Selection of optimal alternative graft source: mismatched unrelated donor, umbilical cord blood, or haploidentical transplant

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Only 30% of patients who require an allogeneic hematopoietic cell transplant will have an HLA-matched sibling donor. A search for an unrelated donor will be undertaken for patients without a matched family donor. However, many patients, particularly patients of diverse racial and ethnic backgrounds, may not be able to rapidly identify a suitably matched unrelated donor. Three alternative graft sources, umbilical cord blood (UCB), haploidentical (haplo)–related donor, and mismatched unrelated donor (MMUD) are available. UCB is associated with decreased GVHD, but hematologic recovery and immune reconstitution are slow. Haplo-HCT is characterized by donor availability for transplantation and after transplantation adoptive cellular immunotherapy but may be complicated by a high risk of graft failure and relapse. A MMUD transplant may also be an option, but GVHD may be of greater concern. Phase 2 studies have documented advances in HLA typing, GVHD prophylaxis, and infection prevention, which have improved survival. The same patient evaluated in different transplant centers may be offered MMUD, UCB, or haplo-HCT depending on center preference. In this review, we discuss the rationale for donor choice and the need of phase 3 studies to help answer this important question. (*Blood*. 2012;119(9):1972-1980)

Introduction

Patient 1 is a 62-year-old woman of Hispanic and Native American descent with a history of breast cancer, treated with surgery and chemotherapy. She is in complete remission; 5 years later, she develops acute myelogenous leukemia (AML) with monosomy 7 karyotype. She attains a complete remission, has an Eastern Cooperative Oncology Group performance status of 1, and reduced intensity conditioning (RIC) allogeneic hematopoietic stem cell transplantation (HCT) is recommended. She has 3 siblings, but none is a HLA full (8/8 HLA- A,-B,-C,-DR) match. One sibling is a haploidentical (haplo) match. Her HLA typing is entered into the National Marrow Donor Program (NMDP), but no fully matched donor is identified. An unrelated donor with a single allele level mismatch at HLA-B is identified. Search of the umbilical cord blood (UCB) registries reveals 2 HLA 4/6 (-A,- B, -DR matches) UCB units with a combined cell dose of 5.3×10^7 nucleated cells/kg.

Most transplant physicians would agree that the only curative therapy for therapy-related AML is allogeneic HCT, and many would favor an RIC regimen for this patient. However, this patient might be offered a haplo-HCT from her sibling at one transplant center, a double UCB transplant (dUCBT) at a different center, and a mismatched unrelated transplant (MMUD) in another part of the country. All of these options have curative potential but significant mortality and morbidity. How is this patient to decide? What can her hematologists do to assist her?

Only 30% of patients will have a matched sibling donor. The NMDP was established in 1986 and now boasts more than 16 million volunteer donors.[1] Today, approximately 60% of white, but only 20% to 45% of black and other minority patients, will be able to find an 8/8 matched unrelated donor (MUD) at HLA-A, -B, -C, and -DR. An estimated 5000 patients each year are candidates for MMUD, UCBT, or haplo-HCT.[2] These 3 alternative graft sources have never been compared in a randomized fashion. In this review, we address the outcome data for each approach in adults with hematologic malignancies, comparing differences in GVHD, relapse, infection, second malignancies, and cost. We discuss current graft selection strategies and future developments.

UCB transplantation

UCB was first successfully transplanted into a child with Fanconi anemia in 1988.[3] Expanding on the success in pediatric UCBT pioneered by Drs Kurtzberg, Gluckman, Wagner, Broxmeyer, and others, the field grew; by 2011, more than 25 000 UCBTs have been performed worldwide and more than 500 000 UCB units have been donated for public use.[2,4] UCB is readily available and donors can be found for a diverse patient population.[5] For example, in New York, Barker et al studied 525 patients; 56% of UCBT patients were of non-European descent, compared with 23% of MUD patients.[5]

Single UCB transplantation

Myeloablative or high intensity transplant

Improvements in patient selection, UCB unit choice, and infection prophylaxis have led to improved UCBT outcomes. Ooi et al reported outstanding results with 5-year disease-free survival (DFS) of 60% to 70% in selected acute leukemia patients receiving myeloablative single unit UCBT (sUCBT).[6] Several European centers, with a more diverse population, have reported DFS of 40% to 50%.[7,8] Both HLA match and cell dose

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Table 1. Selected myeloablative transplant adult studies

