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Haploidentical Bone Marrow Transplantation with Post-Transplant Cyclophosphamide/Bendamustine in Pediatric and Young Adult Patients with Hematologic Malignancies

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A B S T R A C T

More than half of patients undergoing hematopoietic cell transplantation at our institution are ethnic or racial minorities, making the search for matched unrelated donors more challenging. Since the introduction of haploidentical bone marrow transplant (haplo-BMT) into our pediatric BMT program in 2015, 69.2% of recipients have been minorities. Herein, we describe our experience with the first 13 pediatric and young adult patients with hematologic malignancies who have undergone T cell–replete haplo-BMT after myeloablative conditioning (MAC) at our institution. We have previously documented that in experimental haplo-BMT, post-transplant bendamustine (PT-BEN) is at least as effective as post-transplant cyclophosphamide (PT-CY) against graft-versus-host disease (GVHD) and elicits superior graft-versus-leukemia (GVL) effects. We report on, for the first time in humans, 4 patients treated with PT-CY and PT-BEN after haplo-BMT as part of our ongoing institutional phase I/II study (NCT02996773). The remaining 9 patients reviewed in this report received PT-CY. Our findings indicate that MAC haplo-BMT is well tolerated by children and young adults with advanced hematologic malignancies with no observed nonrelapse mortality or grades III to IV GVHD. All patients who underwent haplo-BMT remain alive and disease-free with a median follow-up of 15.6 months (range, 1.5 to 31.2). Preliminary findings from our ongoing clinical trial demonstrate that partial substitution of PT-BEN for PT-CY is feasible and safe after haplo-BMT as an immune modulatory strategy to alleviate GVHD and potentially more effectively preserve GVL.

INTRODUCTION

Haploidentical hematopoietic cell transplantation (haplo-HCT) has emerged as a safe and effective treatment for patients with hematologic malignancies. The most widely used approach, particularly in North America, is T cell–replete haplo-HCT with post-transplant cyclophosphamide (PT-CY) [1–5]. Although there have been numerous reports of haplo-HCT with PT-CY in adults, there have been very limited primarily pediatric publications to date [6–8]. Jaiswal et al. [7] reported on the use of PT-CY after a chemotherapy-based myeloablative conditioning (MAC) regimen and unmanipulated peripheral blood HCT in pediatric leukemia patients in India. Berger et al. [6] described their pediatric haploidentical bone marrow transplantation (haplo-BMT) experience from 5 Italian centers, with 58% of patients receiving MAC and the remaining reduced-intensity conditioning (RIC), all followed by PT-CY. Klein et al. [8] from Johns Hopkins recently summarized their pediatric and young adult outcomes after haplo-BMT for advanced hematologic malignancies conditioned with their well-known RIC regimen followed by PT-CY. The 1- or 2-year disease-free survival (DFS) in these studies ranged from 32% to 61%.

Haplo-HCT has particularly benefited minority patients who are often unable to find a matched unrelated donor (MUD). About half of the patients undergoing HCT at our institution are ethnic or racial minorities. Thus, our pediatric BMT

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program started offering haplo-BMT to our patients in 2015. We describe our experience with the first 13 pediatric and young adult patients with hematologic malignancies who underwent T cell–replete haplo-BMT after MAC. We have previously documented that in experimental haplo-BMT, post-transplant bendamustine (PT-BEN) is at least as effective as PT-CY against graft-versus-host disease (GVHD) and improves graft-versus-leukemia (GVL) effects [9]. We report on, for the first time in humans, 4 patients treated with a combination of PT-CY and PT-BEN (PT-CY/BEN) after haplo-BMT as part of our ongoing institutional phase I/II study. The remaining 9 patients in this report received PT-CY. Impressively, all 13 patients who underwent haplo-BMT remain alive and disease-free with a median follow-up of 15.6 months (range, 1.5 to 31.2).

