Addition of mycophenolate mofetil to a calcineurin inhibitor and post-transplant cyclophosphamide results in lower incidence of extensive chronic graft-versus-host disease in HLA-matched allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia in complete remission

Published in:
Bone Marrow Transplantation

Publication status and date:
Published: 01/08/2025

DOI (link to publisher):
10.1038/s41409-025-02610-5

Document Version
Publisher's PDF, also known as Version of record

ARTICLE

Addition of mycophenolate mofetil to a calcineurin inhibitor and post-transplant cyclophosphamide results in lower incidence of extensive chronic graft-versus-host disease in HLA-matched allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia in complete remission: a matched-pair analysis on behalf of the Acute Leukemia Working Party of the EBMT

Giorgia Battipaglia[1,2]✉, Myriam Labopin[3,4,5], Aleksandr Kulagin[6], Jurgen Versluis[7], Goda Choi[8], Ellen Meijer[9], Montserrat Rovira[10], Gwendolyn van Gorkom[11], Mi Kwon[12], Yener Koc[13], Jan Vydra[14], Patrizia Chiusolo[15], Amit Patel[16], Simona Piemontese[17], Jaime Sanz[18], Annalisa Ruggeri[17], Arnon Nagler[2,19], Fabio Ciceri[17] and Mohamad Mohty[3,4,5]

Whether one or two agents added to post-transplant cyclophosphamide (PTCy) are needed in HLA-matched allogeneic hematopoietic stem cell transplantation (allo-HSCT) with peripheral blood stem cells (PBSC) is debated. We retrospectively compared PTCy in association with a calcineurin inhibitor (PTCy+CNI) or with a CNI plus mycophenolate mofetil (PTCy+CNI+MMF) in adult patients transplanted for acute myeloid leukemia in first complete remission and receiving PBSC in the period from 2010 to 2020. Propensity score matching was performed using exact matching for donor type (related or unrelated) and the nearest neighbor for other variables (i.e. age, adverse cytogenetics, Karnofsky performance status, patient and donor cytomegalovirus serology, conditioning intensity). Each group comprised 146 patients, with 63% in total undergoing matched unrelated-allo-HSCT. Median follow up was longer for PTCy+CNI (36 [IQR 31–39] months versus 25 [IQR 19–30] months for PTCy+CNI+MMF, $p < 0.01$). At 2 years, PTCy+CNI was associated with a higher incidence of extensive chronic GVHD (16% [95% CI 10–22] versus 6% [95% CI 3–12] for PTCy+CNI+MMF, $p < 0.03$) while no differences were observed for all the other transplant outcomes. Addition of MMF to PTCy and CNI may help to prevent extensive chronic GVHD in HLA-matched allo-HSCT with PBSC.

Bone Marrow Transplantation (2025) 60:1146–1151; https://doi.org/10.1038/s41409-025-02610-5

INTRODUCTION

Despite major transplant improvements, graft-versus-host disease (GVHD) still represents one of the leading causes of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT) even in the setting of human leukocyte antigen (HLA) matched transplantation [1, 2]. The standard GVHD prophylaxis has historically been based on the use of a calcineurin inhibitor (CNI) alone or more frequently in association with methotrexate (MTX) or mycophenolate mofetil (MMF) [3]. More recently, with the increasing use of peripheral blood stem cells (PBSC) as the stem cell source, the addition of antithymocyte globulin (ATG) to the standard GVHD prophylaxis has been shown to help prevent chronic GVHD (cGVHD), as well as allowing earlier immunosuppressive agents withdrawal [4–6]. However, active interest in the development of new GVHD prophylaxis strategies resulting in the reduction of the duration and of the number of drugs used is ongoing. Use of post-transplant cyclophosphamide (PTCy), initially pioneered by Luznik et al. in the haploidentical setting, has opened a new chapter in the GVHD prophylaxis conception [7]. Due to the favorable results obtained with this strategy in the presence of HLA mismatches, its use has been extended to other donor types [8–10]. Despite use of PTCy being shown to be feasible in the HLA-matched setting, early closure of studies investigating its use as a single agent for GVHD prevention has led to the conclusion that adjuvant immunosuppressors should be added to PTCy even in the absence of HLA mismatches [11]. This conclusion was also confirmed in a study by our group whereby the addition of two immunosuppressive agents to PTCy allowed more favorable transplant outcomes [9]. However, the latter study included both PBSC and bone marrow as stem cell sources and different drugs combined with PTCy in patients

A full list of author affiliations appears at the end of the paper.

