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Outcomes after Haploidentical Hematopoietic Cell Transplantation with Post-Transplantation Cyclophosphamide: A Systematic Review and Meta-Analysis Comparing Myeloablative with Reduced-Intensity Conditioning Regimens and Bone Marrow with Peripheral Blood Stem Cell Grafts

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A B S T R A C T

Haploidentical hematopoietic cell transplantation (haplo-HCT) with post-transplantation cyclophosphamide (PTCy) may be the sole available curative option for several hematologic malignancies. However, the best choice of conditioning regimen and graft source has not been established. This study was conducted to compare myeloablative conditioning (MAC) regimens with reduced-intensity conditioning (RIC) regimens and peripheral blood stem cell (PBSC) grafts with bone marrow (BM) grafts in the haplo-HCT setting with PTCy. We performed a systematic review and meta-analysis of studies comparing MAC with RIC and PBSC with BM in the haplo-HCT. The search was conducted in PubMed and TRIALS on February 2, 2021, without a date limit. We excluded studies with >30% non-PTCy graft-versus-host disease (GVHD) prophylaxis and >30% nonmalignant diseases. We screened 570 abstracts from PubMed and TRIALS and selected 20 for full-text review and 17 for inclusion in the qualitative and quantitative analyses. For PBSC versus BM grafts, we found no difference in overall survival (OS; hazard ratio [HR], 1.05; $P = .61$; nPBSC = 1983; nBM = 2124), progression-free survival (PFS; HR, 0.95; $P = .52$; nPBSC = 2663, nBM = 2769), graft-versus-host disease (GVHD)-free relapse-free survival (GRFS; HR, 1.16; $P = .07$; nPBSC = 1454; pBM = 1647), or nonrelapse mortality (HR, 1.14; $P = .13$; nPBSC = 1664; nBM = 1862). Relapse was lower with the use of PBSC grafts (HR, 0.84; $P = .001$; nPBSC = 2663; nBM = 2769). The rates of acute GVHD (aGVHD) and chronic GVHD (cGVHD) were higher with PBSC grafts (aGVHD grade II-IV: HR, 1.67; $P < .001$; nPBSC = 2663; nBM = 2802; aGVHD grade III-IV: HR, 1.82; $P < .001$; nPBSC = 1826; nBM = 2000; cGVHD: HR, 1.46; $P = .002$; nPBSC = 2686; nBM = 2815). Engraftment was higher with PBSC grafts (HR, 1.27; $P < .001$; nPBSC = 1461; nBM = 1717). Comparing MAC and RIC, the use of MAC was associated with less relapse (HR, 0.70; $P < .001$; nMAC = 1929; nRIC = 2662), higher nonrelapse mortality (HR, 1.24; $P = .002$; nMAC = 2016; nRIC = 2790), but better PFS (HR, 0.86; $P = .002$; nMAC = 1929; nRIC = 2662). There were no differences between the 2 conditioning regimens in OS (HR, .95; $P = .32$; nMAC = 2123; nRIC = 3155), GRFS (HR, 0.97; $P = .67$; nMAC = 1182; nRIC = 1330), grade II-IV aGVHD (HR, 1.01; $P = .81$; nMAC = 2099; nRIC = 3090), or cGVHD (HR, 1.05; $P = .44$; nMAC=1929; nRIC = 2662). This analysis shows that the use of BM grafts is associated with comparable outcomes as seen with PBSC grafts despite a lower incidence of GVHD and a higher relapse rate. The use of MAC regimens is associated with improved PFS. These results suggest that for fit patients, MAC remains the optimal conditioning regimen in terms of mortality, and that the use of PBSC grafts may further decrease relapse risk and hasten engraftment, provided that further strategies can be incorporated to decrease GVHD. Prospective comparisons are awaited.

INTRODUCTION

Haploidentical hematopoietic cell transplantation (haplo-HCT) with post-transplantation cyclophosphamide (PTCy) is emerging

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as a new standard in the Western world for haplo-HCT. The procedure is relatively straightforward and easily reproducible [1], obviating the need for expensive T cell depletion techniques and greatly expanding the pool of donors.

Haplo-HCT is defined as partially HLA-mismatched transplantation and at least 1 haplotype matched, usually 2 or 3 HLA antigens mismatched (HLA-A, HLA-B, HLA-DR) [2]. PTCy acts in vivo by depleting alloreactive T cells while relatively sparing nonalloreactive T cells that are partially responsible for immune reconstitution [2]. Two recently published meta-analyses have shown that haplo-HCT with PTCy is at least as effective as HCT from unrelated donors for malignant diseases [3,4], and it has been used in patients lacking an HLA-identical sibling donor.

Luznik et al. [1] pioneered the use of PTCy in the setting of reduced-intensity conditioning (RIC) using bone marrow (BM) as stem cell source. That study was associated with a low incidence of graft-versus-host disease (GVHD) and low nonrelapse mortality (NRM) for older patients, although disease recurrence was rather high, partly because of the high-risk disease profile. Subsequently, other protocols using myeloablative conditioning (MAC) and peripheral blood stem cells (PBSCs) have been established in the haplo-HCT with PTCy setting for younger patients high risk of disease, demonstrating its feasibility.

