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Alternative donor allogeneic hematopoietic cell transplantation for acute myeloid leukemia

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Abstract

Allogeneic hematopoietic cell transplantation (alloHCT) provides a potentially curative therapy for patients with high-risk or chemorefractory acute myeloid leukemia (AML). Historically, the applicability of alloHCT has been limited as only 30–35% of patients have human leukocyte antigen (HLA)-matched siblings and outcomes using other donor types have been markedly inferior due to excess toxicity, graft failure, graft-versus-host disease, and consequently non-relapse mortality. Advances in HLA typing, graft-versus-host disease prophylactic approaches, and other transplantation techniques have successfully addressed these historical challenges. Herein, we review recent alloHCT studies using volunteer unrelated donors, umbilical cord blood units, or HLA-haploidentical donors, specifically focusing on studies that compared outcomes between donor sources. Although none are randomized and most are retrospective, these analyses suggest that current outcomes for AML patients using most alternative donor types are comparable to those seen using HLA-matched-siblings.

Introduction

The curative potential of allogeneic hematopoietic cell transplantation (alloHCT) in treating patients with acute myeloid leukemia (AML) was first demonstrated over 50 years ago. Although cure was achievable in some patients with chemorefractory disease, alloHCT demonstrated a more dramatic benefit when used to treat AML patients earlier in their disease course.¹ In fact, relapse was lower after alloHCT than after consolidation

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chemotherapy,² suggesting that some patients with AML in first complete remission might benefit by proceeding directly to alloHCT.^{3, 4} Even so, many patients suffered non-relapse mortality (NRM),⁵ stemming from a number of challenges to the success of alloHCT. These included graft failure, graft-versus-host disease (GVHD) in both its acute and chronic forms, and post-grafting opportunistic infections related to long-lasting deficiencies in both humoral and cellular immunity.

Encouraging results with alloHCT were restricted to the minority of patients who had an HLA-matched-sibling donor (MSD). A suitable unrelated donor (whether HLA-matched-unrelated donor [MUD], one-locus HLA-mismatched-unrelated donor (mmUD), or umbilical cord blood [UCB] unit) can be found for most individuals.⁶ Furthermore, HLA-haploidentical (haplo) related donors are available for nearly all individuals. Nevertheless, outcomes were less favorable when alternative donors were used,^{7–11} establishing HLA-matched-sibling donors as the gold standard donor source. However, improvements in transplantation approaches over the past few decades have led to markedly improved outcomes after alternative donor alloHCT [Figure 1], now challenging whether MSD alloHCT still achieves superior outcomes. Herein, we review the expanding role of alternative donor alloHCT in the treatment of AML patients.

HLA-Matched-Unrelated Donors

Since HLA-matching has been prioritized in donor selection, a patient without an HLA-matched-related donor potentially could benefit from alloHCT using a volunteer HLA-matched-unrelated donor. Index cases from the early 1980s proved the feasibility of this approach for treating acute leukemia.¹² Although initial studies suggested relative equivalence with MSD alloHCT,¹³ a large, prospective case-control, multi-institutional study showed inferior engraftment, higher rates of grade II-IV acute and extensive chronic GVHD, and worse survival for unrelated donor alloHCT compared with MSD alloHCT.^{10, 11}

Given discrepancies in results between studies and the inclusion in some studies of HLA-mismatched- unrelated donors (mmUDs), large registry-based analyses were undertaken to evaluate the relative equivalence of MUD versus MSD alloHCT. The first compared alloHCT patients reported to the International Bone Marrow Transplant Registry between 1985 and 1991.¹⁴ Each of graft failure, grades II-IV and III-IV acute GVHD, chronic GVHD, and NRM (>50%) were higher for all alternative donors (MUDs, one locus mmUDs, or one- or two-locus HLA-mismatched related donors) when compared with MSDs. A later registry study from the Center for International Blood and Marrow Transplant Research (CIBMTR) reported on alloHCT for 4099 (941 8/8 MUDs and 3158 MSDs) adult patients with AML, ALL, or CML performed between 1995 and 2004.¹⁵ GVHD, particularly grade II-IV acute GVHD, was slightly more common in the MUD cohort. For AML patients, MUD allografting was associated with higher rates of both NRM and relapse, resulting in significantly lower DFS and questioning whether there indeed was a superior graft-versus-leukemia effect associated with MUD compared with MSD allografting.

