COMMENT

GVHD prophylaxis with post-transplant cyclophosphamide results in lower incidence of GVHD and allows faster immunosuppressive treatment reduction compared to antithymocyte globulin in 10/10 HLA-matched unrelated allogeneic hematopoietic cell transplantation

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Antithymocyte globulin (ATG) as part of graft-versus-host disease (GVHD) prophylaxis for peripheral blood stem cells (PBSC) transplant significantly reduced the risk of GVHD and thus progressively became a standard, notably for unrelated donor (UD) allogeneic cell transplantation (allo-HCT) [1, 2]. More recently, GVHD prophylaxis with post-transplant cyclophosphamide (PT-Cy) was introduced in the setting of haploidentical allo-HCT (haplo-HCT), with low incidence of GVHD despite the HLA donor-recipient disparity [3]. Based on these very promising results in haplo-HCT, PT-Cy was then reported in the setting of UD allo-HCT in various situations of patients and disease groups [4–7]. At Paoli Calmettes Institute, we started using PT-Cy in mismatched UD allo-HCT in 2014 and previously reported significantly better GVHD prevention and outcomes compared to historical control of patients receiving ATG [8]. More recently, a multicenter prospective randomized trial showed that GVHD prophylaxis with PT-Cy was highly effective in matched UD (MUD) allo-HCT [9]. We thus used PT-Cy as our new standard GVHD prophylaxis in this setting since 2020. Here, we report our single center experience in a retrospective historical control comparison versus ATG based GVHD prophylaxis. All patients gave general informed consent for transplantation, data collection, and subsequent retrospective analyses. Study was conducted in accordance with Helsinki declaration and was approved by our institutional review board (IRB: CASPER-IPC 2021-002 retrospective project, accepted January 2021).

We analyzed 30 consecutive patients who received PBSC MUD allo-HCT with PT-Cy as GVHD prophylaxis from April 2020 to July 2021. PT-Cy (50 mg/kg/day) was given on days+3 and 4, reduced at 40 mg/kg/day for patients ≥65 years. Cyclosporine A (CSA) and mycophenolate mofetil (MMF) were given as additional GVHD prophylaxis starting on day+5 and granulocyte-colony stimulating factor (G-CSF) was administered from day+5 to neutrophil recovery. In the absence of GVHD, MMF was discontinued at day+35 and CSA was progressively tapered from day+60 to day+120. We compared these patients to an historical cohort of 64 consecutive patients undergoing PBSC MUD allo-HCT between 2014 and March 2020 using a homogeneous platform of fludarabine, 2-day i.v. busulfan (FB2) and ATG (Thymoglobuline®, 2.5 mg/kg/day on day −3 and day −2) plus CSA without G-CSF, as previously described [4].

There was no significant difference in baseline characteristics except for conditioning regimens that were non myeloablative (NMAC, low dose TBI based), reduced intensity (RIC) and myeloablative (MAC) versions of the TBF regimen in 70%, 17%, and 13% of the PT-Cy group patients, respectively (100% FB2 in ATG group, Supplementary file: Table 1). 39 (41%) and 55 (59%) patients had lymphoid and myeloid disorders. DLI were administered to 20 patients (21%), including 13 (43%) and 7 (11%) in the PT-Cy and ATG group, respectively. Statistical analyses were performed as usually for post allo-HCT outcomes, except that we only consider the pre-DLI GVHD events (Supplementary file: statistical analyses). Median follow up was 19 (95% CI: [17–24]) and 52 (95% CI: [47–60]) months in the PT-Cy and ATG groups, respectively.

All patients engrafted. Despite the use of G-CSF in the PT-Cy group, median time from allo-HCT to neutrophil recovery (>0.5 G/L) was 19 and 17 days in the PT-Cy and ATG groups, respectively ($p = 0.049$). The cytotoxicity of PT-Cy may explain this difference, that is, although statistically significant, not of high clinical relevance. Median time from allo-HCT to platelet recovery (>20 G/L) was 26 and 10 days in the PT-Cy and ATG group, respectively ($p < 0.001$). We did not observed any major hemorrhagic event in the PT-Cy group.