Despite the increasing use of haplo-HCT with PTCy, some questions remain: does myeloablative conditioning regimen yield superior results compared with reduced-intensity, and should PBSC grafts be preferred over BM grafts?

In the unrelated donor setting, the randomized BMT-CTN 0201 study has shown similar survival outcomes with PBSC and BM grafts, with a higher engraftment rate with the former and a lower rate of chronic GVHD (cGVHD) with the latter [5]. Haplo-HCT with PTCy has been associated with better overall survival compared with double-cord blood transplantation, owing mainly to a higher NRM with cord blood [6]. The objective of the present study was to systematically review the literature and compare graft sources and conditioning regimens used in haplo-HCT with PTCy.

METHODS

This systematic review and meta-analysis followed the PRISMA statement [7]. There were 2 review questions: (1) do myeloablative conditioning regimens yield superior PFS compared with reduced-intensity conditioning, in patients with hematologic malignancies?, and (2) does peripheral blood stem-cell graft yields superior PFS, compared with bone marrow, in patients with hematologic malignancies? The search was conducted in PubMed and Cochrane CENTRAL and performed on 2nd Feb 2021 without any date limit. Detailed search strategy is in the supplemental file. All studies that compared PBSC with BM and MAC with RIC in the Haplo-HCT setting were included. There was no time or age restriction. We excluded studies with more than 30% of non-malignant diseases, with more than 30% of non-PTCy-based GVHD prophylaxis, and studies whose patients have probably been included in subsequent publications. Only observational studies were available. Study selection and data extraction were performed independently by L.J.A. and M.N.K., and disagreements between the reviewers were solved through discussion.

The primary outcome was PFS, and secondary outcomes were overall survival (OS), graft-versus-host disease (GVHD)-free relapse-free survival (GRFS), relapse, GVHD (acute grade II-IV, acute grade III-IV, chronic and extensive chronic), relapse, NRM, and neutrophil engraftment. PFS was defined as progression or death, whichever occurred first. NRM was defined as death in a patient in remission. Acute GVHD (aGVHD) was usually graded with the Glucksberg [8] or MAGIC [9] criteria, both of which are highly correlated. When chronic GVHD (cGVHD) was staged by the National Institutes of Health's consensus criteria [10], we considered "moderate" and "severe" cGVHD to be equivalent to "extensive" cGVHD. Neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count $>500/mm^3$. When PFS was not reported, we estimated it based on the NRM and the relapse incidence rates. We extracted hazard ratios (HRs) and their corresponding standard errors (SEs) based on the confidence interval (CI) or *P*value. When HR was not available, we estimated the log(HR) for survival (S) by the $\log(-\log(S_B)) - \log(-\log(S_A))$ transformation for survival outcomes and by the $\log(-\log(1 - CIF_B)) - \log(-\log(1 - CIF_A))$ for cumulative incidence function (CIF) outcomes [11], or by the transformation of the log-transformed relative risk (logRR) [12]. The corresponding variances were estimated by the sum of the variances and/or the delta method. Additional details are provided in the Supplementary Material. We used a random-effects model when heterogeneity was high ($I^2 > 50\%$) and a fixed-effects model otherwise. BM graft and RIC served as the reference categories.

We used the all-but-one method for sensitivity analysis. We identified 3 Center for International Blood and Marrow Transplant Research (CIBMTR) and 3 European Society for Blood and Marrow Transplantation (EBMT) studies that could have overlapping patients; thus, we also excluded 2 of these studies at a time to see whether the results held—an unplanned analysis. We also performed another sensitivity analysis in which we assumed that studies that have not reported outcomes had an HR of 1 for aGVHD grade III-IV; we excluded studies that did not prespecify grade III-IV aGVHD or extensive cGVHD analysis, and this sensitivity analysis makes sense only for outcomes with statistically significant results. Publication bias was assessed by visual inspection of funnel plots, and the trim and fill method was applied in the presence of evidence of publication bias. The risk of bias was assessed with the Newcastle-Ottawa Scale (Supplementary Material).

This study received no third-party funding. All analyses were performed with R version 3.6.2, with the "meta" and "msm" packages (R Foundation for Statistical Computing, Vienna, Austria). This systematic review is registered at PROSPERO (CRD42021234696), an international database of prospectively registered systematic reviews.

RESULTS

We screened 570 abstracts and selected 20 for a full-text review. Of these, we excluded 3 [13-15], 2 because of probable redundant publication and 1 with <70% of subjects receiving PTCy-based GVHD prophylaxis, leaving 17 for inclusion in our analyses [16-32]. Three studies were single center, 7 were multicenter, and 7 were registry studies. Thirteen studies were included in the PBSC versus BM analysis, and 11 studies were included in the MAC versus RIC analysis. Study profiles are provided in Table 1 and Supplementary Material, and the main results are summarized in Table 2. Forest plots are shown in Figures 1-5 and Supplementary Material.

PBSCs versus BM

OS (HR, 1.05; $P = .61$), PFS (HR, 0.95; $P = .52$), and GRFS (HR, 1.16; $P = .07$) were not different with the use of PBSC or BM grafts (Figure 1). There was a 16% reduction in relapse risk (HR, 0.84; $P = .001$) with the use of PBSC grafts compared with BM grafts (Figure 2). There was no significant difference in NRM between the 2 graft sources (HR, 1.14; $P = .13$).