Based on these and other studies, MUDs standardly have been considered a second-tier donor source. However, simultaneous to the second study above, advances in HLA typing were improving outcomes for MUD alloHCT. HLA typing originally had been performed by serologic methods for HLA-A, HLA-B, and HLA-DR only. The importance of HLA-C serologic matching was later recognized, although “permissive” mismatching in HLA-C may exist that do not deleteriously affect outcomes.¹⁶ By the mid-1990s, it was discovered that serologic typing was inferior to DNA-based typing.^{17, 18} In fact, one study published in 1998 performed HLA typing by both serologic and DNA methods and found that only 45% of patients who were serologically matched were in fact HLA-matched by DNA testing of HLA-A, -B, and DRB1.¹⁹ Furthermore, HLA-C and -DQ testing had not been performed serologically, and 41% of donor-recipient pairs were found to be incompatible at those loci by DNA testing.¹⁹

Therefore many patients from earlier studies of “MUD” alloHCT may not have in fact received 8/8 HLA-matched allografts. Even single HLA-mismatches in HLA-A, -B, -C, and – DRB1 were found to be associated with worse survival,^{20, 21} in addition to the negative effects of specific HLA-locus-mismatching on the incidences of graft failure, GVHD, and relapse.^{19–22} HLA matching at HLA-DQ, HLA-DP, and low expression HLA-DR loci also may impact outcomes, although effects of mismatching at these loci is much more prominent in alloHCT using 6/8 or 7/8 mmUDs.^{23, 24} Beyond better HLA typing, improved supportive care has played an important role in improving outcomes for unrelated donor alloHCT. Furthermore, the incorporation of anti-thymocyte globulin (ATG)^{25, 26} or more recently post-transplantation cyclophosphamide (PTCy)^{27, 28} into GVHD prophylactic approaches may alleviate some of the increased alloreactivity associated with MUD compared with MSD allografting.

Overall, with these advances in transplantation approaches, survival outcomes for AML patients treated with MUD alloHCT currently appear only slightly lower than those seen for patients receiving MSD alloHCT, and these small differences do not typically reach statistical significance [Table 1].^{28–36} While most studies do show higher rates of grade II–IV acute GVHD with MUDs, grade III–IV acute GVHD and NRM appear similar between the two donor types.^{28, 30, 32–34} Inconsistent effects on chronic GVHD have been reported; likely MUD allografting is associated with increased chronic GVHD, but this risk appears to be mitigated by the addition of ATG [Table 1].²⁶ Interestingly, given the greater alloreactivity and associated GVHD that accompanies female-into-male allografting, male MUDs may be associated with nearly identical results as female MSD alloHCT.³⁴

Ultimately, these studies are limited by most being retrospective with the few prospective studies not incorporating randomization of the donor source. Biologic randomization may alleviate some potential sources of bias but introduces others. For example, the time from diagnosis to transplant may be longer with MUD alloHCT or the threshold for MSD alloHCT may be lower than for MUD allografting due to perceived differences in the relative toxicities and outcomes between the two donor types. Even so, the 2–4 month delay in procuring a MUD allograft can make MUDs a non-viable donor option for many patients with aggressive AML in fragile remissions. Furthermore, it is much more challenging to re-access an unrelated donor for adoptive cell therapeutic strategies to prevent or treat relapse.

Umbilical Cord Blood

The potential of UCB to be used as a donor source for alloHCT was developed through the work of Broxmeyer and colleagues. In a study reported in 1989, these investigators examined over 100 human UCB units.³⁷ Firstly, they determined that UCB-derived hematopoietic progenitor cells remained viable and functionally active for at least three days when stored at 4°C or even room temperature, allowing the routine transportation and cryopreservation of UCB to be performed. Secondly, the number of progenitor cells obtained from a single UCB unit was comparable to that reported necessary for successful engraftment of bone marrow alloHCT. These properties of UCB allowed the establishment of UCB banks that could provide HLA-matched or partially-HLA-mismatched-unrelated UCB parallel to that provided by the National Marrow Donor Program (NMDP) for volunteer unrelated donors. Although 75% of European-descent patients have an 8/8 MUD in the NMDP registry, such a donor is available for only 16–19% of African-Americans.⁶ Nevertheless, greater than 80% and 95% of adult and pediatric patients, respectively, of any ethnicity will have an available 4/6 HLA-matched (intermediate level at HLA-A and -B and high resolution at HLA-DRB1) UCB unit.⁶