Received: 21 October 2024 Revised: 15 January 2025 Accepted: 16 April 2025
Published online: 13 May 2025

diagnosed with either acute lymphoblastic leukemia or acute myeloid leukemia (AML).

METHODS

This is a retrospective study from the Acute Leukemia Working Party (ALWP) of the European Society of Blood and Marrow Transplantation (EBMT), which is a working group of more than 600 transplant centers, mostly located in Europe, that are required to report annually all consecutive transplantations and follow-up data. Data are entered, managed, and maintained in a central database with internet access; each EBMT center is represented in this database. There are no restrictions on centers for reporting data, except for those required by law on patient informed consent, data confidentiality and accuracy. Quality control measures include several independent systems: confirmation of validity of the entered data by the reporting team, cross-checking with the National Registries, and regular in-house and external data audits. Patients provide informed consent authorizing the use of their personal information for research purposes. Each patient provides informed consent for transplant according to the ethical principles of the Declaration of Helsinki. The study was approved by the Institutional Review Board of the ALWP of the EBMT.

Study design and eligibility criteria

Included in the current study were adult patients aged ≥18 years at transplant, diagnosed with AML and undergoing their first allo-HSCT in first complete remission (CR). Only patients transplanted from a matched related donor (MRD) or fully matched unrelated donor (MUD) receiving PBSC were eligible. Transplant outcomes of patients receiving PTCy-based GVHD prophylaxis with a CNI (PTCy+CNI group) were compared to those also receiving MMF (PTCy+CNI+MMF group). Concomitant use of ATG or ex-vivo T-cell depletion represented exclusion criteria. Transplants were performed during the period 2010–2020.

Definitions

Cytogenetic risk was defined according to MRC criteria [12]. Performance status was graded according to the Karnofsky performance status (KPS) scale and was defined as poor when it was <90. The conditioning regimen was defined according to data reported by EBMT centers as myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC) [13].

The primary endpoint of the study was the cumulative incidence of acute GVHD (aGVHD) and cGVHD. Secondary endpoints included leukemia-free survival (LFS), overall survival (OS), refined GVHD/relapse-free survival (GRFS), relapse incidence (RI) and non-relapse mortality (NRM).

Severity of aGVHD was graded according to the modified Glucksberg criteria and cGVHD according to the revised Seattle criteria [14, 15].

Engraftment was defined as achieving an absolute neutrophil count $\geq 0.5 \times 10^9$/L for three consecutive days. The probability of being alive without evidence of relapse or progression defined LFS. Overall survival was defined as the time from allo-HSCT to death, regardless of the cause. Refined GRFS was defined according to Ruggeri et al., i.e. being alive with neither grade III-IV aGVHD nor severe cGVHD, nor disease relapse at any time point [16]. Relapse was defined as the presence of at least 5% of bone marrow blasts and/or reappearance of the underlying disease. Death without evidence of relapse or progression defined NRM.

Statistical analysis

Patient-, disease- and transplant-related characteristics were compared using the Chi-squared test or Fisher exact test for categorical variables, and the Mann–Whitney test for continuous variables. Probabilities of OS, LFS and GRFS were calculated using the Kaplan–Meier method [17]. Cumulative incidence functions (CIF) were used to estimate RI and NRM in a competing risk setting. To study GVHD, death and relapse were considered as competing events. The follow-up time was calculated using the reverse Kaplan–Meier method. Endpoints were censored at 2 years for all comparisons in order to take into account the difference of follow-up between the 2 groups. Univariate analyses were performed using the log rank test for OS, LFS and GRFS, while the Gray's test was used for CIF [18]. Multivariate analysis was performed using a Cox proportional-hazards model which included variables differing significantly between the groups, factors known to be associated with outcomes, plus a center frailty effect to take into account the heterogeneity across centers. Propensity score matching was performed to reduce or eliminate confounding effects. Matching was done without replacement. For each patient receiving PTCy+CNI+MMF, one matched control receiving PTCy+CNI was identified using exact and propensity-score matched criteria. Exact matching was used for donor type while the nearest neighbor was used for age, adverse cytogenetics, performance status, patient and donor CMV serology status and intensity of the conditioning regimen. Matching was done using calipers of width equal to 0.2 of the standard deviation. After matching, we checked that standardized mean difference were less than 0.10 for all covariates included in the propensity. Comparisons between matched groups were performed using Cox model and **c**luster-robust standard errors was used to account for dependence between observations within matched pairs. All tests were two-sided and *P* values <0.05 were considered as statistically significant. Analyses were performed using the R statistical software version 3.2.3 (available online at http://www.R-project.org), and propensity score matching was performed using the 'MatchIt' package.