Reference	Donor source	N	TRM, %	OS, %	DFS, %
Aversa[45]	Haplo	104	40	41	48 AML in CR; 46 ALL in CR; 5 no CR
Grosso[47]	Haplo	27	22	48	NR
Huang[49]	Haplo	250	19-51	27-73	25-71
Laughlin[12]	sUCB	150	63	26	23
Laughlin[12]	7/8 MMUD/BM	83	70	20	19
Eapen[13]	sUCB	165	37	NR	43
Eapen[13]	MMUD	406	38	NR	44
Brunstein[15]	dUCB	128	34	NR	51
Brunstein[15]	MMUD	52	27	NR	38

CR indicates complete remission; ALL, acute lymphoblastic leukemia; and NR, not reported.

are important for UCBT outcomes; patients who receive fully matched (6/6 HLA -A, -B, -DR) UCB units have superior survival, regardless of cell dose.[9] An analysis of 514 patients treated with myeloablative sUCB found a 1-year survival of 37%, with older age, more advanced disease, and limited center experience predictive for worse survival.[10]

No randomized trials have compared myeloablative UCB with other graft sources, but several large retrospective studies have been published (Table 1). Takahashi et al compared 100 UCB recipients with 71 recipients of matched related donor (MRD) transplant.[11] There was no difference in transplant-related mortality (TRM), relapse, or leukemia-free survival (LFS). In 2004, Laughlin et al showed comparable survival between sUCBT and MMUD, but MUD patients did better.[12] In 2010, Eapen et al, reporting for the Center for International Blood and Marrow Transplant Research (CIBMTR), compared outcomes of 165 recipients of myeloablative sUCBT with 888 MUD peripheral blood stem cell (PBSC) recipients and 472 MUD bone marrow (BM) recipients. TRM was higher for the UCBT cohort, but overall survival (OS) and DFS were comparable.[13]

dUCBT

Myeloablative transplant

dUCBT has become more popular for adults in the United States partially because of the heavier weight of Americans (~ 10 kg heavier than Europeans and 15 kg heavier than Asians). The Minnesota group pioneered this approach, reporting a 1-year DFS of 57% and a 13% incidence of acute GVHD grade 3 or 4.[14] There are no randomized studies in adults comparing sUCBT with dUCBT; however, the BMT Clinical Trials Network (CTN) is investigating this question in children. The Minnesota and Seattle groups showed comparable LFS among 536 patients receiving dUCBT, MRD, MUD, or MMUD.[15] TRM was higher, but relapse was lower, in the UCB recipients.

UCBT: reduced intensity transplant

The median age of patients with AML is 68 years; therefore, an RIC or nonmyeloablative approach is an attractive option. The Eurocord group analyzed 176 hematologic malignancy patients treated with a fludarabine-based RIC sUCBT.[16] DFS was 41% at one year. Extending the dUCBT experience to RIC HCT, Brunstein reported a 38% 3-year DFS for patients treated with fludarabine, cyclophosphamide, and low-dose total body irradiation (TBI; Table 2).[17] Our Massachusetts General Hospital (MGH)/Dana Farber Cancer Institute (DFCI) group, using an RIC regimen of fludarabine, melphalan, and rabbit antithymocyte globulin (ATG), reported a 1-year disease-free survival of 67%.[18] Subsequent studies showed a very low rate (9%) of grades 2 to 4 GVHD using sirolimus and tacrolimus for GVHD prophylaxis.[19] Chen et al showed comparable survival among MUD and dUCB in patients receiving an RIC HCT at DFCI/MGH.[20] TRM was highest for the UCB patients, but the relapse rate was lower, suggesting a decreased risk of relapse without an increase in GVHD.

Two parallel phase 2 trials studying RIC alternative donor HCT were completed by the United States BMT CTN.[21] Fifty patients were treated in each study; all patients received an RIC regimen of fludarabine, cyclophosphamide, and low-dose TBI. Nonrelapse mortality (NRM) was higher after UCBT (24% for UCB vs 7% for haplo), but the relapse rate was higher after haplo-HCT (31% for UCB vs 45% for haplo). The 1-year DFS was comparable at 46% for UCBT and 48% for haplo-HCT. The CTN is currently planning a randomized study between haplo-HCT and UCBT. Thus, retrospective RIC studies have shown comparable survival among UCBT and haplo-SCT, and UCBT and MUD.

Table 2. Selected reduced intensity adult studies

Reference	Donor source	N	TRM, %	OS, %	DFS, %
Rizzieri[51]	Haplo	49	31	31	43
Luznik[52]	Haplo	68	15	36	26
Brunstein[21]	Haplo	50	7	62	48
Brunstein[21]	dUCB	50	24	54	46
Brunstein[17]	dUCB	110	19	45	38
Chen[20]	dUCB	64	26	46	30
Ho[35]	MMUD	33	48	30	16
Nakamae[36]	MMUD/MMRD	59	36	29	28
Koreth[41]	MMUD	23	0	78	57

MMRD indicates mismatched related donor.