Early studies demonstrated the feasibility of the UCBT approach.³⁸ However, the ideal transplantation platform for UCBT has been debated. One major factor has been one-versus-two-unit UCBT for adults. The stem cell dose obtainable from many UCB units is often considered too low for engrafting larger adults. The use of double-unit UCBT (dUCBT) has demonstrated encouraging results, but it remains unclear whether an adequately-sized single-unit UCBT (sUCBT) is sufficient. Several studies have retrospectively^{39–42} or prospectively⁴³ compared sUCBT versus dUCBT. Engraftment was similar in all studies. All but one⁴³ report showed an increased risk of grade II–IV acute GVHD with dUCBT, but grade III–IV acute and chronic GVHD were less consistently higher after dUCBT. Three of the five studies showed lower relapse after dUCBT.^{39, 42, 43} NRM was similar between sUCBT and dUCBT in all studies, and only one report showed a survival advantage to dUCBT.³⁹ The optimal conditioning intensity for UCBT also is uncertain. A recent retrospective study showed, as expected, higher NRM but lower relapse and thus similar overall survival (OS) after myeloablative conditioning compared with reduced-intensity conditioning (RIC) UCBT.⁴⁴ Meanwhile, another retrospective study showed a survival advantage for AML patients receiving myeloablative conditioning.⁴⁵

Regardless of disagreement as to the optimal UCBT platform, a number of analyses have compared outcomes between UCBT and alloHCT using MSDs or MUDs. An early registry study from the CIBMTR examined outcomes for children with acute leukemia undergoing bone marrow or single-unit UCB alloHCT from HLA-matched or HLA-mismatched donors.⁴⁶ This study found similar survival for all groups, but the highest survival actually was seen with HLA-matched UCBT. However, an HLA-matched UCB unit is not available for most individuals,⁶ particularly adults who may require a large single-unit or double-unit UCBT. Within the last several years, a plethora of retrospective studies including AML patients have compared outcomes after unrelated (and generally HLA-mismatched) UCBT with outcomes after MSD and/or MUD alloHCT [Table 2].^{47–57} These studies consistently showed delayed neutrophil and platelet engraftment with higher incidences of non-

engraftment in patients treated with UCBT. The effects on acute GVHD were less uniform with several showing reduced grade II–IV but not grade III–IV acute GVHD after UCBT. Chronic GVHD rates were consistently lower after UCBT, although these differences were not always statistically significant. However, these studies are complicated by differing percentages of patients within each cohort who received ATG, which was generally more frequently given to UCBT recipients. Almost all studies revealed higher NRM after UCBT, while the impact on relapse differed between studies. Due to the high NRM, most studies showed lower DFS and OS after UCBT, although in many cases the differences were not statistically significant. These studies conclude that UCBT is a reasonable alternative donor option when a MSD donor is not available. Whether unrelated UCB or MUD donors should be preferentially used when both are available is unclear at this time.

Recent work in UCBT has focused on reducing the high NRM associated with the approach, particularly via improving the rapidity of engraftment and improving post-transplantation immune reconstitution. Co-culturing UCB cells with mesenchymal stromal cells prior to infusion resulted in nucleated cell expansion and reduced both graft failure and time to engraftment.⁵⁸ An alternative strategy has involved infusing both an UCB unit and a haplo allograft.^{59–61} Although this approach resulted in rapid engraftment, two of the three published studies still showed high NRM of 28% and 35%. Overall, low chronic GVHD and potentially lower relapse with UCBT have made it a promising transplantation platform to continue to refine. Furthermore, this donor source is rapidly available to more than 80% of patients of any ethnicity without the need for further donor evaluation or matching.⁶

HLA-Haploidentical Donors

HLA-haploidentical (haplo) alloHCT initially generated poor outcomes, largely related to high rates of graft failure and GVHD.^{7–9} The Fred Hutchinson Cancer Research Center group compared alloHCT outcomes between 1975–1986 using either MSD or partially HLA-mismatched-related donors, with the latter group having higher incidences of graft failure (12%) and GVHD (>50% grade III–IV acute GVHD) as well as inferior survival (~10% for two- or three-locus HLA-mismatched alloHCT),^{8,9} reflecting the intense bi-directional T-cell alloreactivity associated with HLA-mismatching.^{8,9} Several investigative groups have since overcome these barriers to HLA-haploidentical alloHCT (haploHCT), among which three strategies have been the most developed.

The Memorial Sloan-Kettering and the University of Perugia groups pioneered the strategy of T-cell depletion (TCD), which was initially performed through negative selection by soybean agglutination and erythrocyte rosetting^{62,63} and more recently has involved CD34-positive selection.⁶⁴ TCD was accompanied by a “mega-dose” of CD34⁺ cells following intensive myeloablative and immunoablative conditioning, all designed to promote engraftment.^{62–64} Engraftment was 90–95% with this approach, and both acute and chronic GVHD were <10% despite no additional post-grafting GVHD prophylaxis. Relapse was not higher than would be expected for patients with high-risk or advanced hematologic malignancies undergoing T-cell-replete alloHCT, potentially related to natural killer cell alloreactivity.⁶⁴ However, NRM was quite high at 37–53%, largely related to infection.^{62–64} Efforts to improve immune reconstitution after TCD haploHCT, including CD3/CD19-

negative selection⁶⁵ or reintroduction of lower levels of both conventional and regulatory T cells,⁶⁶ have not thus far been successful in substantially reducing this high NRM. A European Blood and Marrow Transplant (EBMT) study of 173 AML patients treated with TCD haploHCT showed 2-year NRM rates of 36%, 54%, and 66% for patients in CR1, CR2, or advanced disease at the time of alloHCT.⁶⁷ Relapse rates were 16%, 23%, and 32%, respectively, resulting in DFS rates of 48%, 21%, and 1%, respectively.

