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Haploidentical bone marrow and stem cell transplantation: experience with post-transplantation cyclophosphamide

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Abstract

Allogeneic blood or bone marrow transplantation (BMT) is a potentially curative therapy for high-risk hematologic malignancies not curable by standard chemotherapy, but the procedure is limited by the availability of human leukocyte antigen-matched donors for many patients, as well as toxicities including graft-versus-host disease. Our group has developed the use of high-dose post-transplantation cyclophosphamide (PTCy) to selectively remove alloreactive T cells without compromising engraftment. This protocol has allowed for successful transplantation of HLA-haploidentical (haplo) grafts, thus expanding the donor pool for the many patients who would not otherwise be a candidate for this life-saving procedure. In this review we will summarize the data that led to the development of PTCy, then focus on the outcomes of haploBMT trials with PTCy across different transplant platforms for patients with malignant hematologic diseases, and finally we will discuss emerging evidence that suggests equivalency of haploBMT with PTCy compared with more traditional transplants.

Introduction

Pioneering early clinical studies by the Seattle bone marrow transplant team demonstrated that of all potential sources of allogeneic (allo) blood or bone marrow transplants (BMT), those from human leukocyte antigen (HLA)-matched siblings produce the best transplantation outcomes with respect to graft-versus-host disease (GVHD), overall survival (OS), and progression-free survival (PFS). Unfortunately, many patients who are candidates for alloBMT will not have an optimal donor - that is, a donor who is matched at high resolution at the *HLA-A*, *HLA-B*, *HLA-C*, and *HLA-DRB1* loci located on the short arm of

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chromosome 6. For patients who lack an HLA-matched sibling, there are 3 alternative sources of stem cells for alloBMT: (1) unrelated donors, (2) umbilical cord blood (UCB), and (3) partially HLA-mismatched, or HLA-haploidentical (haplo) related donors. Since any patient shares exactly one HLA haplotype with each biologic parent or child and half of siblings, an eligible haplo donor can be rapidly identified in nearly all cases. The fundamental clinical obstacle to haploBMT arises from intense, bi-directional responses from T cells responding to allogeneic HLA molecules resulting in unacceptably high incidences of graft rejection or GVHD. Indeed, early studies using T cell replete haploBMT and standard GVHD prophylaxis with methotrexate and calcineurin inhibitors (CNI) such as tacrolimus reported high toxicity relative to HLA-matched transplants,^{1–4} in particular acute grade III/IV GVHD and graft rejection. After it was discovered that T cell depletion (TCD) of the donor graft prevents GVHD after alloBMT in mice,⁵ there was substantial interest in preventing GVHD after HLA haploBMT using *ex vivo* TCD. While this technique was indeed successful in reducing the incidence and severity of GVHD, there was a compensatory increase in the risk of graft failure, disease relapse, and non-relapse mortality (NRM).^{6–8} However, in the last two decades several novel methods for haploBMT have been developed that yield encouraging results with high rates of engraftment, effective GVHD control and favorable outcomes. Approaches using *ex vivo* TCD with ‘megadose’ CD34⁺ cells^{9,10} or combining granulocyte colony-stimulating factor-primed allografts with intensive pharmacological immunosuppression and *in vivo* TCD with antithymocyte globulin^{11–13} will be the focus of other manuscripts in this volume. Herein we will focus on haploBMT with post-transplantation cyclophosphamide (PTCy) and review the outcomes in patients with hematologic malignancies treated with this approach.

Pre-clinical rationale behind PTCy

Based on studies published by several groups in the 1960s–1990, our group became interested in PTCy to induce immunologic tolerance in the context of alloBMT as a method to suppress GVHD without causing global immunosuppression.¹⁴ In 1963, Berenbaum showed that cyclophosphamide (Cy) administration prolonged the survival of allogeneic skin grafts in mice, especially if the drug was given 1–3 days after placement of the skin graft.¹⁵ At Johns Hopkins, Santos and Owens found that Cy suppressed the incidence and severity of GVHD in rats given allogeneic spleen cells, especially if dosing was commenced on day 2 after the splenocyte infusion.¹⁶ Nomoto and colleagues at Kyushu University developed a method for inducing tolerance to major histocompatibility antigens (MHC) by giving mice an intravenous injection of MHC-matched, allogeneic splenocytes followed in 2–3 days by an intraperitoneal injection of high-dose Cy.^{17,18} Colson et al. demonstrated in a mouse model of partially MHC-mismatched BMT that the dose of conditioning total body irradiation (TBI) required for stable engraftment was decreased when mice were given Cy two days post BMT, regardless of the degree of MHC-mismatch.^{19,20}