The future of cord blood

Several centers have attempted ex vivo expansion to improve engraftment and immune recovery. The MD Anderson Cancer Center is investigating expansion of one UCB unit with mesenchymal stem cells.[22,23] Encouraging results have been reported by Delaney et al using a Notch ligand-based system.[24] Direct intrabone marrow injection of sUCB may speed engraftment.[25] Our DFCI/MGH group is studying dimeric prostaglandin E_2 in cord blood homing.[26] Preliminary results indicate expedited neutrophil engraftment and preferential engraftment with the treated cord.[26]

Summary of UCBT

The advantages of UCBT are the readily availability of UCB units and the low risk of GVHD and relapse. Disadvantages include the cost and the slow immune recovery, which contributes to infections and TRM.

Mismatched unrelated donor transplant

HLA-mismatched HCT is imprecisely defined in the literature but typically involves a 1 or 2 HLA-locus mismatch at class I (HLA-A, -B, -C) and/or class II (HLA-DRB1; ± -DQ, -DP). HLA-mismatched HCT is appealing for patients lacking HLA matches as donor availability is considerably enhanced. In the NMDP registry, 68% of black patients would have an available 7 of 8 HLA-matched donor, compared with 20% with an available 8 of 8 HLA-matched donor (NMDP oral communication, 2011). However, HLA-mismatched HCT has been associated with impaired outcomes after myeloablative and RIC HCT.

Myeloablative conditioning

The Japan Marrow Donor Program (JMDP) reported higher mortality with allele or antigen-level mismatch at HLA-A and/or -B, but not HLA-C or -DRB1, although its applicability to the more diverse non-Japanese populations remained in question.[27,28] A large CIBMTR retrospective study compared HLA-mismatched BM versus 8 of 8 HLA-matched (HLA-A, -B, -C, -DRB1) unrelated donor HCT and documented worse NRM, acute GVHD, and overall and DFS with increasing degree of antigen and/or allele-level HLA-mismatch.[29] The 1-year survival of 8 of 8, 7 of 8, and 6 of 8 HLA-matched cohorts was 52%, 43%, and 33%, respectively, in low-risk disease, an absolute unadjusted survival difference of 9% to 10% for each HLA-locus mismatch ($P < .001$).

French BM registry data reported that mismatch at HLA-A, -B, -C, -DRB1, or -DQB1 was associated with significant decrement in survival.[30] Reports from the International Histocompatibility Working Group also identified impaired survival with HLA-DQB1 mismatch, whereas HLA-DPB1 mismatch was associated with increased acute GVHD ($P < .001$) but reduced relapse risk ($P = .01$).[31,32] There was greater survival impairment of an HLA mismatch seen in low- versus intermediate- or high-risk disease ($P < .0001$, $P = .02$, and $P = .43$, respectively).[31] Similar outcome impairment was reported for 1-antigen HLA-mismatched (HLA-A, -B, -C, -DRB1) PBSC transplantation.[33] Retrospective analyses compared outcomes after myeloablative sUCB versus MUD and MMUD BM transplantation, suggesting that sUCB outcomes were comparable with MMUD, and in one of the 2 studies, equivalent to MUD.[12,34]

RIC

The impact of HLA mismatch in RIC HCT is less well defined but is associated with high rates of acute GVHD, NRM, and impaired survival after 1 or 2 locus-mismatched RIC HCT (Table 2). In a retrospective report from the DFCI, HLA-C disparity compared with HLA-matched transplantation was associated with increased grade 3 or 4 acute GVHD (33% vs 12%, $P = .01$), increased NRM (48% vs 16%; $P = .0001$), and worse 2-year OS (30% vs 51%, $P = .008$).[35] CIBMTR data confirmed impaired survival of HLA-C antigen mismatch compared with 8 of 8 HLA-matched RIC PBSC transplantation (relative risk = 1.40, 95% CI, 1.01-1.95, $P = .04$).[32] A prospective study of T-replete 1 or 2 locus HLA-mismatched RIC PBSC grafts and calcineurin inhibitor-based GVHD prophylaxis described similarly poor outcomes, with rates of grades 2 to 4 acute GVHD of 69%, grade 3 or 4 acute GVHD of 26%, NRM of 47%, and 2-year OS of 29%.[36]