A second approach (called the GIAC protocol) was developed by the Peking University group in Beijing, China, and incorporated granulocyte colony-stimulating factor (G-CSF) treatment of the donor, the use of both T-cell-replete PBSC and bone marrow allografts, and intensive pharmacologic immunosuppression including ATG.^{68–70} This strategy resulted in universal engraftment and favorable NRM and relapse rates. However, cumulative incidences of GVHD were quite high, particularly chronic GVHD which occurred in up to 74% of patients.⁶⁹ A report by an Italian group of a modification of this approach through using only BM allografts and adding basiliximab was successful in reducing chronic GVHD to 17% but resulted in a 7% rate of graft failure and a NRM of 36%.⁷¹ Outcomes for AML patients treated with the GIAC protocol have appeared quite encouraging. One large report from the Peking group showed relapse rates for standard-risk and high-risk AML patients of 12% and 20%, respectively, resulting in DFS rates of 71% and 56%, respectively.⁷⁰ Four reports from three Chinese groups have shown similar DFS after haploHCT using the GIAC protocol compared with outcomes using MSD alloHCT [Table 3].^{68, 72–74} In fact, one study of patients with very high-risk acute leukemia even showed better survival due to lower relapse after haploHCT.⁷³ Grade II–IV acute GVHD occurred more frequently after haploHCT in all four studies. Chronic GVHD and NRM rates were similar between haploHCT and MSD alloHCT in three of the four studies.

A third approach was developed at Johns Hopkins Hospital and involved the administration of high-dose cyclophosphamide on days +3 and +4 after infusion of a T-cell-replete bone marrow allograft.^{75, 76} This PTCy strategy appears to work, at least in part, by eliminating proliferative, alloreactive T-cells, while preserving regulatory T-cells.^{76, 77} While graft failure was seen (2–13%),^{75, 78} given low intensity conditioning, most patients with graft failure quickly experienced autologous reconstitution.⁷⁵ NRM, severe acute GVHD, and particularly chronic GVHD were quite low. Relapse was relatively high,^{75, 78} although studies by other centers using higher intensity conditioning seemed to provide more acceptable relapse rates while reducing graft failure and not significantly impacting NRM or GVHD.^{79, 80} No AML-specific outcomes have yet been published for PTCy haploHCT. However, the Hopkins experience using RIC has shown chronic GVHD of 16%, NRM of 10%, and OS of 52% at 4 years for AML patients in remission without measurable residual disease at haploHCT (Margaret Showel, personal communication).

Three retrospective studies including AML patients have compared outcomes between haploHCT using PTCy with MSD or MUD alloHCT not using PTCy and have shown that GVHD and survival outcomes were similar with haploHCT [Table 4].^{79–81} Recent unpublished registry data also have shown equivalence between outcomes using PTCy haploHCT and MUD alloHCT (Ciurea et al., American Society of Hematology, 2014). One of the published studies compared outcomes across five different donor types (also including

mmUD and UCB) treated at the same institution over a seven year period.⁸⁰ Those latter two groups had worse survival than the other three groups (MSD, MUD, haplo) with survival after UCBT being statistically lower than after MSD alloHCT. These differences in outcomes were largely reflective of slower immune reconstitution and higher NRM for MUD, mmUD, and UCB alloHCT. There was no statistical difference in relapse rates across treatment groups. Two parallel prospective studies of alternative donor transplantation, one using PTCy haploHCT and the other using UCBT, was recently reported.⁷⁸ Eligibility criteria were standardized between the two protocols, and each used similar RIC-based transplantation platforms. Engraftment, acute and chronic GVHD, and NRM all were better after PTCy haploHCT. However, relapse rates were lower after UCBT, leading to statistically similar progression-free and overall survival rates between the two studies. These outcomes have spurred an ongoing randomized phase III study directly comparing UCBT versus PTCy haploHCT for the treatment of advanced hematologic malignancies.

