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ARTICLE

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Cytogenetic and molecular risk-driven conditioning intensity in acute myeloid leukemia patients undergoing stem cell transplantation with post-transplant cyclophosphamide: a study from the acute leukemia working party of the EBMT

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We retrospectively analyzed the impact of conditioning intensity on transplant outcomes according to their cytogenetic/molecular risk in a cohort of 1823 patients with acute myeloid leukemia (AML) and intermediate- or adverse-risk cytogenetics in first complete remission (CR1). These patients received their first hematopoietic stem cell transplantation (HSCT) using post-transplant cyclophosphamide (PTCy). The intermediate-risk cytogenetic group included 1386 (76%) patients, and 608 (34%) had mutated FLT3-ITD. Myeloablative conditioning was used in 930 patients (51%), while 1130 (62%) received an intensified conditioning (score ≥2.5) based on the transplant conditioning intensity (TCI) score. Conditioning intensity using the myeloablative/reduced intensity stratification did not impact transplant outcomes across the entire cohort. However, a higher TCI score was associated with a lower risk of relapse, with no effect on survival. In specific cytogenetic risk groups, a higher TCI score did not influence outcomes in the adverse-risk group. In the intermediate-risk group, the impact varied with FLT3-ITD status. Patients with FLT3-ITD mutation who received a higher TCI showed a beneficial effect on relapse, leukemia-free survival (LFS), and overall survival. Conversely, in FLT3-ITD wild-type patients, more intense conditioning had a detrimental effect on graft-versus-host disease-free, and relapse-free survival with no effect on other outcomes. In conclusion, for AML patients in CR1 undergoing HSCT with PTCy, it is crucial to consider cytogenetic risk and molecular status when selecting the conditioning regimen. Intensive conditioning should be considered for patients with intermediate-risk cytogenetics and mutated FLT3-ITD but should probably be avoided for those with wild-type FLT3-ITD.

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INTRODUCTION

The conditioning regimen is a crucial component of the hematopoietic stem cell transplant (HSCT) procedure, yet the impact of conditioning intensity on outcomes in acute myeloid leukemia (AML) remains controversial. A phase III randomized trial by the Blood and Marrow Transplant Clinical Trials Network showed improved survival with fully myeloablative conditioning (MAC) compared to reduced intensity conditioning (RIC) in AML patients [1]. While some retrospective studies have suggested similar survival rates [2–4], these findings generally support the use of intensive conditioning as the standard of care for fit AML patients at high risk of relapse. However, certain limitations for applying these recommendations still remain.

Firstly, the definitions of RIC and MAC [5, 6] are somewhat arbitrary and may be outdated, especially for novel conditioning regimens. The Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) has enhanced the RIC/MAC classification by introducing a tool that assigns intensity weight scores to commonly used conditioning regimen components, resulting in a transplant conditioning intensity (TCI) score [7].

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In addition, there is insufficient information to guide the appropriate conditioning intensity in specific settings. For instance, transplant platforms using post-transplant cyclophosphamide (PTCy) have successfully controlled graft-versus- host disease (GvHD), making conditioning intensity especially pertinent in this scenario. Furthermore, the impact of conditioning intensity on transplant outcomes likely varies with the risk of relapse. In this regard, MAC has shown significant benefits for patients with detectable residual disease prior to allogeneic HSCT [8]. However, its effects across different cytogenetic and molecular risk categories of AML remain underexplored.

The aim of our study was to investigate the impact of conditioning intensity, using TCI score, in different AML subgroups according to their cytogenetic and molecular profile receiving HSCT with PTCy as GvHD prophylaxis. We analyzed data from the EBMT database stratifying patients by their cytogenetic and molecular risk profiles.

PATIENTS AND METHODS

Study design and data source

This is a retrospective registry-based analysis on behalf of the ALWP of the EBMT. The EBMT is a voluntary working group of more than 650 transplantation centers that are required to report all consecutive stem cell transplantations and follow ups once a year. In the EBMT registry, there is an internal quality control program regarding accuracy and consistency of entered data and audits are regularly performed using queries on missing/incorrect data and follow-up requests. All transplantation centers are required to obtain written informed consent from patients before data registration with the EBMT in accordance with the 1975 Declaration of Helsinki. The ALWP of the EBMT approved this study.

