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

Leonardo Javier Arcuri1,2,*, Nelson Hamerschlak1, Vanderson Rocha3, Carmem Bonfim4, Mariana Nassif Kerbauy1

1 Bone Marrow Transplantation Unit, Hospital Israelita Albert Einstein, Sao Paulo, Brazil
2 Bone Marrow Transplantation Unit, Hospital das Clinicas, Faculty of Medicine, Sao Paulo University, Sao Paulo, Brazil
3 Service of Hematology, Transfusion, and Cell Therapy and Laboratory of Medical Investigation in Pathogenesis and Directed Therapy in Onco-Immuno-Hematology (LIM-31), Hospital das Clinicas, Faculty of Medicine, Sao Paulo University, Sao Paulo, Brazil
4 Bone Marrow Transplantation Unit, Universidade Federal do Parana, Curitiba, Brazil

ABSTRACT
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 = 1826; nBM = 2124), progression-free survival (PFS; HR, 0.95; P = .52; nPBSC = 2686; nBM = 2769), graft-versus-host disease (GVHD)-free relapse-free survival (GRFS; HR, 1.16; P = .07; nPBSC = 1454; nBM = 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 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, 0.95; P = .32; nMAC = 2123; nRIC = 3155), grade II-IV aGVHD (HR, 0.97; P = .67; nMAC = 1182; nRIC = 1330), grade II-IV cGVHD (HR, 1.01; P = .41; nMAC = 2099; nRIC = 3080), or GVHD-free survival (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.

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INTRODUCTION
Haploidentical hematopoietic cell transplantation (haplo-HCT) with post-transplantation cyclophosphamide (PTCy) is emerging...
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 yield 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-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) and 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).
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

<table>
<thead>
<tr>
<th>Comparisons and Outcomes</th>
<th>HR</th>
<th>95% CI</th>
<th>I², %*</th>
<th>k²</th>
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<th>BM/RIC, n</th>
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<tr>
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<td>53</td>
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<td>0.82-1.11</td>
<td>60</td>
<td>13</td>
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<td>0.76-0.94</td>
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<td>13</td>
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<td>2769</td>
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<td>11</td>
<td>1664</td>
<td>1862</td>
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<td>1.42-2.33</td>
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<td>2000</td>
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<td>1929</td>
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<tr>
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<td>1330</td>
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</tbody>
</table>

Statistically significant results are in bold type.

* Outcomes with an I² > 50% were analyzed with a random-effects model.

† Number of comparisons (not studies).
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
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...
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 reported in unrelated donor transplantation [5].

Whether the small decrease in relapse rate that we found without a clear benefit in PFS justifies the systemic 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.

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.

ACKNOWLEDGMENTS

Financial disclosure: This study received no third-party funding.

Conflict of interest statement: There are no conflicts of interest to report.

Authorship statement: M.N.K. was responsible for the study design, data extraction, and writing and revising the final manuscript. L.J.A. was responsible for the study design, data extraction, analysis, and writing and revising of the final manuscript. C.B., V.R., and N.H. were responsible for writing and critically revising the final manuscript.

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