With these results as background, we sought to develop a strategy to administer PTCy that would permit the sustained engraftment of partially HLA-mismatched (haploidentical) grafts without severe GVHD. This objective was achieved in a mouse model of MHC-mismatched alloBMT using pre-transplant conditioning with fludarabine (a highly immunosuppressive purine analog) and low-dose TBI, and GVHD prophylaxis with high-dose PTCy.^{21,22} These

results, together with the observation that hematopoietic stem cells express high levels of aldehyde dehydrogenase which confers cellular resistance to cyclophosphamide,^{23,24} provided the rationale to proceed with the first clinical trial, and also served as a platform for future laboratory studies to decipher the mechanisms behind this novel approach.^{25,26}

Early PTCy experience at Johns Hopkins Hospital

The first phase I/II clinical trial of haploBMT with PTCy to treat high-risk hematologic malignancies was initiated in 1999, and outcomes of the first 13 patients were published in 2002. Conditioning was based on a nonmyeloablative (NMA) regimen comprised of fludarabine and low-dose TBI as developed by Storb and colleagues in Seattle²⁷ and used in our pre-clinical rodent studies.^{21,22} The protocol allowed for the addition of cyclophosphamide to the conditioning regimen with flexibility for dose adjustment if failure to engraft was an issue. GVHD prophylaxis consisted of cyclophosphamide administered as a single-dose on day +3 post-transplant, tacrolimus, and mycophenolic acid mofetil (MMF). Two of the first three patients transplanted after conditioning without cyclophosphamide rejected their grafts. Thus, cyclophosphamide was added to the conditioning regimen according to a Bayesian continual reassessment model at a total dose of 29 mg/kg given on days -5 and -6. Engraftment was achieved in 8 of the next 10 patients, so the pre-transplant cyclophosphamide dose in the conditioning regimen was fixed for future trials.²⁸ Autologous hematopoietic recovery occurred in 3 of 4 patients who rejected their grafts. Acute GVHD occurred in 6 of 8 engrafted patients on the phase II portion of the trial, and 5 patients responded to therapy.²⁸

With ongoing collaborations between the groups at Hopkins and Seattle, a phase II trial of haploBMT using PTCy continued and a modification was made to the regimen by increasing the dose of PTCy to a total of 100 mg/kg given on days +3 and +4 with the intention of decreasing the incidence of GVHD. With two doses of PTCy the cumulative incidences of grades II-IV and grades III-IV acute GVHD by day 200 were 34% and 6%, respectively. There was no difference in the incidence of severe acute GVHD between one or two doses of PTCy. Furthermore, there was a trend toward a lower incidence of extensive chronic GVHD among recipients of two versus one dose of PTCy. Primary graft failure occurred in 13% of the patients. The cumulative incidences of NRM and relapse at one year were 15% and 51%, respectively. Actuarial OS and event-free survival (EFS) at two years after transplantation were 36% and 26%, respectively.²⁹ Subsequent analysis by Kasamon et al.³⁰ of 185 patients who underwent NMA haploBMT at Johns Hopkins demonstrated no association between the degree of mismatching at five HLA loci and the risk of acute GVHD or NRM. Updated results from the growing Hopkins experience using two doses of PTCy for GVHD prophylaxis after haploBMT were published in 2011 by Munchel et al.,³¹ showing similar outcomes in a larger number of patients. Collectively, these early clinical outcome data suggest that PTCy has been successfully translated from basic science research and preclinical models into clinical practice.