Patient eligibility

Included were all adults (age ≥ 18 years) with AML in first complete remission (CR1) reported via the ProMISe data entry system to the EBMT database, who underwent a first allogeneic HSCT between January 2010 and December 2022, using an unmanipulated graft and PTCy as GvHD prophylaxis. Patients had to have complete information on conditioning, cytogenetics, and FLT3/NPM1 status. Patients with favorable-risk cytogenetics were excluded due to the low number of such patients.

Endpoints and definitions

The primary endpoint was leukemia-free survival (LFS). Secondary endpoints included acute and chronic GvHD, disease relapse, non-relapse mortality (NRM), GvHD-free and relapse-free survival (GRFS), and overall survival (OS). GRFS was defined as survival without disease relapse and severe acute or chronic extensive GvHD. OS was defined as the time between the date of transplant and death. LFS was defined as survival without relapse or progression, and was calculated until the date of first relapse, death from any cause, or the last follow-up. Relapse was defined as leukemia recurrence at any site. NRM was defined as death from any cause other than relapse. Conditioning intensity was measured using the transplant conditioning regimen intensity MAC/RIC classification[6] and TCI score [7]. Low TCI was defined as a TCI score <2.5 and high TCI as a score ≥2.5. Cytogenetic and molecular risk groups were classified according to the 2017 European LeukemiaNet (ELN) classification [9]. Pre-transplant measurable residual disease (MRD) was declared by the center using locally defined assays and cut-offs.

Statistical analysis

GRFS, LFS, and OS were estimated using the Kaplan-Meier method [10]. Survival probabilities at 2 years are given as percentages and 95% confidence intervals (95% CIs). Cumulative incidence functions were used to estimate acute GvHD, chronic GvHD, relapse incidence, and NRM [11, 12]. Competing risks were death for relapse incidence and relapse for NRM, relapse or death for acute GvHD and chronic GvHD. Univariate analyses were performed using the log-rank test for LFS, GRFS, and OS and Gray's test for cumulative incidence estimates. Multivariate analyses were performed using the Cox proportional-hazards model [13]. All multivariable analysis were adjusted on patient, disease and transplant characteristics including: patient´s age at transplantation, Karnofsky performance status, hematopoietic cell transplant specific comorbidity index (HCT-CI), cytogenetic risk group, FLT3-ITD and NPM1 mutational status, transplantation year, conditioning regimen intensity according to the TCI score (high for score ≥ 2.5 vs. low for score < 2), donor type, stem cell source, donor-recipient CMV serostatus, donor-recipient gender mismatch, and in-vivo T-cell depletion. Pre-transplant therapy was not included due to lack of information. Complete case analysis was performed for MRD analysis as the number of missing was too high. Moreover, taking into account for the low number of events, only univariate analysis was performed for MRD subgroups. To consider the heterogeneity in the effect of a characteristic or a treatment across centers, we introduced a random effect into the Cox multivariate models [14]. In order to know if the effect of TCI was similar for patients whatever their FLT3-ITD status, we included potential interactions between FLT3-ITD and each other covariate included in the Cox model. We considered that there was an interaction when the p value was less that 0.10. The significance level was fixed at 0.05 and p values were two-sided. Statistical analyses were performed using the R statistical software version 4.2.3 (R Foundation for Statistical Computing, Austria, Vienna; available online at http://www.R-project.org).

RESULTS

Patient, disease, and transplantation characteristics

Patient, disease, and transplant characteristics are summarized in Table 1. A total of 1813 patients were included, with a median age of 55 years (range, 18–75). Among them, 194 (11%) received transplants from matched sibling donors (MSD), 563 (31%) from matched unrelated donors (MUD), and 1056 (58%) from haploidentical family donors. Regarding cytogenetic risk groups, 1386 patients (76%) were classified as intermediate risk, while 427 (24%) were classified as adverse risk. FLT3-ITD and NPM1 mutations were detected in 608 (34%) and 578 patients (32%), respectively. MAC was administered to 930 patients (51%). According to TCI score, 1130 patients (62%) received an intensified conditioning regimen (score ≥ 2.5). The most frequently used GvHD prophylaxis was PTCy combined with mycophenolate-mofetil and a calcineurin inhibitor.

