HHS Public Access

Author manuscript

Bone Marrow Transplant. Author manuscript; available in PMC 2015 May 07.

Published in final edited form as:

Bone Marrow Transplant. 2015 May ; 50(5): 619–627. doi:10.1038/bmt.2015.1.

Alternative donor transplant of benign primary hematologic disorders

J Tolar[1], **P Sodani**[2], and **H Symons**[3]

[1]Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA

[2]Department of Hematology, Tor Vergata Hospital, Rome, Italy

[3]Department of Pediatrics, John Hopkins Hospital, Baltimore, MD, USA

Abstract

Hematopoietic SCT is currently the only curative therapy for a range of benign inherited and acquired primary hematologic disorders in children, including BM failure syndromes and hemoglobinopathies. The preferred HLA-matched sibling donor is available for only about 25% of such children. However, there has been substantial progress over the last four decades in the use of alternative donors for those without a matched sibling—including HLA-matched unrelated donors, HLA-haploidentical related donors and unrelated-donor umbilical cord blood—so that it is now possible to find a donor for almost every child requiring an allograft. Below, we summarize the relative merits and limitations of the different alternative donors for benign hematologic conditions, first generally, and then in relation to specific disorders, and suggest recommendations for selecting such an alternative donor.

INTRODUCTION

There are unique considerations, as described below, that must be taken into account when planning for hematopoietic SCT (HSCT) for a primary benign hematologic disorder. The preferred source for HSCT is a matched sibling donor (MSD), but there are other options when one is not available. Table 1 describes the advantages and disadvantages of the alternative donor options —matched unrelated donor (URD), umbilical cord blood (UCB) and HLA-'half-matched' related (haploidentical or haplo)—as they pertain to these considerations. Others have compared advantages and disadvantages of alternative donor sources in a similar manner.[1]

TRANSPLANT TIMING

Unlike HSCT for hematologic malignancies, HSCT for benign hematologic disorders does not always carry with it the same time pressure. For patients with worrying infectious

Correspondence: Dr H Symons, Johns Hopkins Hospital, 1650 Orleans St, CRB I 2M52, Baltimore, MD 21287, USA. Hsymons2@jhmi.edu.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

histories or organ dysfunction, HSCT can be very urgent; but for others, HSCT can be planned in a less hurried manner. Haplo-HSCT donors and UCB units are rapidly accessible, but the obstacles for URD HSCTs include identifying a 'suitable' donor and the speed with which a graft can be acquired. Further, if a donor is identified, then issues including unavailability or a change in the desire to donate can arise. The frequency with which an URD can be identified may be around 50% for Caucasians, but the likelihood falls to ≤ 10% for those of certain ethnic or mixed race backgrounds.[2]

GRAFT CELL DOSE

Wagner *et al.*[3] found that UCB with $CD34^+$ cells/kg ≥ 1.7×10^5 is associated with improved OS and decreased TRM. Grafts with > 2.7×10^5 CD34 cells/kg have been associated with even lower rates of TRM and higher $CD34^+$ cell dose partially overcomes the negative impact of HLA for each level of HLA disparity. For example, in recipients of UCB grafts mismatched at two HLA loci, patients who received transplants of ≥1.7×10^5 CD34 cells/kg had a higher survival (0.61, $n = 30$) than those receiving a lower cell dose (0.11, $n = 9$).[3] Subsequently, Cairo *et al.*[4] reviewed 268 UCB transplants (UCBTs) between 1994 and 2005, including those for BM failure syndromes (BMFs, 48%), ultimately recommending a cell dose with ≥4.9×10^7 nucleated cells (NC)/kg at collection and 3.5×10^7 NC/kg at infusion, and avoiding grafts with > 2 HLA mismatches, particularly with infusion cell doses < 3.5×10^7 NC/kg.

