Received: 24 March 2025 | Accepted: 17 July 2025

DOI: 10.1111/bjh.70050

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

ORIGINAL PAPER

Transplantation & Cellular Therapy

Impact of the addition of antithymocyte globulin to post-transplantation cyclophosphamide in haploidentical transplantation with peripheral blood compared to post-transplantation cyclophosphamide alone: A retrospective study on behalf of the Cellular Therapy and Immunobiology Working Party of the European Society for Blood and Marrow Transplantation

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Summary

In the setting of haploidentical haematopoietic cell transplantation (HCT), post-transplant cyclophosphamide (PTCy) has dramatically reduced the incidence of graft-versus-host disease (GVHD) and non-relapse mortality. To further reduce GVHD incidence, the addition of antithymocyte globulin (ATG) to PTCy was evaluated in retrospective and non-comparative prospective studies showing promising results. We conducted a large retrospective analysis of the European Society for Blood and Marrow Transplantation (EBMT) registry to evaluate this approach. We analysed haploHCT with peripheral blood stem cells performed for haematological malignancies between 2014 and 2021. GVHD prophylaxis included either PTCy alone or PTCy+ATG. Four thousand five hundred and nineteen patients were analysed in the PTCy only group versus 675 with PTCy+ATG. Median follow-up was 29.80 months. In univariate analysis, 2-year GVHD-free, relapse-free survival (GRFS), relapse-free survival (RFS), overall survival (OS), cumulative incidence of relapse, non-relapse mortality (NRM) and chronic GvHD (cGVHD) were, respectively: 40.5% versus 37.5% ($p = 0.098$), 50.9% versus. 45.8% ($p = 0.015$), 56.9% versus 52.5% ($p = 0.01$), 24.2% versus 28.1% ($p = 0.032$), 25% versus 26.1% ($p = 0.49$) and 28.4% versus 18.5% ($p < 0.001$). aGVHD did not differ. After multivariable adjustment, OS and RFS were lower in the PTCy+ATG group: HR = 1.18 ($p = 0.037$) and HR = 1.18 ($p = 0.027$) and patients receiving PTCy+ATG had less cGVHD: HR = 0.68 ($p = 0.004$). In that retrospective analysis, the addition of ATG

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to PTCy for GVHD prophylaxis in haploHCT was associated with a reduction of cGVHD but also a worse OS and RFS.

KEYWORDS
BMT, cell therapy, GVHD

INTRODUCTION

In the setting of allogeneic haematopoietic cell transplantation (HCT) for haematological malignancies, the use of a haploidentical donor has been historically limited due to a high incidence of severe graft-versus-host disease (GVHD) leading to unacceptable non-relapse mortality (NRM).[1,2] In 2008, a group from Baltimore and Seattle described a new platform for haploidentical HCT (haploHCT) using post-transplant cyclophosphamide (PTCy) as GVHD prophylaxis in patients receiving a bone marrow graft.[3] Since then, this approach has demonstrated its efficacy for the prevention of severe acute and chronic GVHD, allowing a wider use of haploidentical donors.[4,5] On the other hand, in allogeneic HCT with a matched sibling donor (MSD) or a matched unrelated donor (MUD), adding a low dose of antithymocyte globulin (ATG) to the conditioning regimen has been proven to reduce the incidence of GVHD with an acceptable toxicity profile and no excess of relapse.[6,7] Therefore, given the higher incidence of GVHD using peripheral blood stem cells (PBSCs), in an attempt to further reduce this incidence in patients receiving haploHCT with a PBSC graft, the addition of a low dose of ATG to PTCy has been evaluated.[8–14] An EBMT registry study conducted in acute myeloid leukaemia (AML) in CR receiving a haploHCT showed a lower incidence of all grade chronic GVHD but no difference for extensive chronic GVHD with the use of ATG plus PTCy compared to PTCy alone. In addition, no difference was found in terms of acute GVHD (aGVHD), overall survival (OS), leukaemia-free survival (LFS), non-relapse mortality (NRM) and GVHD-free, relapse-free survival (GRFS).[15] Nonetheless, to this day, no large retrospective study or prospective trial has compared the classical PTCy approach to the dual T-cell depletion in that setting.

To compare the efficacy of PTCy alone or combined with ATG in haploHCT with PBSC graft, in a large cohort of patients, we performed a retrospective analysis within the EBMT centres taking into account every haematological malignancy regardless of the remission status at the time of transplantation.

