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ARTICLE

# Better leukemia-free survival with allogeneic than with autologous HCT in AML patients with isolated trisomy 8: a study from the ALWP of the EBMT

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## Abstract

The indication for performing an allogeneic hematopoietic stem cell transplantation (allo-HCT) in patients with isolated trisomy 8 AML in first complete remission (CR) is still debated. Here, we compared outcomes of such patients given either allo-HCT or autologous (auto)-HCT. Inclusion criteria consisted of adult patients with de novo AML, isolated trisomy 8, first HCT between 2000 and 2018, CR1 at transplantation, and either auto-HCT or allo-HCT with a HLA-identical sibling donor (MSD) or a 10/10 HLA-matched unrelated donor (UD 10/10). A total of 401 patients met the inclusion criteria. They underwent an auto-HCT ($n = 81$), allo-HCT with a MSD ($n = 186$) or allo-HCT with a 10/10 UD ($n = 134$). At 3 years, relapse incidence, nonrelapse mortality and leukemia-free survival (LFS) were 59%, 5%, and 37%, respectively, in auto-HCT recipients; 31% ($P < 0.001$), 14% ($P = 0.04$), and 55% ($P = 0.033$), respectively, in MSD recipients and 29% ($P < 0.001$), 13% ($P = 0.15$), and 59% ($P = 0.03$), respectively, in UD 10/10 recipients. In multivariate analysis, in comparison to auto-HCT, MSD and UD 10/10 were associated with a lower risk of relapse (HR = 0.47, $P < 0.001$ and HR = 0.40, $P < 0.001$, respectively) translating to better LFS (HR = 0.69, $P = 0.04$ and HR = 0.60, $P = 0.03$, respectively). There was also a similar trend for overall survival (HR = 0.73, $P = 0.12$ and HR = 0.65, $P = 0.08$).

## Introduction

Trisomy 8 is one of the most frequent cytogenetic abnormality in acute myeloid leukemia (AML), occurring in 10–15% of AML patients and being the sole genetic abnormality in ~5% of AML [1, 2]. Although allogeneic hematopoietic stem cell transplantation (allo-HCT) has been frequently used in first complete remission (CR) in younger, fit AML patients with isolated trisomy 8 [3, 4], there has been a paucity of data comparing allo-HCT to autologous hematopoietic stem cell transplantation (auto-HCT) or consolidation chemotherapy in these patients [2].

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Specifically, the only large study reported to date assessing the impact of allo-HCT (versus other approaches) included data from 131 patients with trisomy 8 or trisomy 8 plus one additional aberration, and who were treated between 1993 and 2002 in 1 of 8 German AMLSG trials [5]. Among them, 72 patients were eligible for post-remission therapy and received either high-dose cytarabine ($n = 43$), auto-HCT ($n = 10$), or allo-HCT ($n = 19$, including 14 with a HLA-matched sibling donor (MSD) and 5 with an unrelated donor (UD)). In multivariate analysis, allo-HCT was associated with better leukemia-free survival (LFS) but was not a prognostic factor for overall survival (OS).

It is now well established that the curative power of allo-HCT relies largely on immune-meditated graft-versus-leukemia effects [6–8]. Prior studies have observed that CD34+ cells from patients with myelodysplastic syndrome harboring trisomy 8 are more sensitive to Fas-mediated apoptosis [9]. One could argue that this might increase their susceptibility to graft-versus-leukemia effects [10]. In contrast, AML blasts from isolated trisomy 8 patients were shown to exhibit lower expression of several proapoptotic genes than AML blasts from AML patients with a normal karyotype [11], perhaps limiting their susceptibility to be killed by donor immune cells.

Based on these considerations, in the current study we elected to compare transplantation outcomes of AML patients with isolated trisomy 8 in first CR who underwent auto-HCT versus allo-HCT from either a MSD or a 10/10 HLA-matched unrelated (UD 10/10) donor.

## Patients and methods

### Inclusion criteria

This is a retrospective study from the acute leukemia working party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). The EBMT registry is a voluntary working society of more than 600 transplant centers, participants of which are required once a year to report all consecutive HCT and follow-up. Audits are routinely performed to check for data accuracy.

Inclusion criteria included adult patients (defined as ≥18 years of age at transplantation), de novo AML, isolated trisomy 8, first HCT between 2000 and 2018, CR1 at transplantation, and either auto-HCT or allo-HCT with either a MSD or an UD 10/10.