RESULTS

Overall, 484 patients fulfilling the inclusion criteria were identified, comprising 234 in the PTCy+CNI and 250 in the PTCy+CNI+MMF group. The associated CNI was cyclosporine in 59% and 41% in the PTCy+CNI and PTCy+CNI+MMF groups, respectively. The baseline characteristics, results of uni- and multivariate analysis of the whole population are outlined in Supplementary Tables 1–3. After pair-matching, each group comprised 146 patients, with a longer median follow-up of 36 (IQR 31–38) compared to 25 (IQR 19–30) months in PTCy+CNI and PTCy+CNI+MMF, respectively ($p < 0.01$). Demographics and transplant characteristics of the matched pair population are summarized in Table 1. HLA unrelated donors were represented by 63% of cases in both groups. Conditioning regimen distribution was represented by MAC in 57% and 53% in the PTCy+CNI and PTCy+CNI+MMF, respectively. Busulfan-fludarabine based regimens were frequently used in the PTCy+CNI group (41%) while both busulfan-fludarabine (53%) and TBI-based conditioning (52%) were the most represented regimens in the PTCy+CNI+MMF group. A poor performance status at transplant was present in 34% in PTCy+CNI and 31% in PTCy+CNI+MMF groups. While no differences were observed in the cumulative incidences of 180-days grade II-IV (28% [95% CI 21–36] for PTCy +CNI versus 20% [95% CI 14–27] for PTCy+CNI+MMF, $p = 0.07$) and grade III-IV aGVHD (6% [95% CI 3–11] for PTCy+CNI versus 9% [95% CI 5–15] for PTCy+CNI+MMF, $p = 0.36$), addition of MMF resulted in a significantly lower incidence of extensive cGVHD at 2 years in the PTCy+CNI+MMF group, this being 6% (95% CI 3–12) compared to 16% (95% CI 10–22) in PTCy+CNI group ($p < 0.03$). No differences were observed for cGVHD of all grades at 2 years in the two groups (28% [95% CI 21–36] for PTCy+CNI versus 35% [95% CI 26–44] for PTCy+CNI+MMF, $p = 0.14$) (Table 2). No significant differences in post-transplant survival were observed with NRM being 8% (95% CI 4–13) compared to 13% (95% CI 8–20) in PTCy +CNI versus PTCy+CNI+MMF, respectively ($p = 0.14$, Fig. 1a). Similarly, RI did not differ being 30% (95% CI 23–38) versus 27% (95% CI 19–35) in PTCy+CNI and PTCy+CNI+MMF, respectively ($p = 0.86$, Fig. 1b). Death was mainly attributable to AML (69% and 57% of deaths in PTCy+CNI and PTCy+CNI+MMF, respectively) followed by GVHD and infections (Supplementary Table 1). Leukemia-free survival and OS at 2 years were 62% (95% CI 53–69) and 67% (95% CI 59–75) in the PTCy+CNI and 60% (95% CI 51–68) and 64% (95% CI 54–72) in the PTCy+CNI+MMF groups, respectively ($p = 0.53$ for LFS and $p = 0.48$ for OS, Fig. 2a, b). Furthermore, 2-years GRFS was 49% (95% CI 40–57) and 52% (95% CI 42–60) for PTCy+CNI and PTCy+CNI+MMF, respectively ($p = 0.98$, Fig. 2c).

DISCUSSION

Graft-versus-host disease incidence is influenced by several factors, the first being the prophylaxis schedule used, but also the type of conditioning regimen, patients and disease-related factors [19]. It has been also widely reported that the stem cell

Table 1. Patient, disease and transplant characteristics in the pair-matched population.

Characteristic (%)	PTCy+CNI (n = 146)	PTCy+CNI+MMF (n = 146)	*p*-value
Median age at allo-HSCT, years (range)	53 (18–76)	55 (20–74)	0.68
F/M gender ratio	84 (58) / 62 (43)	88 (60) / 58 (40)	0.63
Secondary AML	20 (14)	23 (16)	0.62
Cytogenetic risk			
Not adverse	112 (77)	114 (78)	0.78
Adverse	34 (23)	32 (22)	
Karnofsky performance status <90	49 (34)	45 (31)	0.62
Donor type			
HLA-identical sibling	54 (37)	54 (37)	1
HLA-matched unrelated donor	92 (63)	92 (63)	
Associated CNI			0.16
Cyclosporine	85 (58)	73 (50)	
Tacrolimus	61 (42)	73 (50)	
Female donor into male recipient	25 (17)	29 (20)	0.55
Patient CMV serology			
Negative	38 (26)	36 (25)	0.79
Positive	108 (74)	110 (75)	
Donor CMV serology			
Negative	66 (45)	64 (44)	0.81
Positive	80 (55)	82 (56)	
Median year of transplant (range)	2018 (2011–2020)	2019 (2013–2020)	0.047
Conditioning regimen			
MAC	83 (57)	77 (53)	0.48
RIC	63 (43)	69 (47)	
Median follow up, months (IQR)	36 (31–38)	25 (19–30)	0.002