DATA AND METHODS

Data selection and definitions

This study included 5194 adult patients (≥18 years at transplantation) with haematological malignancies that underwent a first haploHCT between 1 January 2014 and 31 December 2021. Patients received a PBSC graft and a GVHD prophylaxis based on a calcineurin inhibitor and mycophenolate mofetil combined with either PTCy alone or PTCy + ATG. Any haematological malignancies (AML, acute lymphoblastic leukaemia, myelodysplastic syndrome, myeloproliferative neoplasm, chronic leukaemia and lymphoma) and conditioning regimens were included. Patients with missing or not valid information on conditioning were excluded. Clinical data were collected and stored by the EBMT Registry. The following variables are derived from the data: the Disease Risk Index (DRI)[16] is used as an independent disease risk classification system and has been validated for allogeneic HCT.[17] Two other variables were created, CMV serostatus patient and donor match (−/− vs. other combinations) and patient donor sex match (male–female vs. other combinations). The study was approved by the Cellular Therapy and Immunobiology Working Party of the EBMT.

End-points

For the analysis the following end-points were used: OS, relapse-free survival (RFS), and cumulative incidences of grade II–IV and grade III–IV aGVHD, chronic GvHD (cGVHD), extensive cGVHD, relapse, NRM and neutrophil recovery. OS was defined as the time from HCT to death from any cause. RFS is defined as the time from transplant to relapse or death, whichever occurred first (patients with continuous progression are set to have a relapse at 2 months, and for those with missing relapse timing, times were imputed by randomly drawing from the relapse timing distribution in the data). Cumulative incidence of relapse and NRM were defined as time from transplant to, respectively, relapse and death without prior relapse, with respectively NRM and relapse as competing events. For all GVHD end-points, death, relapse and second allogeneic transplant were considered competing events. In case of missing time of onset of aGVHD, event times are imputed by randomly drawing from grade specific aGVHD distributions from the data. aGVHD grading was based on the modified Glucksberg criteria and cGVHD on the revised Seattle criteria.[18,19] GRFS is defined as time from transplant until relapse, death, aGVHD (grade III–IV) or extensive chronic GvHD (If date of turning to extensive cGVHD is not known, first cGVHD incidence is used), whichever occurred first.[20] Neutrophil recovery was defined as the first of three consecutive days in which the absolute neutrophil count (ANC) exceeded 0.5 G/L. For cumulative incidence of neutrophil recovery,

death was considered a competing event. Artificial censoring at 5 years was applied for all outcomes.

Statistical methods

For continuous variables, the median and interquartile range (IQR) were reported, whereas for categorical variables, numbers and percentages were stated. Kaplan–Meier curves for survival outcomes (RFS, OS and GRFS) and cumulative incidence curves for outcomes with a competing risk (relapse, NRM, GvHD end-points and neutrophil and platelet recovery) were calculated for patients with PTCy + ATG versus PTCy only as GVHD prophylaxis to display differences in survival and cumulative incidences between the treatment groups. For statistical comparisons, log-rank tests were used to compare Kaplan–Meier curves, while Gray's test was applied for comparing cumulative incidence curves. Multivariable (cause-specific) Cox proportional hazards models are employed to investigate the association of GVHD prophylactic treatment (PTCy + ATG vs. PTCy only) with the above-described end-points. Apart from the binary treatment variable, the following variables were included in the models as potential confounders: donor and patient age, year of transplant, Karnofsky score, donor patient sex match, DRI, CMV serostatus match, total body irradiation (TBI) and conditioning intensity (myeloablative vs. reduced intensity). A missing indicator for donor age was added as a variable, and for Karnofsky score and CMV serostatus match, a category for missing was included in order to avoid exclusion of a substantial number of patients. Those with missing on other variables were excluded (complete case analysis). To account for potential unobserved heterogeneity across different hospital/centres, we included a frailty term in our Cox proportional hazards model. Specifically, we modelled the hazard function using a shared frailty approach, with the frailty term representing the random effects associated with each hospital/centre. As non-proportional hazards were detected for the association of treatment with both neutrophil and platelet recovery; for both these analyses, treatment was included as a time-dependent covariate (time split of 0–0.5, 0.5–1 and 1+ months), but stratified by hospital/centre (rather than shared frailty).

For the group of patients with PTCy + ATG, it was investigated whether dosage had an impact on the above-described end-points. A binary variable indicating whether a patient had received a relatively low dosage (thymoglobulin <5 mg/kg or grafalon <30 mg/kg) versus a higher dosage; otherwise, the same confounding variables as in the previous models were included in the (cause-specific) Cox proportional hazards models. Given the relatively high number of missing or invalid dosages (around 33%), missing imputation was applied as a robustness test, using the Multivariate Imputation by Chained Equations (MICE) approach for imputation. Dosage, confounding variables and additionally event indicators plus Nelson-Aalen estimators[21] were used in the imputation model. Fifty imputed datasets were generated and the MICE algorithm was run 20 times; each of the datasets was analysed and then summarised using Rubin's rules to obtain final estimates of the regression coefficients, their standard errors and significance levels. All analyses were performed using R version 4.4.1 with the survival, PRODLIM and MICE packages.

