blood advances

Related haploidentical donors are a better choice than matched unrelated donors: Counterpoint

Bronwen E. Shaw

Center for International Blood and Marrow Transplant Research, Froedtert & the Medical College of Wisconsin, Milwaukee, WI

This article has a companion Point by Fuchs.

In this article, I will argue that a transplant using a matched unrelated donor (UD) remains the first choice for patients lacking an HLA-identical sibling donor and should be prioritized above a related haploidentical (haplo) donor.

The first successful UD transplant was performed in the United States in 1973. Since then, >60 000 UD transplants have been performed, with long-term survivors of >25 years. As a community, we are very experienced in the practice of UD transplantation, and numerous studies have now shown that survival following a UD transplant is not different from that using an HLA-identical sibling.[1,2]

Several studies have recently compared the outcomes for patients receiving related haplo transplants (concentrating predominately on the posttransplant cyclophosphamide [PTCY] approach) with those receiving UD transplants (Table 1), and all 10 of these studies show no significant difference in overall survival between donor types. However, this should be interpreted with caution, as all of these studies are retrospective, nonrandomized comparisons. The numbers of patients studied are small, particularly in the haplo setting (a total of 813 patients are reported in 10 studies, but individual patients may be represented more than once), such that individual studies are almost certainly underpowered to detect significant differences in outcomes. Additionally, the haplo transplants are performed in more recent years and in some studies have a shorter median follow-up. Importantly, the patient characteristics in many of the studies differ significantly between groups, particularly regarding not only the choice of stem cell source (bone marrow [BM] vs peripheral blood stem cells [PBSCs]) but also in some cases disease risk, comorbidities, and time to transplant. Finally, in all cases, the graft-versus-host disease (GVHD) prophylaxis differs (consistently PTCY for all haplo recipients, but more traditional pharmacological agents in the UD recipients).

While survival in all studies is similar, other outcomes, including engraftment, relapse, and GVHD, do differ.

Engraftment

Numerous publications have shown that engraftment and/or immune reconstitution is delayed after haplo transplant compared with UD transplant,[3,4] and 6 out of 8 (not reported in 2) comparative studies (Table 1) report slower neutrophil and/or platelet engraftment with haplo donors.[5-10]

Relapse

Early studies using the PTCY approach raised a concern regarding an increased relapse risk compared with contemporary approaches.[11-13] This has not in general been borne out in more recent studies, and in the comparative studies shown in Table 1, only 1 study showed a higher incidence of relapse in the haplo setting (acute myeloid leukemia [AML] patients receiving reduced-intensity conditioning).[7] Conversely the incidence of relapse in Hodgkin lymphoma was lower in the haplo setting than in UD setting.[14]

It has been suggested, however, that relapse after haplo may differ from that seen in other settings. Bashey et al[15,16] reported that the postrelapse survival was significantly worse after PTCY haplotransplant than after transplantation using UDs (17% vs 63%, $P < .001$). Although none of these patients were treated with donor lymphocyte infusions (DLIs), the outcome in haplo transplants remained worse even when those receiving DLIs in the UD setting were excluded from the analysis.

An interesting phenomenon recently reported in relapsed patients has been termed “HLA loss relapse.” In this situation, leukemic cells can escape from the donor’s antileukemic T cells through loss of the mismatched HLA haplotype. This was first identified in patients relapsing after haplo transplantation.[17,18] In a more recent study from a single center, Crucitti et al[19] evaluated the incidence in 233 consecutive

Table 1. Retrospective studies comparing outcomes using related haplo donors vs matched unrelated donors

