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REVIEW

Haploidentical *vs* cord blood transplantation for adults with acute myelogenous leukemia

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Abstract

Hematopoeitic cell transplantation is established as a curative treatment for patients w acute myelogenous leukemia. Haploidentical family donor and umbilical cord blood (UCB) are alternative sources of stem cells for patients lacking a matched sibling or unrelated donor. The early challenges of transplant complications related to poor engraftment and graft-*vs*-host disease have been overcome with new strategies such as using 2 units and increased cell dose in UCB and T-cell depletion and post transplantation cyclophosphamide in haploidentical transplantation. The outcomes of alternative transplantation for acute leukemia were compared to other traditional graft sources. For patients lacking a matched sibling or unrelated donor, either strategy is a suitable option. The choice should rely mostly on the urgency of the transplantation and the available cell dose as well as the expertise available at the transplant center. This manuscript reviews the options of alternative donor transplantation and highlights recent advances in each of these promising transplantation options.

Key words: Umbilical cord blood transplantation; Haploidentical transplantation; Leukemia

Core tip: Allogeneic hematopoeitic cell transplantation is a curative treatment for patients with acute leuekemia. Many patients lack a suitable matched donor and require another stem cell source. The choice between cord blood and mismatched relative is challenging as there is no direct comparison between the two transplantation modalities. This manuscript highlights the studies and current innovative approaches with either modality with an emphasis on the recent studies aiming at decreasing complications, enhancing engraftment and speeding immune recovery.

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INTRODUCTION

Allogeneic hematopoeitic cell transplantation (HCT) is a potential curative treatment for patient with leukemia. The preferable donor is a fully matched sibling; however, two thirds of patients needing transplant lack this donor option[1]. In the absence of sibling donors, most centers choose a matched unrelated volunteer donor as the next option. Report from the National Marrow Donor Program's registry indicates an 8/8 HLA-matched adult unrelated donor is available for 51% of Whites, 30% of Hispanics, 20% of Asians and 17% of African-Americans[2]. Hence, a 30% of all patients requiring HCT lack a suitable matched donor. The high relapse risk of many leukemia patients lacking a matched donor has led to the use of alternative sources of stem cells such as unrelated donor umbilical cord blood (UCB) and haploidentical

family donors.

First attempts with alternative HCT carried a high risk of mortality, engraftment complications and graft *vs* host disease[3]. Progress in recent years has significantly improved the outcomes post alternative donor HCT. The improved outcomes are mostly credited to better donor selection, vigorous T-cell depletion in haploidentical transplantation, use of post infusion cyclophosphamide in haploidentical setting and use of 2 units in adult UCB transplantation (DUCBT) and introduction of more suitable conditioning regimens.

This article will review the recent advances in alternative donor HCT for acute leukemia in adults, describe the outcomes of HCT using these alternative donor sources and discuss ongoing studies in alternative HCT.

UMBILICAL CORD BLOOD TRANSPLANTATION

UCB offers several benefits over unrelated adult donors[1,4]. UCB is safe for the donor as it is collected from the placenta during delivery. UCB units are readily available with less risk of transmission of infections, in particular cytomegalovirus (CMV), since most units are CMV negative. It permits a higher HLA disparity between donor and recipient when compared to MUD or related donors[5,6]. Finally, UCB HCT may carry less risk of chronic GVHD compared to other cell sources[7-10]. The main limitations associated with UCB are related to the small number of progenitor cells in each unit and the lack of access to donor lymphocytes for donor lymphocyte infusion (DLI), if needed. UCB constitutes a significant proportion of unrelated donor transplantations in children (40%) compared to only 10% in adults.