RESULTS

Population characteristics

A total of 5194 patients fulfilled the inclusion criteria and were analysed, with 4519 patients in the PTCy only group and 675 in the PTCy + ATG group. Median follow-up was 29.80 months (IQR: 16.1–48.07); 30.75 (IQR: 16.82–48.95) in the PTCy group versus 24.15 (IQR: 12.16–40.41) in the PTCy + ATG group. Patients and transplantation characteristics are shown in Table 1. Some significant differences were found in terms of underlying diagnosis, and the Disease Risk Index (DRI) was slightly higher in the PTCy + ATG group. Moreover, patients received TBI more frequently in the PTCy only group (32% vs. 18% $p < 0.001$). Regarding the CMV serological status, the combination donor negative/recipient negative was more frequent in the PTCy + ATG group (25% vs. 17% $p < 0.001$) and the combination donor positive/recipient positive was more frequent in the PTCy only group (53% versus 47% $p < 0.001$). The rest of the characteristics were similar.

GRFS, OS, RFS

There was no significant difference in the probability of GRFS for 2 years between the PTCy only and PTCy + ATG group: 40.5% (95% confidence interval (CI) [38.9–42.1]) versus 37.5% (95% CI [33.2–41.8]) ($p = 0.098$). Two-year RFS was significantly better in the PTCy only group, being 50.9% (95% CI [49.3–52.4]) versus 45.8% (95% CI [41.5–50.1]) ($p = 0.015$). Similarly, 2-year OS was significantly higher in the PTCy only group: 56.9% (95% CI [55.4–58.5]) versus 52.5% (95% CI [48.2–56.8]) ($p = 0.01$). Two-year cumulative incidence of relapse was lower in the PTCy only group: 24.2% (95% CI [22.8–25.5]) versus 28.1% (95% CI [24.2–31.9]) ($p = 0.032$). 2-year NRM did not differ: 25% (95% CI [23.6–26.3]) in the PTCy only group versus 26.1% (95% CI [22.5–29.8]) in the PTCy + ATG group ($p = 0.49$) (Figure 1).

After multivariable adjustment, GRFS was not statistically different between groups: HR = 1.14 (95% CI [0.99–1.32]) ($p = 0.062$) while OS and RFS were lower in the PTCy + ATG group: HR = 1.18 (95% CI [1.01–1.38]) ($p = 0.037$) and HR = 1.18 (95% CI [1.02–1.36]) ($p = 0.027$) respectively. Two-year cumulative incidence of relapse was not significantly different: HR = 1.21 (95% CI [1–1.48]) ($p = 0.055$). NRM did not differ significantly: HR = 1.15 95% CI [0.93–1.43] ($p = 0.189$) (Table 2).

TABLE 1 Descriptive table of patients and transplantation characteristics for the two groups.

Characteristics	PTCy only *N* = 4519	PTCy + ATG *N* = 675	*p*-value
Patient sex			0.2
Male	2792 (62%)	435 (65%)	
Female	1726 (38%)	239 (35%)	
Missing	1	1	
Donor sex			0.3
Male	2777 (62%)	430 (64%)	
Female	1726 (38%)	239 (36%)	
Missing	15	1	
Patient age	55 (40, 64)	55 (41, 64)	>0.9
Donor age	37 (28, 47)	38 (29, 49)	0.066
Missing	126	6	
Year transplant			0.074
2014	174 (3.9%)	17 (2.5%)	
2015	315 (7.0%)	32 (4.7%)	
2016	381 (8.4%)	54 (8.0%)	
2017	524 (12%)	88 (13%)	
2018	585 (13%)	97 (14%)	
2019	712 (16%)	126 (19%)	
2020	899 (20%)	131 (19%)	
2021	929 (21%)	130 (19%)	
Diagnosis			
AML	2076 (46.4%)	341 (50.5%)	
ALL	525 (11.6%)	59 (8.7%)	
MDS	610 (13.5%)	122 (18.1%)	
MPN	271 (6%)	45 (6.7%)	
B-cell lymphoma	635 (14.1%)	53 (8%)	
T-cell lymphoma	244 (5.4%)	39 (5.8%)	
Other	158 (3.5%)	16 (2.4%)	
Disease risk index			<0.001
Low	350 (7.7%)	25 (3.7%)	
Intermediate	2836 (63%)	415 (61%)	
High	1092 (24%)	186 (28%)	
Very high	241 (5.3%)	49 (7.3%)	
Karnofsky score			0.8
≤80	1181 (28%)	168 (27%)	
≥90	3112 (72%)	454 (73%)	
Missing	226	53	
CMV status			<0.001
D−/R−	755 (17%)	163 (25%)	
D−/R+	347 (7.9%)	48 (7.3%)	
D+/R−	947 (22%)	139 (21%)	
D+/R+	2347 (53%)	312 (47%)	
Missing	123	13	
Conditioning intensity			0.075
MAC	1981 (44%)	269 (40%)	
RIC	2522 (56%)	398 (60%)	
Missing	16	8	
Conditioning type			<0.001
Fludarabine + Busulfan	969 (22%)	174 (26%)	
Fludarabine + Busulfan + Thiotepa	1550 (34%)	239 (35%)	
Fludarabine + TBI	1150 (25%)	70 (10%)	
Other	850 (19%)	192 (29%)	
Received TBI	1423 (32%)	119 (18%)	<0.001
Missing	40	2	