METHODS

From October 2015 to March 2018, 13 pediatric and young adult patients with hematologic malignancies underwent haplo-BMT at Banner University Medical Center in Tucson, Arizona. University of Arizona institutional review board approval was obtained to review and report our findings. All patients were treated by the pediatric BMT service except for the oldest patient (26 years), who was transplanted by our adult BMT colleagues.

Seven patients with acute lymphoblastic leukemia (ALL) were conditioned with fractionated total body irradiation (TBI) of 200 b.i.d. given on days −8, −7, and −6 (1200 cGy total dose with lungs shielded to 900 cGy by custom Cerrobend blocking), followed by fludarabine 30 mg/m^2 on days −5, −4, −3, and −2 [1]. The remaining 6 patients (3 with myeloid leukemias, 1 with acute undifferentiated leukemia, and 2 with lymphomas) received busulfan at .8 mg/kg i.v. every 6 hours for a total of 12 doses (days −8 to −6), targeting an average area under the curve of 1000 to 1100 μMol/min for the duration of the course. Busulfan pharmacokinetics of the first dose were performed at the Seattle Cancer Care Alliance Laboratory. The seventh and remaining doses were modified to achieve the average exposure of 1000 to 1100 μMol/min. Busulfan was followed by fludarabine 30 mg/m^2 on days −5, −4, −3, and −2 and melphalan 100 mg/m^2 on day −2 [10].

Nine patients received PT-CY 50 mg/kg on days +3 and +4. The other 4 patients were treated on an institutional review board–approved phase I/II single-institution clinical trial through the University of Arizona Cancer Center (NCT02996773). Two patients (cohort 1) received PT-CY 50 mg/kg on day +3. On day +4 they received 40 mg/kg PT-CY, immediately followed by PT-BEN 20 mg/m^2. Two additional patients (cohort 2) received PT-CY 50 mg/kg on day +3 and 20 mg/kg on day +4 immediately followed by PT-BEN 60 mg/m^2. For GVHD prophylaxis, all patients were started on mycophenolate mofetil on day +5 at 15 mg/kg per dose every 8 hours i.v. or p.o. with a maximum dose of 1000 mg until day +28. Tacrolimus was initiated on day +5 i.v. or p.o. every 12 hours, adjusting the dose to maintain levels of 7 to 12 ng/mL. Granulocyte colony-stimulating factor was started on day +5 at 5 μg/kg/day until an absolute neutrophil count of 2.5 × 10^9/L was achieved for 3 consecutive days.

Donors were parents or siblings who were HLA-haploidentical based on high-resolution typing at HLA-A, -B, -Cw, -DRB1, and -DQB1. Nine of the donors were 5/10 antigen matches, 3 were 6/10, and 1 was 7/10. None of the patients had anti-donor HLA antibodies. Seven major and 1 minor ABO incompatibilities required donor RBC reduction using Hespan (B. Braun Medical Inc. Irvine, CA 92614-5895 USA) (6% hetastarch in .9% sodium chloride injection) for RBC sedimentation [11]. Day of myeloid engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count of .5 × 10^9/L. Day of platelet engraftment was considered the first of 3 consecutive days with platelet counts of ≥20 × 10^9/L with no platelet transfusions administered in the previous 7 days.

RESULTS

Patient, Disease, and Transplant Characteristics

Thirteen pediatric and young adult patients with a median age of 19.4 years (range, 4.6 to 26.1) underwent haplo-BMT at our institution. Patient characteristics are summarized in Table 1. Ethnic and/or racial minorities constituted 69.2% of all patients, most of whom were Hispanic (53.8%). There were 10 males and 3 females. Lansky/Karnofsky performance status scores ranged from 70 to 100 with a median of 90.