Laughlin *et al*[3] reported on 68 patients [15 with acute lymphoblastic leukemia (ALL), 19 acute myeloid leukemia (AML) and 17 chronic leukemia] who received myeloablative UCB transplantation[3]. Engraftment was better for patients with a nucleated cell dose $\geqslant 2.4 \times 10^7$/kg. Median time to engraftment was 27 d. Five patients experienced primary graft failure. CD34+ cell dose ($\geqslant 1.2 \times 10^5$/kg) was associated with a higher event free survival (EFS). EFS was not influenced by HLA matching (3-6/6) or patient age. This study established the safety of UCB transplantation in adults despite limited cell content and a more HLA mismatch than what has been reported in pediatrics[11]. The COBLT study prospectively evaluated the outcomes of UCB transplantation[12]. This study evaluated 34 adult subjects [AML = 19, ALL = 9, CML = 3, myelodysplastic syndrome (MDS) = 1]. Patients had a myeloablative conditioning (MA) with total body irradiation (TBI) plus cyclophosphamide and busulfan or melphalan with 4-6/6 HLA matched UCB units. The required cell dose was $> 1 \times 10^7$ nucleated cells/kg. Overall, 34 % had primary graft failure and 6 mo survival was only 30%. The reasons for higher mortality and complications with initial studies of UCB were due to patient selection and long duration from diagnosis to transplantation. However, these reports established the importance of cell dose for successful UCB HCT and set the background for future studies of strategies to limit complications (*e.g.*, double umbilical cord blood transplantation, *ex vivo* expansion).

Double umbilical cord blood transplantation

The use of two UCB units was started at the University of Minnesota to overcome the cell dose limitation of single UCB units[3,13,14]. DUCBT has yielded better engraftment, lower mortality and improved disease free survival comparable to other hematopoietic cell sources[15].

A recent report from Minnesota group assessed 536 patients who received HCT with HLA MRD (n = 204), HLA allele matched or 1 antigen mismatched unrelated donor (MUD = 152, MMUD = 52) or HCT using 4-6/6 HLA matched two UCB units (n = 128) after myeloablative conditioning[15]. Disease free survival (DFS) was similar for the different graft sources (UCB 51%, MUD 48%, MRD 33%, and MMUD 38%). UCB recipients had a lower relapse risk but a higher TRM. Another study from Minnesota suggested that using double UCB units carries a lower risk of relapse and a higher risk of acute GVHD when compared to single unit UCB transplantation[16,17].

BMT-CTN 0501 is a myeloablative study that randomizes 1 *vs* 2 UCB grafts for children with leukemia. BMT-CTN 0604 study addressed RIC regimen in the DUCBT setting. Longer follow up from both studies will help improve our understanding of the use of DUCBT.

UCB outcomes

UCB has been compared to other donor sources in the myeloablative setting (Table 1). Transplant outcomes post UCB used to be inferior but recent series show similar outcomes for UCB when compared to other graft sources. The differences in outcomes between prior and current studies is related to many reason, the most important being an increase in the minimum acceptable cell dose in the cord unit to proceed with transpantation[18].

Laughlin *et al*[5] compared outcomes of 450 patients receiving 5-6/6 HLA matched unrelated donor transplants to 150 patients receiving 4-6/6 UCB transplants through the CIBMTR registry. The median time to neutrophil engraftment was delayed with UCB (27 d) compared to 18 d among 6/6 and 20 d among 5/6 HLA-matched unrelated bone marrow. Acute GVHD and relapse rates were similar between UCB and 6/6 MUD. UCB had higher TRM and poorer LFS. MUD had a better overall survival at 3 years (33% *vs* 23%) compared to UCB HCT. When UCB was compared to 5/6 MMUD, UCB was shown to have a lower risk of acute GVHD, but a similar risk of TRM, relapse, and LFS. Rocha *et al*[6] on the other hand; reported that UCB had a lower risk of GVHD and similar rates of relapse, TRM and LFS. Both authors suggested UCB as a reasonable stem cell source in the absence of 6/6 MUD.