Only one study published to date has compared different haploHCT approaches. An MD Anderson group examined their institutional outcomes from two successive clinical trials: one of TCD and the other of PTCy haploHCT. Although the patients were not treated concurrently and thus follow-up was shorter for the PTCy-treated patients, platelet engraftment, T-cell reconstitution, infectious complications, chronic GVHD, and particularly 1-year NRM (42% versus 16%) were significantly better for PTCy-treated patients. Progression was similar between the groups (36% versus 34%) leading to substantially better 1-year progression-free and overall survival for PTCy recipients (OS: 30% versus 64%). Different haploHCT approaches have not yet been compared prospectively, and all current approaches have their own challenges to address. Even so, haploHCT using any transplantation platform has the advantages of rapid donor availability for nearly all patients and the ready availability of the donor for further adoptive cell therapeutic strategies.

Conclusion

Given initial reports showing inferior outcomes with other donor sources, HLA-matched-sibling donors historically have been the preferred donor source. However, as only approximately one-third of patients have an HLA-matched-sibling donor, several alternative donor transplant strategies have been developed. Expanded registries both for volunteer unrelated donors and UCB units have enhanced access to alternative donor transplantation. Furthermore, advances over the past few decades in areas such as HLA typing, supportive care, and better prevention of GVHD have led to marked improvements in outcomes for alternative donor transplantation. Nevertheless, despite numerous retrospective studies showing relative equivalence between most alternative donor sources and MSDs, a MSD likely still will be used preferentially when available. This is particularly true as no randomized studies have been completed to directly compare MSDs with any alternative donor. However, the important prognostic impact of donor factors other than HLA-matching (e.g. age, sex, CMV serostatus, or natural killer cell alloreactivity) on post-transplantation outcomes is becoming increasingly recognized. Therefore, given the recent success of alternative donor transplantation, it is foreseeable that in the near future HLA-matching may no longer be the top priority in donor selection.

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Figure 1. Timeline of important milestones in alternative donor allogeneic hematopoietic cell transplantation

For all milestones, the year of manuscript publication was used. Early unsuccessful transplantations were not included. MTX=methotrexate, GVHD=graft-versus-host disease, HLA=human leukocyte antigen, HCT=allogeneic hematopoietic cell transplantation, HaploHCT=HLA-haploidentical HCT, SCID=severe combined immunodeficiency, MUD=HLA-matched-unrelated donor, ALL=acute lymphoblastic leukemia, ATG=anti-thymocyte globulin, CsA=cyclosporine-A, NMDP=National Marrow Donor Program, UCBT=umbilical cord blood transplantation, TCD=T-cell depletion, PTCy=post-transplantation cyclophosphamide, MSD=HLA-matched-sibling donor, TCR=T-cell receptor, MAC=myeloablative conditioning, PBSCs=peripheral blood stem cells, MSCs=mesenchymal stromal cells.

Selected recent comparative studies of MSD versus MUD T-cell-replete allogeneic cell transplantation for AML patients.

Table 1

Reference Number	Years of Study	# of Patients		% AML Patients		Patient Ages	HLA Locus Matching	% Given ATG		Relapse And Survival Outcomes Reported At, Years	Graft Failure, %		Acute GVHD, II-IV, CI %		Acute GVHD, III-IV, CI %		Chronic GVHD, CI %		NRM, CI %		Relapse, CI %		DFS, %		OS, %	
15 ^a	1995–2004	3158	941	40	36	18–60	8	1	5	5	NR	NR	34	52	16	21	42	49	24 [*]	40 [*]	15	22	61 [*]	38 [*]	NR	NR
29	1995–2004	168	51	100	100	50–73	8	38	61	5	NR	NR	39	30	19	14	22	15	↔	↔	↔	↔	33	30	↔	↔
30 ^b	1995–2006	226	254	100	100	<1–74	8	8	27	3	NR	NR	38 [*]	54 [*]	19 [*]	25 [*]	43 [*]	59 [*]	21	26	37	40	42	34	45	37
31 ^c	1998–2004	62	89	100	100	19–61	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	↔	↔	↔	↔	NR	NR	↔	↔
32 ^d	1996–2007	135	62	100	100	18–69	10	6	13	5	NR	NR	64	77	21	16	50	50	↔	↔	~30	~25	~60	~55	~65	~58
33 ^e	2000–2003	181	55	NR	NR	<55	10	0	0	2	0	0	46 [*]	61 [*]	19	29	NR	NR	24	29	20	16	56	55	64	58
28 ^f	2004–2011	78	60	100	100	18–64	10	0	0	3	3	8	37 [*]	50 [*]	10	18	6	15	18	23	37	36	45	41	57	48
34 ^g	2004–2011	1855	1360	100	100	18–77	8	17	58	2	2	2	24 [*]	27 [*]	10	10	50	38	20	21	29	33	51	46	57	52

* Indicates outcomes that are significantly different between MSD and MUD cohorts. Results indicate differences in univariate analysis unless multivariate analysis was performed and contradicted the univariate results.