### Definitions

Reduced intensity conditioning (RIC) was defined as regimens combining fludarabine with either <6 Gy total body irradiation (TBI), ≤8 mg/kg busulfan, or ≤140 mg/m$^2$ melphalan, or with other nonmyeloablative drugs as previously reported [12, 13]. Acute and chronic graft-versus-host disease (GVHD) was graded according to previously reported criteria [14].

### Statistical analyses

Analyses were carried out on data from all patients meeting the inclusion/exclusion criteria. Start time was the day of either auto-HCT or allo-HCT for all endpoints. Patients were censored at the time of last follow-up. Relapse was defined as the presence of 5% bone marrow blasts and/or reappearance of the underlying disease. Nonrelapse mortality was defined as death without evidence of relapse or progression. OS was defined as the time from allo-HCT to death, regardless of the cause. Events in the composite endpoint LFS included relapse and death, whichever occurred first. The Kaplan–Meier method was used to estimate the probabilities of OS and LFS.

Cumulative incidence functions were used to estimate relapse incidence and nonrelapse mortality in a competing risk setting. Relapse and death were treated as competing events for analyses assessing cumulative incidences of acute or chronic GVHD.

Univariate analyses were performed using Gray's test for cumulative incidence functions and the log-rank test for OS and LFS.

Multivariate Cox models were used to adjust the comparison of transplantation outcomes between patients given an auto-HCT versus either an allo-HCT with MSD or an an allo-HCT with a UD 10/10 donor. Factors included in the model consisted of time from diagnosis to transplantation, patient age, and year of transplantation. Further, in order to take into account the heterogeneity in the effect of a characteristic or a treatment across centers, we introduced a random effect (also named frailty effect) in Cox multivariate models [15]. Then, the same random effect was shared by all patients within the same center. All tests were two sided. The type I error rate was fixed at 0.05 for determination of factors associated with time to event outcomes. Statistical analyses were performed with SPSS 19 (SPSS Inc, Chicago, IL), and R 3.4.3 (R Development Core Team, Vienna, Austria) software packages.

## Results

### Patients

Data from 401 patients meeting the inclusion/exclusion criteria of the study were included in the current analysis. Eighty-one received an auto-HCT, and 320 an allo-HCT from either a MSD ($n = 186$) or an UD 10/10 ($n = 134$).

Age at transplantation and Karnofsky performance status were comparable in the three groups (Table 1). In contrast, median year of transplantation was earlier in auto-HCT patients (2006) than in MSD (2011) or UD 10/10 (2015) patients (global $P < 0.001$). The stem cell source was peripheral blood stem cells in 94% of auto-HCT patients, 76% of MSD patients, and 85% of UD 10/10 recipients (global $P = 0.002$). The proportion of patients with mutated NPM1 or FLT3-ITD was comparable within the 3 groups. Finally, among allo-HSCT recipients, the proportion of patients given grafts after RIC regimen was 48% in MSD and 58% in UD 10/10 patients, respectively.

## Engraftment and GVHD

Graft failure occurred in one auto-HCT (1%), four MSD (2%), and two UD 10/10 (1%) patients, respectively. Median time to achieve 500 neutrophils was 14 days (IQR 12–17 days) in auto-HCT patients, 16 days (IQR 14–20 days) among MSD patients, and 18 (IQR 15–21 days) among UD 10/10 recipients (global $P < 0.001$).

Among MSD patients, grade II, III and IV acute GVHD was observed in 27 (15%), 7 (4%), and 5 (3%) patients, respectively. In UD 10/10 recipients the figures were 29 (22%), 11 (8%), and 5 (4%), respectively. The 2-year cumulative incidence of chronic GVHD was 42% in MSD recipients and 43% in UD 10/10 patients.

## Relapse and nonrelapse mortality

The 3-year cumulative incidence of relapse was 59% (95% confidence interval (CI): 46–69%) in auto-HCT patients, 31% (95% CI: 24–38%) in MSD recipients ($P = 0.0002$ in comparison to auto-HCT), and 29% (95% CI: 20–38%) in UD 10/10 recipients ($P < 0.0001$ in comparison to auto-HCT) (Fig. 1). These observations held true in FLT3 wild-type patients, in those with wild-type NPM1 and in those with both FLT3 and NPM1 wild-type (Supplementary Table 1). In addition, these observations held also true in patients transplanted from 2000 to 2009 as well as in those transplanted from 2010 to 2018 (Supplementary Table 2). Further, combining data from MSD and UD 10/10 patients, there was no impact of conditioning intensity on the relapse risk ($P = 0.75$). In multivariate analysis, in comparison to auto-HCT, allo-HCT with MSD (Hazard ratio (HR) = 0.47, 95% CI: 0.31–0.72; $P = 0.0006$) or UD 10/10 (HR = 0.40, 95% CI: 0.24–0.67; $P = 0.0005$) were each associated with a lower risk of relapse (Table 2) while there was no interaction between donor type and year of transplantation and the risk of relapse.