Note: *p*-values based on Kruskal test for continuous variables (Wilcoxon rank sum test when 'by' variable has two levels), Pearson's chi-square test for categorical variables with all expected cell counts ≥5, and Fisher test for categorical variables with any expected cell count <5.

Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; RIC, reduced intensity conditioning; TBI, total body irradiation.

GVHD

Cumulative incidence of grade II–IV and grade III–IV aGVHD at day 100 was 32.2% (95% CI [30.8–33.6]) and 11.1% (95% CI [10.1–12]), respectively, in the PTCy only group versus 30.2% (95% CI [26.7–33.8], $p = 0.31$) and 13.2% (95% CI [10.6–15.9], $p = 0.10$), respectively, in the PTCy + ATG group. The 2-year cumulative incidence of cGVHD was significantly higher in the PTCy only group: 28.4% (95% CI [27.0–29.8]) versus 18.5% (95% CI [15.2–21.9]) in the PTCy + ATG group ($p < 0.001$). Similarly, the 2-year cumulative incidence of extensive cGVHD was significantly higher in the PTCy only group: 12.2% (95% CI [11.2–13.2]) versus 7.8% (95% CI [5.5–10.1]) in the PTCy + ATG group ($p = 0.002$) (Figure 2). In multivariable analysis, we confirmed that PTCy + ATG was associated with a lower cumulative incidence of cGVHD: HR = 0.68 (95% CI [0.53–0.89]) ($p = 0.004$) but not for extensive cGVHD: HR = 0.71 (95% CI [0.48–1.04]) ($p = 0.079$). The multivariable model found no evidence for a difference in grade II–IV and grade III–IV aGVHD: HR = 0.87 (95% CI [0.70–1.06]) ($p = 0.17$) and HR = 1.20 (95% CI [0.90–1.59]) ($p = 0.226$) respectively (Table 3).

Haematopoietic recovery

In univariate analysis, the day 28 cumulative incidence of neutrophil recovery was slightly higher in the PTCy + ATG group, being 91.7% (95% CI [89.5–93.8]) versus 89.7% (95% CI [88.8–90.6]) in the PTCy only group ($p < 0.001$). It was confirmed in the multivariable analysis. Platelet recovery did not differ significantly (data not shown).

