follow soon (11). Successful reconstitution of cellular and humoral immunity has been demonstrated in the majority of patients treated. So far over 60 PID patients have been treated within gene-therapy trials. In the early days serious side-effects were reported related to insertion of the retroviral vector into a proto-oncogene (LMO2) resulting in the development of T-cell leukemia in 5 of 20 patients treated in the two SCID-X1 gene therapy studies (12). Modifications to vector design, used in current trials, may overcome the problems associated with these initial trials. The role of gene therapy alongside conventional HCT (or enzyme replacement therapy for ADA-SCID) is shown in the figures designed by the EBMT-IEWP (5).

Inborn errors of metabolism (IEM)

IEM comprise an assorted group of inherited diseases, some of which are due to disorders of lysosomal or peroxisomal function which may be benefitted by HCT. In these disorders, onset in infancy or early childhood is typically accompanied by rapid deterioration, resulting

in early death in the more severe phenotypes. Timely diagnosis and immediate referral to an IEM specialist are essential steps in optimal management. Treatment recommendations are based on the diagnosis, phenotype, rate of progression, prior extent of disease, family values and expectations and the risks and benefits associated with available therapies, including HCT. International collaborative efforts are of utmost importance in determining modalities of therapy and HCT for these rare diseases, and have improved outcomes significantly over the last decades. Clear guidelines on whom and how to transplant are now available (5, 13). Here we will focus on cell source used in HCT in IEM, providing an international perspective on progress, limitations, and future directions.

Although this can be argued, MPS-1 (Hurler's disease), which is the most frequently transplanted IEM, is often used as the "example" disease in the development of guidelines. This is mainly because all other IEM that benefit from HCT are very rare. Until a decade ago HCT in MPS-1 was limited by high rates of graft-failure and transplant-related mortality (14). International collaborative studies identified predictors for graft-failure, including T-cell depleted grafts and reduced intensity conditioning, while busulfan with therapeutic drug monitoring appeared to be a predictor for higher "event free survival" in comparison to prior experience (2, 14-16). These data have led to an EBMT transplant protocol/guideline (13, 17). These guidelines include standardized myeloablative conditioning regimens (currently fludarabine + exposure targeted busulfan) and the use of CB as a preferred graft-source, second only to non-carrier matched sibling BM. This transplant protocol with well-matched grafts resulted in significantly improved engraftment and a survival rate of over 90% in larger experienced HCT-centers specialized in transplanting MPS patients, who also have standardized long term follow up programs (18).

Over the past decade, unrelated CB has been used with increasing frequency as a graft source for HCT in children with an IEM. Similar to PID, CB offers several advantages (see section PID) over BM or PB of which reduced time to transplant in neurodegenerative diseases is a very important one. Recent collaborative cell source comparison studies suggest that the highest "event free survival-rates (EFS)" are achieved in patients receiving an identical matched sibling donor or an identical (6/6) unrelated cord blood, followed by 5/6 matched CB or 10/10 matched unrelated donor. Interestingly, almost all CB recipients had full-donor chimerism associated with normal enzymes levels, while mixed chimerism was more frequently seen in matched sibling and MUD donors (2). It is also important to recognize that most matched sibling donors are carriers, influencing post-transplant enzyme levels, which appear to be important for long-term outcomes, including neurocognitive outcomes (19, 20).

In 2003 IV "enzyme replacement therapy (ERT)" became available for MPS-1. HCT remains the treatment of choice in patients with the Hurler phenotype of the disease as ERT does not cross the blood brain barrier. It is however studied in combination with HCT, aiming to reduce the toxicity of the HCT. The combination of ERT and HCT for MPS IH children has been evaluated in single and multi-center studies and found that although ERT was well tolerated, the combination of ERT and HCT did not affect rates of survival, engraftment, or HCT-associated morbidity within the entire cohort (21, 22). However the studied population was not a high-risk population of patients. Patients in a very poor clinical

condition, especially those with cardiac dysfunction (23), may improve significantly on ERT, making them eligible for HCT. Currently, many transplant centers are administering ERT to MPS IH patients prior to HCT and continuing it until either start of the conditioning or achievement of donor-derived engraftment.

As for other NMD, gene-therapy protocols are being developed: e.g. Biffi and colleagues demonstrated clinical benefit to such an approach in infantile MLD (24). Whether gene-therapy is superior to HCT needs to be determined after longer-term follow up. There are several other similar gene-therapy approaches that are quite close to clinical trials (e.g. MPS-3, MPS-1, X-ALD) (25-27). As well as more effectively treating transplant refractory illness, gene-therapy may further improve outcomes of currently treated conditions by improving enzyme delivery and by reducing transplant risk (e.g. no GVHD risk). Of course the efficacy of such an approach should be prospectively evaluated against conventional therapies especially in terms of safety and long term stability of gene expression.