The most common diagnosis was ALL, with 5 of 7 ALL patients receiving transplant in second complete remission (CR), all of whom were minimal residual disease negative. Three patients had intrachromosomal amplification of chromosome 21, and 1 was Philadelphia chromosome positive. The ALL patient receiving haplo-BMT in first CR achieved minimal residual disease negative status with blinatumomab after primary induction failure following 2 chemotherapy regimens [12]. Similarly, the patient receiving haplo-BMT in fourth CR had previously relapsed 75 days after an unrelated cord blood transplant and subsequently had 4 failed infusions of chimeric antigen receptor (CAR) T cells but achieved a minimal residual

Table 1
Patient Characteristics

	All Patients (N = 13)	PT-CY (n = 9)	PT-CY/BEN20 (n = 2)	PT-CY/BEN60 (n = 2)
Median patient age at BMT, yr (range)	19.4 (4.6-26.1)	19.4 (4.6-24.4)	20.9 (15.6-26.1)	15.3 (9.2-21.4)
Males/females	10/3	7/2	1/1	2/0
Race/ethnicity				
Hispanic	7 (53.8)	5	1	1
Native American	1 (7.7)	1		
African American	1 (7.7)	1		
White	4 (30.8)	2	1	1
Diagnosis and disease stage				
ALL CR1	1	1		
ALL CR2	5	3	1	1
ALL CR4	1	1		
AML CR1	1	1		
AML CR2	1	1		
AUL CR1	1			1
CML CP	1	1		
NHL PR	1		1	
HD PR	1	1		
Pretransplant conditioning				
TBI-FLU	7 (53.8)	5	1	1
BU-FLU-MEL	6 (46.2)	4	1	1
Prior BMT (diagnosis, months pre-haplo)				
UCB (ALL, 18)	1	1		
Auto (HD, 11)	1	1		
Median Lansky/Karnofsky score (range)	90 (70-100)	90 (80-100)	90 (90)	80 (70-90)

Values are n (%) unless otherwise defined. AML indicates acute myeloid leukemia; AUL, acute undifferentiated leukemia; CML, chronic myeloid leukemia; CP, chronic phase ; NHL, non-Hodgkin lymphoma; PR, ; HD, Hodgkin disease; FLU, fludarabine; BU, busulfan; MEL, melphalan; UCB, umbilical cord blood; Auto, autologous.

Table 2
Patient, Donor Graft Characteristics, Engraftment, and GVHD

	All Patients (N = 13)	PT-CY (n = 9)	PT-CY/BEN20 (n = 2)	PT-CY/BEN60 (n = 2)
Median donor age, yr (range)	27 (16.3-47.7)	38.4 (16.3-47.7)	35.7 (26.1-45.3)	26.4 (25.8-27)
Donors males/females	8/5	5/4	2/0	1/1
Recipient/donor				
Male/mother	4 (30.8)	3		1
Male/father	3 (23.1)	2	1	
Male/brother	3 (23.1)	2		1
Female/father	1 (7.7)	1		
Female/brother	1 (7.7)		1	
Female/sister	1 (7.7)	1		
Median bone marrow cells infused				
$CD45^+$ 10^8/kg	2.57 (1.14-6.18)	2.50 (1.14-6.18)	3.62 (2.41-4.82)	4.79 (3.70-5.87)
$CD34^+$ 10^6/kg	3.50 (1.50-7.45)	3.10 (1.50-6.35)	5.0 (2.55-7.45)	5.28 (3.67-6.89)
RBC incompatibility	8 (61.5)	5	1	2
CMV status recipient/donor				
Positive/positive	9	7	1	1
Positive/negative	4	2	1	1
Days post-BMT				
ANC > 500/μL	16 (12-26)	16 (13-26)	16 (15-17)	13.5 (12-15)
Platelets > 20,000//μL	27.5 (16-176)	28 (25-176)	27.5 (22-33)	21 (16-26)
Transfusions received				
Platelets	14 (2-42)	16 (7-42)	17 (14-20)	6 (2-10)
PRBCs	3 (0-14)	5 (1-14)	3 (0-6)	2 (1-3)
Day post-BMT discharged	28 (18-39)	28 (20-39)	24.5 (18-31)	29.5 (26-33)
GVHD				
Acute grade II/IV	4 (30.8)	3	1	0
Acute grade III/IV	0	0	0	0
Chronic (all)	3 (23.1)	3	0	n/a
Extensive chronic	2 (15.4)	2	0	n/a

Values are n (%) unless otherwise defined. PRBCs indicates packed red blood cells.

disease negative status (fourth CR) after blinatumomab treatment [12]. Two patients had acute myeloid leukemia, 1 of whom developed a t(9;11),11q23 positive secondary leukemia 8 months after completion of chemotherapy for osteogenic sarcoma [10]. Three patients had measurable disease at the time of haplo-BMT, 2 with refractory lymphoma and 1 with chronic myelogenous leukemia with a T315I mutation and previously failed treatment with 3 different tyrosine kinase inhibitors. For 2 of 13 patients, haplo-BMT was their second transplant (Table 1).