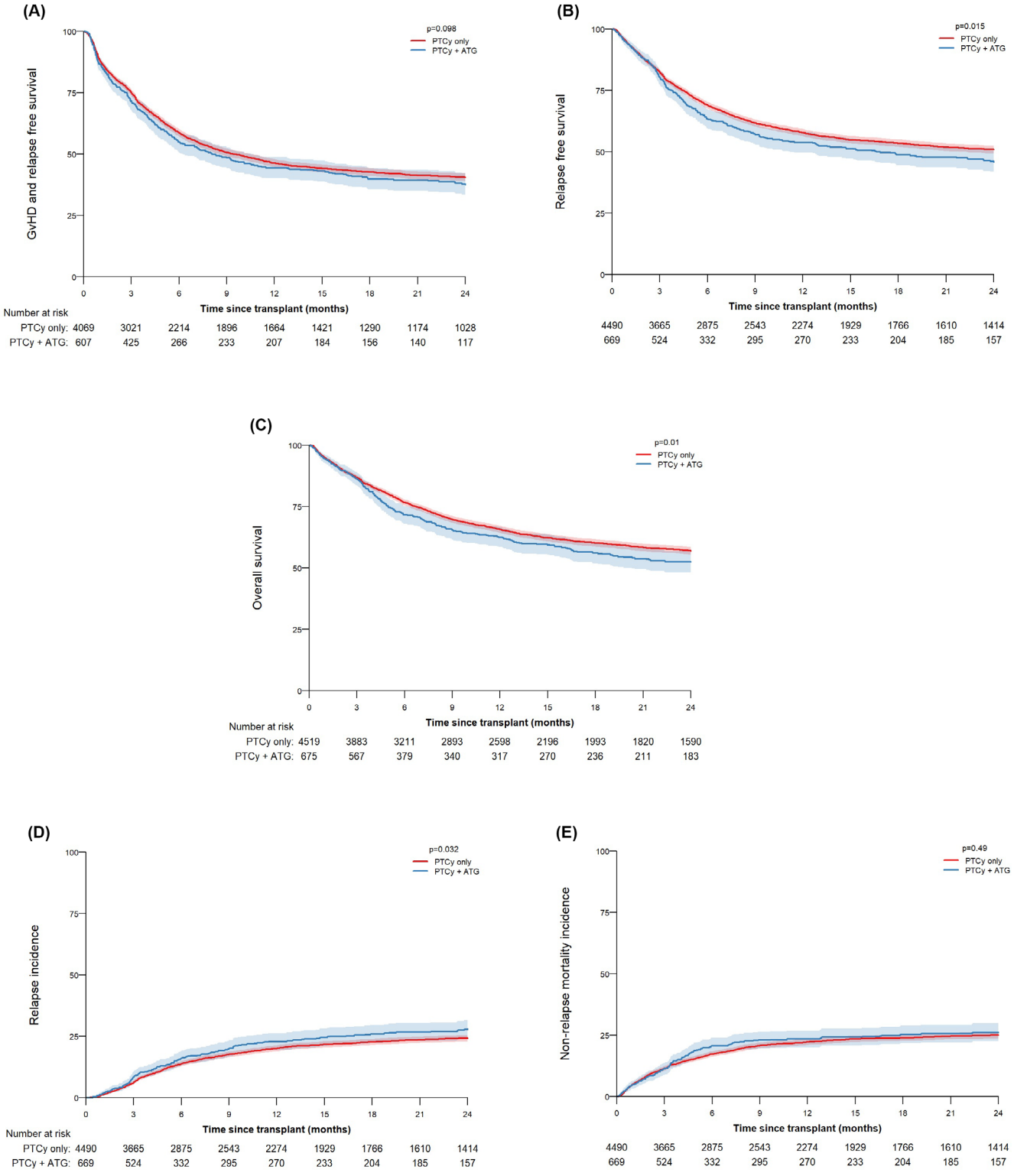

FIGURE 1 Survival curves showing incidence comparison between post-transplant cyclophosphamide (PTCy) only and PTCy + antithymocyte globulin (ATG) for GVHD-free, relapse-free survival (GRFS) (A), relapse-free survival (RFS) (B), overall survival (OS) (C), RI (D) and non-relapse mortality (NRM) (E). GVHD, graft-versus-host disease.

Impact of ATG dosage

Given the wide range of ATG doses used in combination with PTCy, we then decided to evaluate whether patients receiving lower doses of ATG in the PTCy + ATG group had different outcomes from those receiving higher doses. We did not find any significant difference in OS, RFS, relapse incidence (RI), aGVHD or cGVHD (Tables S1 and S2). NRM was increased

TABLE 2 Cox proportional hazards models for OS, RFS, RI, NRM and GRFS.