Bone marrow failure syndromes (BMFS)

BMFS may be inherited or acquired. Disorders are listed in Table 2 and genetic causes indicated if known. Many BMFS initially affect isolated cell lines but eventually result in multi-lineage failure. Chronic transfusions and supportive care ameliorate symptoms. BMFS progress to hematopoietic malignant transformation in 4-21% of patients, a risk averted by successful HCT (28-30). On the flip side, HCT only cures the hematopoietic component of cancer predisposition in disorders such as Fanconi Anemia (FA) and Dyskeratosis Congenita (DC). Acquired severe aplastic anemia (SAA) can be treated with immunosuppressive therapy (IST) but relapse and late failures occur in 30% (30). HCT should be considered in BMFS based on disease severity, the risk benefit ratio of transplant variables such as donor source, clinical status and tolerability of therapy.

MSD HCT has the best outcomes in SAA (cure rates of 82-90%) with mortality similar to patients receiving IST, and graft rejection of 9-11% (31-33). Unrelated donor (URD) HCT outcomes are now similar especially when performed at a young age (<20 years), using reduced intensity conditioning (RIC) incorporating anti-thymocyte globulin (ATG) or alemtuzumab. The latter has a survival benefit especially and lower GVHD rates (11% vs 25%) (34, 35). Bone marrow is the gold standard as higher GVHD rates are seen with PBSC at all ages (32, 36). HCT has the advantage over IST that 5 year failure free survival rates are >85% but <60% with IST (37, 38). A trial underway with the Bone Marrow Transplant Clinical Trials Network (BMT CTN) will determine the minimum dose of cyclophosphamide necessary for the conditioning. Children have better survival than adults (95% vs 76%) (37). Mismatched unrelated donor transplants can now achieve 70-80% DFS with current regimen but with higher GVHD rates (39). Recipients of African origin also have higher GVHD rates (72%) and lower survival OS (58%) (40). Toxicity parameters such as gonadal dysfunction, growth impairment, cataracts, avascular necrosis and hypothyroidism are higher with URD (41). These need to be discussed adequately pre-HCT.

Unrelated CBT for SAA has high rates of graft rejection (17%) with lowered dose preparation and overall, lower survival (42). A nucleated cell dose of $>3.9 \times 10^7/\text{kg}$, and immunosuppressive regimens (fludarabine, melphalan and TBI) can overcome this problem

(43, 44). CBT has the advantage of lower cGVHD if TRM and rejection are offset in other ways. Haploidentical transplants have recently reported 71% survival at early follow up, with cGVHD rates similar to MUD HCT (21%) (45). Post HCT cyclophosphamide may abrogate this complication (46). Haploidentical transplants with CB derived mesenchymal stem cells and anti-CD25 antibodies support engraftment but do not avert aGVHD risks (47).

Inherited BMFS (IBMFS) though rare, also have excellent outcomes with MSD HCT (48, 49). Standard URD transplants are associated with higher GVHD (24-50%) and TRM (30-39%). Fludarabine based RIC regimens can successfully offset toxicities and support engraftment (50). Ex vivo T cell depletion to offset GVHD is an alternate strategy (51). Both T depleting protocols and UCBT are associated with increased graft rejection (39%) compromising DFS (75% BM; 61% CB) resulting in the need for increased conditioning, cell dose ($>6.1 \times 10^7/\text{kg}$), and early HCT (<5 years of age). Progression to MDS or AML reduces DFS to 27-57%. RIC approaches are very important in DC and FA with DNA susceptibility where late mortality (OS 49% at 20 years) is high from organ toxicity (hepatic, renal, pulmonary failure) (52, 53). HCT results are better before clonal evolution, radiation, and when performed at <10 years of age. Fludarabine containing regimen have increased OS to 64% recently but the probability of secondary malignancy ($>20\%$ at 20 years) (28) remains a concern. HCT can salvage patients with clonal abnormalities more effectively before established MDS or AML (54).

Hemoglobinopathies

There are about 100,000 people living with sickle cell disease (SCD) and 1000 living with thalassemia in the United States, but millions more world-wide in countries with poor tracking systems for prevalence. MSD HCT has a high cure rate ($>90\%$) and should be offered to all patients who can avail of this opportunity in childhood when outcomes are best (55, 56). In those that do not, the availability of a donor, stage of the disease, patient age, and organ function are critical considerations that drive transplant outcomes (57). Transplant approaches have evolved in a quest to improve outcomes in alternative donor settings, avoid late toxicities such as gonadal and growth failure, and expose recipients to lower doses of chemotherapy as part of preparative regimen (58, 59). The acceptance that stable mixed chimerism is able to eradicate disease in the presence of high red cell chimerism is key to the acceptance of RIC transplants and further refinement towards safety (60, 61).