Expanding the use of PTCy, single-center experiences

Several other centers rapidly adopted PTCy and made various modifications to the original protocol such as increasing the intensity of conditioning or substituting peripheral blood stem cells (PBSCs) for bone marrow as the graft source. These developments were driven in part by concerns that the original NMA conditioning was insufficient to control aggressive hematologic malignancies, and that use of PBSCs may provide ease of protocol acceptance in centers where this graft source is preferred, as well as to decrease the rejection rate due to higher donor T cell dose in comparison to BM. These modifications will be discussed in turn (see also Table 1). The San Martino Hospital group reported outcomes³² for a cohort of 148 patient with variety of hematologic malignancies who underwent haploBMT with MA conditioning followed by PTCy. They recently published updated results that confirmed early encouraging outcomes, with the incidence of severe GVHD at 4%, OS at 4 years of 53%, and only 1% graft failure. The relapse rate was 27% in this trial with MA conditioning.³³ The BMT group at Northside Hospital in Georgia also tested MA conditioning using fludarabine, busulfan, and cyclophosphamide, and engrafted patients with PBSC followed by PTCy. The rate of grade II–IV acute GVHD was 30% while the incidence of chronic GVHD was 35%. NRM was 10%, and the relapse rate was 40% in this cohort of high-risk hematologic malignancy patients. Overall survival at one year was 69%.³⁴ In a subsequent manuscript by Solomon et al. the same group of investigators reported outcomes using a conditioning method with myeloablative doses of TBI (1200 cGy) and fludarabine, and continued using PBSC for engraftment. In this study of 30 patients there was no graft failure, and the rates of acute GVHD grade II–IV, grade III–IV, and chronic GVHD were 43%, 23%, and 56%, respectively. At a median follow-up of 2 years 78% of patients were alive.³⁵ Investigators at Thomas Jefferson University developed an innovative protocol that separated the infusion of T cells and CD34⁺ stem cells after TBI-based myeloablative conditioning. PBSCs were collected from donors over several days, and T cells and CD34⁺ cells were sorted *ex vivo*. After completing conditioning with TBI, patients received a fixed dose of 2×10^8 CD3⁺ donor T cells per kg, then after a rest period of two days alloreactivity was ablated with two doses of PTCy, followed by infusion with CD34⁺ PBSCs. The authors' goal for this 2-step approach was to deliver a fixed dose of T cells and to avoid exposing the stem cells to cyclophosphamide.³⁶ Results of patients who were in remission at the time of haploBMT have been encouraging with NRM of 4%, a low relapse rate of 22%, and excellent overall survival of 77% at two years.³⁷ Together, these studies demonstrate the PTCy can be successfully used in haploBMT with MA conditioning and using PBSC as the graft source.

Other groups continued to pursue strategies with PBSC grafts, while utilizing reduced intensity conditioning (RIC) with the objective to decrease NRM and maintain eligibility for older patients and those with compromised organ function. Investigators at Seattle, London, and Sydney reported outcomes of 55 patients with advanced hematologic malignancies who underwent haploBMT after RIC with fludarabine and low-dose TBI and using PBSCs for the graft. The rate of acute GVHD was somewhat higher in this study with 61% of patients having grade II–IV acute GVHD, but chronic GVHD was typically low at 16%. The rate of relapse in this cohort was 28% at 2 years, and OS was 48%.³⁸ Sugita et al.³⁹ recently

reported outcomes of 31 patients who received haploidentical PBSC grafts also after RIC conditioning. The NRM in that study was 23%, but this can be partially explained by the rate of graft failure which was 13%,³⁹ likely due to the inclusion of poor-risk patients including 13 patients who had prior alloBMT. Despite the inclusion of challenging patient population OS, relapse, and disease-free survival rates were 45%, 45%, and 34%, respectively, at 1 year.

With the goal to assess the impact of PBSC versus BM allografts Castagna et al. retrospectively analyzed outcomes of 69 patients (46 receiving BM and 23 receiving PBSC) undergoing haploBMT with PTCy. The results from this albeit small study suggested that all major transplantation outcomes did not statistically differ between the groups.⁴⁰ Investigators from Australia reported that outcomes may be better after the use PBSCs, but the number of patients was small (n=36) and the number of doses of PTCy between the two graft sources differed.⁴¹ Overall these data suggest that RIC followed by haploPBSC transplantation is associated with similar outcomes to transplants using bone marrow, but these are early results and need to be interpreted with caution and followed over time. An interesting phenomenon that is seen with the use of PBSCs is high fevers that characteristically occur several days after stem cell infusion. They can also occur with bone marrow, but are typically less severe. These fevers are generally culture-negative, and are thought to be cytokine-mediated secondary to uncontrolled alloreactivity. They tend to abate within hours to days of PTCy administration.⁴² While prospective randomized studies have not yet been done, these reports demonstrate that PTCy can successfully be used in the haplo setting for patients who receive either MA or NMA conditioning, and who receive grafts from bone marrow or PBSCs.

