POINT-COUNTERPOINT

blood advances

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

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This article has a companion Counterpoint by Shaw.

When a person seeks to purchase a product in the marketplace, be it a car or an apple, 2 product characteristics are decisive: price and quality. If a customer perceives 2 varieties of apples to be of equal quality, then the cheaper variety will be preferred and purchased. For patients who lack an HLA-matched sibling donor, bone marrow transplant physicians often must choose between a well-matched unrelated adult donor (MUD) or an HLA-haploidentical (haplo) relative. In the past, the choice was fairly easy: outcomes after transplantation using MUDs approached those from matched sibling donors[1-3] and both donor types were easily superior to the poor survivals seen using haplo donors.[4] However, haplo transplant outcomes have improved dramatically with modern methods of graft-versus-host disease (GVHD) prophylaxis including the combination of antithymocyte globulin, cyclosporine, methotrexate, and mycophenolate mofetil[5] or high-dose, posttransplantation cyclophosphamide.[6] It is now possible to say that haplo donors are a better choice than MUDs because grafts from haplo donors offer the same or better quality at a lower price than grafts from MUDs.

Unrelated donor stem cell grafts are more expensive than related donor stem cell grafts because of the costs associated with maintaining unrelated donor registries, performing searches, and providing the logistics to get the donor to a transplant center and the graft to the patient. Fortunately, the cost of acquiring unrelated donor stem cells is not a barrier to transplantation in much of the developed world, and unrelated donor transplants outnumber transplants from related donors in the United States[7] and in Europe.[8] However, the fact remains that many developing countries have not established registries of unrelated donors because of the associated costs, and these countries benefit substantially from the haplo donor option.

Table 1 lists other practical advantages of haplo over unrelated donors. The most salient advantage of the haplo donor option is donor availability. There is significant ethnic variation in the availability of unrelated donors, ranging from about 19% for African Americans to 80% or more for Caucasians of Northern European origin. In contrast, nearly all patients have an available haplo donor because all biologic parents and children of a patient are haplo and each sibling or half-sibling has a 50% chance of being haplo. The major limitation to the availability of haplo donors is the presence of antidonor HLA antibodies, usually in parous women against paternal HLA antigens present in the children.[9] Even if such antibodies are present, they can oftentimes be removed by a desensitization procedure to permit transplantation.[10] Haplo donor availability increases further if one considers transplantation from extended family members such as aunts, uncles, nieces, and nephews, who on average have a 50% chance of being haplo, or cousins, who have a 25% chance of being haplo.

Some patients need to get to transplant quickly because their remission is not expected to last or because their health status is precarious and likely to deteriorate. In such circumstances, the transplant is considered urgent and there is a need to obtain and infuse the product as quickly as possible. There has been a dramatic improvement in the speed with which unrelated donor transplantation registries can mobilize donors for transplantation, but delays are unavoidable. We simply do not know how many patients become ineligible for transplantation while waiting for a MUD graft to arrive. In 2008, more than 34 000 patient searches were initiated for a stem cell donor, but only 9747 patients received an unrelated adult donor stem cell transplant.[11] It seems reasonable to assume that some of the patients did not make it to transplant because a suitably matched donor could not be identified and mobilized in time. In contrast, haplo donors are readily available and usually are highly motivated to donate to their family member, especially in the case of parent-to-child transplantations. The logistical advantages of related over unrelated donors extend to subsequent cellular therapies, such as donor lymphocyte infusion to treat posttransplantation relapse. Finally, unrelated donor products must be shipped to their destination and can degrade between the time of collection and the time of infusion. The effects of

Table 1. Logistical comparison of related haplo vs HLA-matched unrelated donors

	MUD	Haplo
Donor availability	20%-80%[18]	>95%
Time to graft acquisition	Slower	Faster
Time between collection and infusion	Longer	Shorter
Ease of repeat donations	Harder	Easier

"cold ischemia" time on transplant outcomes are unknown, but are unlikely to weigh in favor of unrelated over haplo grafts.