Thalassemia

The focus is currently on (1) reducing toxicities with newer preparative regimens and improving outcomes in high risk (Pesaro risk score 3; hepatomegaly >5 cm in patients >7 yrs) recipients - DFS is 54% in the former and 24% in the latter risk group (62, 63), (2) reducing graft rejection rates and (3) expanding donor pools while maintaining outcomes.

Advances in HCT have included decreased graft rejection with the addition of ATG and the incorporation of hydroxyurea, azathioprine and thiotepa into preparative regimens (even with mismatched donors) (64, 65). Treosulfan and fludarabine based MUD HCT in children has reduced toxicity and good outcomes (82% OS) (66). Unrelated CBT after ablative

busulfan produced good outcomes (73% DFS) in a Taiwanese report (67). USA based on registry data however have inferior results with CBT (21% DFS) due to graft rejection and higher treatment related mortality (68).

RIC regimens are attractive in thalassemia to reduce toxicity and maintain organ function especially if graft rejection is minimized. Recently, a RIC based trial (URTH trial) was completed in the US and used hydroxyurea, alemtuzumab, fludarabine, melphalan and thiotepa in the conditioning regimen. It successfully enrolled both 8/8 matched marrow and 5-6/6 matched UCBT with 78% DFS and 4% graft rejection (69). Haploidentical transplants for thalassemia following CD34 selection have reported fair success (14 of 22 DFS; no GVHD) (70). A recent refinement includes α/β + T cell and CD19+ B cell depletion with successful engraftment, DFS 91% and TRM 9% (8). Longer term follow up of these patients for late outcomes and immune reconstitution is of interest.

Sickle cell disease (SCD)

Over 1000 HCT procedures have been performed for SCD to date worldwide. The majority (85%) of transplants reported to the center for international bone marrow transplant research (CIBMTR) registry are from matched sibling donors. Because of improved tracking of long term disease consequence (cardiopulmonary mortality in the third and fourth decades), there is continued interest in expanding HCT to encompass alternative donors while decreasing SCD sensitive complications – hepatic sinusoidal obstruction syndrome, posterior reversible encephalopathy syndrome, hypertensive crises, GVHD, and endocrine/fertility problems. Reduced intensity transplants designed to increase tolerability even with underlying disease morbidity have met with early success (95% OS in children; 87% OS in adults) in the MSD setting (59, 71).

URD HCT is less utilized in SCD due to the concern for mortality and GVHD. Since cure is the goal, it is logical to consider careful HCT trials in patients with “severe” disease. Typically this has been defined as neurologic involvement, chronic debilitating pain or recurrent acute chest syndrome despite intervention, inability to tolerate transfusions, and progressive organ damage (eyes, kidneys, joints, etc.)(72). In any of the above situations, transplant outcomes are likely to be better at a younger age (<16 years) and prior to the development of irreversible organ damage that HCT may not be able to reverse. A MUD transplant trial using RIC (alemtuzumab, fludarabine and melphalan) was just completed by the Bone Marrow Transplant Clinical Trials Network (BMT CTN) (the SCURT Trial) based on our experience with RIC for NMD and is in follow up for marrow transplants; cord blood transplants were associated with a higher rate of graft rejection with this RIC approach (73). Limitations to this approach include the paucity of matched voluntary donors for recipients of African origin (16-19%) and the difficulty subjecting recipients to transplant risks prior to the development of significant disease or age progression which is when outcomes are likely to be better (74).

MUD marrow transplants are planned in an upcoming trial for young adults (age range 15-40 years) using reduced toxicity conditioning with busulfan, fludarabine and ATG to determine tolerability and outcome (the STRIDE trial). Expansion of donor source is underway. A single-antigen mismatched donor can be identified in 70% of patients (74). A

multi-institution phase I trial utilizing RIC and investigating abatacept based GVHD prophylaxis is underway with 7/8 matched donors in patients with severe disease that benefit from transplant-based intervention [NCT00920972]. Cord blood transplants from unrelated donors resulted in high rates of graft rejection and disease recurrence (68, 73).

Immunosuppressive regimens to enhance engraftment using cord products with the higher cell dose ($>4.0 \times 10^7/\text{kg}$ TNC) are under trial [NCT00920972]. Products matched at 5/6 HLA loci are considered acceptable and available to 23% adults and 56% of children where utilization is limited by cell dose. Cord expansion strategies (75, 76) using notch signaling molecules or nicotinamide are under investigation to optimize cord products for transplant following expansion. Mesenchymal stem cell facilitated cord transplantation has not yielded an engraftment/survival advantage in the SCD setting (77). As for haploidentical donors, a RIC approach followed by post-transplant cyclophosphamide was tolerated well with no mortality but had 43% graft rejection; a good start with room for improvement (78). Haplo-identical transplantation is also under investigation for SCD using ablative conditioning and CD34 selected peripheral blood cells (79). Thus, efforts are ongoing to improve outcomes with both cord and haploidentical transplants to expand donor sources.