The median age of the donors was 27 years (range, 16.3 to 47.7) (Table 2). Thirty-eight percent of the donors were siblings, 31% fathers and 31% mothers. Six of 10 male patients (60%) and 2 of 3 female patients (66.6%) received cells from male donors. The median number of bone marrow $CD34^+$ cells infused was 3.5×10^6/kg (range, 1.5 to 7.45). All patients and 9 donors were cytomegalovirus (CMV) seropositive (Table 2).

Outcomes after Haplo-BMT

Post-transplant immunosuppression, engraftment, and chimerism

Nine patients received PT-CY 50 mg/kg on days +3 and +4. As part of an institutional phase I/II trial (NCT02996773), 4 patients received PT-BEN with de-escalation of PT-CY on day +4 (2 at CY 40 mg/kg with BEN 20 mg/m^2 and 2 at CY 20 mg/kg with BEN 60 mg/m^2; Table 1). Neutrophil engraftment occurred at a median of 16 days post-BMT (range, 12 to 26) (Table 2 and Figure 1). Platelet engraftment (≥20,000/μL) took place at a median of 27.5 days (range, 16 to 176) (Table 2 and Figure 2). PT-CY/BEN did not adversely affect neutrophil or platelet engraftment (Table 2). Two PT-CY patients received suboptimal numbers of $CD34^+$ cells (1.5 and 1.55×10^6/kg). Both achieved timely myeloid engraftment (days +16 and +17), but 1 displayed delayed platelet engraftment (day +54). Another PT-CY patient received adequate $CD34^+$ cells (4.62×10^6/kg) but had delayed platelet engraftment, likely from secondary infections including CMV reactivation requiring ganciclovir. All patients had complete donor chimerism on day 28, 11 of 11 assessable patients on day 100 and at 6 months after haplo-BMT. No graft failures were observed.

Post-transplant complications

Patients were hospitalized from the start of the conditioning regimen through engraftment and were discharged when they were able to tolerate adequate oral nutrition, fluids, and medications. The median time to discharge was 28 days (range, 18 to 39), which was similar between patients receiving PT-CY or PT-CY/BEN (Table 2). Eight patients required hospitalization again during the first 100 days after haplo-BMT, 3 requiring 2 admissions. Patients receiving PT-CY/BEN accounted for only 1 of 11 rehospitalizations. The most common cause of

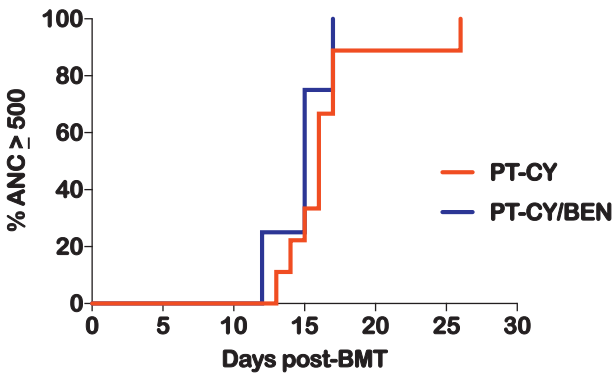

Figure 1. Time to an absolute neutrophil count (ANC) of 500. Time in days from haplo-BMT to achieving an ANC of at least $.5 \times 10^9$/L. Defined as the first of 3 consecutive days with an ANC of $.5 \times 10^9$/L. PT-CY versus PT-BEN, not significant.