PTCy post-transplant cyclophosphamide, *CNI* calcineurin inhibitor, *MMF* mycophenolate mofetil, *allo-HSCT* allogeneic hematopoietic stem cell transplantation, *M* male, *F* female, *AML* acute myeloid leukemia, *CMV* cytomegalovirus, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *IQR* interquartile range.

source significantly impacts GVHD development, with PBSC being related to a higher risk especially of cGVHD [20]. Early immune modulation with the combination of several drugs for GVHD prophylaxis can impact its onset, even when occurring later as cGVHD, and can potentially affect long-term immune reconstitution and tolerance patterns.

Use of a CNI in association with MTX or MMF has for years represented a major cornerstone in GVHD prophylaxis and has remained the standard even in recent times, especially in the US [3]. The same holds only partially true in the EU and Canada where the addition of ATG to standard immunosuppressive agents in the HLA-matched setting with the use of PBSC has shown to successfully prevent GVHD, also allowing an earlier withdrawal of immunosuppressive agents [4, 5]. The recent expansion in the use of PTCy outside the haploidentical setting, has shown promising results [8–10]. While initial attempts at using PTCy alone in allo-HSCT from HLA-matched donors with PBSC as the stem cell source was a failure, resulting in a high incidence of GVHD with early closure of clinical trials, subsequent studies have shown not only the feasibility but also the superiority of this approach when added to standard GVHD prophylaxis agents [11, 21, 22]. However, despite the clinical utility of PTCy, its exact mechanism of action in allo-HSCT and the best agent(s) it should be associated with, are not fully elucidated. In the recently published HOVON-96 trial the addition of PTCy to tacrolimus and MMF compared to tacrolimus and MTX without PTCy resulted in a significantly higher GRFS and a lower severe aGVHD or cGVHD, with a concomitant higher proportion of immunosuppressive agents withdrawal at 1 year after a RIC-based HLA-matched allo-HSCT with PBSC [21].

In a study by our group, use of PTCy alone was compared to PTCy in association to one (CSA, MMF or MTX) or two agents (CSA+MMF or CSA+MTX) in HLA-matched allo-HSCT, with a clear superiority of the use of two agents [9]. However, several limitations of this study are the inclusion of bone marrow and PBSC as stem cell sources and inclusion of both AML and ALL patients, with varying disease status at transplant. Furthermore, the addition of MTX or MMF to PTCy, compared to the addition of CsA, may not provide the same power for GVHD prophylaxis. Lastly, several patients who had concomitantly received ATG were included.

Therefore, in the current study we aimed to explore in a more homogeneous cohort, whether the addition of a CNI alone or a CNI with MMF may impact transplant outcomes when used with PTCy for HLA-matched allo-HSCT. Our analysis only focused on AML in CR1 and only included PBSC as the stem cell source, with

Table 2. Cumulative incidences of GVHD (a) and 2-year survival outcomes (b) in the pair-matched population.

a)

	180-d grade II-IV aGVHD [95% CI]	180-d grade III-IV aGVHD [95% CI]	2y-cGVHD, any grade [95% CI]	2y-cGVHD, extensive [95% CI]
PTCy+CNI	28% [21–36]	6% [3–11]	28% [21–36]	16% [10–22]
PTCy+CNI+MMF	20% [14–27]	9% [5–15]	35% [26–44]	6% [3–12]
HR (95% CI)	0.65 (0.40–1.03)	1.48 (0.64–3.44)	1.41 (0.89–2.21)	0.38 (0.17–0.89)
p-value	0.07	0.36	0.14	0.026

b)

	LFS [95% CI]	OS [95% CI]	GRFS [95% CI]	RI [95% CI]	NRM [95% CI]
PTCy+CNI	62% [53–69]	67% [59–75]	49% [40–57]	30% [23–38]	8% [4–13]
PTCy+CNI+MMF	60% [51–68]	64% [54–72]	52% [42–60]	27% [19–35]	13% [8–20]
HR (95% CI)	1.14 (0.76–1.72)	1.18 (0.74–1.87)	1 (0.72–1.40)	0.96 (0.61–1.50)	1.81 (0.82–4.03)
p-value	0.53	0.48	0.98	0.86	0.14

d days, *aGVHD* acute graft-versus-host disease, *CI* confidence interval, *y* years, *cGVHD* chronic graft-versus-host disease, *PTCy* post-transplant cyclophosphamide, *CNI* calcineurin inhibitor, *MMF* mycophenolate mofetil, *LFS* leukemia-free survival, *OS* overall survival, *GRFS* graft-versus-host disease/relapse-free survival, *RI* relapse incidence, *NRM* non-relapse mortality.