The rates of grade II-IV aGVHD (HR, 1.67; $P < .001$), aGVHD grade III-IV (HR, 1.82; $P < .001$), cGVHD (HR, 1.46; $P = .002$), and extensive cGVHD (HR, 1.44; $P = .06$) were higher with PBSC grafts compared with BM grafts. Engraftment was significantly higher with PBSC grafts (HR, 1.27; $P < .001$).

MAC versus RIC Regimens

OS (HR, 0.95; $P = .32$) and GRFS (HR, 0.97; $P = .67$) were not different between recipients of MAC regimens and recipients of RIC regimens. On the other hand, PFS was increased with the use of MAC regimens (HR, 0.86; $P = .002$).

The risk of relapse was lower with MAC regimens (HR, 0.70; $P < .001$), whereas NRM was lower with RIC regimens (HR, 1.24; $P = .002$).

There was no difference between the 2 conditioning regimens in the incidence of grade II-IV aGVHD (HR, 1.01; $P = .81$) or cGVHD (HR, 1.05; $P = .44$), whereas there was a higher incidence of grade III-IV aGVHD (HR, 1.38; $P = .02$) with MAC. The rate of extensive or moderate/severe cGVHD was not different between the 2 conditioning regimens (HR, 1.11; $P = .45$). There was no evidence of a difference in engraftment between the 2 regimens (HR, 1.00; $P = .96$).

Table 1
Relevant Studies

Study	N	Median Age, yr	Diseases	Included in	
				PBSC vs BM	MAC vs RIC
Bashey et al., 2017 [16]	687	54.9	AML, ALL, MDS, NHL, or HL	Y	Y
Bazarbachi et al, 2020 [17]	474	41	Lymphoma	Y	Y
Bradstock et al., 2015 [18]	36	48	Various	Y	N
Castagna et al., 2014 [19]	69	47.3	Hematologic malignancies	Y	N
Huselton et al., 2018 [20]	148	52.1	Various	N	Y
Im et al., 2020 [21]	384	61	AML, ALL, MDS, or CML; MAC	Y	Y
Im et al, 2020 [21]	262	42.9	AML, ALL, MDS, or CML; RIC	Y	Y
Jacque et al., 2017 [22]	176	44	Hematologic malignancy	Y	N
Mariotti et al., 2019 [23]	91	31	Hodgkin lymphoma	Y	N
Modi et al., 2020 [24]	89	58	Hematologic malignancies	N	Y
Mussetti et al., 2018 [25]	234	47.0	Hematologic malignancies	Y	N
Nagler et al., 2020 [26]	314	36.5	ALL	Y	Y
O'Donnell et al., 2016 [27]	86	49	Hematologic malignancies	Y	N
Pagliardini et al., 2019 [28]	100	58	AML	N	Y
Ruggeri et al., 2018 [29]	451	45	AML and ALL	Y	Y
Santoro et al., 2019 [30]	912	58.8	AML	Y	Y
Solomon et al., 2019 [31]	689	–	ALL, AML or MDS; 18-54 yr	Y	Y
Solomon et al., 2019 [31]	636	–	ALL, AML or MDS; 55-70 yr	Y	Y
Sugita et al., 2019 [32]	127	58	Hematologic malignancies	N	Y
Total	5965	50.8		13*	11*

ALL indicates acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; CML, chronic myelogenous leukemia.
* Number of studies.

Sensitivity and Risk of Bias Analyses

A risk of bias table and funnel plots are provided in the Supplementary Material. Imputation of missing SEs did not change any results. Likewise, considering missing point estimates as HR = 1 and imputing SEs did not change any results. Excluding 2 of the 3 CIBMTR studies substantially reduced the HR for cGVHD (14%, 12%, and 13% in terms of HR and 39%, 32%, and 36% in terms of logHR) and for extensive cGVHD (11% and 9%

Table 2
Main Results

Comparisons and Outcomes	HR	95% CI	*I2*, %*	k†	PBSC/MAC, n	BM/RIC, n
PBSC vs BM grafts						
OS	1.05	0.88-1.25	53	12	1983	2124
PFS	0.95	0.82-1.11	60	13	2663	2769
Relapse	**0.84**	0.76-0.94	26	13	2663	2769
NRM	1.14	0.96-1.36	10	11	1664	1862
aGVHD grade II-IV	**1.67**	1.50-1.86	18	13	2663	2802
aGVHD grade III-IV	**1.82**	1.42-2.33	37	11	1826	2000
cGVHD	**1.46**	1.14-1.85	62	14	2686	2815
Extensive cGVHD	1.44	0.99-2.08	50	9	1716	1865
Engraftment	**1.27**	1.15-1.40	14	11	1461	1717
GRFS	1.16	0.99-1.37	54	7	1454	1647
MAC vs RIC						
OS	0.95	0.87-1.05	44	13	2123	3155
PFS	**0.86**	0.79-0.95	11	12	1929	2662
Relapse	**0.70**	0.62-0.79	0	12	1929	2662
NRM	**1.24**	1.08-1.43	33	12	2016	2790
aGVHD grade II-IV	1.01	0.91-1.13	42	12	2099	3090
aGVHD grade III-IV	**1.38**	1.06 -1.78	17	8	1132	1720
cGVHD	1.05	0.92-1.20	38	12	1929	2662
Extensive cGVHD	1.11	0.85-1.46	45	7	1070	1645
Engraftment	1.00	0.91-1.09	0	9	1284	1906
GRFS	0.97	0.85-1.11	0	7	1182	1330

Statistically significant results are in bold type.
* Outcomes with an I^2 >50% were analyzed with a random-effects model.
† Number of comparisons (not studies).