HLA MISMATCHES

A retrospective look at 663 URD transplants for non-malignant disorders revealed that double, but not single, high-resolution HLA mismatches at the HLA-A, -B, -C and -DRB1 loci, but not at the HLA-DQ or -DP loci, were associated with increased mortality.[4] There was no association between HLA mismatch and acute GVHD, in contrast to the Japanese severe aplastic anemia (SAA) study, which showed a significantly higher incidence of grade II-IV acute GVHD (aGVHD) in multivariate analysis with HLA mismatching (single allele C or DRB1/DQB1 and multiple allele mismatches).[5]

Haplo-HSCT for hematologic malignancies is now comparable to HLA-matched transplants in terms of graft failure and GVHD risk. A variety of methodologies have helped achieve these results, including megadose G-CSF-mobilized PBSCs,[6] depletion of T cells,[7] graft engineering, anti-thymocyte globulin (ATG)-based GVHD prophylaxis,[8] and post-transplantation cyclophosphamide (PT/CY).[9–16] However, in exchange for successful engraftment and GVHD rates, regimens that have depleted T cells, utilized megadose PBSCs and/or ATG are associated with slower immune reconstitution, increased TRM and infectious morbidity. Haplo-HSCT for hematologic malignancies using T cell-replete grafts with PT/CY have decreased TRM and infectious complications[10,12] and for non-malignant conditions ($n = 9$), we have had no TRMs with a median follow-up time of 15 months (Symons, unpublished data).

ENGRAFTMENT

Historically, graft failure has been more problematic with alternative donors. Antibodies directed against donor-disparate HLA antigens increase graft failure as reported with alternative donors,[17] particularly problematic for heavily transfused patients. Isoimmunity can be a concern especially in SAA, where hematopoietic targeted isoimmunity is likely responsible for the disease.[18]

The ability to achieve stable mixed donor chimerism (MC) is curative in some benign hematologic disorders such as hemoglobinopathies. In fact, as little as 10% donor chimerism in sickle cell disease (SCD) and 10–20% in thalassemia can eradicate disease. For thalassemia, the percentage of RHCs (residual host hematopoietic cells) 2 months post transplant was predictive of graft rejection, with nearly all patients rejecting when RHCs exceeded 25%.[19–21] In SAA and Fanconi anemia (FA), progressive MC increased late graft rejection and poor survival after MSD, haplo and URD HSCT.[22] Emerging evidence supports the importance of looking at lineage-specific chimerism, for example, erythroid chimerism to help guide clinical decision making.[23] Evidence looking at MC in other inherited BMFs has not been studied; however, it is likely that anything less than complete engraftment increases the risk of leukemia from the remaining recipient hematopoiesis.

DONOR LYMPHOCYTE INFUSIONS

The potential for secondary marrow aplasia and GVHD with associated mortality fuels the debate over DLI for falling chimerism and/or graft failure and data are scarce.[24–27] Limited data with escalating doses of DLI starting at 1×10^7 for thalassemia patients after MSD HSCT has had some success in MC (75–90% donor), but not in patients with < 75% donor chimerism.[28] Another report demonstrated that 8/13 recipients who had MC with < 75% donor after 2 months eventually lost their grafts despite DLI. Considerations for DLI include (1) patients with host chimerism > 25% at the 2-month mark; (2) MC < 75% donor at Day 30 and transfusion dependence; and (3) > 20% decrease in the percentage of donor cells at subsequent evaluations and a decrease in Hb.[26] Prospective studies of DLI after alternative donor HSCT for non-malignant conditions are warranted.

INTENSITY OF PREPARATIVE REGIMEN

The main role of the preparative regimen in non-malignant conditions is to sufficiently immunosuppress the host in order to allow engraftment of donor cells. Ideally, this could be achieved with a reduced-intensity conditioning (RIC) regimen, as opposed to a fully myleoablative regimen, to minimize both short- and long-term side effects. Historically, however, graft rejection has been problematic with RIC alternative donor regimens, especially with heavily transfused, alloimmunized patients. Reduced toxicity, yet marrow ablative regimes such as those using treosulfan,[29–34] have also been beneficial in minimizing specific side effects such as liver-related complications. Table 2 describes RIC regimens for non-malignant diseases and their outcomes, which are improving.