The day-100 cumulative incidence of grade 2–4 acute GVHD was significantly lower in the PT-Cy group (23% vs. 45%, $p = 0.014$, Fig. 1a). This was confirmed in multivariate analysis (Reference: ATG HR = 1, PT-Cy: HR = 0.42, 95%CI = [0.18-0.97]; $p = 0.043$, Supplementary file: Tables 3 and 4). This risk reduction in acute GVHD was observed with the same magnitude in patients younger and older

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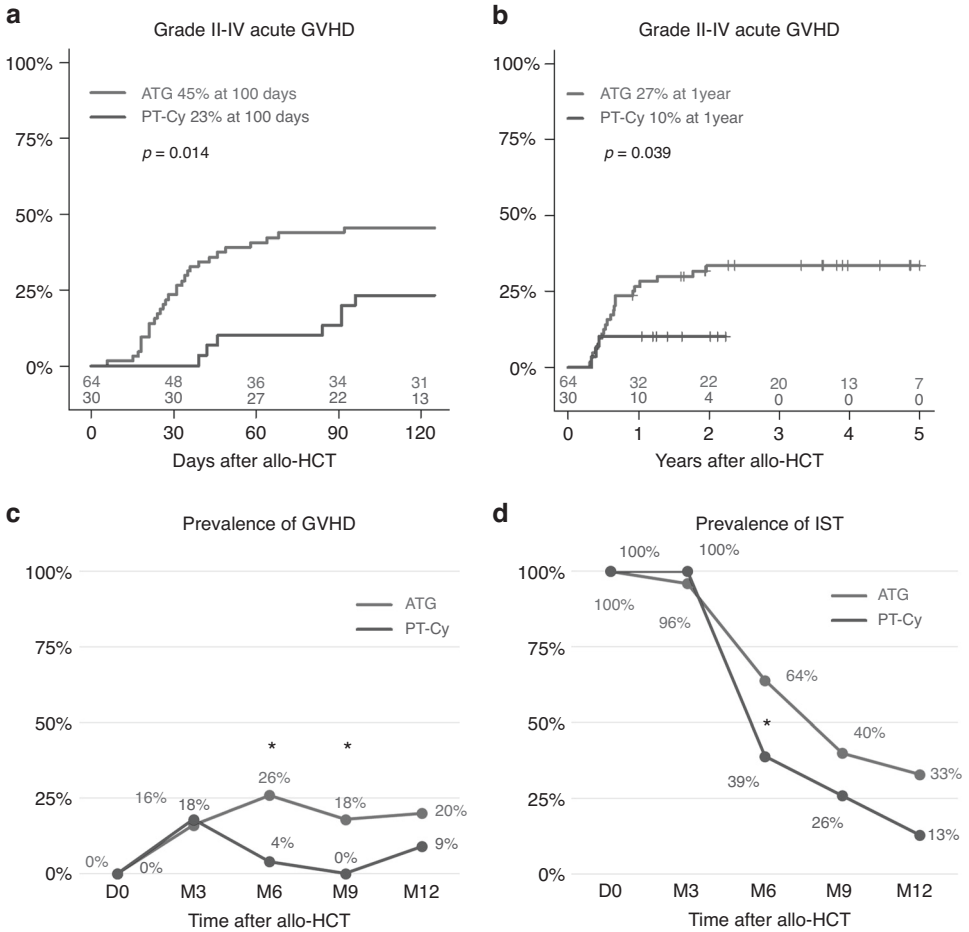

Fig. 1 GVHD after allo-HSCT. Cumulative incidences of grade 2–4 acute GVHD (**a**) and moderate to severe chronic GVHD (**b**). Prevalence of GVHD (**c**) and immunosuppressive treatments [IST] (**d**) during the first year post allo-HCT, in the PT-Cy and ATG groups. (*$p < 0.05$).