	OS		RFS		RI		NRM		GRFS	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
PTCy + ATG	1.18 (1.01–1.38)	**0.037**	1.18 (1.02–1.36)	**0.027**	1.21 (1.00–1.48)	0.055	1.15 (0.93–1.43)	0.189	1.14 (0.99–1.32)	0.062
Age (per 10 years)	1.19 (1.15–1.23)	**<0.001**	1.13 (1.10–1.17)	**<0.001**	1.01 (0.97–1.05)	0.7	1.30 (1.24–1.37)	**<0.001**	1.08 (1.05–1.12)	**<0.001**
Donor age	1.00 (1.00–1.01)	**0.025**	1.00 (1.00–1.00)	0.281	1.00 (0.99–1.00)	0.143	1.01 (1.00–1.01)	**0.003**	1.00 (1.00–1.01)	**0.037**
Year of transplants	0.96 (0.93–0.98)	**<0.001**	0.95 (0.93–0.98)	**<0.001**	0.96 (0.93–0.99)	**0.005**	0.95 (0.92–0.98)	**0.002**	0.97 (0.95–0.99)	**0.003**
DRI—low	0.91 (0.75–1.12)	**<0.001**	1.05 (0.88–1.25)	**<0.001**	0.97 (0.75–1.25)	**<0.001**	1.17 (0.92–1.49)	**0.005**	1.08 (0.92–1.27)	**<0.001**
DRI—high	1.61 (1.46–1.77)		1.58 (1.44–1.73)		2.09 (1.84–2.37)		1.18 (1.03–1.35)		1.51 (1.38–1.65)	
DRI—very high	2.64 (2.26–3.08)		2.54 (2.19–2.95)		3.99 (3.30–4.82)		1.46 (1.14–1.87)		2.18 (1.87–2.54)	
Donor sex mismatch	1.09 (0.98–1.20)	0.105	1.08 (0.98–1.19)	0.104	0.96 (0.84–1.10)	0.557	1.23 (1.07–1.40)	**0.002**	1.16 (1.06–1.27)	**<0.001**
Karnofsky—≥90	0.58 (0.53–0.64)	**<0.001**	0.62 (0.57–0.68)	**<0.001**	0.72 (0.63–0.82)	**<0.001**	0.54 (0.47–0.62)	**<0.001**	0.66 (0.60–0.72)	**<0.001**
CMV—other combination	1.15 (1.02–1.30)	**0.014**	1.13 (1.01–1.26)	**0.011**	1.07 (0.92–1.24)	0.264	1.21 (1.03–1.42)	**0.022**	1.01 (0.91–1.11)	0.467
RIC conditioning	0.98 (0.88–1.09)	0.723	0.99 (0.90–1.09)	0.871	1.07 (0.93–1.22)	0.336	0.90 (0.79–1.04)	0.16	0.92 (0.84–1.01)	0.066
TBI	0.96 (0.86–1.07)	0.452	0.98 (0.89–1.09)	0.763	1.09 (0.95–1.25)	0.209	0.87 (0.75–1.01)	0.062	0.98 (0.89–1.08)	0.689

Abbreviations: ATG, antithymocyte globulin; GRFS, GVHD-free, relapse-free survival; GVHD, graft-versus-host disease; NRM, non-relapse mortality; OS, overall survival; PTCy, post-transplant cyclophosphamide; RFS, relapse-free survival; RIC, reduced intensity conditioning; TBI, total body irradiation.

p values under 0.05 are presented in bold.

in patients who received a higher dose of ATG (HR = 1.70, 95% CI [1.07–2.69], $p = 0.024$) and extensive cGVHD was decreased (HR = 0.37, 95% CI [0.15–0.95, $p = 0.038$]); nevertheless, robustness test analysis was conducted using missing imputation and did not confirm these results (Tables S3 and S4).

Stratified analysis

To refine our results and account for the heterogeneity of our cohort, we performed stratified analyses by subgroup. We did not find any specific impact of ATG based on the underlying disease (myeloid neoplasm, acute lymphoblastic leukaemia or lymphoma) or CMV serostatus (Figures S1 and S2). In contrast, when we performed a stratified analysis based on DRI index (high or very high vs. low or intermediate), we found that the lower OS and RFS associated with the use of ATG + PTCy seem to be restricted to patients with a high or very high DRI (Figure S3).

DISCUSSION

PTCy for GVHD prophylaxis in haploHCT has emerged as a gold standard[4,5] widening the access to transplantation for many patients without MSD or MUD and replacing cord blood transplantation to a certain extent.[22] On the other hand, PBSCs are more frequently used than BM due to their easier utilization and better acceptability by donors; however, PBSCs also increase the risk of GVHD,[23,24] which remains a major cause of NRM.[3–5] The combination of ATG with PTCy in haploHCT with PBSCs demonstrated a low incidence of GVHD, notably cGVHD.[10,11] In the current study, we did not find any difference in GRFS between PTCy alone and PTCY + ATG, yet we showed a better OS and RFS in the PTCy alone group on both univariate and multivariate analyses. The discrepancies between our results and those of Battipaglia et al. might be related to the different populations, as the previous EBMT study included only AML in CR, and it is possible that the impact of the addition of ATG to PTCy may differ from one haematological malignancy to the other. On the other hand, it could be explained by the much larger population we analysed, leading to a higher statistical power. It is not clear whether in our analysis, the excess of mortality in the PTCY + ATG group comes from an increase in NRM, RI or both since neither of these two parameters alone differed significantly between groups.

In some previous studies, the use of high-dose ATG was associated with an increased risk of relapse and/or NRM,[7,25,26] so we further analysed the dose and type of ATG in our PTCy + ATG group. Unfortunately, this information was available in only 67% of cases. On that sample, we found a very wide range of dosage of grafalon or thymoglobulin. We compared patients who received relatively high doses of ATG versus a lower dose, but we were not able to demonstrate any significant difference in clinical outcomes, probably due to the incompleteness of data.