COST

Overall HSCT costs, duration of hospitalization and donor acquisition fees vary by graft source. A recently published single-institution report of pediatric allogeneic HSCT concluded that for 2004–2006, the mean costs per day survived, as well as graft acquisition fees, were highest with URD and UCB recipients.[35] The authors concluded that an URD source adds approximately $100 000 to the cost of the first 3 months of HSCT medical care. Using haplo donors spares the graft acquisition fees associated with MUDs and UCB (> $80 000). Additionally, haploBMT with PT/CY is technologically simple and does not involve costly T cell-depletion procedures.[9]

BM FAILURE SYNDROMES

The idea of disease-specific HSCT protocols was driven by the BMFs, for example, de-escalation of HSCT conditioning SAA and tailoring the HSCT to accommodate the alkylator sensitivity in FA. These advances, introduced in the treatment of BMFs, continue to influence and advance the field of HSCT.

SEVERE APLASTIC ANEMIA

In the 1970s, BMT was first used to treat SAA,[36] thus making BMT the prototypical stem cell therapy. Outcomes of pioneering HSCT protocols, graft selection and supportive care in SAA have improved remarkably over the last three decades.[37–40] Because of the careful collection and analysis of data, it has been possible to optimize recommendations on: (1) conditioning regimens, (2) HLA matching and (3) age groups for whom the HSCT from URDs may be considered as a first-line therapy.

Recent efforts have focused on limiting exposure to CY during conditioning to maintain efficacy while decreasing early and late regimen-related toxicities. Early data from the BMTCTN (Bone Marrow Transplant Clinical Trials Network) trial of CY de-escalation demonstrated that both high-dose CY therapy (150 mg/kg) and omission of CY result in excess mortality and graft failure, respectively.[39,40] The treatment with middle-dose cohorts (50 and 100mg/kg) has been completed and will be reported later this year.

Next, the review of HSCT outcomes from 7/8 and 8/8 HLA-matched URDs showed that regimen-related toxicities, rates of GVHD and survival rates are comparable. Furthermore, outcomes of these HLA-matched URD transplants for younger adults are approaching those of HLA genotypically identical transplants.[41–44] Additionally, the Hopkins group has utilized pharmacokinetically adjusted BU and CY with HLA-matched or haplo donors and PT/CY for nine patients with SAA who failed at least one prior treatment regimen. All patients engrafted, none developed GVHD, and one patient died of TRM (A Dezern, personal communication). In general, it is customary for immunosuppressive therapy to continue through 1 year post transplant for SAA patients.[45]

Evidence is emerging in support of the extension of inclusion criteria for first-line URD HSCT to adults up to 40 years of age. Using HSCT as frontline therapy limits risks of infection, allosensitization and iron overload that occur during pre-HSCT

immunosuppressive therapy.[46–48] With viral load monitoring, preemptive therapy with anti-CD20 antibody (rituximab) can be given (for EBV viremia), and with the advances in T-cell mediated eradication of many viruses, prevention and treatment of DNA viral infections is within reach. UCBT, however, may require new approaches such as combination with haploidentical graft or cell dose optimization.[49–51] Outcomes using alternative donors for SAA are shown in Table 3.

DYSKERATOSIS CONGENITA

For those Dyskeratosis congenita (DC) individuals with aplastic anemia who never respond or lose their response to androgen therapy, HSCT can be curative.[52,53] Historically, individuals with BMFs in DC had poor outcomes due to physical (for example, sinusoidal obstruction syndrome/veno-occlusive disease[54] and interstitial pneumonia) and immune (for example, GVHD) side effects of HSCT. Gadalla *et al.*[55] reviewed data on 34 individuals with DC who were treated with allogeneic HSCT (half had MSDs) between 1981 and 2009. HLA mismatch was associated with increased mortality; half of the deaths occurred late after HSCT (some of pulmonary failure) and the 10-year probability of survival was 30%.

