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Comparable outcomes with marrow or peripheral blood as stem cell sources for hematopoietic cell transplantation from haploidentical donors after non-ablative conditioning: A matched-pair analysis

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In the setting of myeloablative conditioning and conventional post-grafting immunoprophylaxis for graft-versus-host disease (GvHD) with a calcineurin inhibitor and methotrexate, randomized studies of bone marrow (BM) versus peripheral blood (PB) as the allograft source in transplantation from HLA-matched related donors (1) or unrelated donors (2) showed comparable outcomes with the exception of an absolute increase of 6-15% in the incidence of chronic GvHD after transplantation of PB. However, in the setting of non-ablative conditioning, a recent retrospective study from the Center for International Blood and Marrow Transplant Research (CIBMTR) showed that rates of acute GvHD, chronic GvHD and overall survival were similar after transplantation of BM compared to PB (3). In

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order to test whether outcomes were similar after haplo-BM and haplo-PB transplants using non-ablative conditioning with the Hopkins regimen (4), we compared data from a multi-center phase II trial of haplo-BM conducted in the US (Blood and Marrow Transplant Clinical Trials Network 0603 [5,6]) to published and unpublished data from phase II trials of haplo-PB transplants in the US, Europe and Australia (7-9) by means of a matched-pair analysis. Patients 70 years of age or younger who met the eligibility criteria for BMT CTN 0603 were matched for age ± 10 years and for low-intermediate-high disease risk index (DRI). DRI is a composite of disease, disease status and cytogenetic risk (acute leukemia and MDS) that has been shown to independently risk stratify survival in heterogeneous adult patient cohorts with hematologic malignancy regardless of conditioning intensity or graft source (10).

Patient, disease and transplant characteristics of the cohorts are shown in Table 1. The median age at transplantation was 49 years. Recipients of haplo-PB transplants were more likely to report 3 or more significant co-morbidities using the HCT-CI score compared to haplo-BM transplants (47% vs. 28%). As shown in Table 1 there were differences in distribution of diseases transplanted and disease status at transplantation. However, approximately 75% of patients in both cohorts were assigned intermediate DRI. Follow-up was substantially longer in the haplo-BM compared to haplo-PB cohort (median 60 months versus 39 months, respectively). Of the 19 patients alive at last follow-up after haplo-BM transplant, 17 (89%) have over 3 years of follow-up and the remaining 2 patients, 30 and 32 months; among haplo-PB recipients, 18 of 29 patients (62%) have over 3 years of follow up, 6 patients (21%) and 5 patients (17%) have been followed for 2-3 years and 1-2 years, respectively.

As reported previously (5, 7, 8), the median time to neutrophil recovery was 17 days (range: 12 – 83 days) after haplo-BM and 18 days (range: 13-30 days) after haplo-PB transplants; the median time to platelet recovery was 25 days (range: 8-92 days) after haplo-BM and 24 days (range: 12-134 days) after haplo-PB transplants. Donor chimerism (≥95% at D28) was 86% after haplo-BM and 93%, after haplo-PB transplants.

Table 2 shows transplantation outcomes by treatment group. There were no significant differences in the rates of grade II-IV acute GvHD after haplo-BM and haplo-PB transplants. None of the recipients of haplo-BM transplants developed grade III-IV acute GVHD. The day-100 incidence of grade III-IV acute GvHD after haplo-PB transplantation was 5% (95% CI 1-14). Similarly, the 2-year incidence of chronic GvHD or its severity did not differ after transplantation of haplo-BM and haplo-PB. Among recipients of haplo-BM, global severity (11) was graded as mild (n=1), moderate (n=7) and severe (n=2). Global severity was graded as mild (n=4), moderate (n=2), and severe (n=1) among recipients of haplo-PB. No new cases of chronic GvHD were observed after 2 year post-transplant in either cohort. There was no significant difference in the incidence of non-relapse mortality and overall survival but the incidence of relapse was lower after haplo-PB compared to haplo-BM transplants.

In this report, we did not find a significant difference in the rate or global severity of chronic GvHD after haplo-BM or haplo-PB transplantation. Other studies using post-transplant cyclophosphamide as GvHD prophylaxis after ablative or reduced-intensity conditioning and

transplantation with either HLA-matched related or unrelated donors have also observed no increase in the incidence or global severity of chronic GvHD after transplantation with PB grafts (12, 13). Regulatory T-cells are thought to play a role in modulating GvHD (14). The fact that regulatory T-cells are resistant to cyclophosphamide (15) may be a possible explanation for the low incidence of severe chronic GvHD with a regimen of GvHD prophylaxis which includes post-transplant cyclophosphamide.

This study is limited by its modest sample size and disease heterogeneity. However, we attempted to adjust for the heterogeneity by matching BM and PB recipients for DRI and patient age. Acknowledging these limitations, we observed comparable overall survival after transplantation of haplo-BM and haplo-PB in the multi-center setting (7, 9). The lower relapse rates observed after transplantation of haplo-PB deserves exploration in a larger cohort of patients with relatively homogenous malignant hematologic disease. Plausible explanations for our observation in the current analysis include differences in diseases between treatment groups and unknown or unmeasured factors that may have influenced relapse. With increasing numbers of haploidentical donor transplantation for hematologic malignancy the question of optimal graft type merit further exploration in larger homogenous datasets.