While the data discussed above confirm that the use of PTCy across different platforms appears to be protective against severe acute and chronic GVHD, concerns have been raised about its potential effect on the graft-versus-tumor response. While it is difficult to compare outcomes between studies, the disease risk index (DRI) is a new tool for predicting progression-free survival (PFS) after alloBMT.^{43,44} This metric was developed to improve the interpretation of BMT data involving a wide range of diseases, disease stages, and transplantation techniques. Using this tool McCurdy and colleagues analyze risk-stratified outcomes of 372 consecutive patients who received haploBMT at Hopkins according to the refined DRI. They reported that risk-stratified survival outcomes after NMA haploBMT with PTCy appear comparable to those of reduced-intensity conditioned, HLA-matched BMT as reported in the original DRI studies.^{43,44} Patients after haloBMT with PTCy, when grouped by the original DRI into low-risk, intermediate-risk, and high/very high-risk groups, had 3-year PFS estimates of 65%, 39%, and 25%, and corresponding 3-year OS estimates of 73%, 49%, and 37%, respectively.⁴⁵ These data from the largest cohort of patients who have undergone HLA-haploBMT after NMA or RIC suggests that this transplantation platform yield outcomes similar to those with HLA-matched donors.

With HLA-mismatch no longer an insurmountable barrier with PTCy, another major challenge in the field is treatment of older patients. Kasamon et al.⁴⁶ addressed this question in a retrospective analysis of 271 consecutive patients receiving NMA haploBMT with PTCy who were between the ages of 50–75 years old, with a mean age of 61. These patients

had a variety of hematologic malignancies. Although there was no younger cohort for comparison in the study, the results are very similar to those from previous reports in younger cohorts as seen in Table 1. NRM for the entire cohort was 12% at one year, and was not significantly different when patients were sub-grouped by age, with the oldest group being 70–75 years old. The rate of relapse was 46%, PFS and OS were 37% and 47% at 3 years respectively, and again did not differ in patients at the younger or older ends of the cohort.⁴⁶ The safety of haploBMT with PTCy in older patients was recently confirmed by Blaise et al.⁴⁷ in a study that compared outcomes after haploBMT to age-matched controls receiving grafts from matched related or unrelated donors. There was no statistically significant difference in outcomes between matched related or haploBMT groups except there was a lower incidence of severe chronic GVHD with haploBMT.⁴⁷ This important work demonstrates that older adults can safely be offered NMA haploBMT, and currently at our institution there is no official upper age limit for BMT. Older patients are considered on an individual basis and are offered transplant so long as they meet criteria for end-organ function and performance status.

Expanding the use of haploBMT with PTCy to lymphomas

A key study by Burroughs et al.⁴⁸ compared the outcomes of patients with relapsed Hodgkin lymphoma (92% of whom had failed autologous transplant) who had undergone NMA conditioning and transplantation with either haplo donors using PTCy or HLA-matched siblings or unrelated donors. GVHD prophylaxis after transplantation with matched donors was a CNI plus MMF. Although the number of patients in each group was relatively small, it appeared that outcomes after haploBMT were no worse, and possibly superior to those after transplantation from matched donors. Two-year NRM was similar for haplo and unrelated donors (9% and 8%, respectively) compared to 21% for related donors. EFS at 2 years was 51% for haplo donors compared to 23% and 29% for matched related and unrelated donors, respectively.⁴⁸ A more recent, single-institution, retrospective analysis of 26 patients with poor-prognosis Hodgkin lymphoma was undertaken in Italy by Raiola and Castagna.⁴⁹ This was a particularly challenging cohort as all patients had previously undergone auto-transplant and 65% went into the procedure with active disease. All subjects received NMA conditioning, haploBMT and PTCy on days +3 and +4 along with CNI and MMF for GVHD prophylaxis. In this challenging population, the incidence of GVHD and NRM was low while DFS and OS at 3 years were robust at 63% and 77%, respectively. The relapse rate was 31%,⁴⁹ which was impressive considering the proportion of patients who went into transplant with active disease. Finally, a retrospective analysis of 44 consecutive patients with peripheral T cell lymphoma was reported by Kanakry et al, which included 18 patients who underwent NMA haploBMT and the rest receiving MA conditioning and/or HLA-matched graft.⁵⁰ The patients receiving RIC were on average older. One-year NRM was 10% for patients undergoing MA conditioning versus 8% for RIC, and 11% for patients undergoing RIC haploBMT. The relapse rate at one year was 38% for patients with MA HLA-identical BMT and 34% for RIC haploBMT, again demonstrating no difference in outcomes regardless of conditioning or degree of HLA matching.