In the last decade however, fludarabine-based conditioning with reduced-intensity alkylator and radiation dosing has dramatically improved the regimen-related toxicity, resulting in an OS of more than 75%.[52,55,56] Remarkably, long-term survival has been possible even for individuals with the severe variant of DC (Hoyeraal-Hreidarsson syndrome)[52] (personal experience, J Tolar). Post-HSCT, immunosuppression for DC and SAA patients is generally continued for 270 days and then weaned over 6–8 weeks.[43,52,57,58]

FANCONI ANEMIA

In FA, genome instability leads to a complex and varied phenotype including exhaustion of hematopoietic stem cells and predisposition to myelodysplasia and leukemia. Constitutional chromosome fragility in FA, however, necessitates significant modifications of the classical HSCT: administration of alkylator at much lower doses (total CY dose from 200 to 20 mg/kg)[59] and use of an antimetabolite fludarabine that is myelosuppressive but does not cause inter-strand cross-links.[60–62] Further, addition of ATG and graft T-cell depletion has been widely used to limit the risk of severe GVHD.[63] This has resulted in greatly improved outcomes of URD HSCT for FA in the last two decades, from approximately 30% to more than 90%.[43] Simultaneously, this platform is a foundation for the recent treatment-optimization strategies, including thymic shielding to decrease the risk of opportunistic infections via enhanced immune reconstitution, haplo-HSCT with PT/CY, and de-escalation of TBI.[43,57,64,65] Results of alternative donor transplants for FA are shown in Table 4.

THALASSEMIA

At present, allogeneic HSCT is the only cure for β-thalassemia major. The results of transplants from HLA-matched related donors by Lucarelli risk class[66] and alternative donor outcomes are reported in Table 5. In URD HSCT, rates of graft failure, aGVHD and cGVHD are still unacceptably high and novel strategies are needed.[32–34] Limited experience with URD HSCT have shown more encouraging results, suggesting that improvements in

donor selection and conditioning regimens have increased safety. HSCT with treosulfan-reduced toxicity conditioning for 60 patients (40 URDs) revealed promising results, especially in comparison with other URD HSCTs[32–34] with low rates of graft failure, TRM, GVHD and promising DFS.[30]

Recently, Gaziev *et al.*[67] described promising results (Table 5) in 16 patients with phenotypically matched or 1-antigenmismatched (MM) donors compared with 66 MSD HSCTs. The entire HLA-MM group had sustained engraftment. DFS and TRM were not statistically significant at 94 and 6% ($P = 0.24$) for the HLA-MM group.

The potential benefits of UCBT are the low risk of graft viral contamination and the decreased incidence of GVHD, however, the small number of stem cells in the UCB product can be problematic for engraftment. Some have received UCB transplantation in combination with BM or peripheral progenitor cells[68] or with double cord products.[68,69] Since data are scarce and rates of rejection high, if unrelated UCB is the only option, consider storing the patient's own BM in case of graft failure. It is reasonable to prioritize other donor sources over unrelated UCBT for thalassemia at this time. Additional data for transplants with unrelated UCB are required for definitive conclusions.

Using hydroxyurea and azathioprine to eradicate BM during the 2 months before haplo-HSCT, along with G-CSF and EPO to facilitate the effects of hydroxyurea, may promote engraftment.[70] In particular, grafts that contain megadoses of positively selected $CD34^+$ progenitor cells from G-CSF-mobilized haplo-PBSCs combined with 2×10^5 haplo-BM mononuclear cells/kg may help engraftment, limit GVHD, and reduce the incidence of post transplant lymphoproliferative disorder.[70,71] In a trial of 43 children with thalassemia who were transplanted from haplodonors, OS is 89% and EFS is 58% (P Sodani, personal communication, Table 5). However, post-transplant infectious complications and relapse remain the most important barriers yet to be overcome in this setting.