The relative impact of HLA disparity at individual loci remains controversial. JMDP data indicated higher mortality with mismatch at HLA-A and/or -B, but non-Japanese registries have reported variant results: some confirming mismatches at HLA-B or -C as better tolerated than those at HLA-A or -DRB1, but others reporting worse survival for HLA-C but not HLA-A mismatches.[27,28,31,33] In addition, individual reports of the JMDP and Italian Bone Marrow Donor Registry have identified specific "high-risk" nonpermissive allele mismatches at HLA-A, -B, -C, -DR, and -DPB1 that individually increase acute GVHD risk and NRM and impair survival.[37,38] The data suggest that antigen or allele-level HLA-mismatch probably has a similar deleterious impact. Although HLA-A, -B, -C, and -DRB1 are considered relevant loci, there is less certainty about HLA-DPB1 or -DQB1. Although there is a possibility of enhanced graft-versus-tumor effect with increasing HLA disparity, as suggested by the finding that MMUD outcomes may not be as impaired in higher risk disease, this finding has not been prospectively evaluated.

The future of mismatched unrelated transplantation

In the myeloablative setting, the use of a proprietary ATG (Fresenius) has been shown to reduce acute and chronic GVHD risk without impairing NRM or survival.[39] In the RIC setting, however, critically dependent on immunologic graft-versus-tumor effect for cure, in vivo T-cell-depletion (eg, ATG, alemtuzumab) appears to impair disease-free survival.[40] Novel T-replete RIC regimens are currently being studied in Boston, where the addition of bortezomib to a calcineurin inhibitor-based regimen has been prospectively tested in 45 patients undergoing MMUD HCT with GVHD, NRM, and survival outcomes in the range reported for HLA-matched donors.[41,42]

Summary of mismatched unrelated donor transplant

The advantages of mismatched unrelated donor transplant include more available grafts, particularly for minority patients, and in some studies, a lower risk of relapse. Disadvantages include a high risk of GVHD.

Haplo-HCT

Haplo-HCT is a favorable option for several reasons, including the ready availability of a related donor for HCT and for subsequent adoptive cellular immunotherapy, lack of search or cord blood

banking fees, and the increased donor availability as many patients will have a parent or child that could serve as a haplo-donor. Haplo-HCT has been limited by historically high rates of graft rejection, GVHD, TRM, and poor immune reconstitution, resulting in a high incidence of serious opportunistic infection. Both myeloablative and RIC transplant strategies have been attempted, and selected experiences are summarized in Tables 1 and 2.

Myeloablative conditioning

Early attempts with myeloablative haploidentical HCT and pharmacologic GVHD prophylaxis with methotrexate (with or without cyclosporine) were complicated by high rates of graft rejection, hyperacute GVHD, and TRM.[43] HLA-one antigen-mismatched HCT outcomes were not significantly different from those of HLA-matched related donor transplantation (higher incidences of GVHD but similar OS), but HLA-2/HLA-3 antigen-mismatched transplants were associated with prohibitive mortality risks.[44] More recent approaches using myeloablative conditioning and vigorous ex vivo T-cell depletion have resulted in a very low incidence of acute and chronic GVHD and favorable event-free and OS probabilities for patients with acute leukemia. Aversa et al described their experience with TBI, thiotepa, fludarabine, and ATG conditioning and ex vivo T-cell depleted "megadose" peripheral blood stem cell transplantation.[45] Among 104 patients with AML (N = 67) or acute lymphoblastic leukemia (ALL; N = 37), engraftment was achieved in 100 of 101 evaluable patients. Acute and chronic GVHD occurred in 8 and 5 of 70 evaluable patients, respectively. NRM probability was 38% primarily resulting from opportunistic infections.

Another myeloablative haplo-HCT strategy has involved the ex vivo induction of alloantigen specific anergy by the coculturing of host and donor BM mononuclear cells with either CTLA-4-IG or anti–B-7.1 and B7.2 antibodies. Davies et al conducted sequential trials of haplo-HCT using this ex vivo anergization strategy in 24 patients with advanced hematologic disorders.[46] Grade C or D acute GVHD and chronic GVHD were seen in 5 and 1 patients, respectively. Eight of the 24 patients were disease-free at a median of 7 years after transplantation. Grosso et al[47] recently described an approach involving in vivo T-cell tolerization using TBI, then donor peripheral blood T cells followed by cyclophosphamide. Patients then received ex vivo CD34-selected peripheral blood stem cells. The probabilities of grades 2 to 4 acute and chronic GVHD were 59% and 16%, respectively. NRM was 23%. OS probability was 48% at 3 years.[47]