Single unit UCB transplantation outcomes were compared to MUD peripheral blood stem cells (PBSC) and

Table 1 Hematopoietic cell transplantation after myeloablative conditioning in adult patients comparing umbilical cord blood and other donor sources

Year	Graft type	Number of patients	Median age	ANC > 500/μL (median, d)	aGVHD II-IV(%)	Extensive cGVHD (%)	100 d TRM (%)	Relapse rate (%)	Survival (%)
2004[5]	UCB	150	16-60	27	41	51	63	17 (3 yr)	26 (3 yr)
	MUD BM	367	16-60	20	48	35	46	23	35
	MMUD BM	83	16-60	18	51	40	65	14	20
2004[6]	UCB	98	25	26	26	30	44	23 (2 yr)	36 (2 yr)
	MUD BM	584	32	19	39	46	38	13	42
2007[19]	UCB	100	38	22	60	23	8	17 (3 yr)	NA
	MRD (BM and PB)	71	40	17	55	30	4	26	
2008[10]	UCB	148	29	NA	NA	NA	41	26 (2 yr)	35 (2 yr)
	MUD PB	518	35	NA	NA	NA	27	30	45
	MMUD PB	210	NA	NA	NA	NA	42	24	36
	MUD BM	243	29	NA	NA	NA	26	28	48
	MMUD BM	111	NA	NA	NA	NA	37	26	38
2009[62]	UCB AML	173	38	NA	32	8	32 (2 yr)	31 (2 yr)	43 (2 yr)
	MUD BM	311	38	NA	35	20	22	24	60
	UCB ALL	114	34	NA	28	10	24	31	49
	MUD BM	222	32	NA	42	17	25	24	57
2010[15]	MRD	204	40	NA	65	47	24 (5 yr)	43 (5 yr)	NA
	MUD	152	31	NA	80	43	14	37	NA
	MMUD	52	31	NA	85	48	27	35	NA
	DUCB	128	25	NA	60	28	34	15	NA

ANC: Absolute neutrophil count; aGVHD: Acute graft versus host disease; cGVHD: Chronic graft versus host disease; TRM: Treatment related mortality; UCB: Umbilical cord blood; MUD: Matched unrelated donor; BM: Bone marrow; MMUD: Mismatched unrelated donor; NA: Not available; MRD: Matched related donor; PB: Peripheral blood stem cells; AML: Acute myeloid leukemia; ALL: Acute lymphoblastic leukemia; DUCB: Double umbilical cord blood.

bone marrow in a multiregistry study[10]. Graft sources included 4-6/6 HLA matched single unit UCB (n = 165), 8/8 HLA matched PBSC (n = 632), 8/8 HLA matched bone marrow (n = 332), 7/8 HLA matched PBSC (n = 256) and 7/8 HLA matched bone marrow (n = 140). Endpoints included hematopoietic recovery, TRM, LFS and GVHD. Both acute Grade Ⅱ-Ⅳ and chronic GVHD were lower in UCB than in PBSC MUD, while only chronic was lower in UCB than in 8/8 matched bone marrow patients. TRM was higher after UCB than after 8/8 allele matched PBSC (HR 1.62, P = 0.003) or bone marrow transplantation (HR = 1.69, P = 0.003). Overall, LFS was comparable between UCB and 7-8/8 allele matched unrelated donor.

A recent report from Minnesota and Fred Hutchinson group in Seattle showed that myeloablative DUCBT has comparable leukemia free survival as matched and 1 antigen mismatched unrelated donor.

UCB has also been compared to related donor transplantation. Takahashi *et al*[19] reported on 171 adults who received single unit UCB (n = 100), 5-6/6 HLA matched related donor bone marrow transplant (n = 55) or 5-6/6 HLA matched related donor PBSC HCT (n = 16). UCB recipients had a delayed hematologic recovery and a lower incidence of grade Ⅲ-Ⅳ acute and extensive chronic GVHD. Both UCB and related donor transplantation had similar relapse, TRM and DFS.

In summary, there is enough evidence to suggest UCB as an acceptable source of stem cells for patients requiring myeloablative HCT but lack a suitable matched donor.

UCB Transplantation after reduced-intensity conditioning

Older patients with AML requiring allogeneic HCT are at increased risk of complications with myeloablative conditioning. Studies with RIC UCB had variable TRM and this variability could be related to different study populations[20-22]. Overall, most studies have reported OS and DFS that is similar to HCT using other stem cell sources.