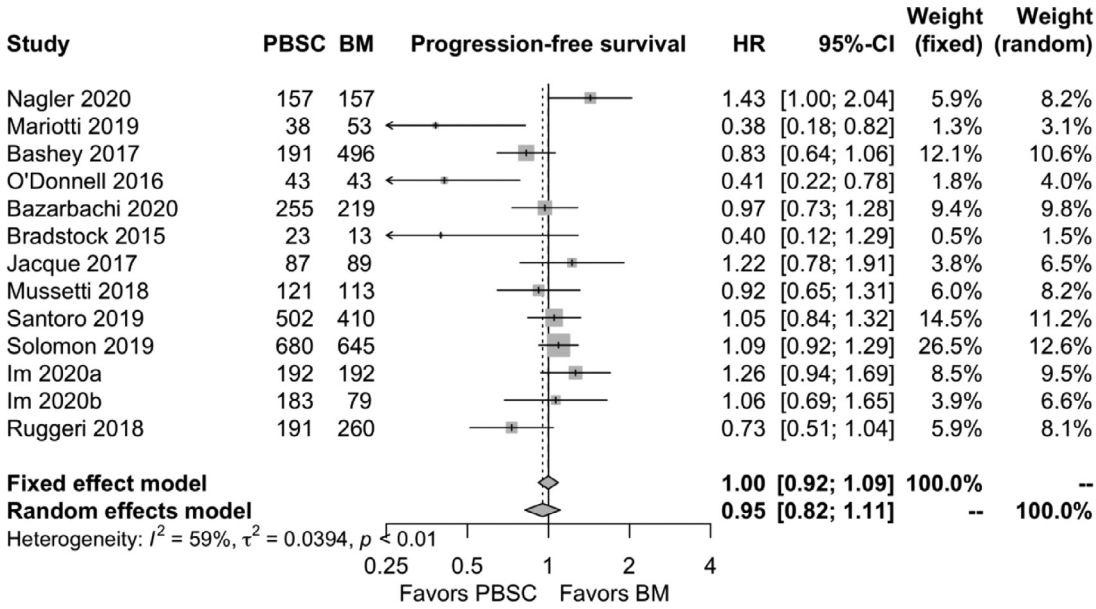

Figure 1. PFS in haplo-HCT and PTCy with PBSC grafts versus BM grafts.

in terms of HR and 32% and 26% in terms of logHR; only 2 reported extensive cGVHD). Other sensitivity analyses did not substantially change any other result. Key sensitivity analyses are described in Supplementary Material.

DISCUSSION

Our results show that MAC regimens are associated with a lower relapse rate and increased PFS compared with RIC, despite higher NRM. Our results also show that the use of mobilized PBSC grafts in haplo-HCT with PTCy achieved better disease control compared with the use of BM as a graft source, although this did not translate into an improved PFS or OS. However, the use of PBSCs was associated with higher incidences of aGVHD and cGVHD. Engraftment was also higher with PBSC grafts.

We have shown that the use of MAC was associated with a lower incidence of relapse (HR, 0.70; 95% CI, 0.62 to 0.79; $P<$ .001) but higher NRM (HR, 1.24; 95% CI, 1.08 to 1.43; $P=$ .002); however, the final result was improved PFS (HR, 0.86; 95% CI, 0.79 to 0.95; $P=$ .002) using MAC instead of RIC. A randomized trial that included 272 relatively fit patients with myelodysplastic syndrome or acute myelogenous leukemia (AML), age <65 years and with <5% blasts, who underwent matched related or unrelated donor HCT found similar results: a lower relapse incidence and a higher NRM, also translating into a higher PFS (HR, 0.47; P < .001) [33]. Our results in the haplo-HCT with PTCy setting suggests that MAC regimens should be the standard conditioning for fit patients.