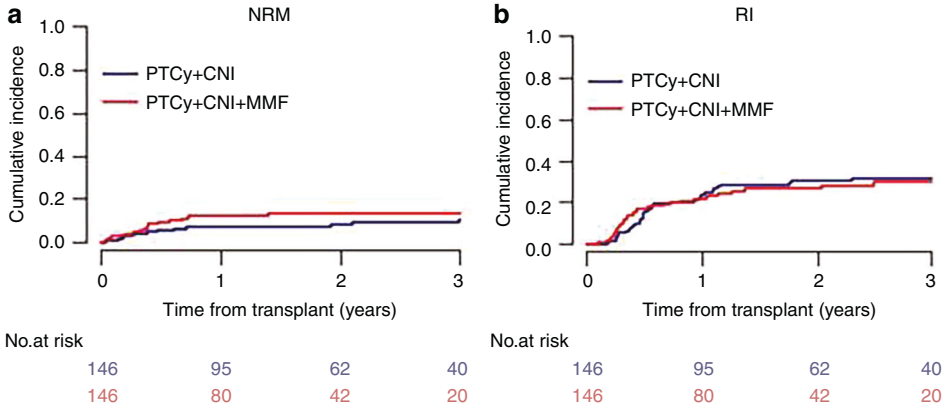

Fig. 1 Transplant outcomes according to graft-versus-host disease prophylaxis. Non-relapse mortality (**a**) and relapse incidence (**b**).

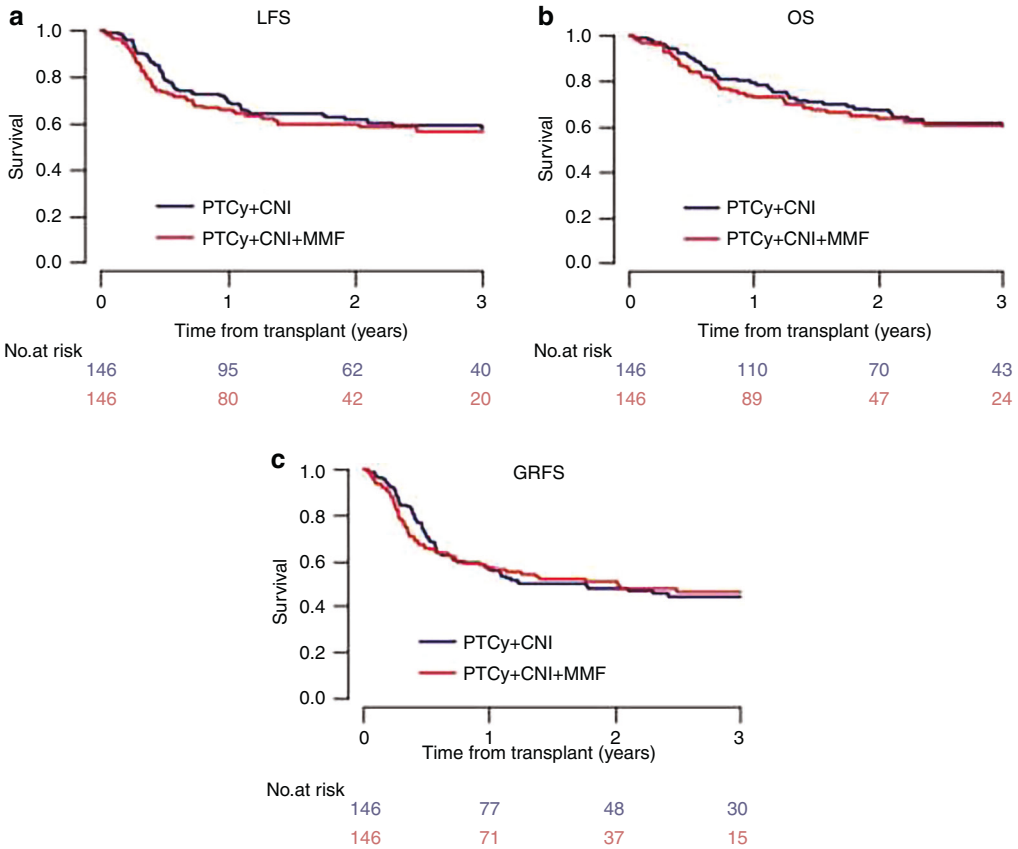

Fig. 2 Transplant outcomes according to graft-versus-host disease prophylaxis. Leukemia-free survival (**a**), overall survival (**b**) and graft-versus-host disease/relapse-free survival (**c**).