A Minnesota study evaluated older patients after UCB transplantation and compared their outcomes to matched related donors, MUD and Mismatched URD. The TRM was higher (35% *vs* 27%), LFS was lower (28% *vs* 35%) and overall survival was lower (30% *vs* 43%) among UCB recipients when compared to MUD transplantation[23]. This study and other reports establish the efficacy of UCB after RIC for patients who are not eligible for myeloablative conditioning.

Other factors in selecting cord blood units

The selection of cord blood units has been traditionally based on low resolution typing of HLA-A, B and high resolution at DRB1 and on the total nucleated cell dose. Recent studies have evaluated the importance of high resolution HLA typing, HLA-C match and KIR ligand status. Eapen *et al*[24] found that patients who had units matched at HLA-A, B, DRB1 and HLA-C had better 3 year TRM (9%) and 3 year OS (57%) than patients who were matched at HLA-A, B, DRB1 but with mismatch at HLA-C (TRM 26%; OS 51%) and better outcomes than those with a mismatch on HLA-C with additional mismatch at HLA-A, B, DRB1 (TRM 31%, OS 37%)[24].

Allele level typing was recently analyzed through a combined CIBMTR and Eurocord registry databases. The investigators showed that the frequency of neutrophil recovery was lower for recipients of mismatches at 3 or more alleles. Nonrelapse mortality was higher with units mismatched at 1 to 5 alleles compared with matched units. Overall mortality was not different except for those that received units mismatched at 5 alleles[25]. The author concluded that cord blood transplantation with ≥ 3 allele level mismatches should be avoided.

When a fetus is exposed to non-inherited maternal antigen (NIMA) in utero, fetal T regulator cells are induced to that haplotype. It was hypothesized that recipients who are matched to donor NIMA may have lower mortality post transplantation. 5 year TRM was lower and OS was better among NIMA matched UCBT compared to NIMA mismatched UCBT (TRM 18% *vs* 32%, P = 0.05; OS 55% *vs* 38%, P = 0.04)[26]. It was suggested that NIMA matching can be considered in a patient with multiple UCB units harboring adequate cell dose.

The role of Donor killer cell immunoglobulin-like receptor (KIR) ligand incompatibility has shown variable conclusions. A study from Eurocord showed that patients receiving UCB units mismatched at KIR-ligand had lower relapse and better leukemia-free survival[27]. The results were significant for patients with AML, where recipients of KIR-ligand mismatched in the GVH vector had a better LFS (73% *vs* 38%, P = 0.004) and incidence of relapse (5% *vs* 36%, P = 0.005). This finding was not reproduced in a recent analysis by the Japan society for HCT[28] or by an earlier study from Minneapolis in the myeloablative setting[29]. In the same analysis, Minnesota group found that KIR ligand mismatch is associated with increased grade Ⅲ-Ⅳ acute GVHD and increased risk of death in the reduced intensity setting.

Recent advances in UCB transplantation

Recent work in UCBT is aimed at achieving faster neutrophil engraftment and minimizing early TRM. Direct injection of stem cells into the marrow cavity was hypothesized to reduce systemic "wasting" of such cells. In one unit UCBT, intra-bone marrow injection was associated with lower risk of acute graft *vs* host disease with a sustained engraftment[30]. These results were not reproducible in the DUCBT setting where one of the two units was injected directly into the bone marrow[31].

New methods to enhance engraftment focus on *ex vivo* expansion and co-infusion of purified committed hematopoietic progenitors. One trial evaluated the effects of co-infusion of highly purified "of the shelf" CD34+ progenitors from healthy volunteers. The aim of this strategy was to assess if the additional CD34+ cells will help enhance neutrophil recovery without leading to long term engraftment. Ex vivo expansion is also receiving more support. One expansion method include co-cultures of UCB derived $CD34^{+}CD38^{-}$ precursors with immobilized Notch I ligand[32]. A study by de Lima *et al*[33] reported on 31 patients who received *ex vivo* expanded UCB with cocultures from mesenchymal stem cells. Time to engraftment was significantly improved at 15 d compared to 24 d for patients with unmanipulated cord infusion[34]. The role of *ex-vivo* expansion in UCB transplantation is still an ongoing process.

