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CORRESPONDENCE

Post-transplant cyclophosphamide in acute leukemia patients receiving more than 5/10 HLA-mismatched allogeneic hematopoietic cell transplantation from related donors: A study on behalf of the ALWP of the EBMT

To the Editor:

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative procedure for patients with high-risk hematological malignancies, however, it may be encumbered by severe complications, of which graft-versus-host disease (GvHD) remains one of the most life-threatening. Many strategies for GvHD prevention are implemented, with large use of calcineurin inhibitors (CNI) associated with either methotrexate or mycophenolate mofetil (MMF), anti-thymocyte globulin (ATG), and post-transplant cyclophosphamide (PTCy).[1] PTCy was first validated in the setting of haploidentical transplant, but its use has since been extended as a platform of GvHD-prophylaxis also in matched related or unrelated donor transplant with favorable results, especially if combined with traditional CNI-based therapy.[2,3]

Donor-recipient human leukocyte antigen (HLA) compatibility plays a key role in successful allo-HSCT as HLA-matching has a direct impact on the risk of GvHD, non-relapse mortality (NRM), and survival. Suitable, matched or haploidentical donors are not always available or accessible, even in the era of the international registries.[4] Therefore, there is a need for new strategies that could negate the barrier of HLA-mismatching, allowing allo-HSCT from non "traditionally compatible" donors.

The purpose of this study is to evaluate retrospectively, PTCy-based GvHD prevention for patients with acute leukemia receiving a traditionally prohibitive highly mismatched allo-HSCT. Hence, we analyzed the outcome of patients affected by acute leukemia, recorded in the European Society for Blood and Marrow Transplantation (EBMT) registry, who received allo-HSCT with an HLA-mismatch greater than 5/10, and PTCy as GvHD-prophylaxis.

This is a retrospective registry-based analysis on behalf of the Acute Leukemia Working Party (ALWP) of the EBMT.

We analyzed a cohort of adults (age ≥18 years) with acute myeloid or lymphoblastic leukemia (AML/ALL), independent of status of disease at transplant, reported to Promise-EBMT, who underwent allo-HSCT from a donor with more than 5 HLA-mismatches and using GVHD prophylaxis including PTCy, between 2010 and 2020.

The primary endpoint was overall survival (OS). Secondary endpoints were neutrophil engraftment, acute GvHD (aGvHD) and chronic GvHD (cGvHD), relapse incidence (RI), NRM, GvHD-free and relapse-free survival (GRFS), and leukemia-free survival (LFS). The definitions of our endpoints and the statistical tools used are illustrated in Supplementary Material.

Fifty-nine eligible patients were identified (Characteristics described in Table S1). Most patients were diagnosed with AML ($n = 44$, 33 de novo and 11 secondary), 14 with ALL (4 Ph-positive) and one with mixed phenotype acute leukemia. At time of transplant, 42 (72%) patients were in complete remission (CR) and 16 (28%) had active, relapsed, or refractory disease. Myeloablative conditioning (MAC) was used in 54% of cases. Sixty percent of patients in CR and 50% of patients not in CR received MAC respectively. The main stem cell source was peripheral blood (64%), no cord blood was used. All donors were related to recipients. The median follow-up was 20 (range, 14–39) months.

PTCy was associated with one or two immunosuppressive drugs according to the center policy, with cyclosporin (CSA) and MMF being the most common combination (62%). In five patients PTCy and a single agent were used, either CSA or MMF or tacrolimus. Only a minority of patients (14%) received in vivo T-cell depletion with ATG.

Most patients (85%) received a 4/10 HLA-matched transplant, the majority with two mismatches in the same locus, most often C or DQ. In two cases the donor was fully unmatched (0/10).

During the analysis period 24 (41%) patients died. The causes of death were: relapsed/refractory leukemia (55%), infection (25%), interstitial pneumonia (8%), hemorrhage (4%), aGvHD (4%), and non HSCT-related complications.

Two-year OS was 56%, while LFS and GFRS were, respectively, 54% and 47%. NRM was 19% and RI was 28%.

A univariate analysis comparing patients in CR and patients with active disease was performed: the first subgroup had a better outcome, especially regarding OS, LFS, GFRS, and RI, with a rate of 66%, 66%, 59%, and 10%, respectively, at the 2-year timepoint (Figure 1). However, it should be noted that among the patients not in CR, only six were alive at last follow-up, and only two at 2 years (Table S2).