than 60 years (Supplementary file: Fig. 1). The 1-year cumulative incidence of chronic GVHD was significantly lower in the PT-Cy group (all grades: 13% vs. 33%, $p = 0.029$; moderate to severe: 10% vs. 27%, $p = 0.039$, Fig. 1b), but multivariate analysis did not confirm this finding (Supplementary file: Tables 3 and 4). At 1 year, there was no significant difference in non-relapse mortality (NRM, PT-Cy vs. ATG: 3% vs. 11%, $p = 0.169$), relapse incidence (PT-Cy vs. ATG: 20% vs. 11%, $p = 0.628$), progression free survival (PT-Cy vs. ATG: 77% vs. 78%, $p = 0.638$) and overall survival at 1-year (PT-Cy vs. ATG: 87% vs. 83%, $p = 0.602$). Causes of death, univariate and multivariate analyses are available in the Supplementary file: Tables 2, 3, 4, and 5. Taken together, our results showed that PT-Cy significantly reduces the incidence of grade II-IV acute GVHD compared to ATG, without significantly increasing the risk of relapse in the same magnitude.

Beyond classical post allo-HCT outcomes, we aimed to assess quality of life (QOL) in survivors. As surrogates, we analyzed the prevalence of GVHD features and immunosuppressive treatments (IST) among disease-free patients at difference time points after allo-HCT. PT-Cy decreased the prevalence of GVHD (at 6 months, PT-Cy vs. ATG: 4% vs. 26%, $p = 0.030$, Fig. 1c) and allowed faster IST tapering compared to ATG (patients living with IST at 6 months, PT-Cy vs. ATG: 39% vs. 64%, $p = 0.049$, Fig. 1d). These benefits in GVHD and IST prevalence may also support the use of PT-Cy in a cost effectiveness point of view. To explore this point, we calculated for a theoretical patient of 70 kg of body weight that the cost of ATG was 36 times more expensive that PT-Cy plus G-CSF. As surrogate of cost, we analyzed the delay between the time of allo-HCT and discharge from the hospital. We observe that it was significantly longer in the PT-Cy group (median in days [IQR] PT-Cy: 28 [23–32] vs. ATG: 23 [21–28], $p = 0.015$). This may be explain in part by the longer hematological recovery in the PT-Cy group. In addition, we do not observe significant difference in the median number of days of subsequent hospitalization during the first 6 months post allo-HCT (median in days [IQR]: PT-Cy 9 [IQR: 4–27] and 9 [IQR: 0–24], $p = 0.361$, calculated on patients who survived at least 6 months)

Gao et al. reported in a meta-analysis that PT-Cy significantly reduced the incidence of acute GVHD compared to ATG leading to lower NRM and better PFS and OS, without impact on chronic GVHD and relapse [10]. However, PT-Cy was mostly given to patients receiving haplo-HCT while UD patients mostly received ATG. In the non haplo-HCT setting, the recent prospective randomized study of Brissot et al. did not find significant difference in GVHD prevention using ATG or PT-Cy for patients undergoing allo-HCT after FB2 RIC regimen [11]. It is important to note that this study includes both matched related and UD allo-HCT. Recently, a registry database analysis from the ALWP of EBMT did not show significant difference between PT-Cy and ATG based GVHD prophylaxis in MUD allo-HCT [12]. This study included patients receiving MAC regimen in a large proportion, and 10% of patients received bone marrow as graft. These differences with our population who mostly received NMAC and RIC for PBSC allo-HCT may explain in part the different conclusions.

Our study has some obvious limitations, specially related to its retrospective design. In addition, the low number of patients makes difficult the interpretation of some results, notably in the multivariate analysis showing interestingly low HRs for PT-Cy but

large 95%CIs. The samples sizes does not allow firm conclusions, notably in case of non-significant difference that should not be interpreted as an equivalence.

We conclude that PT-Cy is an effective GVHD prophylaxis in 10/10-HLA MUD allo-HCT that allows reducing the prevalence of GVHD and IST as compared to ATG. Although our study adds justification to extend the use of PT-Cy beyond the setting of haplo-HCT, a comparative prospective trial in the specific context of MUD is still needed.

DATA AVAILABILITY

On request to the corresponding author.

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AUTHOR CONTRIBUTIONS

FD and RD collected and analyzed data. FD and RD wrote the manuscript. All authors included patients. All authors edited the manuscript and approved the submission.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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