Transplant outcomes

Patient outcomes after HSCT are shown in Table 2. For the overall cohort, the 180-day cumulative incidence of acute GvHD grade II–IV and III–IV was 27% (95% CI, 25–29) and 8% (95% CI, 7–10), respectively. The 2-year cumulative incidence of chronic and chronic extensive GvHD was 35% (95% CI, 33–38) and 15% (95% CI, 13–17), respectively. The 2-year cumulative incidence of relapse and NRM was 21% (95% CI, 19–23) and 16% (95% CI, 14–17), respectively. The LFS, OS, and GRFS at 2 years was 63% (95% CI, 61–66), 69% (95% CI, 66–71), and 52% (95% CI, 49–55), respectively.

In multivariable analysis, older patient age (hazard ratio [HR] per 10 years 1.15; 95% CI 1.07–1.24) and adverse-risk cytogenetics (HR 1.42; 95% CI 1.17–1.72) were associated with worse LFS. FLT3-ITD (HR 0.99; 95% CI 0.79–1.23), NPM1 (HR 0.87; 95% CI 0.69–1.1), and donor type (MUD: HR 1.15; 95% CI 0.83–1.59; haploidentical: HR 1.2; 95% CI 0.88–1.62) had no effect on LFS.

Impact of conditioning intensity on transplant outcomes

Overall cohort. Conditioning intensity, as determined by the MAC/RIC stratification, did not impact transplant outcomes. However, a higher TCI score was associated with a lower risk of relapse (HR 0.74; 95% CI 0.57–0.98). There was no significant effect on NRM (HR 1.32; 95% CI 0.97–1.81), LFS (HR 0.97; 95% CI 0.8–1.19), OS (HR 1; 95% CI 0.81–1.25), or GRFS (HR 1.05; 95% CI 0.87–1.26).

Cytogenetic and molecular-risk groups. Multivariable analyses of transplant outcomes according to conditioning intensity and stratified by cytogenetic and molecular-risk categories are shown in Table 3.

Table 1. Patient, disease, and transplant characteristics.

	n (%)
No. of patients	1813
Follow-up in months, median (IQR)	26 (24–29)
Age in years, median (range)	55 (18–75)
Male gender	1000 (55)
CMV seropositive	1294 (72)
Karnofsky performance score ≥ 90 at transplant	1361 (77)
HCT-CI	
0	749 (48)
1–2	3912 (25)
≥3	429 (27)
Missing	244
Cytogenetic risk	
Intermediate	1386 (76)
Adverse	427 (24)
FLT3-ITD	
Wild-type	1205 (67)
Mutated	608 (34)
NPM1	
Wild-type	1235 (68)
Mutated	578 (32)
Pre-transplant MRD	
Positive	371 (41)
Negative	531 (59)
Missing	911
Type of donor	
Matched sibling	194 (11)
Unrelated	563 (31)
Haploidentical	1056 (58)
Stem cell source	
Peripheral blood	1504 (83)
Bone marrow	309 (17)
Conditioning intensity according to MAC/RIC classification	
Myeloablative	930 (51)
Reduced intensity	883 (49)
Conditioning intensity according to TCI score	
Low (<2.5)	683 (38)
High (≥2.5)	1130 (62)
In-vivo T-cell depletion	225 (12)
Graft-versus-host disease prophylaxis	
PTCy + calcineurin inhibitor + MMF	1240 (68)
PTCy + calcineurin inhibitor	276 (15)
PTCy + sirolimus + MMF	125 (7)
PTCy + other	172 (10)

IQR interquartile range, *CMV* cytomegalovirus, *HCT-CI* hematopoietic cell transplant specific comorbidity index, *MRD* measurable residual disease, *MAC* myeloablative conditioning, *RIC* reduced intensity conditioning, *TCI* transplant conditioning intensity, *PTCy* post-transplant cyclophosphamide, *MMF* mycophenolate mofetil.

Table 2. Transplant outcomes of the entire cohort.

Outcome[a]	Overall % (95% CI)
Acute GvHD	
Grade II–IV	27 (25–29)
Grade III–IV	8 (7–10)
Chronic GvHD	
Overall	35 (33–38)
Extensive	15 (13–17)
Non-relapse mortality	16 (14–17)
Relapse incidence	21 (19–23)
Leukemia-free survival	63 (61–66)
Overall survival	69 (66–71)
GvHD-free and relapse-free survival	52 (49–55)

[a]Acute GvHD: 180-day cumulative incidence; Chronic GvHD, non-relapse mortality and relapse incidence: 2-year cumulative incidence; Leukemia-free survival, overall survival, and GvHD-free and relapse-free survival: 2-year survival probability.