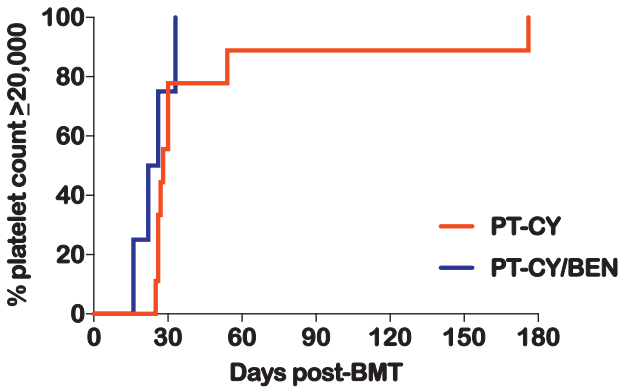

Figure 2. Time to a platelet count of 20,000. Time in days from haplo-BMT to achieving a platelet count of at least 20×10^9/L. Defined as the first of 3 consecutive days with platelet counts $\geq 20 \times 10^9$/L with no platelet transfusions administered in the previous 7 days. PT-CY versus PT-BEN, not significant.

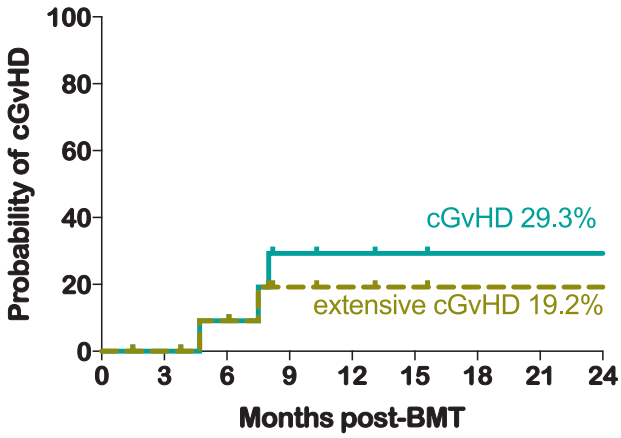

Figure 4. Two-year probability estimates of all c GVHD and of extensive cGVHD.

hospitalization was fever and/or infection. There were no transfers or admissions to the Intensive Care Unit (ICU) during the first 100 days after haplo-BMT.

Graft-versus-host disease

All patients received mycophenolate mofetil from days +5 to +28. Tacrolimus was discontinued at a median of 149 days after haplo-BMT (range, 95 to 222). The incidence of grades II to IV and grade III to IV acute GVHD (aGVHD) was 30.8% and 0%, respectively. Of the 4 patients with grade II GVHD, only 1 required treatment with systemic steroids, whereas the others responded to topical creams (Figure 3). One of the 3 patients receiving PT-CY/BEN (cohort 1) had grade II aGVHD (stage II skin) that resolved with steroid creams and tacrolimus ointment (Table 2). The incidence of chronic GVHD (cGVHD) and extensive cGVHD to date is 23.1% and 15.4%, with 2-year probabilities estimated at 29.3% and 19.2%, respectively (Figure 4). All 3 patients with cGVHD responded to treatment, 2 are off immunosuppression and the third is on a prednisone taper. None of the PT-CY/BEN patients has developed cGVHD, but the follow-up is short for cohort 2 (1.5 and 3.8 months).

Infections

There were 5 bacteremias in 5 patients before day +28 (3 in PT-CY and 2 in PT-CY/BEN), all of which responded to appropriate antibiotic therapy (Table 3). There were no bacteremias documented in any patient between days 29 and 100, whereas 5 occurred between days 101 and 365 in 3 patients, all of whom received PT-CY. Two patients with cGVHD had 2 infections each in this time period. One of these patients, with extensive cGVHD, also developed a fungal infection, coccidioidomycosis, which is endemic in southern Arizona, and responded to azoles [13]. This was also the only patient who required ICU admission, occurring on day +178 post-BMT for *Stenotrophomonas* bacteremia (Table 3).