A novel study by Kanakry and colleagues examined prioritizing donor selection by factors other than HLA-typing.⁵¹ The investigators developed a protocol to prioritize donors by Fc

gamma receptor 3A (FCGR3A) polymorphisms, which have been shown *in vitro*⁵² and *in vivo*^{53,54} to influence the response to rituximab in patients with CD20-expressing lymphomas. The authors hypothesized that prioritizing FCGR3A receptor polymorphism over HLA-typing would not affect safety and may lead to improved survival. Of the 83 patients with B cell lymphomas in the study, 69 received haploidentical grafts. The safety profile did not seem to be affected by the donor selection criteria as GVHD was low and NRM was 10% at one year. At two years of follow up, PFS and OS for the haplo group were 63% and 73%, respectively.⁵¹ Although the authors failed to demonstrate a better response in patients receiving grafts with particular FCGR3A polymorphisms, the excellent safety profile for all groups in this trial gives credibility to the provocative concept that HLA need not be of utmost priority in donor selection.

Comparative studies of haploBMT with PTCy vs other alternative donor transplants

Following encouraging results with the first PTCy trials, the Bone Marrow Transplant Clinical Trials Network (BMT CTN) sponsored a multicenter phase II trial of haploBMT (CTN 0603) for high-risk hematologic malignancies after RIC. The study was run in parallel with a phase II trial (CTN 0604) of RIC and transplantation of two units of unrelated umbilical cord blood (dUCB) as the donor source. The goal of the study was to show that the promising results achieved in single-center trials could be replicated in a multi-institutional cooperative group setting. Participating centers enrolled patients with UCB, haplo, or both depending on the centers' preferences. The day +56 cumulative incidence of neutrophil recovery was 94% after dUCB transplantation and 96% after haploidentical BMT. The 100-day cumulative incidence of grade II–IV acute GVHD was 40% after dUCB transplantation and 32% after haploidentical BMT. The 1-year cumulative incidences of NRM and relapse after dUCB transplantation were 24% and 31%, respectively, with corresponding results of 7% and 45% after haploidentical BMT. The one-year probabilities of OS and PFS were 54% and 46% after dUCB transplantation and 62% and 48% after haploidentical BMT (see Table 2).⁵⁵ Similar results showing equivalency of outcomes was reported by two other groups that retrospectively reviewed their institutional data. Raiola et al. published the results of 459 consecutive hematologic malignancy patients who underwent transplant using a variety of graft sources including alternative or HLA-matched donors. The comparison between alternative donors including mismatched unrelated donors (mMUD), UCB, and haplo donors will be reviewed here, and comparison to matched transplants is discussed below. Selected results are presented in Table 2. The median number of days to engraftment for the 3 alternative donor groups was 16, 23, and 18, respectively, and the longer time to engraftment in the UCB cohort was statistically significant, as is typically seen with this type of donor. The incidence of moderate to severe GVHD was under 30% in all groups, and in fact was lowest in the haplo group at 15%. Actuarial overall survival was greater than 40% in each group, and again trended towards superiority in the haplo group at 52%.⁵⁶ El-Cheikh and colleagues in France conducted another comparison of haploBMT with PTCy versus UCB. The analysis included a relatively large number of patients with 81 in the UCB arm and 69 in the haplo arm, and again it was not randomized. It should be noted that there was a much higher proportion of leukemia patients in the UCB arm, and

more lymphoma patients in the haplo arm. The rates of engraftment, NRM, and GVHD were not different between the groups, but all measures trended towards favoring recipients of haploidentical grafts using PTCy. Overall survival was superior in the PTCy group, with 69% of patients alive at 2 years as compared to 45% in the UCB group.⁵⁷