the exclusion of patients concomitantly receiving ATG for GVHD prophylaxis. In order to reduce or eliminate confounding effects, a matched pair analysis was performed with exact matching for donor type, this being MUD in most cases (63%).

Our results show that the addition of CNI alone or CNI+MMF represent valid strategies, with no major differences in the main transplant outcomes between the two groups. However, they importantly highlight that the addition of MMF results in lower incidence of severe cGVHD. This is a non negligeable result with practical implications since cGVHD remains one of the major causes of long-term morbidity and late mortality in allo-HSCT survivor, especially in its extensive form [23]. Indeed, one study showed that patients experiencing limited cGVHD had a 4 year survival rate of 83%, compared with 45% in patients with extensive cGVHD and this difference was primarily due to the lower RI and mortality in the cohort with limited cGVHD [24]. One should not forget that GVHD prophylaxis regimens relying on the use of ATG, especially in EU countries, have also been shown to effectively prevent cGVHD in both matched related and unrelated donor transplantation, with comparative studies with PTCy providing conflicting results on which is the best strategy to use [6, 25, 26].

The negative implications of extensive cGVHD are also explained by the prolonged use of immunosuppressive agents needed for its treatment, which is often associated with several adverse effects on long-term quality of life and functional abilities with one study showing that among patients with cGVHD initiating new systemic therapy, 62% will experience a clinical impairment or decline in functionality associated with disability by

18 months [27]. Despite new, effective, and well-tolerated targeted therapies that have been developed, they continue to be used empirically after lack of response to systemic corticosteroids and/or a CNI is established [28–30]. Furthermore, rate of complete and or durable responses are unsatisfactory.

Our results should be taken with caution due to the limitations of a retrospective registry-based analysis with lack of comprehensive data such as timing of immunosuppressive agents withdrawal, evaluation of quality of lilifethat is essential when talking about cGVHD) and details on GVHD organ distribution. However, despite these, they highlight that potentiating GVHD prophylaxis by addition of a CNI and MMF to PTCy, may result in a lower incidence of extensive cGVHD without significant modification of other transplant outcomes.

DATA AVAILABILITY

The final analysis dataset will be available upon specific request to the Working Party Chair.