A concern regarding conditioning intensity is that different age subgroups may have different outcomes. A retrospective

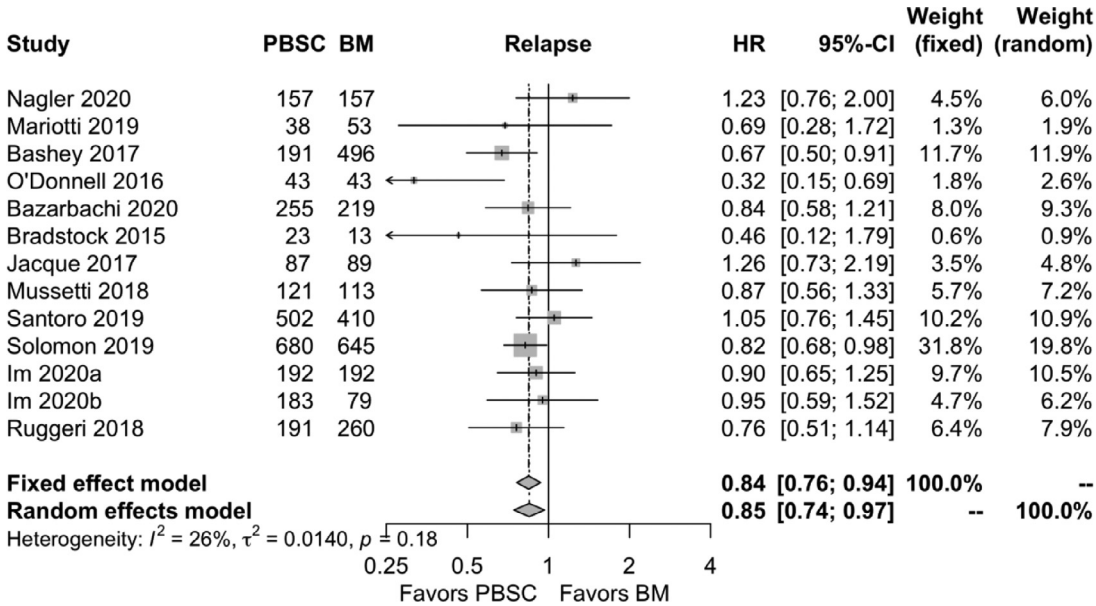

Figure 2. Relapse in haplo-HCT and PTCy with PBSC grafts versus BM grafts.

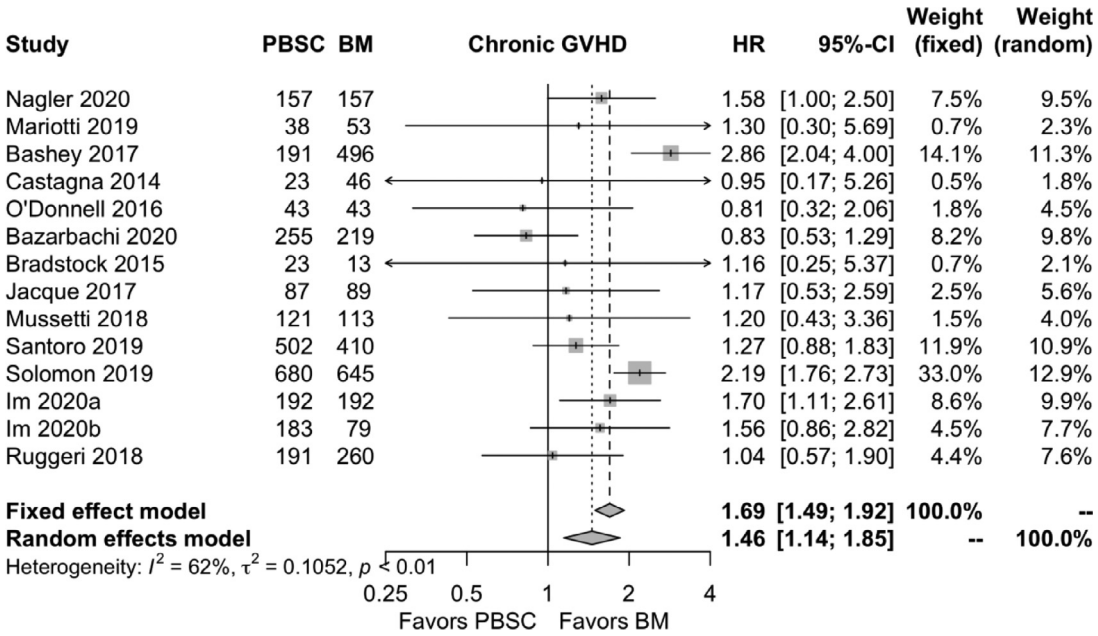

Figure 3. cGVHD in haplo-HCT and PTCy with PBSC grafts versus BM grafts.

analysis of 912 AML patients age ≥45 years who underwent haplo-HCT with either MAC or RIC showed no difference in outcomes according to age stratification (45 to 55 years, 55 to 60 years, or >60 years) [30], whereas a retrospective CIBMTR analysis including 1325 eligible patients showed greater disease-free survival with MAC regimens in younger patients (18 to 54 years) but not in patients age 55 to 70 years [31]. Moreover, we note that only approximately 14% of the diseases included were lymphomas, and we cannot draw definite conclusions in this population. Moreover, it is important to highlight that different conditioning protocols were used in the different studies included in this meta-analysis. Whether different drugs used in MAC regimens have high or low toxicity profiles should be further evaluated to decrease the NRM and maintain disease control after haplo-HCT.