Myeloablative haplo-HCT approaches without ex vivo T-cell depletion have also been recently described. Multiple investigators have described a strategy using aggressive multiagent conditioning regimens, polyclonal ATG for in vivo T-cell depletion, and posttransplant GVHD pharmacoprophylaxis.[48-50] Huang et al recently described 250 patients who received conditioning with busulfan, cytarabine, cyclophosphamide, semimustine, and ATG, and post-HCT GVHD prophylaxis with mycophenolate mofetil, cyclosporine, and methotrexate.[49] A total of 249 of the 250 patients achieved full donor chimerism. Grades 2 to 4 acute and chronic GVHD incidences of 46% and 54%, respectively, were reported. Three-year LFS probabilities were excellent, especially for patients with standard-risk disease: for AML, LFS probabilities were 71% and 56% for standard- and high-risk patients, respectively; and for ALL, 60% and 25% for standard- and high-risk patients, respectively.

RIC

RIC haplo-HCT approaches have also been evaluated. Rizzieri et al administered a conditioning regimen of fludarabine, cyclophosphamide, and alemtuzumab for in vivo T-cell deletion.[51] Posttransplant GVHD prophylaxis consisted of mycophenolate mofetil with or without cyclosporine. The incidence of GVHD was low with this approach, as 16% of patients developed grades 2 to 4 acute GVHD and 8% chronic GVHD. One-year relapse-free and OS probabilities were 43% and 31%, respectively. Posttransplant high-dose cyclophosphamide was used by Luznik et al to deplete alloreactive (both in the GVH and HVG direction) T cells after conditioning with low-dose TBI, fludarabine, and cyclophosphamide for a variety of hematologic malignancies.[52] A 13% rate of graft failure was observed. Grades 2 to 4 acute GVHD developed in 34% of patients, and chronic GVHD developed in 25% and 5% of patients who received one or 2 doses of posttransplant cyclophosphamide, respectively. Two-year event-free survival and OS probabilities were 26% and 36%. At MGH, sequential trials initially used cyclophosphamide, equine ATG, and thymic radiation, with the later substitution of a monoclonal anti CD2 antibody (MEDI-507) for ATG for better T-cell depletion, with the intent to induce stable mixed chimerism as a platform for delayed donor lymphocyte infusion. Graft rejection and GVHD were limiting complications.[53,54] Using a similar conditioning strategy at MGH with both ex vivo T-cell depletion (by CD 34^+ cell selection) and in vivo T-cell depletion (using MEDI 507), we found that stable mixed chimerism was reliably achieved with minimal GVHD, and long-term survival has been achieved in approximately one-fourth of patients with chemorefractory lymphoma (B.D., K.B., S. McAfee, T.S., unpublished data, December 2011). Other fludarabine-and ATG-based RIC regimens for haplo-HCT have been reported with similar, favorable survival outcomes, particularly for standard-risk hematologic malignancies.[55,56] As described above, the CTN phase 2 studies showed comparable survival for UCBT and haplo-HCT; haplo-compared with MMUD HCT has not been well studied.

Future of haploidentical transplantation

Because relapse remains a major limitation of haplo-HCT, several strategies are being developed to reduce the risk of relapse. Transfer of tumor-specific T lymphocytes or donor-derived NK cells is under investigation.[57,58] Novel approaches to the prevention and treatment of infection include the use of donor-derived virus-specific T lymphocytes to treat refractory viral and fungal infections.[59]

Summary of haploidentical transplantation

Haploidentical donor options are available for most patients, and there are no search or acquisition costs. Disadvantages of haploidentical HCT are the necessary technical expertise and cost of ex vivo T-cell depletion (when such methods are used), poor immune reconstitution, and high risk of relapse (after RIC approaches) after transplantation.

Posttransplantation complications

The 3 alternative donor sources (UCB, haplo-HCT, and MMUD) have different posttransplantation complications, as illustrated in Table 3. UCB is associated with a higher risk of infection but often a lower risk of GVHD than haplo-HCT or MMUD. Second

Table 3. Advantages and disadvantages of alternative donor sources

	UCB	Haploidentical-related family member	One locus mismatched unrelated donor
Donor availability	Difficulty to find high-quality units for minorities	Most patients have parent or child as donor	May be lengthy/difficult to find donors, especially for minorities
Cost	US $20 000-$40 000 per cord unit	Low donor acquisition costs	US $20 000-25 000
Availability of donor lymphocytes	No	Yes, readily available	Available, but may be lengthy wait
GVHD	Low risk	May be severe, especially with no T-cell depletion	May be very severe
Infection	High risk, especially viral	High risk	Moderate risk
Product quality	High variability	Low variability	Low variability
Relapse risk	Moderate	High, especially with some forms of T-cell depletion	Moderate

malignancies have been reported more frequently after UCB or haplo-HCT. Cost may be higher with UCB. These sections explore the risks of the common after transplantation complications with the 3 donor sources.