These multicenter studies confirmed the utility of both dUCB and haploidentical bone marrow as alternative donor sources and established equipoise for an ongoing multicenter randomized clinical trial to assess the relative efficacy of these two transplant strategies (CTN 1101). Forty centers around the United States are participating, and nearly 50% of target enrollment has been achieved thus far. Results are expected to become available in approximately 4 or 5 years.

Comparative studies of HLA-matched and alternative donor BMT

Several groups have conducted retrospective studies to compare outcomes from HLA-matched siblings, which is considered the gold standard for transplant, to haploBMT with PTCy. Bashey et al.⁵⁸ published a study comparing 117 patients receiving matched related donor (MRD), 103 receiving MUD, and 53 receiving haploBMT with PTCy. Patients received haplo allografts only if there was no MRD or MUD available within a time frame that the investigators deemed acceptable. The NRM was not different amongst the groups, and was less than or equal to 10% in each group. The rate of relapse, PFS, and OS was also excellent and not statistically different between the groups, with OS being greater than 64% for each cohort. The only significant difference in outcomes was that the haploBMT cohort had a lower incidence of acute and chronic GVHD.⁵⁸ Di Stasi and colleagues⁵⁹ published a retrospective comparison of AML patients receiving MRD, MUD, or haplo with PTCy transplants, and reported similar outcomes showing equivalency of HLA-matched and mismatched BMT. NRM was somewhat higher in this study at 27% at one year for the entire cohort, but the MUD cohort actually had the highest NRM at 34%, compared to 20% and 24% for MRD and haplo, respectively. The rates of relapse and PFS were similar amongst all groups.

As discussed above, the Raiola study also included comparisons to MUD and HLA-matched siblings, the current gold standard for transplant. Surprisingly, the incidence of acute grade II–IV GVHD was significantly lower in the haplo group at 14%, compared with 31% in matched sibling pairs, although the rate of grade III–IV GVHD was not different. The cumulative incidence of NRM for the matched sibling group was 24% compared to 33% for MUD and 18% for haplo, although the differences were not statistically significant. In a multivariate analysis of survival, there was no difference between matched siblings, MUD, or haplo, although mMUD and UCB were inferior.⁵⁶ This study provided additional evidence that GVHD, which had previously limited the success of early T cell replete HLA-mismatched transplants, could be substantially mitigated by PTCy.

The most recent large comparative study between HLA-matched and haploidentical donors was published by Ciurea et al. This study used Center for International Blood and Marrow Transplant Research data to retrospectively evaluate outcomes of MDS/AML patients who underwent BMT using either MUD (n=1,982) or haplo (n=192) donors. Patients in this

study included those who had either MA or RIC, and all haplo transplants utilized PTCy for GVHD prophylaxis. Table 2 shows the combined results of patients receiving MA and RIC although these results are presented separately in the manuscript. In MA transplants, there was no difference in NRM or OS between the groups, but the haplo group did have a lower incidence of acute and chronic GVHD. For patients who underwent RIC transplants, recipients of haplo grafts again had less GVHD, but in this study also had an advantage with respect to NRM.⁶⁰ Taken together, these large studies demonstrate that HLA matching is definitively no longer a barrier to bone marrow transplant for hematologic malignancies. Haploidentical BMT has evolved from being an experimental procedure with high morbidity and mortality to a strategy that can now be performed safely, and may indeed result in outcomes similar to those using HLA-matched donors.