CMV reactivation was common after haplo-BMT and was detected in 8 patients (61.5%), 6 of whom were treated with ganciclovir and/or valganciclovir (Table 4). Five of the 6 patients requiring CMV treatment had concurrent aGVHD and/or cGVHD. Surprisingly, only 1 of the 4 patients receiving a CMV-negative donor reactivated (25%), versus 7 of the 9 who had positive donors (77.7%). Four patients demonstrated adenovirus reactivation. One received treatment with cidofovir, whereas the viremia resolved spontaneously in the others. Human herpes virus-6 reactivation was detected in 7 patients, none of whom required treatment. Low levels of Epstein-Barr virus DNA load (350, 800, and 1500 IU/mL) were identified in 3 patients, resolving in each case without intervention. Two patients developed microscopic hematuria secondary to BK viruria without viremia. Viral reactivations in patients receiving PT-CY/BEN did not appear to be more frequent. One patient was treated for

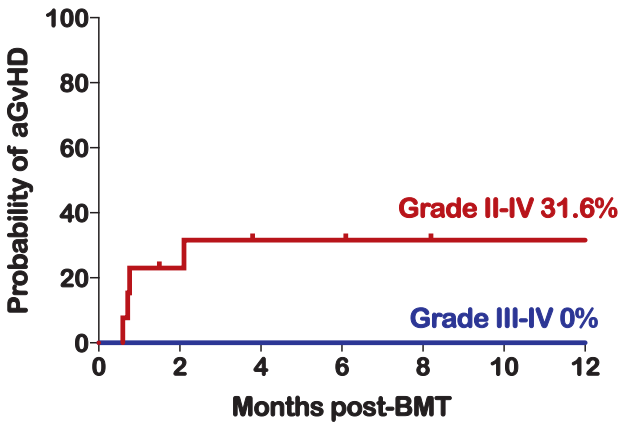

Figure 3. Cumulative incidences of grades II to IV and grades III to IV aGVHD.

Table 3
Bacteremias and Fungal Infections after Haplo-BMT

	Day 0-28	Day 29-100	Day 101-365	PT-CY (n = 9)	PT-CY/BEN (n = 4)
Gram-positive bacteremia					
Coagulase-negative *Staphylococcus*	1			1	
Streptococcus viridans group	3			1	2
Streptococcus pneumoniae			2	2	
Rhodococcus			1	1	
Gram-negative bacteremia					
Escherichia coli			1	1	
Klebsiella pneumoniae	1			1	
Stenotrophomonas maltophilia			1	1	
Fungal					
Coccidioides immitis			1	1	

Table 4
Viral Reactivation after Haplo-BMT

	PT-CY (n = 9)		PT-CY/BEN (n = 4)	
	Treatment	No Treatment	Treatment	No Treatment
CMV	5 (55.6)	2 (22.2)	1 (25)	
Adenovirus	1 (11.1)	3 (33.3)		
HHV-6		6 (66.7)		1 (25)
EBV		3 (33.3)		
BK viremia				
BK viruria		2 (22.2)		1 (25)

Values are n (%) unless otherwise defined. HHV-6 indicates human herpes virus-6; EBV, Epstein-Barr virus.

CMV and was also noted to have low-grade human herpes virus-6 reactivation and BK viruria. The other 3 patients have had no documented viral reactivations to date (Table 4).

Survival

With a median follow-up of 15.6 months (range, 1.5 to 31.2), the DFS and overall survival remain at 100% with no relapses and no nonrelapse mortality (NRM) (Figure 5). Follow-up for the 9 patients receiving PT-CY ranged between 6.1 and 31.2 months, whereas in the PT-CY/BEN patients it was 8.2 and 13.1 months for cohort 1 and 1.5 and 3.8 months for cohort 2.