GVHD

Acute and chronic GVHD remain important sources of morbidity and mortality after HCT and, thus, should factor heavily when faced with the choice of an alternative stem cell donor. Significant advances have been made with improved donor selection and the use of novel prophylaxis regimens for different alternative donors. Several of these studies are outlined in Table 4.

The ability to cross significant HLA barriers safely has made UCBT quite attractive. Currently, standard UCB selection criteria require matching at 4 of 6 major HLA-antigens (A, B, DRB1) with high resolution typing only routinely required for HLA-DRB1.[60] Even with such a degree of HLA disparity, rates of acute and chronic GVHD after UCBT appear to be either similar or decreased compared with HCT from conventional or alternative stem cell sources. The Eapen CIBMTR study, which studied 1525 acute leukemia patients receiving myeloablative HCT, reported a significantly lower rate of both acute and chronic GVHD for sUCBT compared with unrelated PBSC recipients, and significantly decreased rates of chronic GVHD compared with PBSC or BM.[13] Brunstein's myeloablative study of 536 leukemia and MDS patients found similar rates of grades 2 to 4 acute GVHD for dUCBT relative to MRD HCT, but significantly lower GVHD than MUD or MMUD patients, 26% for dUCBT, and 43% to 48% for MUD and MMUD.[15]

In the reduced intensity setting, our Boston group compared RIC dUCBT (n = 64) with RIC MUD HCT (n = 221). Similar rates of grades 2 to 4 acute GVHD were observed in both groups, but patients undergoing dUCBT had a significantly lower incidence of chronic GVHD (54% MUD vs 22% dUCB, $P < .0001$).[20] The Johns Hopkins group, using posttransplantation cyclophosphamide to achieve selective depletion of alloreactive donor T cells after haplo-RIC, reported a 34% incidence of grades 2 to 4 acute GVHD (6% grade 3 or 4) and a very low incidence of chronic GVHD.[52] Recent results from the CTN phase 2 trial using this approach in 50 patients at 17 centers showed an impressively low 22% incidence of grades 2 to 4 acute GVHD (0% grade 3 or 4) and a 13% cumulative incidence of chronic GVHD at one year.[21]

Several groups have reported their experience adding ATG to standard regimens for MMUD HCT. Pidala et al reported on 45 patients undergoing MMUD HCT, all of whom received ATG (thymoglobulin, Genzyme), tacrolimus, and methotrexate and showed a 1% incidence of grade 3 or 4 acute GVHD and a 19% incidence of moderate to severe chronic GVHD.[61] Kim et al reported a retrospective analysis of 49 MMUD patients and showed that patients who received ATG in addition to standard tacrolimus and methotrexate had a lower incidence of grades 2 to 4 acute GVHD (8% vs 29%, $P = .038$) with similar incidences of chronic GVHD.[62] Mead et al presented results using pre-HCT alemtuzumab and post-HCT cyclosporine in 157 RIC patients, 50 of whom were mismatched at 1 to 4 HLA antigens (64% single loci mismatch, 30% 2 loci mismatch). Their results showed similar outcomes between MUD and MMUD HCT with no evidence of any increased risk of acute or chronic GVHD.[63] These studies suggest that rates of acute and chronic GVHD after MMUD HCT can be comparable to MUD and perhaps UCB if additional agents, such as alemtuzumab and ATG, are used; however, large prospective studies are needed to validate the role of ATG in MMUD HCT.

Table 4. Risk of GVHD and relapse

Reference	n	Diseases	Conditioning	GVHD ppx	Relapse, %	II-IV Acute GVHD, %	Chronic GVHD, %
UCB							
Eapen[13]	165	AML, ALL	Various myeloablative	Various	30	30	24
Brunstein[15]	128	AML, ALL, CML, MDS	Flu/Cy/TBI-ablative	CNI + MMF	15	60	26
Chen[20]	64	Various	Flu/Mel/ATG-RIC	Various	43	14	22
Haplo							
Aversa[45]	104	AML, ALL	TBI, TT, Flu, ATG-myeloablative	TCD	25	8	7
Rizzieri[51]	49	Various	Flu/Cy/alemtuzumab-RIC	CsA ± MMF	NA	16	14
Luznik[52]	68	Various	Flu/Cy/TBI-RIC	Cy/Tacro/MMF	58	34	13
MMUD							
Pidala[61]	45	Various	Various	ATG/Tacro/MTX	33	64	35
Kroger[93]	158	Various	Various	F-ATG/CsA/MTX	27	41	41
Mead[63]	50	Various	Flu/Mel/alemtuzumab	CsA	NA	22	39