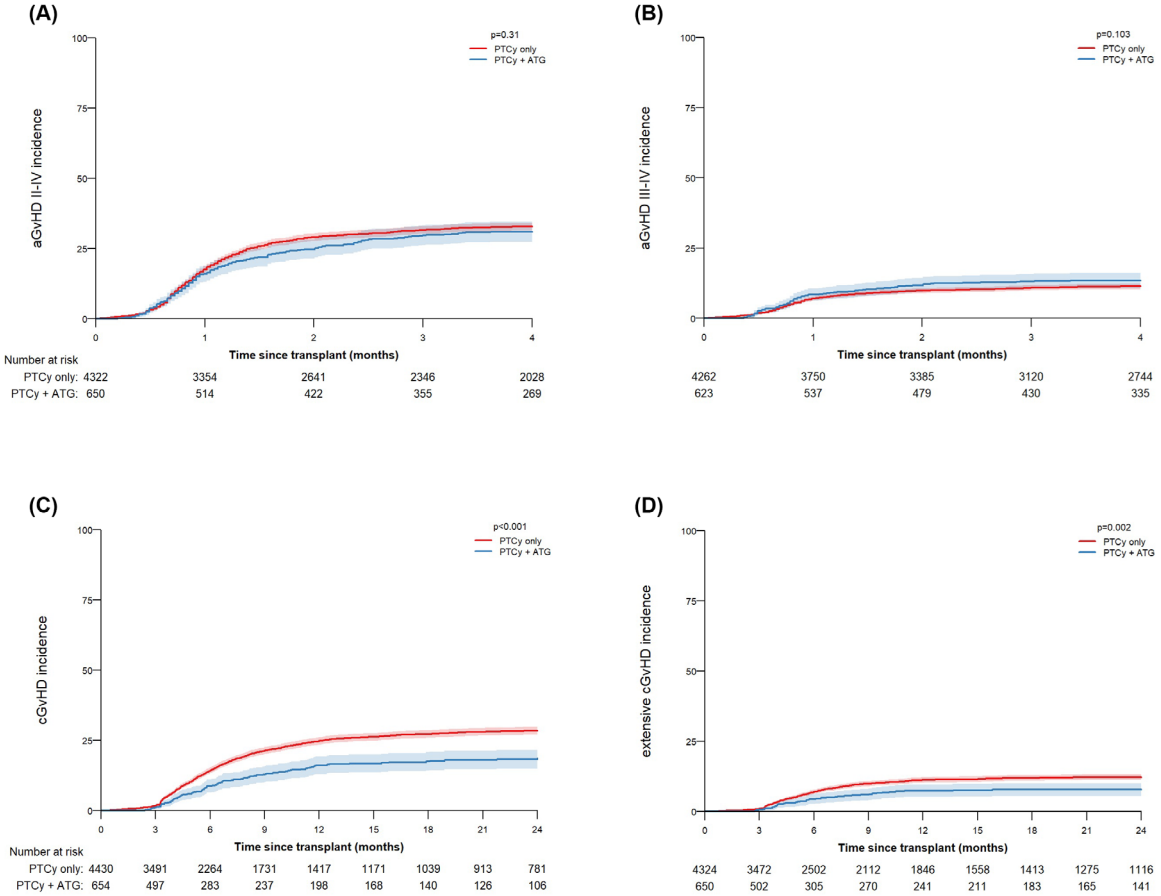

FIGURE 2 Survival curves showing incidence comparison between post-transplant cyclophosphamide (PTCy) only and PTCy + antithymocyte globulin (ATG) for acute GVHD (aGVHD) II–IV (A), aGVHD III–IV (B), chronic GVHD (cGVHD) (C) and extensive cGVHD (D). GVHD, graft-versus-host disease.

TABLE 3 Cox proportional hazards models for aGVHD II–IV, aGVHD III–IV, cGVHD and extensive cGVHD.