Most patients (51/59, cumulative incidence (CIN) 86%, 95% CI: 74–93) attained successful neutrophil engraftment with a median time of 19 (range, 11–37) days. At day 60 the CIN of platelet engraftment was 73% (95% CI: 59–83).

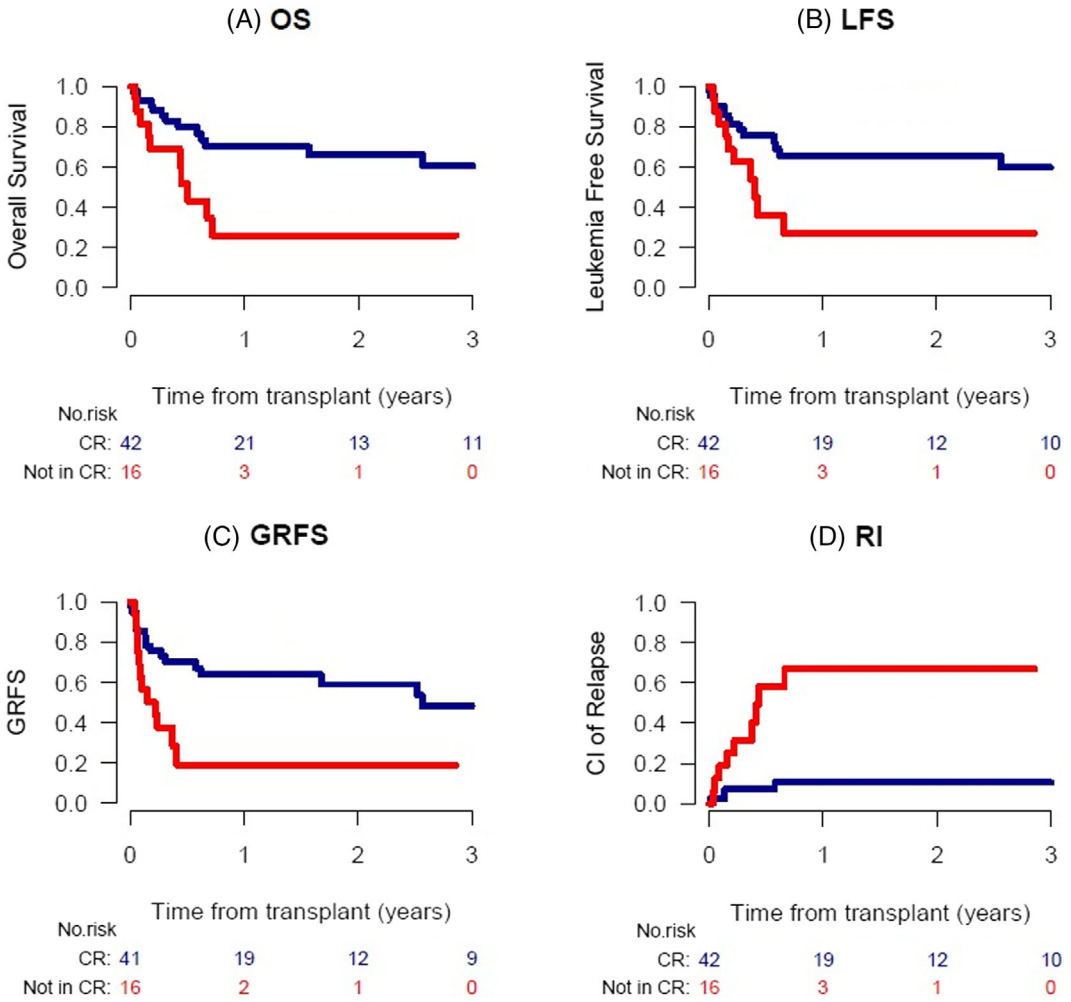

FIGURE 1 Outcomes: (A) overall survival (OS); (B) leukemia-free survival (LFS); (C) graft-versus-host disease-free and relapse-free survival (GRFS); (D) cumulative incidence (CI) of relapse (RI). The blue curve describes the patients in complete response (CR), the red curve describes the patients not in CR.

Primary graft failure was noted in eight patients, who all died within the first 100 days after HSCT. Details regarding graft failure are depicted in Table S3.

Thirty-three (58%) patients were free of any aGvHD. When present, it was usually not severe, with 15 cases of grade I-II versus 9 of grade II-IV. The CIN of grade II-IV aGvHD at day 180 was 30%, while for grade III-IV aGvHD it was 14%.

At 2 years the CIN of cGvHD was 21% with extensive involvement in 7%. The median time of onset of aGvHD and cGvHD was 26.5 (range, 18–149) and 145 (range, 79–470) days respectively.