Reference	Donor	N	Disease	Conditioning for haplo	GVHD prophylaxis	Overall survival (%)	Disease-free survival (%)	Nonrelapse mortality (%)	Acute GVHD (%)	Chronic GVHD (%)	Relapse (%)
Burroughs et al[14] (multicenter)	MRD	38	Hodgkin	NMA (fludarabine, 2-Gy TBI, cyclophosphamide)	CNI/MMF	53	23	21	16	50	56
	(m)MUD	24	Lymphoma		CNI/MMF	58	**29**	8	8	63	**63**
	Haplo	28			PTCY/FK/MMF	58 (2 y)	**51 (2 y)**	9 (2 y)	11 (III/IV)	35 (extensive, 2 y)	**40 (2 y)**
Bashey et al[15] (single center)	MRD	117	Mixed malignancy	NMA (fludarabine, 2-Gy TBI, cyclophosphamide)	NR	76	53	13	8	54	34
	(m)MUD	101		MA	NR	67	52	16	11	**54**	34
	Haplo	53		Fludarabine, busulfan, cyclophosphamide	PTCY/FK/MMF	64 (2 y)	60 (2 y)	7 (2 y)	11 (III/IV, 6 mo)	**38 (extensive)**	33 (2 y)
Di Stasi et al[8] (single center)	MRD	87	AML/MDS	NMA (fludarabine, melphalan, thiotepa)	FK/MTX	NR	36	20	11	31	NR
	(m)MUD	108			FK/MTX +ATG	NR	27	35	**6**	21	NR
	Haplo	32			PTCY/FK/MMF	NR	30 (3 y)	24 (1 y)	**0 (III/IV)**	11 (extensive, 3 y)	NR
Raiola et al[4] (single center)	MRD	176	Mixed malignancy	Multiple different regimens used MA in 77%	CsA/MTX	45	32	24	7	29	40
	MUD	43			CsA/MTX + ATG	43	36	33	3	22	23
	(m)MUD	43			CsA/MTX + ATG	40	34	35	9	19	30
	Haplo	92			PTCY/CsA/MMF	52	43	18	4	15	35
	UCB	103			CsA/MMF + ATG	34 (4 y)	33 (4 y)	35 (1000 d)	1 (III/IV)	23	30
Solomon et al[25] (single center)	(m)MUD	48	Mixed malignancy	MA (Cy-TBI fludarabine)	Tacro/MTX	78	73	23	**63**	**58**	23
	Haplo	30			PTCY/tacro/MMF	71 (2 y)	64 (2 y)	3 (2 y)	**43 (all grade)**	**22 (moderate/severe)**	24 (2 y)
Kanate et al[9] (registry study)	MUD	491	Lymphoma	NMA (fludarabine, 2-Gy TBI, cyclophosphamide)	CNI	62	49	22	60	**62**	28
	MUD	241			CNI +ATG	**50**	**47**	26	56	**37**	36
	Haplo	185			PTCY/CNI/MMF	**60 (3 y)**	**38 (3 y)**	17 (3 y)	52 (all grade, 6 mo)	**15 (all grade, 2 y)**	36 (3 y)
Ciurea et al[7] (registry study)	MUD	1982	AML	Multiple different regimens used MA in 54%	CNI + MMF/MTX	44(RIC)50(MA)	NR	**23 (RIC), 20 (MA)**	**11 (RIC), 13 (MA)**	**52 (RIC), 53 (MA)**	**42 (RIC), 39 (MA)**
	Haplo	192			PTCY/CNI/MMF	46(RIC) 45(MA) (3 y)	NR	**9 (RIC), 14 (MA) (3 y)**	**2 (RIC), 7 (MA) (III-IV, day 90)**	**34 (RIC), 30 (MA) (3 y)**	**58 (RIC), 44 (MA) (3 y)**
Blaise et al[6] (single center)	MRD	47	Mixed malignancy	Multiple different regimens used NMA in 68%	CsA + ATG	78	64	11	13	16	25
	(m)MUD	63		RIC in 32%	CsA + ATG (±MMF)	51	**38**	**34**	25	**14**	31
	Haplo	31			PTCY/CsA/MMF	70 (2 y)	**67 (2 y)**	**10 (2 y)**	10 (III/IV)	**0 (severe, 2 y)**	23 (2 y)
Bashey et al[5] (single center)	MRD	181	Mixed malignancy	Multiple different regimens used	Tacro/MTX ± ATG	72	56	14	28	44	30
	MUD	178			Tacro/MTX ± alemtuzumab	59	50	16	48	**47**	34
	Haplo	116		MA in 40%	PTCY	57 (2 y)	54 (2 y)	17 (2 y)	41 (2 y)	**31 (moderate/severe, 2 y)**	29 (2 y)
Baker et al[10] (single center)	(m)MUD	59	Mixed malignancy	NMA (fludarabine, 2-Gy TBI, cyclophosphamide)	Tacro/MTX or MMF + ATG	403	293	29	8	18	46
	Haplo	54			PTCY/tacro/MMF	465 (median days)	245 (median days)	28 (2 y)	13 (III-IV, day 180)	24 (moderate/severe, 2 y)	44 (2 y)

Bold indicates significant differences between haplo and matched UD.

AML, acute myeloid leukemia; ATG, anti–thymocyte globulin; CNI, calcineurin inhibitor; CsA, cyclosporine; FK, FK506 (tacrolimus); GVHD, graft-versus-host disease; MA, myeloablative conditioning; MDS, myelodysplastic syndrome; MMF, mycophenolate mofetil; MTX, methotrexate; MRD, matched related donor; (m)MUD, (mis)matched unrelated donor; NR, not reported; NMA, nonmyeloablative conditioning; PTCY, posttransplant cyclophosphamide; RIC, reduced-intensity conditioning; tacro, tacrolimus TBI, total body irradiation; UCB, umbilical cord blood.

transplants from partially HLA-mismatched related and UDs. Of 84 relapses, 23 were with HLA loss and, in the haplo setting, accounted for 33% of the relapses. Postrelapse survival was poor, regardless of whether patients had HLA loss or not. In this study, no case of HLA loss relapse was seen in the UD setting. Although case reports have been published in UD,[20-22] to date, this mechanism of relapse in that setting appears to be rare or anecdotal.

GVHD

A fairly consistent finding and major stated benefit to the haplo platform is the reduction in GVHD, in particular chronic GVHD. This has been shown in numerous studies.[23,24] Of the 10 comparative studies, 6 studies show that haplo patients are less likely to experience chronic GVHD (either overall or moderate and/or extensive; Table 1). Severe acute GVHD is more commonly shown to be similar between these groups, although 3 of the 10 studies (Table 1) reported a significant reduction in acute GVHD.