Engraftment can also be improved by increasing stem cell homing. One such method include the use of complement fragment 3a and diprotein A[34,35] that increase homing through stromal cell-derived factor 1 (SDF1). A recent study through the University of Minnesota established safety of infusing C3a primed units but failed to show effect on engraftment[36].

HAPLOIDENTICAL FAMILY DONOR TRANSPLANTATION

Haploidentical transplantation has gained significant interest in the last few years with the introduction of new GVHD strategies such as T cell depletion with high CD34+ doses to overcome risk of graft failure[37,38], and high dose cyclophosphamide post transplantation. Haploidentical donors are usually defined as having ≥ 2 HLA antigen mismatches at HLA-A, -B and -DRB1 loci. Some studies of haploidentical transplantation included family donors with one HLA antigen mismatch[39]. There are several platforms for performing haploidentical transplantation including *ex vivo* T cell depletion prior to infusion, post infusion depletion with drugs such as cyclophosphamide and unmanipulated infusion with vigorous GVHD prophylaxis. With the choice of multiple available donors, selection can be based on factors such as sex, age, cytomegalovirus status (CMV) and killer immunoglobulin receptor (KIR) incompatibility. One advantage over UCB, is the availability of haploidentical donors for more cells if needed.

OUTCOMES OF HAPLOIDENTICAL TRANSPLANTATION IN ACUTE LEUKEMIA

Ex vivo T-cell depleted haploidentical transplantation

The Perugia group evaluated 104 adult leukemia patients who were conditioned with TBI, fludarabine, thiotepa and antithymocyte globulin (ATG)[37]. Grafts were T-cell depleted using CD34+ immunoselection and no post-transplantation GVHD prophylaxis was used. Ninety-one percent of the patients engrafted, and for the seven patients who failed to engraft, engraftment was successful after a second transplant in six cases. Acute GVHD developed in 8% of patients (2% grade Ⅲ-Ⅳ) and five patients developed chronic GVHD. 16/67 AML patients and 10/37 ALL patients relapsed. The event free survival for patients who were transplanted in complete remission was 48% for AML and 46% for ALL. Table 2 Summarizes studies that compared haploidentical transplantation to other donor sources.

Table 2 Haploidentical hematopoietic cell transplantation compared to transplantation from other graft sources

Year	Number of patients	Neutrophil engraftment (median d)	aGVHD II-IV (%)	cGVHD (%)	100 d NRM (%)	Relapse (2 yr)	Survival (%)
2002[63]	MUD BM 81	16	42	57	23	25	58 (2 yr OS)
	MMUD BM 58	15	33	51	45	26	34
	Haplo 48	14	46	50	42	42	21
2005[53]	Haplo-ALL 74	NA	8	NA	49	38	13 (2 yr LFS)
	UCB-ALL 91		26		41	23	36
	Haplo-AML 151		12		58	18	24
	UCB-AML 91		26		24	24	30
2009[48]	Haplo 56	54/56 (13)	27	23	13	22	68 (2 yr LFS)
	MRD 51	48/51 (12)	14	31	8	17	76

aGVHD: Acute graft versus host disease; cGVHD: Chronic graft versus host disease; NRM: Non-relapse mortality; AML: Acute myelogenous leukemia; ALL: Acute lymphoblastic leukemia; NA: Not available; HCT: Hematopoietic cell transplant; MUD: Matched unrelated donor; BM: Bone marrow; MMUD: Mismatched unrelated donor; Haplo: Haploidentical family donor; OS: Overall survival; LFS: Leukemia free survival; UCB: Umbilical cord blood; MRD: Matched related donor.