ALL indicates acute lymphoblastic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; Flu, fludarabine; Cy, cyclophosphamide; Mel, melphalan; TT, thiotepa; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; TCD, T-cell depletion; CsA, cyclosporine A; Tacro, tacrolimus; MTX, methotrexate; F-ATG, Fresenius ATG; and NA, not available.

Relapse

Although significant strides have been made in reducing overall transplant-related mortality in HCT over the past 2 decades, relapse of disease remains the most common cause of failure in patients undergoing HCT.[64] With lower rates of GVHD after UCBT, an initial concern was that increased rates of relapse would be observed because of a weaker graft-versus-malignancy effect. Interestingly, this has not been borne out in the several retrospective comparisons of UCBT to HCT from adult stem cell sources. In the large CIBMTR study, the cumulative incidence of disease relapse was similar despite a significantly lower rate of chronic GVHD in the UCB group.[13] Several analyses have shown a decreased risk of relapse with dUCBT compared with sUCBT.[65,66] In the analysis by Brunstein et al, recipients of myeloablative dUCBT had significantly lower rates of disease relapse at 5 years (15%) compared with recipients of MRD (43%), MUD (37%), and MMUD (35%).[15] Donor lymphocyte infusions, however, are not available for UCBT recipients who relapse. No analysis has suggested that disease relapse is decreased in patients who are recipients of MMUD grafts relative to matched counterparts. Indeed, a large CIBMTR registry study of more than 4500 chronic myelogenous leukemia patients did not find a lower risk of relapse with greater HLA mismatching.[67] Relapse rates after haplo-HCT appear to differ significantly depending on the conditioning and GVHD regimens used. More studies are needed to define whether certain disease groups benefit selectively from mismatching at specific HLA loci with adult donor stem cell sources.

In the RIC setting, analyses have shown similar rates of relapse among dUCB and conventional HCT.[20,68] Preliminary analyses of RIC haplo-HCT with the Hopkins regimen suggested that patients with lymphoid diseases had less relapse than patients with myeloid diseases with especially impressive outcomes for patients with Hodgkin lymphoma.[69] The presence of an HLA-DRB1 antigen mismatch in the GVH direction or the presence of 2 or more class I allele mismatches (composite of HLA-A, -B, and -C) in either direction was associated with significantly lower rates of disease relapse and improved event-free survival without excess NRM.[70] Nevertheless, the relapse rate of 45% at 1-year after RIC haplo-HCT observed in the BMT CTN study raises concern that the successful prevention of GVHD in this manner may inhibit effective graft-versus-malignancy effects.[21] Disease relapse is dependent on the underlying disease, disease risk, and status at the time of HCT and, thus, best determined in a prospective randomized study. Finally, the precise mechanisms of tumor immunity after HCT, which may be different depending on donor type, need to be elucidated to potentially better choose among donor types based on underlying disease.

Immune reconstitution and infectious complications

Despite advances in antimicrobial therapy, severe infections remain a major cause of death after alternative donor HCT, particularly in older patients. The Spanish group compared 48 recipients of single UCBT with 144 recipients of unrelated BM or PBSC HCT.[71] At 3 years, the UCBT group had a higher risk of developing an infection, but infection-related mortality (25%) was similar in the 2 groups. HLA mismatch did not affect outcome in the UCBT group but was associated with a higher mortality in the BMT/PBSC cohort. Ringden et al found a similar rate of bacteremia in UCB and MMUD patients, but TRM was higher for the MMUD patients.[72] The Minnesota group has demonstrated comparable rates of cytomegalovirus infection between dUCBT and MRD transplantation.[73]