We found a small decrease in the risk of relapse with PBSC grafts compared with BM grafts (16% reduction; 95% CI, 0.76 to 0.94; P = .001), which was probably achieved owing to a better graft-versus-disease effect, as demonstrated by the higher rates of all forms of GVHD (HR, 1.67 [95% CI, 1.50 to 1.86; P < .001] for grade II-IV aGVHD; 1.82 [95% CI, 1.42 to 2.33, P < .001] for grade III-IV aGVHD, and 1.46 [95% CI, 1.14 to 1.85; P = .002] for cGVHD). The results did not change when we included only studies that used the same conditioning regimen in both arms or that controlled for conditioning regimen either by matching or by multivariable analyses (Supplementary Material). However, PFS was not improved with the use of PBSC grafts. Recent data collected by the CIBMTR from 5200 adult recipients of 8/8 and 7/8 HLA-matched unrelated donor transplants showed improved 5-year OS in 8/8 HLA-matched

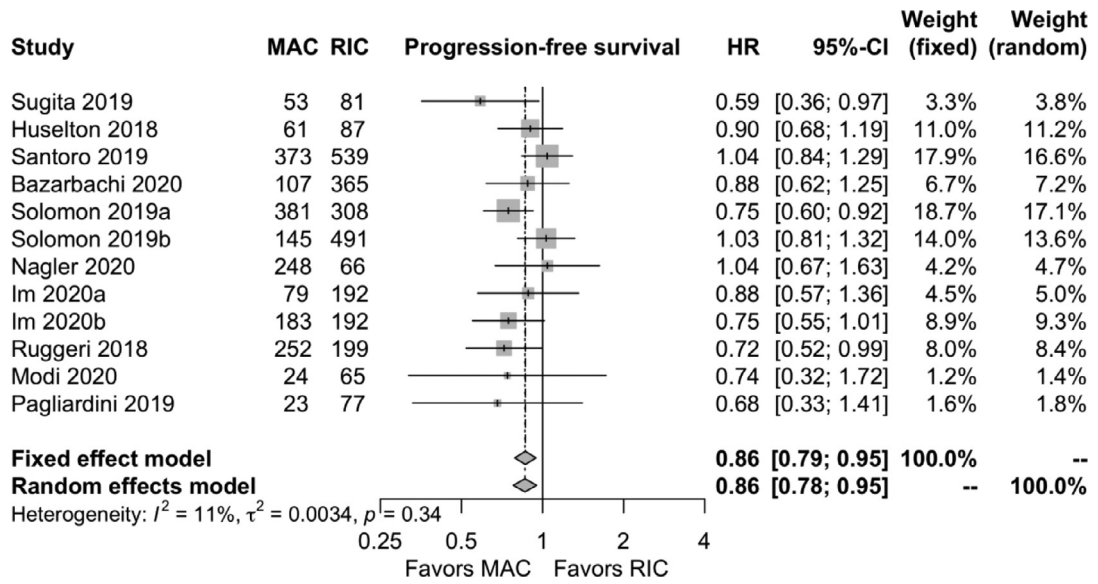

Figure 4. PFC in haplo-HCT and PTCy with MAC versus RIC.

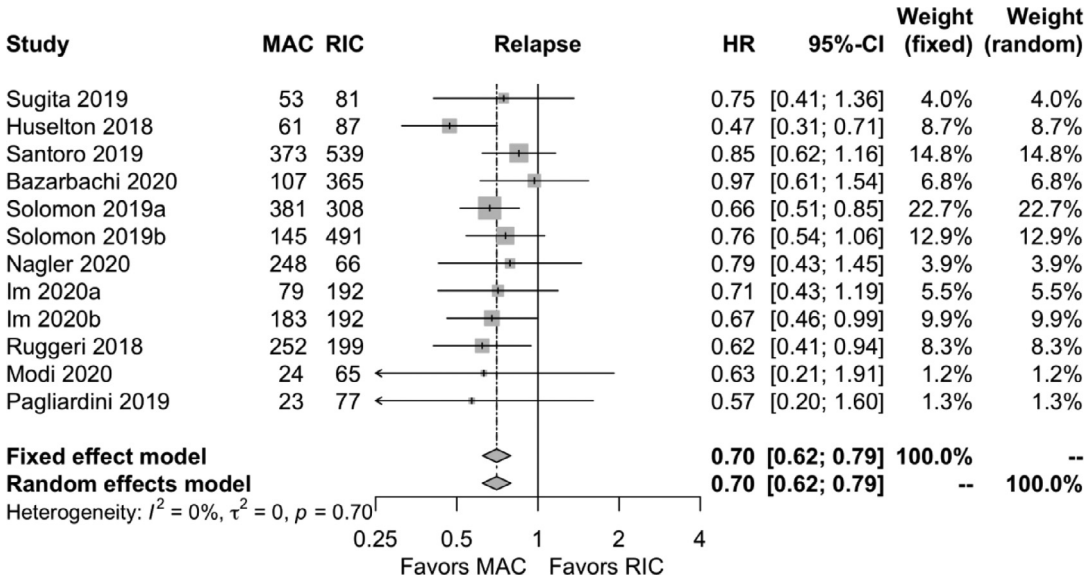

Figure 5. Relapse in haplo-HCT and PTCy with MAC versus RIC.

unrelated donor HCT with BM grafts compared PBSC grafts [34]. Phase III randomized trials in the unrelated [5] and matched sibling [35] settings found no difference in any outcomes, except for a higher rate of cGVHD in patients who received PBSC grafts. However, a Cochrane meta-analysis found a lower relapse rate with matched sibling donor PBSC transplants [36]. In addition, we found higher engraftment with PBSC grafts, a finding previously reports in unrelated donor transplantation [5].