The incidence of MC in 335 patients who received MSD HSCT for thalassemia was 32% at 2 months after transplant.[72] Graft loss occurred in 35/108 (32%) with MC. The risk of graft rejection was only 13% in patients with < 10% RHCs and was 41% in patients with 10–25% RHCs.[19,20] The duration of post-HSCT immunosuppression varies based on clinical outcomes as well as chimerism status, but generally ranges from about 8 months to 1 year post HSCT.[67,70]

Recent literature suggests that it is important to look at erythroid chimerism in mixed chimeras as, despite the presence of few donor NC, the majority of erythrocytes are of donor origin.[23] Moreover, the proportion of donor-derived erythroid precursors is equivalent to that observed in the mature NC, rather than that of the RBC. These results suggest that for patients with MC, a selective advantage of maturation of donor erythroid precursors might successfully offset the problems associated with the recipient’s ineffective erythropoiesis and that evaluation of RBC chimerism might provide relevant clinical information in the routine monitoring of engraftment.[73]

SICKLE CELL DISEASE

There is very little data on URD HSCT for SCD, likely because it is difficult to find a suitable URD. A pilot study looked at six patients who received a RIC prep, unrelated BM or UCB, and MSCs. Although no infusion-related toxicity was seen, the co-transplantation of MSCs was not sufficient for reliable engraftment, with only two patients engrafting.[74]

The experience using UCB is limited. Out of a total of 33 cases reported, two-thirds were in the related donor setting.[75] Unrelated UCB appears to be associated with a greater risk of graft rejection and GVHD, with the largest study consisting of seven patients. This study reported one death, EFS of 43%, five patients with aGVHD and one patient with cGVHD.[75] There has been one report of a double UCBT, which was used in an attempt to augment the total cell dose in a young adult patient with SCD and Hodgkin lymphoma.[76]

Iannone *et al.*[77] described a non-myeloablative HSCT approach in six pediatric patients with SCD and one with thalassemia. Regimen-related toxicity was minimal, but transient donor engraftment occurred in only six patients, suggesting that more intensive conditioning is required. More recently, a non-myeloablative conditioning regimen was reported to be successful in adults with SCD transplanted with MSDs.[78] If RIC can sustain MC with little regimen-related toxicity then it will allow more low-risk patients the option of cure without long-term morbidity. Both the National Institute of Health and Johns Hopkins have used RIC preparative regimens with alternative donors and PT/CY with success.[79] Table 6 presents results for alternative donor transplants for SCD.

Length of immunosuppressive therapy for SCD post transplant varies, with shorter time courses for T cell-depleted grafts given the lower risk of GVHD, and 6 months to 1 year for T cell-replete grafts, with ultimate discontinuation when stable MC or full donor chimerism is achieved.

A subgroup of patients who undergo HSCT for SCD develop lifelong stable MC once donor–host tolerance is established.[75,80] Stable MC was observed in 13 out of 50 patients (26%) who showed SCD-free survival for a median duration of 6.9 years.[73] Among these patients, five had donor MC of < 75% (range of 11–74%), and none of them developed sickle cell-related complications during a 3-year median follow-up period.

SUMMARY

This review is limited to primary benign hematologic disorders and thus does not address HSCT for other non-malignant conditions such as immunodeficiencies and metabolic disorders. Overall recommendations regarding alternative donor HSCT for patients with non-malignant hematologic conditions include transplanting early to minimize graft failure and TRM. Ideally, one should utilize the least intensive preparative regimen and post transplant immunosuppressive regimen to maximize engraftment and immune reconstitution, and minimize GVHD. When time to HSCT is not a priority, URD HSCT should be strongly considered to achieve these goals. When time is a priority and/or an URD is not available, haplo-HSCT should be strongly considered. Although historically haplo-HSCT was associated with unacceptable rates of GVHD, newer regimens have lowered the

rates of GVHD similar to that of MSD HSCT. Additionally, maximizing cell dose for engraftment is more controllable. UCB might confer less GVHD, but also increases the potential for graft failure depending on cell dose. Prospective studies comparing donor sources including URD, UCB (single and double) and haplo-HSCT are warranted to support more definitive recommendations.