↔ Indicates that the exact percentage was not reported but that there was no difference on testing between MSD and MUD alloHCT patients.

^aGVHD rates were not statistically compared. NRM, relapse, and DFS outcomes listed are for the AML cohort only. However, these results were not reported for the entire AML population but by three AML groups divided by disease status at alloHCT. The top line is AML in first complete remission, the second line is AML in second or subsequent complete remission, and the bottom

^bAll patients had AML with unfavorable-risk cytogenetics in first complete remission.

^cThis was a prospective study but donor selection was not randomized. Instead, donor selection was based on donor availability (biologic randomization).

^dIncluded patients with AML in first complete remission. Relapse and survival percentages were not reported explicitly but were shown in figures. Even so, statistical comparisons between MSD and MUD alloHCT were performed. NRM was not shown in a figure nor were percentages reported. However, there was no statistical difference between the two groups in regards to NRM with a hazard ratio of 0.95 (95% confidence interval, 0.32–2.78).

^eThis was a prospective study designed to compare MSD versus MUD alloHCT. Although donor selection was not randomized, entry criteria, conditioning, and GVHD prophylaxis were standardized between the two cohorts. Seventy-eight percent of MSD alloHCT patients and 62% of MUD alloHCT patients had acute leukemia, but the percentage of AML patients was not specifically reported.

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^fData are shown for just AML patients included in this study of AML, ALL, and MDS patients. Of note, the difference in chronic GVHD was statistically significant for the entire cohort (8% for MSD versus 20% for MUD, $p=0.02$), but the difference within the AML subset was not significant ($p=0.1$).

^gThis study compared MUD alloHCT using a male donor and MSD alloHCT using a female donor. Data from the AML cohort only are shown. Seventeen percent and 58% of MSD and MUD alloHCT patients, respectively, received anti-thymocyte globulin.

Abbreviations: MSD=HLA-matched-sibling donor, MUD=HLA-matched-unrelated donor, HL/A=human leukocyte antigen, AML=acute myeloid leukemia, GVHD=graft-versus-host disease, CI=cumulative incidence, NRM=non-relapse mortality, DFS=disease-free survival, OS=overall survival, NR=not reported, alloHCT=allogeneic hematopoietic cell transplantation, ALL=acute lymphoblastic leukemia, MDS=myelodysplastic syndrome.

Table 2

Selected^d recent comparative studies of unrelated UCBT versus T-cell-replete MSD or MUD alloHCT for AML patients.

Ref.	Years of Study	# of Patients			% AML Patients			Patient Ages	# UCB Units	Conditioning Intensity	Acute GVHD, III–V, CI %			Acute GVHD, III–V, CI %			Chronic GVHD, CI %			NRM, CI %			Relapse, CI %			PFS/DFS, %			OS, %		
		MSD	MUD	UCB	MSD	MUD	UCB				MSD	MUD	UCB	MSD	MUD	UCB	MSD	MUD	UCB	MSD	MUD	UCB	MSD	MUD	UCB	MSD	MUD	UCB	MSD	MUD	UCB
47	2000–2005		311	173		100	100	16–69	1	MAC		35	32		NR	NR	28	22*	33*	24		31		54*	36*		60*	43*			
48 ^b	2000–2005	47		43	21		44	55	2–88%	RIC	42		49		NR	NR	17*		28		NR	30			34	43		34			
49 ^c	2000–2009		313	161		94	80	21–69	2	RIC		33*	50*	14	17	18		21*	19	44		49		35*	31		44*	37			
50 ^d	2000–2010	82	35	80	100	100	100	50–74	2–88%	RIC	29	38	39	10	15	14	43	41	23	18	14	24	33*	29*	43*	33	51	53	45		
51	2001–2008	204	152	128	48	33	53	10–67	2	MAC	65	80*	60*	13	14	22	47*	43*	26*	24*	14	34*	43*	37*	15*	NR	NR	NR			
52 ^e	2001–2009	38		60	68		73	55–70	2–95%	RIC	38		45	26		21	61*		33*	25		25	34		47	37		31			
53 ^f	2002–2006		964	165		59	46	16	1	MAC		↑*	↓*		NR	NR	↑*	↓*					↔	↔	↔		NR	NR			
54 ^g	2004–2008		221	64		33	36	19–73	2	RIC		20	14		7	3	54*	22*	27*	10*		34	40		30		50	46			
55 ^h	2007–2010	30	20	39	42		33	22–70	2	RIC	31		26	15	8		35	6*	26	36		23	58		51	62	61				
56 ⁱ	2005–2010		441	205	100	100	100	50–75	2–61%	Both		↔	↔		NR	NR	↑*	↓*	35*		35		39*	28*		43*	30*				
57 ^j	2005–2011	36	13	32	100	100	100	18–69	2–72%	RIC	18*	41*	8	25			35	25	16	22		60*	50*	25*		56	34				

^{*} Indicates outcomes that are significantly different. Results indicate differences in univariate analysis unless multivariate analysis was performed and contradicted the univariate results.