Whether the small decrease in relapse rate that we found without a clear benefit in PFS justifies the systematic use of PBSC grafts instead of BM grafts remains an open question and should be addressed in randomized controlled trials, as should the optimum $CD34^+$ and $CD3^+$ cell doses in the infused product. Importantly, strategies that decrease the incidence of aGVHD and cGVHD in the haplo-HCT setting using PBSC grafts merit further evaluation.

This study has several limitations. It included only observational studies with mainly heterogeneous populations. Nonetheless, we included a total of 5965 patients and ran several sensitivity analyses to be sure about our results. The median age was high in all included studies, so these results should not be extrapolated to children. There was also a lack of standardization in reporting HCT outcomes across the evaluated studies. Some reported outcomes as HRs, others as survival/incidence, with or without *P* values or CIs, and some outcomes were not reported at all. We opted to use reported HRs and estimated HRs by survival/incidence instead of the most frequently performed analysis multiplying survival/incidence by the number of patients, which disregards all censored structure data. We could transform every outcome into an HR, but we had to do it almost manually. As far as we know, there are no packages for automating the conversion. There is an urgent need for standardization in HCT reports. We also could not control the analyses for different concurrent GVHD prophylaxis regimens, disease status, and MAC with or without total body irradiation; however, a large proportion of the HRs were extracted from multivariable analyses.

In summary, we have shown that the use of PBSC grafts in haplo-HCT is associated with decreased relapse incidence but at the cost of higher incidences of all forms of GVHD and did not translate into improved OS or PFS. MAC regimens, despite higher NRM, achieved better disease control and improved PFS. The results of this meta-analysis suggest that for fit patients, MAC remains the optimal conditioning regimen regarding mortality and PBSC may further decrease relapse risk and hasten engraftment, provided further strategies can be incorporated to decrease GVHD. Prospective comparisons are awaited.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2021.06.011.

REFERENCES

1. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, post-transplantation cyclophosphamide. *Biol Blood Marrow Transplant*. 2008;14:641–650.
2. Fuchs EJ. Haploidentical transplantation for hematologic malignancies: where do we stand? *Hematology Am Soc Hematol Educ Program*. 2012;2012:230–236.
3. Arcuri LJ, Aguiar MTM, Ribeiro AAF, Pacheco AGF. Haploidentical transplantation with post-transplant cyclophosphamide versus unrelated donor hematopoietic stem cell transplantation: a systematic review and meta-analysis. *Biol Blood Marrow Transplant*. 2019;25:2422–2430.
4. Gagelmann N, Bacigalupo A, Rambaldi A, et al. Haploidentical stem cell transplantation with posttransplant cyclophosphamide therapy vs other donor transplantations in adults with hematologic cancers: a systematic review and meta-analysis. *JAMA Oncol*. 2019;5:1739–1748.
5. Anasetti C, Logan BR, Lee SJ, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med*. 2012;367:1487–1496.