ACKNOWLEDGEMENTS

This study was supported by grants from the NCI (#1R13CA177155-01), NHLBI (#5U10HL069254-13), Pediatric Cancer Research Foundation, Children's Cancer Fund, NMDP Foundation and St Baldrick's Foundation.

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Table 1

Alternative donor options: advantages and disadvantages

Graft source	Advantages	Disadvantages
Unrelated donor	Historical 'gold standard' Wealth of experience Well-published outcomes Reproducible quality of stem cell product Faster immune reconstitution Donor lymphocytes available	Availability (~50%, ≤ 10% for minorities) Time delay More expensive
Umbilical cord blood	Availability (> 95%) Speed to HSCT No risk to donor Extension of the donor pool Small cryopreserved volume with easy transportability Low risk of infectious disease transmission of latent viruses Decreased GVHD	Low cell number Single use/no DLI available Slower hematopoietic engraftment/immune reconstitution Infection Few large-size and high-quality units compared with URD More expensive Recommendation to have autologous product as back-up
HLA-haploidentical related donor	Availability Speed to HSCT Less expensive Maximize cell dose Faster immune reconstitution Donor lymphocytes available	Less experience Delayed immune reconstitution and expensive (T cell-depleted grafts)

Abbreviations: HSCT =hematopoietic SCT; URD =unrelated donor.

Bone Marrow Transplant. Author manuscript; available in PMC 2015 May 07.

Table 2

Reduced intensity preparative regimens for non-malignant conditions

	***N* (alternative donors)**	**Preparative regimen**	**Immuno-suppression**	**Engraftment**	**aGVHD**	**cGVHD**	**TRM**
Jacobsohn *et al*.[81]	13 (9)	ATG/Flu/BU	CsA/MMF	72% full donor	8%	37%	15%
Shenoy *et al*.[82]	16 (6)	Distal (Day -21) campath/Flu/mel	CsA/MPD or MTX	87.5%	28% (Gr1–2)	0%	4 pts
Law *et al*.[83]	30 (23)	Campath Day -12/BU/Flu	CsA/MTX	91% (2/3 MM URD)	17%	8%	9%
Satwani *et al*.[84]	50 (22 MSD/URD, 28 UCB)	BU/Flu/ ± ATG BU/Flu/Campath Flu/CY/ ± ATG	Tacro/MMF	76% (47% chemo-naïve)	20%	Matched 21%, UCB 6%	19%
Greystoke *et al*.[31]	32 (21)	Treo/Campath or ATG	CsA + MMF or MPD or MTX	88% 86% full	25% (6% severe)	4 pts	4 pts
Beier *et al*.[29]	53 (37)	Treo/Flu+TT or Mel, ATG or campath	CsA + MMF or MTX	All (3 boost, 3 secondary failures)	47% (15% severe)	7%	13%
Parikh *et al*.[85]	15 (15)	Campath/Flu/Mel/TT/HU	Tacro and MMF	12/15	2 patients	1 patient	NA

Abbreviations: aGVHD= acute GVHD; ATG=anti-thymocyte globulin; cGVHD =chronic GVHD; Flu= fludarabine; HU =hydroxyurea; Mel = melphalan; MMF=mycophenolate mofetil; MM URD =mismatched URD; MPD= methylprednisolone; NA=not available; tacro = tacrolimus; treo=treosulfan; TT =thiotepa; UCB= umbilical cord blood; URD=unrelated donor.