^a All studies which began enrolling AML patients after 2000 and which separately reported outcomes for either MSD or MUD recipients (did not mix with partially-HLA-mismatched) were included.

^b ATG was given to 13% of MSD alloHCT recipients and 40% of UCBT recipients.

^c UCBT outcomes were split by those who received TCF conditioning and those who received other conditioning regimens. For outcomes, TCF UCBT is on the top line and UCBT using other conditioning is on the bottom line.

^d ATG was given to 30% of MSD, 86% of MUD, and 29% of UCB alloHCT recipients. DFS was significantly different on unadjusted analysis but was non-significant on adjusted analysis. The unadjusted DFS is shown as the adjusted percentages were not reported. The adjusted OS percentages were reported and are shown.

^e ATG was given to 57% of UCBT patients and 32% of MSD alloHCT patients.

^f ATG was given to 72% of UCBT patients, 28% of BM alloHCT patients, and 18% of PBSC alloHCT patients. Significant differences for acute GVHD were only seen between UCBT and PBSC alloHCT, but not between UCBT and BM alloHCT.

^g Includes 7/8 and 8/8 HLA-matched-unrelated donors. Ninety-one percent of donors were 8/8 HLA-matched with the recipient.

h Two additional patients who received HLA-mismatched-unrelated alloHCT were included in the outcomes. ATG was given to all MSD and MUD recipients and only 6 (15%) of UCB recipients.

i In vivo T-cell depletion was given to 39% of MUD recipients and 32% of UCB recipients. There were no significant differences in outcomes between UCBT patients receiving a single-unit or double-unit except for higher NRM after double-unit UCBT, with a trend towards lower relapse after double-unit UCBT.

j All MSD and MUD recipients but no UCB recipients received ATG.

Abbreviations: UCB=umbilical cord blood, UCBT=umbilical cord blood transplantation, MSD=HLA-matched-sibling donor, MUD=HLA-matched-unrelated donor, HLA=human leukocyte antigen, alloHCT=allogeneic hematopoietic cell transplantation, Ref=reference number, AML=acute myeloid leukemia, GVHD=graft-versus-host disease, CI=cumulative incidence, NRM=nonrelapse mortality, PFS=progression-free survival, DFS=disease-free survival, OS=overall survival, MAC=myeloablative conditioning, RIC=reduced-intensity conditioning, NR=not reported, ATG=anti-thymocyte globulin, TCF=Total body irradiation, Cyclophosphamide, and Fludarabine, BM=bone marrow, PBSC=peripheral blood stem cell.

Table 3

Studies Comparing Haplo AlloHCT Using the GIAC Protocol Versus MSD AlloHCT for AML patients.

Ref.	Years of Study	# of Patients		% AML Patients		Patient Ages	Relapse and Survival Outcomes Reported At, Years	Acute GVHD, II–IV, CI%		Acute GVHD, III–IV, CI %		Chronic GVHD, CI %		NRM, CI %		Relapse, CI %		DFS, %		OS, %	
								MSD	Haplo	MSD	Haplo	MSD	Haplo	MSD	Haplo	MSD	Haplo	MSD	Haplo	MSD	Haplo
68 ^a	2002–2004	135	158	25	22	5–50	2	32*	40*	11	16	56	55	14	22	13	18	71	64	72	71
72 ^b	2003–2005	51	56	31	25	4–59	2	14*	27*	4	7	31	23	8	12	17	22	76	68	80	70
73 ^c	2005–2009	36	81	56	37	5–56	3	24*	49*	4	15	39	62	38	34	49*	26*	15*	42*	20*	42*
74 ^d	2008–2013	90	99	47	29	9–56	5	16*	42*	6*	17*	24	41	5*	30*	34*	14*	64	58	77*	61*

* Indicates outcomes that are significantly different.

^aThe transplantation platform for haplo alloHCT used twice the dose of cytarabine, the inclusion of ATG, and a longer post-transplantation duration of MMF but was otherwise identical to that used for MSD alloHCT.

^bThe conditioning used for MSD alloHCT was busulfan/cyclophosphamide or cyclophosphamide/total body irradiation without ATG. GVHD prophylaxis for haplo alloHCT added an additional dose of methotrexate on day +11, started CsA earlier during conditioning, and continued both CsA and MMF for a longer time period post-transplantation.