DISCUSSION

We report our initial experience with implementation of haplo-BMT in our pediatric BMT program. There are unique features to our experience compared with other pediatric studies with haplo-HCT and PT-CY. First, the nearly universal donor accessibility afforded by haplo-BMT is particularly significant for our program due to our ethnic and racial minority patient demographics. Of all patients undergoing allogeneic HCT on our pediatric blood and marrow transplant unit since 2010, 59% were minorities (49% Hispanic, 6% African American, and 4% Native American). The likelihood of finding an 8/8 antigen (HLA-A, -B, -C, and -DRB1) MUD donor is only 34% to 40% for Hispanics, 16% to 19% for African Americans, and 36% to 52% for Native Americans compared with 75% for whites of European descent [14]. Consequently, there was a critical need to introduce haplo-BMT to our largely minority patient population. Our pediatric BMT program therefore started offering haplo-BMT in 2015. Haplo-BMT replaced mismatched unrelated donor and unrelated cord blood transplants for malignant diseases. Not unexpectedly, haplo-BMT has been applied more frequently in minority patients, which have comprised 69.2% of our haploidentical transplants. During the last 3 years, 56% of allogeneic transplants for hematologic malignancies have relied on haploidentical donors, compared with 28% on matched sibling donors and 16% on MUDs.

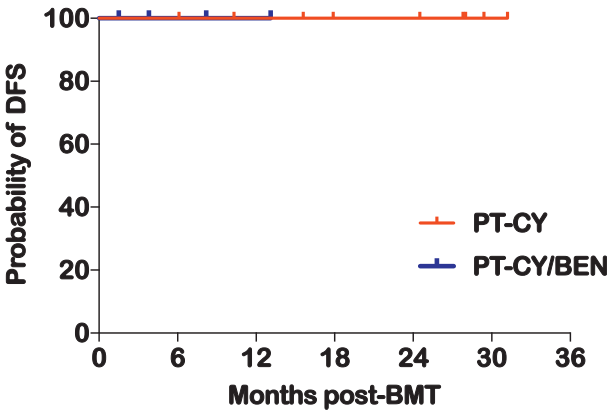

Figure 5. Kaplan-Meier DFS of all patients receiving haplo-BMT.

Second, we report for the first time that other chemotherapeutic agents such as bendamustine may be introduced after BMT to control GVHD. More than half a century ago it was demonstrated that a single dose of CY was able to prolong the survival of a skin allograft from a haploidentical donor if given between the first and fourth day after implantation of the graft [15]. The use of PT-CY originated from experimental HCT in murine models performed at Johns Hopkins University. This approach has been critical in the development of T cell–replete haplo-HCT [16]. PT-CY is effective for several reasons, including its ability to target rapidly dividing alloreactive donor T cells that are responsible for GVHD while not affecting quiescent hematopoietic stem cells due to their relatively high levels of aldehyde dehydrogenase [17,18]. Additional benefits of PT-CY are that it is simple to use and can be applied by any center performing allogeneic HCT. T cell–replete haplo-HCT with PT-CY has therefore emerged as the most widely applied regimen, at least in the United States, because it circumvents the need to manipulate stem cell grafts. Although many of the initial studies focused primarily on adult patients, T cell–replete haplo-HCT with PT-CY is becoming an increasingly used transplant approach in pediatric patients afflicted by both malignant and nonmalignant diseases. Based on our recently published preclinical study in haplo-BMT demonstrating that PT-BEN, when compared with PT-CY, is equally protective against early GVHD and has advantages in late GVHD and GVL [9], our phase I/II trial seeks to challenge the PT-CY dogma. Although our findings are preliminary and limited, we have not observed any differences in engraftment, toxicity, GVHD, infections, or relapse between patients receiving PT-CY and PT-CY/BEN. The trial continues to enroll both pediatric and adult patients evaluating clinical parameters and immune reconstitution.

A third unique feature to our experience is that we used MAC regimens for all patients rather than the Johns Hopkins RIC protocol with PT-CY. For patients with ALL, our institution uses a TBI-based regimen previously described in adult patients by Bacigalupo et al. [1] from Genoa. For myeloid leukemia and lymphoma, we have applied a chemotherapy-based MAC regimen comprised of busulfan, fludarabine, and melphalan. Coincidently, this regimen is similar to the one recently reported by Jaiswal et al. [7] with regard to busulfan, but we use 4 days of fludarabine (30 mg/m^2) instead of 5, given after busulfan rather than concurrently, and a lower dose of melphalan (100 mg/m^2 instead of 140). Both of our regimens have been well tolerated with no transplant-related mortality or admissions to ICU.