Intermediate-risk cytogenetic group: In the intermediate-risk cytogenetic group, a higher TCI score was associated with a lower risk of relapse (HR 0.67; 95% CI 0.48–0.95) but did not significantly affect other transplant outcomes. We subsequently analyzed specific subgroups according to FLT3-ITD status after confirming that there was no interaction between FLT3-ITD and other factors included in the multivariable analysis in the intermediate risk group, including NPM1. We found an interaction between TCI and FLT3-ITD status in the intermediate risk group for LFS (HR 0.64; 95% CI 0.41–1), OS (HR 0.6; 95% CI 0.37–0.97) and relapse (HR 0.57; 95% CI 0.31–1.05). The effect of TCI was not the same according to FLT3-ITD status. Within the intermediate-risk cytogenetic group, for patients with FLT3-ITD mutations, more intense conditioning showed beneficial effects on relapse (HR 0.43; 95% CI 0.26–0.74), LFS (HR 0.58; 95% CI 0.39–0.87), OS (HR 0.58; 95% CI 0.37–0.89), and GRFS (HR 0.67; 95% CI 0.47–0.97) (Fig. 1). In contrast, for FLT3-ITD wild-type patients, more intense conditioning had a detrimental effect on GRFS (HR 1.32; 95% CI 1.02–1.7) but did not impact other outcomes (Fig. 2).

To evaluate the impact of MRD in the intermediate-risk cytogenetic group, we analyzed 753 patients (54%) with available information. Among these, 425 (56%) were MRD-negative and 328 (44%) were MRD-positive, with a similar distribution of conditioning intensity and FLT3-ITD status. MRD negatively influenced the cumulative incidence of relapse (22% vs. 10%, $p = 0.001$), LFS (64% vs. 75%, $p = 0.003$), and OS (70% vs. 80%, $p = 0.007$). However, conditioning intensity did not significantly impact the risk of relapse according to MRD status. In MRD-negative patients, the cumulative incidence of relapse was 9% (95% CI, 5–15) and 11% (95% CI, 7–15) ($p = 0.6$) for patients receiving low and higher TCI, respectively. In MRD-positive patients, the cumulative incidence of relapse was 28% (95% CI, 18–39) for low TCI and 19% (95% CI, 14–26) for higher TCI ($p = 0.09$).

High-risk cytogenetic group: In the high-risk cytogenetic group, conditioning intensity did not influence transplant outcomes.

DISCUSSION

This study shows that for AML patients undergoing HSCT in CR1 with PTCy-based GvHD prophylaxis, the impact of conditioning intensity varies according to the cytogenetic risk and molecular status. While intensifying the conditioning regimen did not affect outcomes in patients with adverse-risk cytogenetics, it reduced relapse and improved LFS in patients with intermediate-risk cytogenetics harboring FLT3-ITD mutations. However, it increased NRM and decreased survival in patients with wild-type FLT3-ITD.

Table 3. Impact of conditioning intensity on outcomes according to cytogenetic risk and FLT3-ITD mutational status.

			Intermediate risk cytogenetics				high-risk cytogenetics	
	Overall HR[a] (95% CI)		FLT3-ITD mutated		FLT3-ITD wild type			
Outcome		*p*	HR[a] (95% CI)	*p*	HR[a] (95% CI)	*p*	HR[a] (95% CI)	*p*
Acute GvHD grade II-IV	1.16 (0.88–1.51)	0.29	1.18 (0.73–1.89)	0.50	0.97 (0.67–1.4)	0.85	1.52 (0.92–2.52)	0.1
Chronic GvHD	1.06 (0.83–1.35)	0.66	0.75 (0.49–1.13)	0.17	1.41 (1.01–1.97)	0.04	0.73 (0.45–1.2)	0.22
Non-relapse mortality	1.32 (0.97–1.81)	0.08	0.92 (0.49–1.7)	0.78	1.39 (0.93–2.08)	0.11	1.89 (0.95–3.77)	0.07
Relapse	**0.74 (0.57–0.98)**	**0.03**	**0.43 (0.26–0.74)**	**0.002**	0.97 (0.62–1.53)	0.90	0.83 (0.51–1.35)	0.45
LFS	0.97 (0.8–1.19)	0.8	**0.58 (0.39–0.87)**	**0.008**	1.17 (0.86–1.57)	0.32	1.11 (0.76–1.63)	0.6
OS	1 (0.81–1.25)	0.97	**0.58 (0.37–0.89)**	**0.012**	1.24 (0.9–1.72)	0.19	1.14 (0.77–1.7)	0.51
GRFS	1.05 (0.87–1.26)	0.76	**0.67 (0.47–0.97)**	**0.035**	**1.32 (1.02–1.70)**	**0.04**	1.08 (0.77–1.53)	0.65