Conclusions

HLA-matched sibling donors have long been the gold standard for allogeneic blood or marrow transplantation, but only 30% of patients have an HLA-matched sibling, while nearly all patients have HLA-haploidentical related donors. The possibility of locating an HLA-matched unrelated donor through donor registries has widened the donor pool, but alloBMT is still unavailable to many individuals. In particular, national registries generally lack a sufficient donor pool for minority populations, and the time to search for and screen a donor can be prohibitive for those in need of rapid transplantation for high-risk malignancies. In addition, not all health systems have the infrastructure to set up and maintain a registry. Alternative donor transplantation approaches including UCB and modern approaches to haploBMT have made donors available to nearly all patients who might require this life-saving procedure. The retrospective evidence presented here suggests that haploBMT with PTCy can produce outcomes that are similar to those with HLA-matched sibling donors. However, there is a major unmet need for a prospective clinical trial to address whether the outcomes after transplantation using haploidentical or HLA-matched donors are in fact equivalent. Finally, with the greatly expanded ability to safely find donors for nearly all patients in need of alloBMT, disease relapse has become the major area for improvement, especially in high-risk and very high-risk patients. PTCy-based haploBMT platforms with associated low incidence of acute and chronic GVHD are perfectly poised for integration of novel immunologic agents and these studies will be the primary focus of the future efforts.

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Table 1
Selected recent studies of haploidentical BMT using PTCy in hematologic malignancy patients.

Study Characteristics				Diseases (n)						GVHD				Outcomes				
Reference	Study period, n, age range (median) (y)	HSC source	Cond.	MDS/AML	ALL	Other	Graft failure	Acute II–IV	Acute III–IV	Chronic	NRM	Relapse	PFS/EFS	OS				
Bacigalupo et al. ^{33a}	2010–2014, n=148, 17–74 (47)	BM	MA	72	28	48	1%	18%	4%	20%	14%	27%	NR	53%				
Solomon et al. ^{34b}	2009–2011, n=20, 25–56 (44)	PB	MA	12	2	6	0%	30%	10%	35%	10%	40%	50%	69%				
Solomon et al. ^{35c}	2012–2014 n=30, 24–60 (46.5)	PB	MA	16	6	8	0%	43%	23%	56%	3%	24%	73%	78%				
Grosso et al. ^{37d}	2006–2009, n=28, 21–65 (47)	PB	MA	16	10	2	0%	39%	4%	22%	4%	21%	NR	77%				
Sugita et al. ^{39e}	2013–2014, n=31, 21–65 (48)	PB	MA	21	8	2	13%	23%	3%	15%	23%	45%	NR	45%				
Raj et al. ^{38f}	2009–2013, n=55, 14–69 (49)	PB	NMA	21	2	32	4%	61%	8%	16%	17%	28%	51%	48%				
McCurdy et al. ^{45g}	2002–2012, n=372, 18–75 (55)	BM	NMA	125	24	223	8%	32%	4%	13%	11%	46%	40%	50%				
Burroughs et al. ^{48h}	1998–2007, n=28, 14–62 (32)	BM	NMA	0	0	28	0%	43%	11%	35%	9%	40%	51%	58%				
Raiola et al. ⁴⁹ⁱ	2009–2011, n=26, 19–61 (31)	BM	NMA	0	0	26	4%	24%	NR	9%	4%	31%	63%	77%				

^a Includes an expanded and updated cohort of patients also reported in reference ³², so are presented instead of that study. Patients had a variety of hematologic malignancies, and 64 (43%) had active disease at the time of transplant.

^b 11 patients had active disease at the time of transplant and 9 were in CR. Due to increased rates of mucositis seen in the first 5 patients, doses of busulfan and fludarabine were decreased for the next 15 patients but the regimen was still considered MA.

^c Patients were recruited prospectively. Outcomes of haploBMT patients reported above were compared with a contemporaneously treated cohort of patients who received MUD at the same institution. Outcomes were similar amongst the groups, with 2-year OS and DFS in the MUD group at 71% and 64%, respectively.

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^p Donors were selected to maximize antihist alloreactivity. No patient had morphologic evidence of disease at the time of transplant. This group utilized a 2-step transplant protocol as described in text.

^e This was a prospective, multi-center study conducted in Japan. 61% of patients were not in remission at the time of transplant, and 42% had undergone prior alloBMT.

^f 44% of patients were not in CR at the time of transplant.

^g Includes an expanded cohort of patients also reported in references 31, 46, 50 so are presented instead of those studies.