Table 3

Alternative donor HSCT for severe aplastic anemia

Study	*N*	Conditioning	Graft failure	aGVHD Gr 2–4	cGVHD	Survival
URD						
Kim *et al.*[86]	40	CY/TBI	5%	30%	38%	75% (3y)
Maury *et al.*[38]	89	Various	14%	50%	28%	42% (5y)
Viollier *et al.*[44]	349	Various	11%	28%	22%	57% (5y)
Kosaka *et al.*[87]	31	CY/ATG/TBI Flu/CY/ATG/TBI	16%	13%	13%	93% (3y)
Perez-Albuerne *et al.*[88]	195	Various	15%	43%	35%	51% (5y)
Bacigalupo *et al.*[89]	100	CY/ATG/TBI Flu/CY/ATG/TBI	17%	18%	27% (−TBI) 50% (TBI)	75% (5y)
Kang *et al.*[90]	28	Flu/CY/ATG	0%	46%	35%	68% (3y)
Yagasaki *et al.*[5]	31	Various	3%	37%	27%	94% (5y)
Lee *et al.*[91]	50	CY/TBI	0%	46%	50%	88% (5y)
Marsh *et al.*[92]	29	Flu/CY/Alem	15%	14%	4%	83% (2y)
Urban *et al.*[93]	7	CY/antiCD3/ATG/TT/Flu/TLI	0%	29%	NR	86% (2y)
Samarasinghe *et al.*[94]	44	Flu/CY/Alem	0%	35%	7%	95% (5y)
UCB						
Yoshimi *et al.*[95]	31	Flu/CY/low TBI		17%	19%	41% (2y)
Peffault de Latour *et al.*[50]	71	48 RIC 22 MAC	34/71	20%	18%	38%(3y) 45% if > 3.9e7 TNC/kg
Liu *et al.*[96]	18	CY/rATG/flu	100%	NA	NA	89% (2y)
Haplo-HSCT						
Im *et al.*[97]	12	$CD3^-$ grafts; Flu/CY/ATG ± TBI	3/12	3/9	2/9	100%
Gormley *et al.*[98] (haplo + UCB	8	$CD34^+/T^-$ haplograft Flu/CY/ATG/TBI	0	2/8	1/8	7/8
Stanhellini *et al.*[99]	73	Various	42%	35%	25%	30% (59% in centers performing >3 haplo-HSCTs/y)
Takahashi *et al.*[100]	25	CY/ATG/TBI or flu/mel/TBI	90%	3/19 3/6	4/19 3/6	100%

Abbreviations: aGVHD= acute GVHD; Alem=alemtuzumab; ATG=anti-thymocyte globulin; cGVHD =chronic GVHD; Flu=fludarabine; HSCT=hematopoietic SCT; MAC=myeloablative conditioning; NA=not applicable; rATG =rabbit anti-thymocyte globulin; RIC= reduced intensity conditioning; TNC= total nucleated cells; TT =thiotepa; UCB=umbilical cord blood; URD=unrelated donor.

Table 4

Alternative donor HSCT for Fanconi anemia

Study	*N*	Conditioning	Graft failure	aGVHD Gr 2–4	cGVHD	Survival
URD						
Wagner *et al.*[62]	98	Flu (46)	NA	16%	31%	52% (3y)
Yabe *et al.*[101]	27	Flu/CY/ATG/TAI	1/26	3/26	8/26	94% (1y)
Guardiola *et al.*[102]	69	CY/XRT/ATG	19% (secondary)	43	17/40	33% (3y)
Davies *et al.*[103]	7	Low-dose CY/TBI	1/5	5/7	2/7	3/7 (9–36m)
Gluckman *et al.*[104]	48 (includes haplo)	CY/XRT/± ATG	24%	51%	46%	295 (2y)
MacMillan *et al.*[61]	29 (5 haplo, 4 UCB)	CY, TBI, ATG	NA	32%	1/29	34% (1y)
UCB						
Gluckman *et al.*[105]	93	Flu/CY/TBI	NA	32%	16%	40% (3y)
Haplo-HSCT						
Thakar *et al.*[64]	3	Flu/CY/2Gy TBI	0	2/3	0	2/3
Zecca *et al.*[65]	12	T^{-}, CD34+/Flu/CY/ATG	17%	17%	35%	83% (5y)

Abbreviations: aGVHD = acute GVHD; ATG = anti-thymocyte globulin; cGVHD = chronic GVHD; Flu = fludarabine; HSCT = hematopoietic SCT; NA = not applicable; T^{-} = T-cell depleted; XRT = radiation therapy; UCB = umbilical cord blood; URD = unrelated donor.