6. Fuchs EJ, O'Donnell PV, Eapen M, et al. Double unrelated umbilical cord blood vs HLA-haploidentical bone marrow transplantation: the BMT CTN 1101 trial. *Blood*. 2021;137:420–428.
7. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *PLoS Med*. 2009;6: e1000097.
8. Weisdorf DJ, Hurd D, Carter S, et al. Prospective grading of graft-versus-host disease after unrelated donor marrow transplantation: a grading algorithm versus blinded expert panel review. *Biol Blood Marrow Transplant*. 2003;9:512–518.
9. Harris AC, Young R, Devine S, et al. International, multicenter standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai Acute GVHD International Consortium. *Biol Blood Marrow Transplant*. 2016;22:4–10.
10. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015;21:389–401.e1.
11. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Stat Med*. 2017;36:4391–4400.
12. Sutradhar R, Austin PC. Relative rates not relative risks: addressing a widespread misinterpretation of hazard ratios. *Ann Epidemiol*. 2018;28:54–57.
13. Mussetti A, De Philippis C, Carniti C, et al. *Role of cell source and graft composition in haploidentical transplantation using post-transplant cyclophosphamide. Presented at the 58th Annual Meeting of the American Society of Hematology*. San Diego, CA; 2016. December 3-6.
14. Nasso D, Labopin M, Ruggeri A, et al. Impact of conditioning regimen on outcomes of T-replete haplo-identical transplantation for patients over 45 years-old with AML: a study on behalf of the Acute Leukemia Working Party of the EBMT. *Haematologica*. 2017;102:132.
15. Piemontese S, Boumendil A, Labopin M, et al. Leukemia relapse following unmanipulated haploidentical transplantation: a risk factor analysis on behalf of the ALWP of the EBMT. *J Hematol Oncol*. 2019;12:68.
16. Bashey A, Zhang MJ, McCurdy SR, et al. Mobilized peripheral blood stem cells versus unstimulated bone marrow as a graft source for T-cell-replete haploidentical donor transplantation using post-transplant cyclophosphamide. *J Clin Oncol*. 2017;35:3002–3009.
17. Bazarbachi A, Boumendil A, Finel H, et al. Influence of donor type, stem cell source and conditioning on outcomes after haploidentical transplant for lymphoma: a LWP-EBMT study. *Br J Haematol*. 2020;188:745–756.
18. Bradstock K, Bilmon I, Kwan J, et al. Influence of stem cell source on outcomes of allogeneic reduced-intensity conditioning therapy transplants using haploidentical related donors. *Biol Blood Marrow Transplant*. 2015;21:1641–1645.
19. Castagna L, Crocchiolo R, Furst S, et al. Bone marrow compared with peripheral blood stem cells for haploidentical transplantation with a non-myeloablative conditioning regimen and post-transplantation cyclophosphamide. *Biol Blood Marrow Transplant*. 2014;20:724–729.
20. Huselton E, Slade M, Trinkaus KM, DiPersio JF, Westervelt P, Romee R. Propensity score analysis of conditioning intensity in peripheral blood haploidentical hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2018;24:2047–2055.
21. Im A, Rashidi A, Wang T, et al. Risk factors for graft-versus-host disease in haploidentical hematopoietic cell transplantation using post-transplant cyclophosphamide. *Biol Blood Marrow Transplant*. 2020;26:1459–1468.
22. Jacque N, Lambert J, Yakoub-Agha I, et al. Comparison of mobilized peripheral blood stem cells versus unmanipulated bone marrow haploidentical transplantation using post-transplant cyclophosphamide: a retrospective study of SFGM-TC in 176 patients. *Blood*. 2017;130(suppl 1):2039.
23. Mariotti J, Devillier R, Bramanti S, et al. Peripheral blood stem cells versus bone marrow for T cell-replete haploidentical transplantation with post-transplant cyclophosphamide in Hodgkin lymphoma. *Biol Blood Marrow Transplant*. 2019;25:1810–1817.
24. Modi D, Kim S, Deol A, Ayash L, Ratanatharathorn V, Uberti JP. Comparison of myeloablative and reduced intensity conditioning regimens in haploidentical peripheral blood stem cell transplantation. *Bone Marrow Transplant*. 2021;56:741–744.
25. Mussetti A, De Philippis C, Carniti C, et al. $CD3^+$ graft cell count influence on chronic GVHD in haploidentical allogeneic transplantation using post-transplant cyclophosphamide. *Bone Marrow Transplant*. 2018;53:1522–1531.
26. Nagler A, Dholaria B, Labopin M, et al. Bone marrow versus mobilized peripheral blood stem cell graft in T-cell-replete haploidentical transplantation in acute lymphoblastic leukemia. *Leukemia*. 2020;34:2766–2775.
27. O'Donnell PV, Eapen M, Horowitz MM, et al. 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. *Bone Marrow Transplant*. 2016;51:1599–1601.
28. Pagliardini T, Castagna L, Harbi S, et al. Thiotepa, fludarabine, and busulfan conditioning regimen before T cell-replete haploidentical transplantation with post-transplant cyclophosphamide for acute myeloid leukemia: a bicentric experience of 100 patients. *Biol Blood Marrow Transplant*. 2019;25:1803–1809.
29. Ruggeri A, Labopin M, Bacigalupo A, et al. Bone marrow versus mobilized peripheral blood stem cells in haploidentical transplants using posttransplantation cyclophosphamide. *Cancer*. 2018;124:1428-1437.
30. Santoro N, Labopin M, Ciceri F, et al. Impact of conditioning intensity on outcomes of haploidentical stem cell transplantation for patients with acute myeloid leukemia 45 years of age and over. *Cancer*. 2019;125:1499–1506.
31. Solomon SR, St Martin A, Shah NN, et al. Myeloablative vs reduced-intensity T-cell-replete haploidentical transplantation for hematologic malignancy. *Blood Adv*. 2019;3:2836–2844.
32. Sugita J, Kagaya Y, Miyamoto T, et al. Myeloablative and reduced-intensity conditioning in HLA-haploidentical peripheral blood stem cell transplantation using post-transplant cyclophosphamide. *Bone Marrow Transplant*. 2019;54:432–441.
33. Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol*. 2017;35:1154–1161.
34. Alousi A, Wang T, Hemmer MT, et al. Peripheral blood versus bone marrow from unrelated donors: bone marrow allografts have improved long-term overall and graft-versus-host disease-free, relapse-free survival. *Biol Blood Marrow Transplant*. 2019;25:270–278.
35. Couban S, Aljurf M, Lachance S, et al. Filgrastim-stimulated bone marrow compared with filgrastim-mobilized peripheral blood in myeloablative sibling allografting for patients with hematologic malignancies: a randomized Canadian Blood and Marrow Transplant Group study. *Biol Blood Marrow Transplant*. 2016;22:1410–1415.
36. Holtick U, Albrecht M, Chemnitz JM, et al. Bone marrow versus peripheral blood allogeneic haematopoietic stem cell transplantation for haematological malignancies in adults. *Cochrane Database Syst Rev*. 2014;4: CD01089.