Another T-cell depleted study evaluated 173 AML patients and 93 ALL patients who received a haploidentical transplantation[40]. Patients received high dose of $CD34^+$ cell with a median of 10×10^6 CD34+ cells/kg and 11.6×10^6 CD34+ cells/kg in AML and ALL patients, respectively. All patients received myeloablative conditioning containing TBI (74% AML and 92% ALL patients received TBI). Transplant related mortality was 66% for AML and 44% for ALL patients. Relapse incidence was 32% in AML and 49% in ALL patients. Among these patients with advanced disease, LFS was only 1% and 7% for AML and ALL, respectively. However, among patients transplanted in complete remission, the outcomes were more encouraging. Ninety-one percent of recipients engrafted with median time to engraftment of 12 d. The incidence of Grade Ⅱ-Ⅳ GVHD was 5% and 18% among AML and ALL patients, respectively. In the AML group, recipients with a parent or sibling donor had lower TRM than other relatives (35% *vs* 65%, $P = 0.03$). The most common cause of TRM was infections, particularly viral infections such as adenovirus and CMV. Among these patients transplanted in remission, leukemia free survival at 2 years was 29% in AML and 23 % in ALL recipients. This multicenter study showed that infusion of high doses of immunoselected CD34+ cells without post-transplant immunosuppression can yield rapid and sustained engraftment and a low risk of GVHD.

A more selective T cell depletion can be performed by the Clini-MACS system. This system removes the α/β T cells and B cells, and keeps γ/λ T cells, natural killer and other cells. Locatelli *et al*[41] reported on this method at the annual European BMT meeting where patients received myeloablative conditioning regimen of TBI, thiotepa, fludarabine and ATG followed by infusion of TCR α/β/CD19 T cell depleted grafts. This approach yielded sustained engraftment, faster immune reconstitution and low incidence of GVHD.

T-cell replete haploidentical transplantation

Di Bartolomeo *et al*[42] studied the outcome of unmanipulated, G-CSF primed bone marrow haploidentical HCT for patients with high risk hematologic malignancies[42]. The most common conditioning regimen used was thiotepa, busulfan and fludarabine in the myeloabaltive settingwith GVHD prophylaxis compromised of 5 drugs: antithymocyte globulin, cyclosporine, methotrexate, mycophenolate mofetil and basiliximab. The 100 d incidence of grade Ⅲ-Ⅳ acute GVHD was 5%, 1 year cumulative incidence of TRM was 36% and 3 year OS was 54% for standard risk patients[42]. This study showed the feasibility of haploidentical transplantation without ex vivo T cell depletion by using a vigorous pre- and posttransplantation pharmacologic GVHD prophylaxis.

A group from china published results of unmanipulated G-CSF primed marrow haploidentical HCT followed by intensive immunosuppression. The incidence of grade Ⅲ-Ⅳ acute GVHD was 13.4% and the 3 year LFS was 70.7% and 55.9% in standard and high risk AML[43]. Another group from china published on the use of mismatched peripheral stem cells without conditioning regimen but post chemotherapy with cytarabine and mitoxantrone and showed an improvement of complete remission rate (80% *vs* 42.8%; $P = 0.06$) when compared to chemotherapy alone[44].

Cyclophosphamide post haploidentical transplantation

A new Platform for RIC haploidentical transplantation was pioneered by john Hopkins university using high-dose post transplantation cyclophosphamide. Cyclophosphamide induced immune tolerance was first studied by Berenbaum *et al*[45] who showed that mice treated with cyclophosphamide had a prolonged survival of mismatched skin graft if given up to the fourth day post grafting. The ability of post-transplant cyclophosphamide to prolong engraftment post a major histocompatibility mismatched skin graft, several immunologists became interested in developing durable chimerism before solid organ transplantation using post-transplant cyclophosphamide[46]. These earlier studies established the fact that post-transplant cyclophosphamide kills T cells that undergo antigen driven proliferation and hence facilitates decrease risk of GVHD post transplantation.