Cord blood contains fewer T cells than other stem cell sources, and cord blood lymphocytes have specific immunologic characteristics, such as different response pattern to cytokines and a greater proportion of naive T cells.[10] In haplo-recipients, there is more NK cell alloreactivity, and NK cell infusions have been used therapeutically after transplantation.[74] In a prospective analysis of immune reconstitution in dUCBT recipients and MUD recipients from the DFCI, Jacobson et al found that CD3 recovery was significantly delayed in the dUCBT group compared with the MUD group for as long as 6 months after HCT, including naive ($CD45RO^-$) and memory ($CD45RO^+$) CD4 T cells, regulatory (CD4CD25) T cells, and CD8 T cells.[75] These unique properties of UCB may contribute to a high risk of infection reported in some studies. Novel strategies to combat infection include the use of virus-specific or trivirus-specific (adenovirus, Epstein-Barr virus, and cytomegalovirus) cytotoxic T lymphocytes.[76] Donor-derived cytotoxic T lymphocytes can be used to combat viral infections in haplo-recipients.[59]

Posttransplant lymphoma and other second malignancies

Second malignancies remain a devastating complication after HCT. A total of 1% of patients in a CIBMTR study of 18 000 BM patients developed posttransplantation lymphoproliferative disorder, with risk factors, including an HLA-mismatched donor and T-cell depletion.[77] UCBT, which are "naturally" T cell depleted have a high incidence of posttransplantation lymphoproliferative disorder, especially with the use of ATG in an RIC regimen.[78,79] Frequent monitoring for EBV and preemptive use of rituximab may reduce the risk and severity of posttransplantation lymphoproliferative disorder after UCBT and MMUD HCT.[80,81] Novel approaches to posttransplantation lymphoproliferative disorder include the use of EBV or trivirus-specific cytotoxic T lymphocytes.[82,83] Donor-derived second myeloid malignancies may be increased after UCBT, perhaps because of naive cells or the use of growth factors.[79,84,85]

Cost and length of stay

Given the current healthcare climate, the cost for the alternative donor graft sources assumes new importance. Costs vary widely from center to center, so the number of hospital days may be a surrogate marker. The Minnesota group compared costs in the first 100 days after myeloablative and RIC transplantation using either UCB or MRD grafts.[86] The median cost per day survived (not including graft acquisition) was $1016 for myeloablative MRD, $2082 for myeloablative UCB, $612 for RIC MRD, and $1156 for RIC UCB. Acquisition of 2 UCB units can cost up to $80 000 prior to the patient entering the hospital; these costs may be related to the large inventory of UCB units, of which only 10% have been used for HCT. Acquisition costs for haplo-HCT are clearly less. The CIBMTR is embarking on a retrospective comparison of length of stay among the different graft sources.

Combination of donor sources

Given the high risk of infection after UCBT, an intriguing strategy is to combine donor sources using both haplo-BM and UCB.[87] The advantage of this approach is the rapid engraftment of the haplo cells to reduce the risk of early infections, followed by sustained hematopoietic engraftment of the UCB.[88] Five-year DFS of 47% has been reported with this strategy.[89]

In conclusion, patients with hematologic malignancies have multiple options for treatment, and multiple choices of transplant

Table 5. Benefits and risks of each graft source

	UCB	Mismatched unrelated donor	Haploidentical transplant
Benefit	Low relapse	Low relapse for high-risk patients	Ready availability
Benefit	Low severe GVHD	Donor lymphocyte available	Low cost
Risk	Cost	GVHD	Relapse (especially RIC)
Risk	Infection	TRM	Infection

donor sources. Table 5 outlines the benefits and risks of each graft source. The field may evolve over the next 5 years so that specific patients may benefit from a particular approach; for example, patients at high risk of infection might receive an MMUD over UCBT, and patients at high risk of relapse might receive UCBT over haplo-SCT. Furthermore, specific diseases might respond differently to different donor sources. Because there are no prospective randomized comparative studies to date, we cannot promote a definitive strategy for donor selection, and clinical trial participation is encouraged. Our center performs UCBT, haplo-HCT, and MMUD HCT for patients without an 8 of 8 or 7 of 8 MRD or an 8 of 8 MUD. We use donor availability, protocol eligibility, patient age, disease, and disease status to decide on the best option for each individual patient. We do tend to favor UCBT given our research interests in this field. The field of alternative donor transplantation is moving forward as work on optimal UCB unit selection and investigation of the role of HLA antibodies, HLA-C, and KIR matching may improve results.[90-92] In the haplo-HCT setting, the use of adoptive immunotherapy to decrease relapse is in progress. MMUD donor selection, with more sensitive HLA typing, will probably improve.

The CTN is embarking on a randomized RIC phase 3 study comparing haplo-HCT and UCB HCT. This study will answer important questions regarding the risks and benefits of these 2 donor sources. Finally, whereas this review focused on alternative donor sources, future randomized studies will be required to compare UCB, haplo, and MMUD to more conventional related and matched unrelated donor sources. We are confident that these studies will allow us to make more informed donor choices for our patients in the future.

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