GvHD graft-versus-host disease, *LFS* leukemia-free survival, *OS* overall survival, *GRFS* GvHD-free and relapse-free survival, *HR* hazard ratio.
[a]Transplant conditioning intensity score ≥2.5 was used as reference.
Bold applies to statiscally significant.

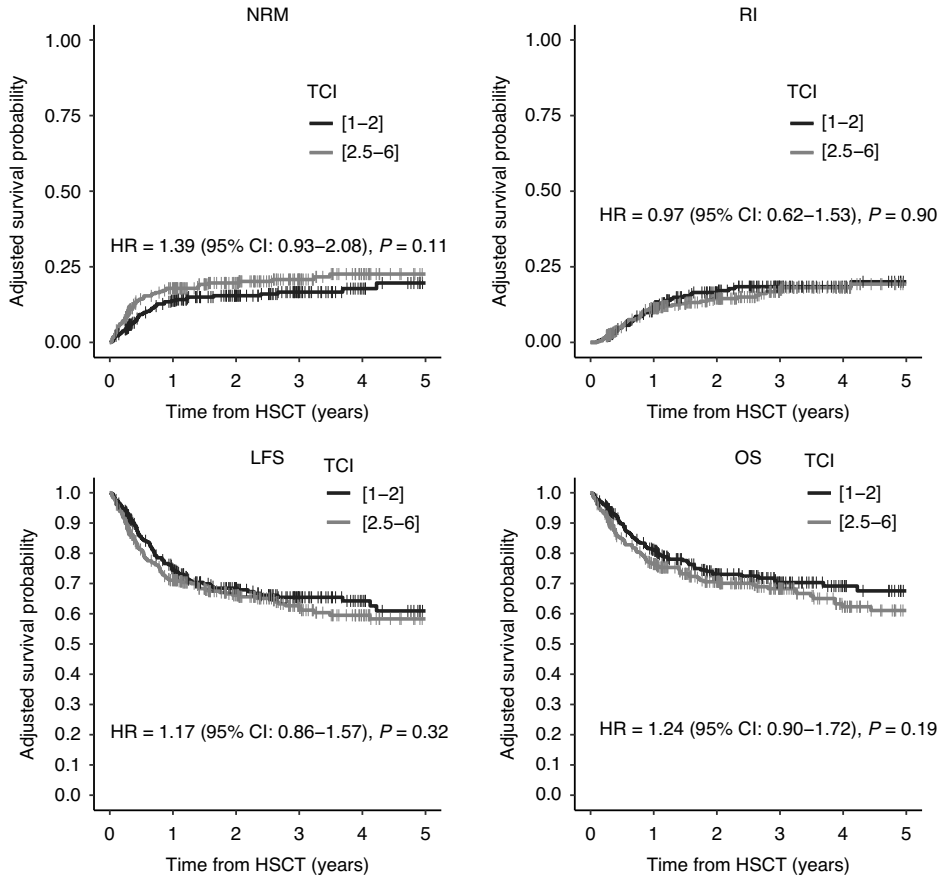

Fig. 1 Adjusted cumulative incidence of non-relapse mortality (NRM) and relapse incidence (RI) and probability of leukemia-free survival (LFS) and overall survival (OS) according to transplant conditioning intensity score for patients with intermediate-risk cytogenetics and FLT3 mutation.

These findings may have significant implications for selecting the appropriate transplant conditioning regimen in this setting.