REFERENCES

1. Boyiadzis M, Arora M, Klein JP, Hassebroek A, Hemmer M, Urbano-Ispizua A, et al. Impact of chronic graft-versus-host disease on late relapse and survival on 7,489 patients after myeloablative allogeneic hematopoietic cell transplantation for leukemia. Clin Cancer Res. 2015;21:2020–8.
2. Gooley TA, Chien JW, Pergam SA, Hingorani S, Sorror ML, Boeckh M, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med. 2010;363:2091–101.
3. Storb R, Deeg HJ, Whitehead J, Appelbaum F, Beatty P, Bensinger W, et al. Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft versus host disease after marrow transplantation for leukemia. N Engl J Med. 1986;314:729–35.
4. Kröger N, Solano C, Wolschke C, Bandini G, Patriarca F, Pini M, et al. Antilymphocyte globulin for prevention of chronic graft-versus-host disease. N Engl J Med. 2016;374:43–53.
5. Walker I, Panzarella T, Couban S, Couture F, Devins G, Elemary M, et al. Addition of anti-thymocyte globulin to standard graft-versus-host disease prophylaxis versus standard treatment alone in patients with haematological malignancies undergoing transplantation from unrelated donors: final analysis of a randomised, open-label, multicentre, phase 3 trial. Lancet Haematol. 2020;7:e100–e111.
6. Battipaglia G, Labopin M, Hamladji RM, Blaise D, Chevallier P, Brissot E, et al. Post-transplantation cyclophosphamide versus antithymocyte globulin in patients with acute myeloid leukemia undergoing allogeneic stem cell transplantation from HLA-identical sibling donors: A retrospective analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Cancer 2021;127:209–18.
7. Luznik L, O'Donnell PV, Symons HJ, Chen AR, Leffell MS, Zahurak M, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transpl. 2008;14:641–50.
8. El Fakih R, Hashmi SK, Ciurea SO, Luznik L, Gale RP, Aljurf M. Post-transplant cyclophosphamide use in matched HLA donors: a review of literature and future application. Bone Marrow Transpl. 2020;55:40–47.
9. Ruggeri A, Labopin M, Bacigalupo A, Afanasyev B, Cornelissen JJ, Elmaagacli A, et al. Post-transplant cyclophosphamide for graft-versus-host disease prophylaxis in HLA matched sibling or matched unrelated donor transplant for patients with acute leukemia, on behalf of ALWP-EBMT. J Hematol Oncol. 2018;11:40.
10. Battipaglia G, Labopin M, Kröger N, Vitek A, Afanasyev B, Hilgendorf I, et al. Posttransplant cyclophosphamide vs antithymocyte globulin in HLA-mismatched unrelated donor transplantation. Blood 2019;134:892–9.
11. Holtick U, Chemnitz JM, Shimabukuro-Vornhagen A, Theurich S, Chakupurakal G, Krause A, et al. OCTET-CY: a phase II study to investigate the efficacy of post-transplant cyclophosphamide as sole graft-versus-host prophylaxis after allogeneic peripheral blood stem cell transplantation. Eur J Haematol. 2016;96:27–35.
12. Grimwade D, Hills RK, Moorman AV, Walker H, Chatters S, Goldstone AH, et al. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood. 2010;116:354–65.
13. Jethava YS, Sica S, Savani B, Socola F, Jagasia M, Mohty M, et al. Conditioning regimens for allogeneic hematopoietic stem cell transplants in acute myeloid leukemia. Bone Marrow Transpl. 2017;52:1504–11.
14. Przepiorka D, Chan KW, Champlin RE, Culbert SJ, Petropoulos D, Ippoliti C, et al. Prevention of graft-versus-host disease with anti-CD5 ricin A chain immunotoxin after CD3-depleted HLA-nonidentical marrow transplantation in pediatric leukemia patients. Bone Marrow Transpl. 1995;16:737–41.
15. Lee SJ, Klein JP, Barrett AJ, Ringden O, Antin JH, Cahn JY, et al. Severity of chronic graft-versus-host disease: association with treatment-related mortality and relapse. Blood. 2002;100:406–14.
16. Ruggeri A, Labopin M, Ciceri F, Mohty M, Nagler A. Definition of GvHD-free, relapse-free survival for registry-based studies: an ALWP-EBMT analysis on patients with AML in remission. Bone Marrow Transpl. 2016;51:610–1.
17. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457–81.
18. Fine JP, Gray RJ. A Proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 2009;446:496–509.
19. Jagasia M, Arora M, Flowers ME, Chao NJ, McCarthy PL, Cutler CS, et al. Risk factors for acute GVHD and survival after hematopoietic cell transplantation. Blood 2012;119:296–307.
20. Anasetti C, Logan BR, Lee SJ, Waller EK, Weisdorf DJ, Wingard JR, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. N Engl J Med. 2012;367:1487–96.
21. Bolaños-Meade J, Hamadani M, Wu J, Al Malki MM, Martens MJ, Runaas L, et al. Post-transplantation cyclophosphamide-based graft-versus-host disease prophylaxis. N Engl J Med. 2023;388:2338–48.
22. Bolaños-Meade J, Reshef R, Fraser R, Fei M, Abhyankar S, Al-Kadhimi Z, et al. Three prophylaxis regimens (tacrolimus, mycophenolate mofetil, and cyclophosphamide; tacrolimus, methotrexate, and bortezomib; or tacrolimus, methotrexate, and maraviroc) versus tacrolimus and methotrexate for prevention of graft-versus-host disease with haemopoietic cell transplantation with reduced-intensity conditioning: a randomised phase 2 trial with a non-randomised contemporaneous control group (BMT CTN 1203). Lancet Haematol. 2019;6:e132–43.
23. Signori A, Crocchiolo R, Oneto R, Sacchi N, Sormani MP, Fagioli F, et al. Chronic GVHD is associated with lower relapse risk irrespective of stem cell source among patients receiving transplantation from unrelated donors. Bone Marrow Transpl. 2012;47:1474–8.
24. Miflin G, Russell NH, Franklin I, Cook G, Milligan DW, Hutchinson RM, et al. An analysis of the effect of chronic GvHD on relapse and survival following allogeneic PBSC transplantation. Cytotherapy 2000;2:423–8.
25. Brissot E, Labopin M, Labussière H, Fossard G, Chevallier P, Guillaume T, et al. Post-transplant cyclophosphamide versus anti-thymocyte globulin after reduced intensity peripheral blood allogeneic cell transplantation in recipients of matched sibling or 10/10 HLA matched unrelated donors: final analysis of a randomized, open-label, multicenter, phase 2 trial. Blood. Cancer J. 2024;14:31.
26. Penack O, Abouqateb M, Peczynski C, Boreland W, Kröger N, Stelljes M, et al. ATG or post-transplant cyclophosphamide to prevent GVHD in matched unrelated stem cell transplantation? Leukemia. 2024;38:1156–63.
27. Hamilton BK, Storer BE, Wood WA, Pidala JA, Cutler CS, Martin PJ, et al. Disability Related to Chronic Graft-versus-Host Disease. Biol Blood Marrow Transpl. 2020;26:772–7.
28. Miklos D, Cutler CS, Arora M, Waller EK, Jagasia M, Pusic I, et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. Blood 2017;130:2243–50.
29. Cutler CS, Lee SJ, Arai S, Rotta M, Zoghi B, Lazaryan A, et al. Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of therapy: the ROCKstar study. Blood. 2021;138:2278–89.
30. Zeiser R, Polverelli N, Ram R, Hashmi SK, Chakraverty R, Middeke JM, et al. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. N. Engl J Med. 2021;385:228–38.