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Table 1

Patient and disease characteristics

Characteristics	Haplo-BM[a,c]	Haplo-PB[b,c]
Number	43	43
Median age, years	49 (7 – 70)	49 (14 – 68)
Age, years		
≤ 18	3 (7%)	2 (5%)
19 – 40	12 (25%)	13 (30%)
41 – 60	19 (45%)	17 (39%)
61 – 70	10 (23%)	11 (26%)
Sex		
Male	29 (67%)	25 (58%)
Female	14 (33%)	18 (42%)
Cytomegalovirus serostatus		
Positive	12 (28%)	12 (28%)
Negative	31 (72%)	31 (72%)
Diseases		
Acute myeloid leukemia	20 (47%)	13 (30%)
Acute lymphocytic leukemia	4 (9%)	3 (7%)
Undifferenciated leukemia	3 (7%)	
Diffuse large B-cell lymphoma	6 (14%)	6 (14%)
Mantle cell lymphoma	2 (5%)	1 (2%)
Anaplastic large cell lymphoma	__	5 (11%)
Peripheral T cell lymphoma	__	3 (7%)
Mycosis fungoides	__	1 (2%)
Non Hodgkin lymphoma, unclassifed	__	3 (7%)
Hodgkin lymphoma	7 (16%)	8 (19%)
Disease status		
Complete remission	33 (77%)	34 (79%)
Partial remission	10 (23%)	9 (21%)
Disease risk index		
Low risk	5 (12%)	5 (12%)
Intermediate risk	32 (74%)	32 (74%)
High risk	6 (14%)	6 (14%)
Co-morbidity index		
0 – 2	31 (72%)	23 (54%)
≥ 3	12 (28%)	20 (47%)
Prior autologus transplantation	9 (21%)	14 (33%)

[a]Data obtained from the Data Coordinating Center for the BMT CTN and CIBMTR. Transplantation occurred between December 2008 and May 2010.

[b] Data obtained from the combined databases of the Institut Paoli Calmettes, Marseille (22 patients), Fred Hutchinson Cancer Research Center, Seattle (9 patients), Westmead Hosptial, Sydney (7 patients) and Guy's and St. Thomas' Hospital/King's College Hospital, London (5 patients). Transplantation occurred between 2009 and 2014.

[c] Institutional Review Boards of each participating institution and the National Donor Program approved the sharing of de-identified patient data in this study

Table 2

Univariate analyses for matched pairs: haplo-BM vs. haplo-PB[a]

Outcomes	Haplo-BM	Haplo-PB	p-value
Number	43	43	
Acute grade II-IV GvHD @ day-100	33% (95% CI 19-47)	40% (95% CI 26-54)	0.50
Chronic GvHD[b]			
@ 1-year	21% (95% CI 10-34)	14% (95% CI 5-26)	0.39
@ 2-year	23% (95% CI 12-37)	19% (95% CI 9-32)	0.63
@ 3-year	23% (95% CI 12-37)	19% (95% CI 9-32)	0.63
Non-relapse mortality			
@ 1-year	5% (95% CI 0-13)	9% (95% CI 3-20)	0.40
@ 2-year	7% (95% CI 1-16)	12% (95% CI 4-23)	0.45
@ 3-year	7% (95% CI 1-16)	12% (95% CI 4-23)	0.45
Relapse			
@ 1-year	49% (95% CI 34-64)	19% (95% CI 9-31)	0.002
@ 2-year	51% (95% CI 36-66)	24% (95% CI 12-38)	0.006
@ 3-year	58% (95% CI 43-73)	24% (95% CI 12-38)	<0.001
Disease-free survival			
@ 1-year	47% (95% CI 32-61)	72% (95% CI 58-84)	0.01
@ 2-year	42% (95% CI 28-57)	65% (95% CI 50-78)	0.03
@ 3-year	35% (95% CI 21-49)	65% (95% CI 50-78)	0.004
Overall survival			
@ 1-year	72% (95% CI 58-84)	81% (95% CI 66-90)	0.30
@ 2-year	58%	66%	0.47
@ 3-year	58% (95% CI 43-72)	66% (95% CI 51-80)	0.47

[a] All patients received conditioning with the Hopkins regimen (4) which included fludarabine 150 mg/m, cyclophosphamide 29 mg/kg and 200cGy TBI. GvHD prophylaxis was cyclophosphamide 50 mg/kg given on post-transplant days +3 and +4 followed on day +5 with tacrolimus (target level 5-10 ng/mL) or cyclosporine (target level 150-300 ng/mL) and 15 mg/kg mycophenolate every 8 hr not to exceed a total daily dose of 3000 mg. Mycophenolate was discontinued after day +35 and the calcineurin inhibitor (tacrolimus or cyclosporine) on day +180 unless continued for treatment of GvHD.

[b] Scored by NIH criteria (11). Previously reported data on chronic GvHD for the haplo-BM cohort (5,6) was scored by the historical Seattle criteria.