There are several reasons other than the donor source that might explain this difference in (predominantly chronic) GVHD between the groups. Firstly, in many of the comparative studies, mismatched UDs are included in the UD comparator group.[6,10,14,15,25] Secondly, BM is more commonly used in the haplo setting. Thirdly, the GVHD prophylaxis is PTCY in all haplo cases and the more traditional calcineurin (CNI)/methotrexate or mycophenolate (MMF) combination in the UD setting, with or without additional TCD depending on the study. This raises the question of whether it is the donor source or the "transplant package" that has the greater association with the reduction in GVHD.

This question has been addressed in a few studies. When restricting the population to those who received BM only in the Center for International Blood and Marrow Transplantation Research (CIBMTR) AML study, there were no differences in the rates of chronic GVHD at 3 years between haplo or UD transplantation using either myeloablative (30% [95% confidence interval (CI_, 21-39]; n = 85 vs 36% [95% CI, 30-43]; n = 231) or reduced-intensity conditioning (34% [95% CI, 24-44]; n = 77 vs 30% [95% CI, 20-41]; n = 80),[7] while a difference had been seen considering both graft sources. Conversely, when restricting their analysis to PBSC recipients only, Bashey et al[5] found that the incidence of moderate-severe chronic GVHD was significantly lower in haplo recipients than UD recipients (2-year CI, 25% vs 48%; $P = .002$), suggesting that the PTCY may play a role in chronic GVHD reduction. In support of this, 2 studies have shown similar rates of acute and chronic GVHD in patients receiving either BM or PBSC with a haplo PTCY (plus CNI and MMF) approach.[26,27]

Several investigators have reported outcomes for patients receiving PTCY in the setting of a matched UD transplant, using either BM (as the sole agent)[28,29] or PBSC (with CNI or MMF).[30,31] In these 4 studies, the incidence of grade III-IV GVHD is between 0% and 19% (>8% in 1 study only), and the incidence of chronic GVHD is between 11% and 22%. These rates compare favorably with historical rates reported in the literature using conventional GVHD prophylaxis or to a reported comparator group including ATG.[31]

Finally, in a retrospective comparative study of haplo and UD transplant recipients, all of whom were treated with PTCY, CNI, and MMF, Rashidi et al[32] reported no significant difference in the incidence of acute or chronic GVHD (there were no significant differences found in any outcome, with the exception of neutrophil engraftment, which was faster after UD transplantation).

Donor factors

By studying thousands of patient-donor pairs, we have gained a better understanding of how to improve outcomes post–UD transplant through the judicious selection of secondary donor characteristics in those with multiple equally HLA-matched donors. It is well understood in this setting that selection of a younger donor improves survival,[33-35] that avoiding disadvantageous HLA-DPB1[36,37] and killer-cell immunoglobulin-like receptor (KIR)[38,39] types improves survival, and that selection by cytomegalovirus status,[37,40,41] ABO type,[34] and sex[34] can mitigate transplant complications. Algorithms to prioritize these factors are being developed. In addition, it is known that the selection of BM over PBSCs reduces chronic GVHD.[42-44] The use of a haplo donor in general offers fewer choices of secondary characteristics, and few studies have addressed donor selection algorithms.[23,45,46] Another important factor is donor-specific antibodies, which present a barrier to transplant in the haplo setting.[45,47,48] The development of posttransplant donor clonal hematopoiesis is another phenomenon recently recognized, which may be more common in haplo transplantation due to the increased use of older donors.[49,50]

In conclusion, through the study of thousands of patients receiving UD transplants over 4 decades, the transplant community has gained an excellent understanding of the expected short- and long-term toxicities and outcomes. We know how to select a UD to maximize good outcomes, and we have a solid backbone on which to investigate newer factors to further this improvement (HLA-DPB1 and KIR). Importantly, we have an extensive registry of volunteer UDs,[51] with multiple protections in place to ensure their participation is clinically, ethically and morally appropriate.[52] Physicians performing haplo transplants should ensure that the health and well-being of their patient's related donors are being given equal consideration.[53]

In contrast, haplo transplants are more recent, and while these clearly show the benefit of extending the possibility of transplant to certain patients, particularly those from ethnic minority groups,[54,55] or when the cost of UD provision is high,[56] long-term outcomes (including cost) are uncertain. Finally, while comparative studies show survival to be similar to UD transplants, these studies are nonrandomized and underpowered, and none to date have shown survival with a haplo donor to be superior. Since an appropriately powered randomized trial to show noninferiority in disease-free survival in haplos would require >3000 patients, this is unlikely to be feasible. For all these reasons, it is currently too early to know whether transplantation with a haplo donor will ultimately be as good or better than transplantation using a matched UD.

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Correspondence: Bronwen E. Shaw, CIBMTR/Froedtert & the Medical College of Wisconsin, 9200 W Wisconsin Ave, Suite C5500, Milwaukee, WI 53226; e-mail: beshaw@mcw.edu.

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