^h This study included relapsed or refractory Hodgkin lymphoma patients who received either MRD, MUD, or haploBMT. Patients were not randomized. Only outcomes of haploBMT are presented here.

ⁱ All patients had previously undergone at least 2 lines of chemotherapy and autologous transplant, and 65% had active disease at the time of transplant.

Table 2

Selected comparisons of haplo BMT with PTCy to other transplant platforms.

Number of pts (n)				Median age (y)		AML/MDS pts (%)		NRM (%)		Relapse (%)		PFS/DFS (%)		OS (%)	
Reference	Year of Study	Do no r 1	Do no r 2	Ha plo a	Do no r 1	Do no r 2	Ha plo	Do no r 1	Do no r 2	Do no r 1	Do no r 2	Do no r 1	Do no r 2	Do no r 1	Do no r 2
Brunstein et al. ^{55b}	2009–2010	50		50	58		48					46		54	62
Bashey et al. ^{58c}	2005–2010	117	101	53	50	51	46	10	10	34	34	53	52	76	64
Di Stasi et al. ^{59d}	2005–2012	87	108	32	60	62	52	20	35	28	23	36	27	NR	NR
Raiola et al. ^{56e}	2006–2012	105	43	92	40	42	45	35	33	30	23	33	36	34	53
El-Cheikh et al. ^{57f}	2010–2013	81		69	47		44	23		38		36		45	69
Ciurea et al. ^{60g}	2008–2012	1982		192	NR		NR	15		40		NR		48	45

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; GVHD, graft-versus-host disease; MA, myeloablative; MDS, myelodysplastic syndrome, MRD, HLA-matched sibling donor; MUD, HLA-matched unrelated donor; mMUD, HLA-mismatched unrelated donor; NMA, nonmyeloablative; NR, not reported; OS, overall survival; PTCy, post-transplantation cyclophosphamide; PBSC, peripheral blood stem cells; PR, partial remission; PTCy, post-transplantation cyclophosphamide; UCB, RIC, reduced intensity conditioning; umbilical cord blood

^a all patients receiving haploidentical grafts received PTCy for GVHD prophylaxis.

^b Donor 1 = UCB, 10 transplant centers enrolled only in the UCB trial, 11 transplant centers enrolled only in the haplo trial, and 6 centers enrolled in both. Patients were not randomized. For eligibility leukemia patients had to be in morphologic CR and lymphoma patients had to be in at least PR before transplant.

^c Donor 1 = MRD, Donor 2 = MUD. Patients in either group received MA or RIC. Included patients with a variety of hematologic malignancies.

^d Donor 1 = MRD, Donor 2 = MUD. Study only included AML/MDS patients, 69% were not in CR at time of transplant. All patients were conditioned with fludarabine and melphalan, and those receiving haploBMT also received thiotepea. OS was not reported.

^e Donor 1 = UCB, Donor 2 = MUD. Study included transplants from MRD, MUD, mismatched unrelated donors, UCB, and haplo donors. Only UCB, MUD, and haplo are presented here due to space constraints. The prioritization of donors was first for HLA-matched sibling, then HLA-matched or mismatched unrelated donor, then UCB, then haplo; although if it was felt the patient could not wait for an unrelated donor or UCB search the transplant proceeded with a haplo donor. Patients received either MA or RIC in both groups. GVHD prophylaxis consisted of cyclosporine and methotrexate for MRD, antithymocyte globulin for MUD, mMUD, and UCB, and PTCy, cyclosporine, and mycophenolate mofetil for haplo. Patients had a variety of hematologic malignancies but all patients with acute leukemia were reported together, so exact percentage of MDS/AML patients is not reported.

^f Donor 1 = UCB. Patients receiving UCB utilized either 1 or 2 units based on the number of cells to achieve a dose $> 3.0 \times 10^7$ nucleated cells/kg. All patients received NMA conditioning.

^g Donor 1 = MUD. All patients had AML. Outcomes in the paper are segregated by conditioning regimen (MA or RIC) and donor type (MUD or haplo). We have combined data for conditioning regimens and present here as aggregate. Most patients receiving haplo graft received bone marrow, and most receiving MUD received PBSC. Neither progression free survival nor disease free survival were reported.