As with other hereditary disorders gene therapy trial efforts for hemoglobinopathies are underway both in Europe and USA from industry and academic institutions (80, 81). The autologous cells used have no GVHD disadvantage. The safety, durability and level of engraftment to provide long-term benefit will be a key factor to their use.

Conclusion

HCT in NMD has become much safer over the last decade resulting in superior survival rates even over 90% in some cases, using unrelated and alternative donors. This has resulted in a dramatically changed life-perspective for patients with historically fatal disorders. More importantly, the use of unrelated and alternative donors has made HCT available to many more patients. In some diseases, such as in IEM, unrelated cord blood is the preferred HCT source. In the upcoming years gene-therapy (autologous CD34+ gene-transduced) will become more important for many of the disorders addressed here. This may further reduce toxicity and more importantly may correct the disease better, such as in IEM. As most of these diagnoses are rare disorders, HCT efforts are best as formal cooperative trials. International collaboration is of utmost importance to be able to improve upon existing knowledge and advance the field.

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Key points

1. Availability of alternate donor stem cell sources and successful use in HCT for NMD has expanded curative options for these disorders.
2. Significant progress has been made toward reduced intensity and reduced toxicity preparative regimens in HCT for NMD.
3. It is essential to plan and track short and long term function and outcomes post HCT for the various groups of NMD.

Table 1

Immune dysfunction disorders

Functional correlate	Genetic diagnosis
SCID phenotypes	
T ⁻ B ⁻ NK ⁻	ADA deficiency, reticular dysgenesis
T ⁻ B ⁻ NK ⁺	RAG, Artemis, Cernunnos, DNA ligase4, DNA PK
T ⁻ B ⁺ NK ⁻	Common gamma chain (X-linked), Jak-3 deficiency
T ⁻ B ⁺ NK ⁺	IL-7Ra deficiency, CD3 defects, coronin 1A defect, unspecified
Non-SCID variants	
CD4-penie	
Zap70 kinase deficiency	
MHC class II deficiency	
Omenn's syndrome	
Cartilage hair hypoplasia	
PNP deficiency	
Nijmegen breakage syndrome	
CD40 ligand deficiency	
Wiskott-Aldrich syndrome	
Hemophagocytic syndromes	
Familial HLH (1-5: PFR, Munc13-4, STX11, Munc18-2]	
Griscelli disease (<i>RAB27a</i>)	
Chediak-Higashi syndrome	
Phagocytic disorders	
IFN-gamma receptor deficiency	
Kostmann disease	
Shwachman-Diamond syndrome	
Granule deficiency	
LAD	
X-linked CGD	
Autosomal recessive CGD	
Autoimmune/immune dysregulation	
Autoimmune lymphoproliferative syndrome	
IPEX syndrome	
IL-10R deficiency	

CGD, chronic granulomatous disease; HLH, hemophagocytic lymphohistiocytosis; IFN, interferon; IL-7Ra, interleukin-7 receptor- α ; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; LAD, leucocyte adhesion deficiency; MHC, major histocompatibility complex; PFR, perforine; PK, protein kinase; PNP, purine nucleoside phosphorylase; RAG, recombination activating genes; SCID, severe combined immunodeficiencies.

Table 2

Disorders of Bone Marrow Failure

Disorder	Genetic mutations	Inheritance
Fanconi Anemia	FA complementation groups (A, B, C, D1 [<i>BRCA2</i>], D2, E, F, G, I, J [<i>BRIP1</i>], L, M, N [<i>PALB2</i>], O [<i>RAD51C</i>], and P [<i>SLX4</i>]).	Yes Autosomal or X-linked recessive
Dyskeratosis Congenita	CTC1, DKC1, TERC, TERT, TINF2, NHP2, NOP10, and WRAP53; short telomeres	Autosomal or X-linked
Shwachmann Diamond Syndrome	SBDS	Autosomal recessive
Congenital Amegakaryocytic Thrombocytopenia	MPL	Autosomal recessive
Severe Congenital Neutropenia	ELANE, HAX1	Autosomal or X-linked
Diamond Blackfan Anemia	RPS19	Autosomal dominant
Paroxysmal Nocturnal Hemoglobinuria	PIGA	Spontaneous mutation
Acquired Severe Aplastic Anemia	-	Immune mediated