Fourth, our outcomes thus far have been excellent, with no grades III to IV aGVHD, no NRM, and 100% DFS. These findings have to be interpreted with caution because our follow-up is short with a median of 15.6 months (Figure 5). Moreover, although our study included patients with advanced disease, comparatively, our cohort appeared to be of lower risk than the previously published pediatric haplo-HCT studies with PT-CY. Jaiswal et al. [7] reported on the use of unmanipulated peripheral blood stem cells in pediatric patients with detectable leukemia at transplant. The NRM in this study was high at 20%, with relapse low at 25%, and a 2-year DFS of 59%. In an Italian multi-institutional study using the Johns Hopkins RIC regimen in most patients, NRM was 9%, with relapse at 24% and a 1-year DFS of 61% [6]. The pediatric group from Johns Hopkins treated pediatric and young adult patients (aged 1 to

25 years) using their haplo-HCT RIC regimen (CY 14.5 mg/kg ×2, fludarabine 30 mg/m^2 ×5, and 200 cGy of TBI) with PT-CY [8]. Engraftment occurred in 94% of patients, whereas grades III to IV aGVHD and cGVHD developed in 13% and 24%, respectively, with an NRM of 13% and relapse rate of 52%. The 1- and 2-year DFS was only 43% and 32%, respectively. This underscores the need for MAC regimens for disease control in pediatric haplo-HCT for refractory and advanced hematologic malignancies.

Haplo-HCT is becoming an accepted transplant modality in pediatrics. Various options exist with respect to the choice of conditioning regimen, graft manipulation, and GVHD prophylaxis. The Europeans have more commonly used T cell–depletion strategies rather than T cell–replete haplo-HCT with PT-CY. A more refined approach to T cell depletion consists of haplo-HCT with $\alpha\beta$ T and B cell–depleted grafts, allowing the transfer of CD34$^+$ stem cells with $\gamma\delta$ T and natural killer cells, both of which are capable of eliciting antileukemic and antipathogenic effects. A German group reported their pediatric results with this approach using a MAC regimen [19]. Engraftment occurred in 88%, grades III to IV aGVHD in 15%, cGVHD in 19% (9% extensive), and relapse in 47% of patients. With a median follow-up of 19 months, the DFS was 51%. Of note, the 10 patients who received their first transplant in CR showed a DFS of 100% at 1 year, illustrating the importance of disease status at the time of transplantation. Locatelli et al. [20] from Italy added to the investigation of $\alpha\beta$ T cell/CD19 B cell–depleted haplo-HCT with 80 acute leukemia pediatric patients in CR. All patients received a myeloablative preparative regimen (75% TBI-based) and no post-transplant GVHD prophylaxis. Two patients experienced primary graft failure (98% engraftment), there was no grades III to IV aGVHD, and only 5% limited cGVHD was observed. NRM was only 5%, and relapse rates were 24%. With a median follow-up of 46 months, the 5-year probability of DFS was 71%. As part of this report, they compared the outcomes of haplo-HCT with their patients receiving matched sibling donor or MUD HCT during the same time period. Haplo-HCT was associated with a lower incidence of grades III to IV aGVHD and cGVHD, and no significant difference in DFS was seen among the 3 transplant groups.

Taken together with the aforementioned published reports, our results strongly indicate that MAC haplo-BMT with PT-CY or PT-CY/BEN is well tolerated by pediatric and young adult patients and offers an excellent alternative to matched donor allogeneic HCT. It is clear that patients in remission have lower rates of relapse. However, research is still needed to determine the optimal donor and graft characteristics and to refine conditioning regimens and GVHD prophylaxis, including agents that may replace PT-CY, such as PT-BEN, thus improving immune reconstitution for enhanced pathogen and disease surveillance.

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