^cThe transplantation platform for the haplo alloHCT included ATG, used twice the dose of cytarabine, omitted a dose of hydroxycarbamide on day –10, and extended the duration/tapering of MMF post-transplantation, but otherwise was identical to that used for MSD alloHCT.

^dMUD alloHCT also was included as a third comparator group in this study. All outcomes were similar between haplo alloHCT and MUD alloHCT recipients. The transplantation platform for HLA-matched alloHCT recipients was busulfan/cyclophosphamide except for those with central nervous system involvement or high white blood cell count at diagnosis in which case it was cytarabine, busulfan, cyclophosphamide, and semustine. Rabbit ATG also was given to MUD alloHCT recipients. The duration of GVHD prophylaxis with MTX, CsA, and MMF was longer for haplo alloHCT recipients.

Abbreviations: Haplo=HLA-haploidentical donor, MSD=HLA-matched-sibling donor, HLA=human leukocyte antigen, alloHCT=allogeneic hematopoietic cell transplantation, AML=acute myeloid leukemia, Ref.=reference number, GVHD=graft-versus-host disease, CI=cumulative incidence, NRM=non-relapse mortality, DFS=disease-free survival, ATG=anti-thymocyte globulin, CsA=cyclosporine A, MMF=mycophenolate mofetil, MUD=HLA-matched-unrelated donor.

Table 4

Studies Comparing Haplo AlloHCT Using PTCy Versus MSD or MUD AlloHCT for AML patients.

Ref.	Years of Study	# of Patients			% AML Patients			Patient Ages			Relapse and Survival Outcomes Reported At, Years	Acute GVHD, II-IV, CI%			Acute GVHD, III-IV, CI%			Chronic GVHD, CI %			NRM, CI%			Relapse, CI %			DFS, %			OS, %		
		MSD	MUD	Haplo	MSD	MUD	Haplo	MSD	MUD	Haplo		MSD	MUD	Haplo	MSD	MUD	Haplo	MSD	MUD	Haplo	MSD	MUD	Haplo	MSD	MUD	Haplo	MSD	MUD	Haplo	MSD	MUD	Haplo
79 ^d	2005–2010	117	101	53	32	36	32	NR			2	27	39	30	8	11	11	54 [*] 11 [*]	54 [*] 12 [*]	38 [*] 4 [*]	13	16	7	34	34	33	53	52	60	76	67	64
80 ^e	2006–2012	176	43	92	NR	NR	NR	15–69			4	31 [*]	21	14 [*]	7	3	4	29 [*]	22	15 [*]	24	33	18	40	23	35	32	36	43	45	43	52
81 ^f	2005–2012	87	108	32	67	66	69	20–76			3	31	29	29	11	6	0	43	30	19	20	35	24	28	23	33	36	27	30	56		66

* Indicates outcomes that are significantly different.

^d Only patients with haplo alloHCT received PTCy. One-third of haplo alloHCT recipients received myeloablative conditioning, and 40% received PBSC allografts. Meanwhile, nearly all patients receiving MSD or MUD alloHCT received PBSCs. For chronic GVHD, the top line is all chronic GVHD and the bottom line is severe chronic GVHD.

^e This manuscript reported outcomes for five donor types and statistical comparisons took into account the presence of all five groups. For simplicity sake, outcomes for HLA-mismatched-unrelated donor and UCB alloHCT are not shown in this table. Of note, those two groups had the lowest survival with the overall survival for UCB alloHCT being significantly lower than MSD alloHCT. Only patients receiving haplo alloHCT received PTCy. MUD recipients received anti-thymocyte globulin. Percentage of patients with acute leukemia were reported (MSD 48%, MUD 43%, and haplo 43%), but the percentages of AML patients were not specified. Only moderate/severe chronic GVHD was reported; those percentages are included in the table.

^f All patients had either AML or myelodysplastic syndrome. All patients received fludarabine and melphalan conditioning, although haplo alloHCT recipients also received thioteпа. Only patients with haplo alloHCT received PTCy.

Abbreviations: Haplo=HLA-haploidentical donor, MSD=HLA-matched-sibling donor, MUD=HLA-matched-unrelated donor, HLA=human leukocyte antigen, alloHCT=allogeneic hematopoietic cell transplantation, PTCy=post-transplantation cyclophosphamide, AML=acute myeloid leukemia, Ref.=reference number, GVHD=graft-versus-host disease, CI=cumulative incidence, NRM=non-relapse mortality, DFS=disease-free survival, OS=overall survival, NR=not reported, PBSC=peripheral blood stem cell, UCB=umbilical cord blood.