Table 5

Transplant outcomes for thalassemia

Study	*N*	Conditioning	Graft failure	aGVHD Grade 2–4	cGVHD	OS (%)	DFS (%)
MSD							
Lucarelli *et al.*[106]	*<17 years:* Class 1–2: 515 Class 3: 73 Adult: 107	BU/CY ± TT BU/CY BU/CY	4% 7% 4%	NA	NA	Class 1–2: 88% Class 3: 87% Adult: 66%	Class 1–2: 85% Class 3: 82% Adult: 62%
URD							
Hongeng *et al.*[32]	49 (21 URD)	BU/CY/ATG	14%	Related:32% Unrelated: 42%	14%	89% (all patients)	Related: 82% Unrelated: 71%
La Nasa *et al.*[33]	68 URD	BU/CY or BU/Flu ± TT	14%	40% (17% Gr 3–4)	18%	79% (class 1–2: 97% Class 3 66%)	66% (class 1–2: 80% Class 3 55%)
La Nasa *et al.*[34]	27	BU/CY or BU/TT/CY	30%	37%	27%	70%	70%
Bernardo *et al.*[30]	40 URD	Treosulfan	9%	14%	1	93%	94%
Gaziev *et al.*[67]	16	0%	6%	19%	13%	94%	94%
UCB							
Jaing *et al.*[69]	51	BU, CY, ATG	21.6%	NA	NA	74.5%	NA
Ruggeri *et al.*[107]	35	MAC (30) RIC (5)	15/35	23% (including sickle cell patients)	16%	8/35	21%
Jaing *et al.*[68]	45 (32 thalassemia)	BU, CY, ATG	6/32 (19%)	76% (all patients)	35% (all patients)	88% (allpatients)	77% (all patients)
Haplo							
Sodani, personal communication	43	Megadose $CD34^+$ PBSCs + haplo-BM MNCs G-CSF/EPO	NA	NA	NA	89%	58% EFS

Abbreviations: aGVHD =acute GVHD; ATG= anti-thymocyte globulin; cGVHD =chronic GVHD; DFS=disease-free survival; G-CSF = granulocyte CSF; MAC=myeloablative; MNCs = mononuclear cells; MSD= matched sibling donor; *N*=number; NA= not available; PBSCs =PB stem cells; RIC= reduced intensity conditioning; TT =thiotepa; UCB=umbilical cord blood; URD=unrelated donor.

Table 6

Alternative donor HSCT for sickle cell disease

Study	*N*	Conditioning	Graft failure	aGVHD Gr 2–4	cGVHD	Overall survival
URD						
Kharbanda[74]	6 (2 thal)	Flu/mel/alem +MSCs	3/6	2/3	NA	33%
UCB						
Adamkiewicz[108]	7	Mixed	1/7	4/7	1	6/7
Mazur[109]	1	Ritux/alem/TT/TBI	0	1	0	100%
Sauter[76]	1	RIC		0	0	100%
Kamani[110]	8	RIC Alem/flu/mel	5/8	2	1	100% (1y)
Radhakrishnan[111]	8	RIC BU/flu/alem	3/8	50%	1	62.5%
HaploHSCT						
Dallas[112]	8	$CD34^{+}$/CD3/BU/TT/CY/OKT3	62%	40%	75%	6/8
Bolanos-Meade[79]	17	ATG/CY/Flu/TBI	43%	1/17	0	100%

Abbreviations: aGVHD = acute GVHD; Alem = alemtuzumab; ATG = anti-thymocyte globulin; cGVHD = chronic GVHD; Flu = fludarabine; HSCT = hematopoietic SCT; mel, melphalan; NA = not applicable; RIC = reduced intensity conditioning; ritux = rituximab; TT = thiotepa; UCB = umbilical cord blood; URD = unrelated donor.