Earlier phase Ⅱ clinical studies with high dose cyclophosphamide were published in 2008 where cyclophos-

phamide 100 mg/kg given was administered over days +3 and +4 post RIC haploidentical marrow transplantation. The conditioning regimen included fludarabine, cyclophosphamide and TBI. Tacrolimus and mycophenolate were used for GVHD prophylaxis. Neutrophil engraftment was achieved at day 15 with very acceptable acute GVHD rates (grade Ⅱ-Ⅳ GVHD was 35%). Relapse rate was 40%-50% at 1 year with DFS of 34%[47]. Overall and EFS at two years were 36% and 26% respectively. A multicenter trial sponsored through the CIBMTR (CTN0603) using haploidentical BMT for high risk hematologic malignancies was run in parallel with another phase Ⅱ trial (CTN 0604) using DUCBT. The probability of 1 year overall and PFS were 54% and 46% after DUCBT and 62% and 48% after haploidentical transplantation[48].

Post-transplant cyclophosphamide was also applied in the myeloablative setting with peripheral blood cell source in the haploidentical setting. A study by the group in Philadelphia used a high dose TBI based conditioning with cytoxan 120 mg/kg given on days -3 and -2 followed by CD34 selected peripheral blood stem cells[49]. The cumulative incidence of NRM was 22%, grade Ⅲ-Ⅳ acute GVDH 7% and the 3 year survival was 27% for patients with active disease at the time of transplant. Other studies with myeloablative haploidentical transplantation using peripheral blood stem cell and post-transplant cyclophosphamide showed similar results of low incidence of acute GVHD and a 1 year of EFS in the range of 50%-60%[50,51].

The use of peripheral blood as a source of stem cells in the nonablative haploidentical setting with post-transplant cyclophosphamide will allow wider applicability of this approach[52].

Haploidentical transplantation vs UCB transplantation

The outcomes of 407 adult leukemia patients (AML = 242; ALL = 165) after UCB or haploidentical HCT were compared by the eurocord group[53]. Compared to haploidentical HCT, recipients of UCB HCT had delayed neutrophil recovery, higher incidence of acute GVHD and similar incidence of relapse, LFS and TRM. A similar analysis among children with ALL showed that UCB HCT had higher rate of graft failure (23% *vs* 11%, $P = 0.07$). Both UCB and haploidentical HCT had similar TRM and DFS but more relapses were seen in the haploidentical group (RR = 1.7, $P = 0.01$)[54]. These studies show that either UCB or haploidentical HCT is an acceptable option for both adult and children with leukemia in the absence of a fully matched sibling or unrelated donor.

A multicenter trial by the Clinical Trials network (BMT-CTN) is comparing the two stem sources in the reduced intensity setting for patients with acute leukemia. This study will hopefully help find some answers on the selective role of each of these procedures among leukemia patients.

Future strategies in haploidentical HCT

T-cell depletion has become the cornerstone of haploidentical transplantation. This usually leads to profound immunodeficiency lasting for 4-6 mo. Adoptive transfer of memory T lymphocytes helps protect against infections in the first months after transplantation. Infusion of virus-specific cell lines (CMV, Epstein-Barr virus, adenovirus and aspergillus) had inconsistent results in preventing and treating infections[55,56]. Other strategies to hasten the post transplantation immune reconstitution without trigerring GVHD have included infusion of donor T cells after engineering with a suicide gene[57], photodynamic purging[58], and the use of anti-CD25 monoclonal antibody to remove alloreactive cells[59]. The Perugia group studied the infusion of haploidentical donor derived regulatory T cells followed by CD34 cells and donor mature T cells in the setting of T cell depleted haploidentical HSCT[60]. With this approach, Perugia group was able to achieve a very low incidence of acute GVHD and a faster immune reconstitution.

More single centers are showing that usage of peripheral stem cell in the haploidentical RIC setting yields equivalent results to bone marrow infusion.

CONCLUSION

Patients with high risk acute leukemia requiring allogeneic HCT and lacking a fully matched related or unrelated donor have alternative options of stem cell sources. Either haploidentical or UCB is an acceptable option in this situation. The choice of best alternative donor is center dependent and several algorithms have been published to address donor selection[40,61]. As studies continue to improve on engraftment rates in UCB, GVHD and relapse rates in haploidentical HCT, the order of donor choices will likely change with time.

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