None of the financial and logistical advantages of related haplo donors over unrelated donors would matter if hematopoietic stem cell transplants from MUDs produced better outcomes. Table 2 shows a number of published, retrospective comparisons of the 2 donor types and, frankly, it is hard to see an advantage of the unrelated donor option. A reasonable interpretation of the data is that haplo stem cell transplantation (SCT) with high-dose, posttransplantation cyclophosphamide (PTCy) is associated with similar overall and progression-free survivals as with MUD SCT, but with perhaps less chronic GVHD. Indeed, a recent study of lymphoma patients receiving either haplo SCT with PTCy or HLA-matched sibling SCT came to the same conclusion.[12] It may be argued that the comparison is unfair because the haplo transplants used PTCy, whereas the MUD transplants did not. Support for this argument comes from recent reports showing good survival and low incidence of chronic GVHD after MUD SCT with PTCy.[13,14] So, it may turn out that PTCy is the great equalizer of adult stem cell sources by abolishing the detrimental effect of HLA or minor histocompatibility mismatches on the outcome of allogeneic SCT.[15]

Concerns have been raised about a higher frequency or worse prognosis of specific complications of haplo SCT or of PTCy, but data so far are reassuring. For example, loss of mismatched HLA occurs in one-third of relapses after haplo SCT, but these relapses have the same prognosis as classical relapse with retention of mismatched HLA.[16] Also, donor stem cells are exposed to the potentially mutagenic effects of PTCy, but in 1 report there were only 5 cases of donor-derived malignancy among 790 recipients of allogenic SCT with PTCy.[17]

Some might say that a prospective, phase 3 trial that randomizes patients to haplo plus PTCy vs MUD is required to establish which donor type is "better." I would argue that such trials are useful for comparing drugs of fixed chemical composition but are inadequate for comparing specific ingredients (haplo vs MUD) of a recipe (conditioning regimen, donor type, stem cell collection method, GVHD prophylaxis). The loser will always claim that the trial results are obsolete because a better recipe is available. Better to let the market decide.

The foregoing discussion should not be cause for despair among advocates of unrelated donor SCT. If HLA matching is no longer the paramount consideration in donor selection, then perhaps other characteristics, such as non-HLA genes or donor age, may come to the fore. For instance, an HIV-infected patient may benefit from a partially HLA-mismatched SCT from an unrelated donor who lacks the CCR5 receptor. An older patient without children may do better with a young, partially HLA-mismatched unrelated donor than with an older, HLA-haploidentical sibling. Rather than squabble over which is the best donor source, transplant physicians should take

Table 2. Retrospective comparisons of outcomes of haplo SCT plus posttransplantation cyclophosphamide vs MUD SCT

Reference	RIC or MAC	N		aGVHD II-IV (%)		cGVHD (%)		NRM (%)		Relapse (%)		Overall survival (%)		Event-free survival (%)	
AML ± MDS		Haplo	MUD	Haplo	MUD	Haplo	MUD	Haplo	MUD	Haplo	MUD	Haplo	MUD	Haplo	MUD
19	MAC	104	1245	**16**	**33‡**	**30**	**53‡**	14	20	44	39	45	50	42	41
	RIC	88	737	**19**	**28***	**34**	**52†**	**9**	**23‡**	**58**	**42†**	46	44	33	35
20	RIC	32	108	–	–	–	–	24	25	33	23	–	–	43	42
21	Mix	52	88	40	36	10	9	27	27	29	43	42	37	44	30
22	Mix	62	21§	40	19	6	5	22	16	31	26	53	58	–	–
Hodgkin lymphoma															
23	RIC	28	38	43	50	35	63	9	8	40	63	58	58	**51**	**29***
Non-Hodgkin lymphoma															
24	RIC	185	491	52	60	**15**	**62‡**	17	22	36	28	60	62	47	49
25	RIC	26	28	–	–	15	29	15	27	19	7	77	71	65	68
Mix															
26	Mix	92	43	14	21	15	22	18	33	35	23	52	43	43	36
27	MAC	30	32	43	63	56	69	3	16	24	28	78	62	73	56
28	RIC	54	59	63	53	32	20	30	29	44	49	–	–	26	22
29	RIC	31	63	**23**	**44***	13	24	10	34	23	31	70	51	**67**	**38***
30	Mix	116	178	41	48	**31**	**47†**	17	16	29	34	57	59	54	50

Significant differences are shown in bold type: *.01 ≤ P ≤ .05; †.001 ≤ P < .01; ‡P < .001.

aGVHD, acute graft-versus-host disease; AML, acute myeloid leukemia; cGVHD, chronic graft-versus-host disease; NRM, nonrelapse mortality; RIC, reduced intensity conditioning (includes nonmyeloablative conditioning); MAC, myeloablative conditioning; MDS, myelodysplastic syndrome.

§Mixture of matched sibling and MUD transplants.

pride in having solved the problem of donor availability and move on to bigger and more exciting challenges, such as preventing relapse and curing solid tumors.

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