	Grade II–IV aGVHD		Grade III–IV aGVHD		cGVHD		Extensive cGVHD	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
PTCy + ATG	0.87 (0.70–1.06)	0.17	1.20 (0.90–1.59)	0.226	0.68 (0.53–0.89)	**0.004**	0.71 (0.48–1.04)	0.079
Age (per 10 years)	1.00 (0.96–1.04)	0.924	0.97 (0.91–1.03)	0.357	1.04 (0.99–1.08)	0.101	1.08 (1.01–1.16)	**0.019**
Donor age	1.01 (1.01–1.02)	**<0.001**	1.02 (1.01–1.02)	**<0.001**	1.00 (1.00–1.01)	**0.031**	1.01 (1.00–1.01)	**0.037**
Year of transplants	0.96 (0.93–0.99)	**0.003**	0.94 (0.90–0.98)	**0.005**	1.01 (0.98–1.04)	0.706	0.98 (0.94–1.03)	0.472
DRI—Low	1.29 (1.07–1.56)	**0.04**	1.20 (0.87–1.67)	0.493	0.93 (0.74–1.17)	0.349	1.24 (0.89–1.73)	0.073
DRI—High	0.98 (0.87–1.10)		1.12 (0.92–1.37)		1.11 (0.97–1.27)		1.30 (1.05–1.60)	
DRI—Very high	1.12 (0.90–1.40)		1.16 (0.81–1.67)		0.93 (0.68–1.26)		1.30 (0.85–1.97)	
Donor sex mismatch	0.86 (0.76–0.98)	**0.02**	0.89 (0.72–1.09)	0.261	1.33 (1.17–1.51)	**<0.001**	1.74 (1.44–2.11)	**<0.001**
Karnofsky—≥90	1.00 (0.88–1.14)	0.34	0.80 (0.65–0.97)	0.089	0.92 (0.79–1.06)	0.28	0.77 (0.62–0.96)	0.062
CMV—other combination	0.88 (0.77–1.00)	0.125	0.76 (0.61–0.93)	**0.025**	0.99 (0.85–1.14)	0.946	1.06 (0.84–1.34)	0.744
RIC conditioning	0.98 (0.87–1.11)	0.766	0.91 (0.75–1.11)	0.362	0.89 (0.77–1.02)	0.086	0.72 (0.58–0.90)	**0.003**
TBI	1.23 (1.08–1.40)	**0.001**	0.96 (0.78–1.18)	0.706	1.02 (0.88–1.17)	0.801	1.06 (0.86–1.32)	0.57

Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; ATG, antithymocyte globulin; DRI, disease risk index; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; PTCy, post-transplant cyclophosphamide; RIC, reduced intensity conditioning; TBI, total body irradiation.

p values under 0.05 are presented in bold.

We acknowledge some limitations to our study. First, the retrospective nature of our work. Second, due to large inclusion criteria, our population was heterogeneous in terms of disease type and status. We also noticed some heterogeneity in the conditioning regimens reported beyond the usual MAC/RIC dichotomy. Moreover, given its retrospective nature, our data do not include the absolute lymphocyte count prior to ATG administration or the exact timing of the ATG infusion, even though both have been shown to influence transplant outcomes.[27–29] Similarly, some important information was not available in the registry, such as the exact schedule and dosage of PTCy, which could have impacted the results.

Nonetheless, this remains the largest retrospective comparison to date of standard PTCy GVHD prophylaxis versus PTCy plus ATG in haploHCT. We found a potential deleterious effect of the PTCy plus ATG approach, which appears to be restricted to patients with a high or very high DRI. In conclusion, prospective trials are warranted to determine which patients may benefit from the addition of ATG to PTCy, as well as the optimal dosing of both drugs.

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ACKNOWLEDGEMENTS

AC conceived the study design and wrote the original draft, JEM performed statistical analysis and wrote the 'Methods' section, FM and AR conceived the study design and reviewed the final draft. All the other authors reviewed and approved the final draft.

CONFLICT OF INTEREST STATEMENT

Florent Malard reports honoraria from BMS, Therakos/Mallinckrodt, Sanofi, JAZZ Pharmaceuticals, Gilead, Novartis, Astrazeneca and MSD, all outside the submitted work. Mohamad Mohty reports grants, lecture honoraria and research support from Adaptive Biotechnologies, Amgen, Astellas, BMS-Celgene, GlaxoSmithKline, Janssen, JAZZ Pharmaceuticals, Novartis, Pfizer, Takeda and Sanofi, all outside the scope of this work. The other authors did not disclose any relevant conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available upon reasonable request to the corresponding authors.

ETHICS STATEMENT

Each patient provided consent for HCT and authorisation for the use of HCT data for research purposes according to the guidelines of the Declaration of Helsinki. The institutional review board of the CTIWP of the EBMT granted ethical approval for this study.

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How to cite this article: Capes A, Mooyaart JE, Blaise D, Bramanti S, Kwon M, Mohty M, et al. Impact of the addition of antithymocyte globulin to post-transplantation cyclophosphamide in haploidentical transplantation with peripheral blood compared to post-transplantation cyclophosphamide alone: A retrospective study on behalf of the Cellular Therapy and Immunobiology Working Party of the European Society for Blood and Marrow Transplantation. Br J Haematol. 2025;00:1–9. https://doi.org/10.1111/bjh.70050