The univariate analysis showed that patients in CR presented lower rates of both acute and cGvHD. At 180 days the aGvHD of grade III-IV was 8% for the patients in CR compared to 40% of those not in CR. The cGvHD rate at 2 years for patients in CR was 27% with extensive involvement in 8%. Only one case (6%) of extensive cGvHD was recorded in patients not in CR.

This study is one of the few to focus on HSCT with more than 5/10 mismatches, the other instances found in the literature are discussed in Supplementary Material.

Due to the scarcity of data available, to better consider the real feasibility of highly mismatched allo-HSCT, we compared our results with the outcome of PTCy in standard haploidentical settings reported in previous registry-based studies of the EBMT.[2,3,5,6]

We observed an OS of 56% at 2 years with an LFS and GRFS of 54% and 47% respectively. If only patients in CR were considered, the rates of OS, LFS, and GRFS at 2 years were 66%, 66%, and 59% respectively. A previous study conducted by the ALWP found comparable survival rates in a large cohort of AML patients who received haploidentical HSCT and PTCy, with an OS of 60.9%, LFS of 55.2%, and GRFS of 45.8% at 2 years.[5] The same study documented successful engraftment at a median time of 19 days, with a rate of 89% of engrafted patients at day +30. A retrospective registry-based comparison of PTCy after haploidentical, matched-related, and matched-unrelated HSCT reported neutrophil recovery in a median of 19, 19, and 20 days, respectively, with a 2-year OS of 61% for haploidentical HSCT.[3] These data suggest that there may be minimal differences in survival and engraftment of a highly mismatched transplant in comparison to standard haploidentical HSCT if PTCy is used. Indeed, the

eight graft failures reported in this study were 6/10 or 7/10 HLA-mismatched, with other concomitant causes of primary graft failure: infection (50%) and leukemia progression (50%) (Supplementary Table 3). Also, the two patients fully mismatched were both alive and in CR at the last follow-up (day +112 and + 378), suggesting that the negative impact of the degree of the mismatch may be lessened by PTCy.

We observed an NRM at 2 years of 19%, reduced to 10% for patients in CR, comparable or lower than in other studies with PTCy.[3,5,6]

Occurrence of aGvHD was higher than otherwise described in haploidentical HSCT.[3,5] This result was expected, as it has been shown that more mismatched HSCTs are associated with a higher rate of aGvHD.[3] However, the rates of cGvHD were lower than in other studies. We found a CIN of cGvHD of 21% at 2 years, with extensive involvement in 7% while other studies have recorded an incidence of 32%–35%, with extensive involvement in 11%–12%.[3,6]

With the limitations of a univariate analysis with few cases we found a net advantage in survival and aGvHD incidence in patients in CR with OS, GFRS, and RI rates comparable or even better than in the standard haploidentical setting previously analyzed.[3,5]

We are aware of the important limitations of this registry-based study, mainly its retrospective nature, the significant variability of patient and disease characteristics, the centers' different policies of transplantation management, and the limited statistical power due to the low number of patients. Our aim was, however, to evaluate in particular contexts, whether this kind of "unorthodox" HSCT could play a role, and our preliminary data provides an interesting starting point for future research.

Although in this initial observation the survival of more than 5/10 HLA-mismatched transplant patients is still lower than in haploidentical HSCT, the use of PTCy would appear to make the difference not insurmountable. Notably, patients in CR presented promising survival rates.

Therefore, we think that in the appropriate setting, PTCy could overcome the block of HLA-mismatching, but further investigations and prospective studies are needed, potentially in both hematopoietic and solid organ transplantation.

AUTHOR CONTRIBUTIONS

Jaime Sanz, Fabio Ciceri, Arnon Nagler, and Mohamad Mohty designed the study. Myriam Labopin performed the statistical analysis. Michele Wieczorek wrote the manuscript. Luca Castagna, Eolia Brissot, Gerard Socié, Anna Maria Raiola, Emanuele Angelucci, Arancha Bermúdez Rodríguez, Ibrahim Yakoub-Agha, Mahmoud Aljurf, Charles Crawley, Jean Baptiste Mear, Maurizio Musso, Renato Fanin, Daniele Avenoso, Pascal Turlure, Cristina Tecchio provided patient data for the study. All coauthors read and validated the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The dataset supporting the conclusions of this article are available in the ALWP of EBMT in Paris, 184 rue du Faubourg-Saint-Antoine.

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SUPPORTING INFORMATION

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