Our study included a large cohort of AML patients from the EBMT registry who underwent HSCT using PTCy as GvHD prophylaxis. Limitations of the study are inherent in its retrospective and registry-based nature. To minimize heterogeneity, we restricted the analysis to patients with AML in CR1. However, certain variables that could impact relapse and influence the selection of the conditioning regimen, such as MRD status, the number of cycles required to achieve CR, and posttransplant strategies, were either incomplete or unavailable, and thus could not be evaluated in our analysis. In the subset analysis of patients with available MRD, MRD status was reported to the registry based on locally defined assays and cut-offs, without centralized evaluation.

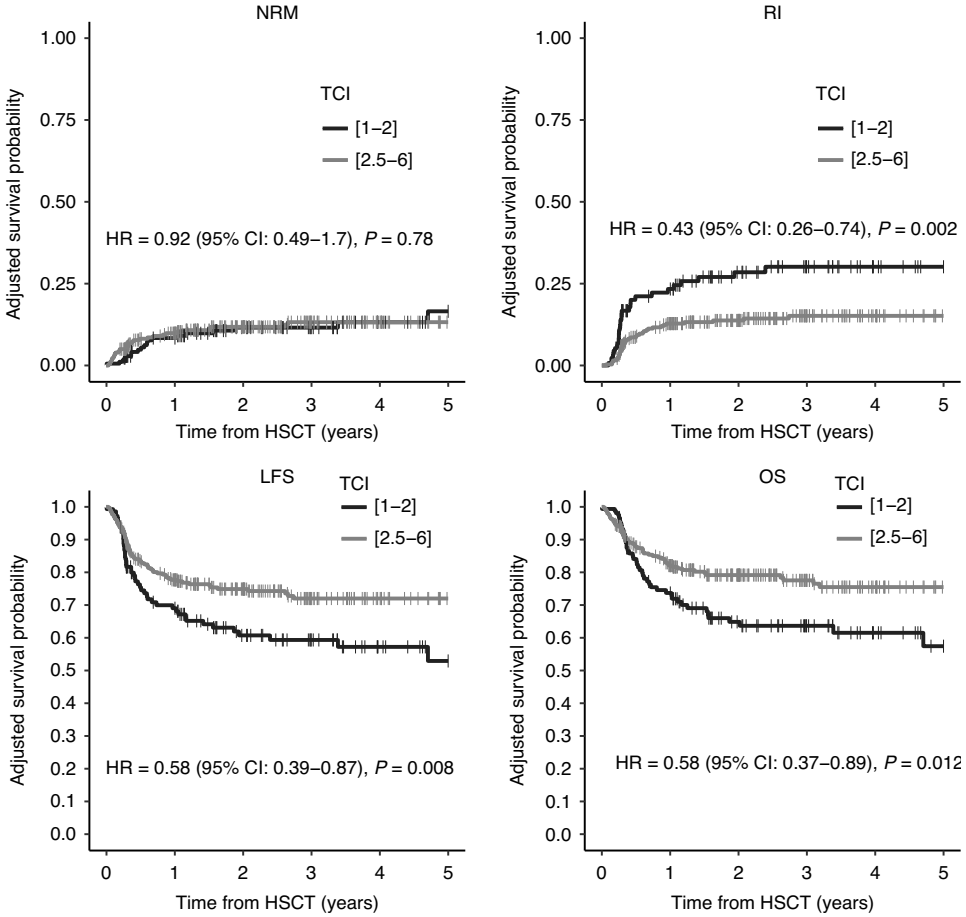

Fig. 2 Adjusted cumulative incidence of non-relapse mortality (NRM) and relapse incidence (RI) and probability of leukemia-free survival (LFS) and overall survival (OS) according to transplant conditioning intensity score for patients with intermediate-risk cytogenetics and wild-type FLT3.

Our study confirms the efficacy of PTCy in HSCT for high-risk AML, offering low rates of acute and chronic GvHD, relapse, and NRM. Not surprisingly, factors such as older age and adverse-risk cytogenetics were associated with decreased survival. Interestingly, unlike previous studies, FLT3-ITD did not negatively impact outcomes. Although the transplant procedure may have played some role in overcoming this previously well recognized adverse-risk feature, this deviation likely reflects the use of FLT3 inhibitors over the past decade, which have improved survival, leading to FLT3-ITD being classified as intermediate-risk in the most recent ELN classification [15]. Furthermore, our study observed similar outcomes after MSD, MUD, or haploidentical HSCT [16–19], showing that PTCy can help overcome the human leukocyte antigen barrier, expanding donor availability and access to HSCT for most patients in need.