ACKNOWLEDGEMENTS

The authors thank Emmanuelle Polge from the office of the ALWP of the EBMT, and the clinical staff and investigators involved in this research, and they especially thank the patients who took part.

AUTHOR CONTRIBUTIONS

GB designed the study and wrote the manuscript, ML performed the statistical analysis, SP, JS, AR, MM, AN and FC revised the manuscript, and all the authors reviewed the final version. AK, JV, GC, EM, MR, GVG, MK, YK, JV, PC, AP, were the principal investigators at the centers recruiting the highest number of patients to the study.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Patients provided informed consent authorizing the use of their personal information for research purposes.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41409-025-02610-5.

Correspondence and requests for materials should be addressed to Giorgia Battipaglia.

[1]Federico II University of Naples, Hematology Department, Naples, Italy. [2]Department of Clinical Medicine and Surgery, Federico II University of Naples, Naples, Italy. [3]EBMT Paris study office, Paris, France. [4]Hematology Department, Hôpital Saint Antoine, Service d'Hématologie et Thérapie Cellulaire, Paris, France. [5]Sorbonne Universités, UPMC Univ Paris 06, INSERM, Centre de Recherche Saint-Antoine (CRSA), Paris, France. [6]First State Pavlov Medical University of St. Petersburg, Raisa Gorbacheva Memorial Research Institute for Paediatric Oncology, Haematology and Transplantation - St-Petersburg, St-Petersburg, Russia. [7]Erasmus MC Cancer Institute, University Medical Center Rotterdam, Department of Haematology - Rotterdam, Rotterdam, The Netherlands. [8]Department of Hematology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. [9]VU University Medical Center, Department of Haematology – Amsterdam, Amsterdam, The Netherlands. [10]Hospital Clinic, BMT Unit, Dept. of Haematology, Institute of Haematology & Oncology, IDIBAPS, Institut Josep Carreras– Barcelona, Barcelona, Spain. [11]Department of Internal Medicine, Division of Hematology, GROW School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands. [12]Department of Hematology, Hospital General Universitario Gregorio Marañon, Instituto de Investigacion Sanitaria Gregorio Marañon, Departamento de Medicina, Universidad Computense de Madrid, Madrid, Spain. [13]Medicana International Hospital Istanbul, Bone Marrow Transplant Unit – Istanbul, Istanbul, Turkey. [14]Institute of Haematology and Blood Transfusion, Prague, Czech Republic. [15]Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico A. Gemelli IRCCS, Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Roma, Italy. [16]Clatterbridge Cancer Centre - Liverpool, Royal Liverpool University Hospital, Clatterbridge Cancer Centre NHS Foundation Trust, Division of Stem Cell Transplantation and Haematology – Liverpool, Liverpool, UK. [17]Ospedale San Raffaele s.r.l., Haematology and BMT, Milano, Italy. [18]Hematology Department, Hospital Universitari i Politècnic La Fe, Departament de Medicina Universitat de Valencia, CIBERONC, Instituto Carlos III, Valencia, Spain. [19]Chaim Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel. ✉email: giorgia.battipaglia@unina.it