Regarding the impact of conditioning intensity on the overall cohort, stratification using MAC/RIC definitions [6] did not show any significant impact on outcomes. This contrasts with two retrospective studies from the ALWP of the EBMT, which described a significant reduction in relapse with MAC that translated into improved survival compared to RIC in the context of PTCy [17, 20]. However, using the TCI score system, we observed a reduced risk of relapse, as previously shown in non-PTCy contexts [2, 4, 21]. Thus, the TCI score system appears to offer more clinically useful stratification of intensity, refining the RIC/MAC classification. Direct comparison between RIC/MAC and TCI scores was not performed and was out of the scope of this study.

The most relevant finding was that the impact of conditioning intensification varied according to cytogenetic risk and FLT3-ITD status. More intense conditioning was beneficial for intermediate-risk cytogenetics with FLT3-ITD due to a reduced risk of relapse. Previous retrospective studies showed no impact of conditioning intensity on relapse in patients with FLT3 mutations [22, 23], although MAC increased antileukemic efficacy in other subsets, such as those with a low/intermediate disease risk index [24] and those with detectable pre-transplant MRD [8]. In view of this information, a recent position statement from the ALWP of the EBMT recommended adapting conditioning based on individual risk factors such as patient age, disease status, or donor type, but not on FLT3 mutations [25]. The use of the TCI score system, which may have better stratified conditioning intensity than the MAC/RIC classification, and the specific focus on PTCy-based GvHD prophylaxis in our study could explain, at least in part, these apparently incongruent findings. However, a recent prospective study confirmed the benefit of post-transplant maintenance with the TKI inhibitor gilteritinib in AML patients with FLT3 mutations and positive MRD [26]. Two key findings emerged from the study. First, participants who received MAC had better OS compared to those who received RIC. Importantly, our analysis demonstrated that the observed protective effect of higher TCI in FLT3+ intermediate-risk patients was independent of MRD status, further underscoring the potential benefit of individualized conditioning approaches in this subset. Our study, however, suggests that higher TCI in the intermediate-risk cytogenetic group was particularly associated with a greater reduction in relapse rates for those with detectable pre-transplant MRD. This observation did not reach statistical significance, likely due to the small sample size of patients with available MRD data and should be interpreted cautiously. Additionally, maintenance therapy showed a positive impact on survival, irrespective of conditioning intensity [26]. Unfortunately, the role of post-transplant FLT3 inhibitor maintenance could not be assessed in our study due to

the lack of availability of such data in the registry. A global retrospective chart review that included the largest European countries, evaluated real-world treatment patterns for FLT3 mutated AML. This study showed that only a minority of patients (18%) received FLT3 inhibitor maintenance therapy [27], likely due to the lack of strong evidence of clinical benefit until recently and drug availability.

In conclusion, cytogenetic and molecular risk should be considered when selecting the intensity of a conditioning regimen for HSCT using PTCy. In this scenario, more intense regimens may be prioritized in intermediate-risk cytogenetics with FLT3-ITD, specially in MRD positive patients, and may probably be avoided in FLT3-wild type. Further studies to confirm these findings are warranted.

DATA AVAILABILITY

The dataset supporting the conclusions of this article are available in the ALWP of the EBMT in Saint Antoine Hospital, Paris.

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AUTHOR CONTRIBUTIONS

JS, ML, AS, MM, SP, and FC: designed the study. ML: performed statistical analysis and helped with the interpretation of the results. JS: wrote the manuscript. JV, DB, JP, JP, JM, GVG, PVDB, HLW, MR, PR, PC, MK, ME, JV, and EB: provided cases for the study. All authors reviewed and approved the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The scientific board of the ALWP of EBMT approved this study. All patients gave written informed consent for the use of their data. All methods were performed in accordance with the relevant guidelines and regulations.

CONSENT FOR PUBLICATION

Not applicable for individual patient data. This is a pooled analysis.

ADDITIONAL INFORMATION

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