The 3-year cumulative incidence of nonrelapse mortality was 5% (95% CI: 1–12%) in auto-HCT patients, 14% (95% CI: 9–20%) in MSD recipients (P = 0.04 in comparison to auto-HCT), and 13% (95% CI: 8–20%) in UD 10/10 recipients ($P = 0.15$ in comparison to auto-HCT) (Fig. 1). These observations held true in patients transplanted from 2000 to 2009 as well as in those transplanted from 2010 to 2018 (Supplementary Table 2). Further, combining data from MSD and UD 10/10 patients, there was no impact of conditioning intensity on nonrelapse mortality ($P = 0.52$). In multivariate analysis, in comparison to auto-HCT, allo-HCT with MSD was associated with a higher nonrelapse mortality (HR = 2.67, 95% CI: 1.0–6.9; $P = 0.04$). Allo-HCT with UD 10/10 showed a trend toward a higher nonrelapse mortality (HR = 2.55, 95% CI: 0.86–7.5; $P = 0.09$) compared with auto-HCT (Table 2). There was no interaction between donor type and year of transplantation and the risk of nonrelapse mortality.

## LFS and OS

The 3-year LFS was 37% (95% CI: 25–48%) in auto-HCT patients, 55% (95% CI: 47–63%) in MSD recipients ($P = 0.03$ in comparison to auto-HCT), and 59% (95% CI: 49–68%) in UD 10/10 recipients ($P = 0.003$ in comparison to auto-HCT) (Fig. 2). These observations held true in FLT3 wild-type patients, in those with wild-type NPM1 and in those with both FLT3 and NPM1 wild-type (Supplementary Table 1). Further, combining data from MSD and UD 10/10 patients, there was no impact of conditioning intensity on LFS ($P = 0.50$). In multivariate analysis, in comparison to auto-HCT, allo-HCT with MSD (HR = 0.69, 95% CI: 0.48–0.99; $P = 0.044$) or UD 10/10 (HR = 0.60, 95% CI: 0.39–0.94; $P = 0.027$) were each associated with better LFS (Table 2). There was no interaction between donor type and year of transplantation and LFS.

The 3-year OS was 50% (95% CI: 38–61%) in auto-HCT patients, 63% (95% CI: 55–70%) in MSD recipients ($P = 0.054$ in comparison to auto-HCT), and 69% (95% CI: 60–78%) in UD 10/10 recipients ($P = 0.01$ in comparison to auto-HCT) (Fig. 2). Further, combining data from MSD and UD 10/10 patients, there was no impact of conditioning intensity on OS ($P = 0.48$). In multivariate analysis, in comparison to auto-HCT, there was no difference between allo-HCT with MSD (HR = 0.73, 95% CI: 0.5–1.1; $P = 0.12$) or with UD 10/10 (HR = 0.65, 95% CI: 0.4–1.1; $P = 0.08$), with respect to OS (Table 2). There was no interaction between donor type and year of transplantation and OS.

Among auto-HCT recipients, the main causes of death were leukemia (56%), infections (19%), and hemorrhage (9%). Among MSD recipients, the main causes of death were leukemia (51%), infections (25%), and GVHD (16%). Among UD 10/10 recipients, the main causes of death were leukemia (38%), GVHD (27%), and infections (22%).

**Table 1** Patient characteristics.

| Variable | Auto-HCT ($n = 81$) | Allo-HCT | | *P* value | |
|---|---|---|---|---|---|
| | | MSD ($n = 186$) | UD 10/10 ($n = 134$) | Auto vs MSD | Auto vs UD 10/10 |
| Follow-up (reverse KM, in months), median (IQR) | 72 (47–124) | 62 (20–98) | 35 (13–57) | 0.20 | <0.001 |
| Patient age at transplant (year), median (Min-Max) | 52 (20–72) | 51 (18–74) | 54 (19–76) | 0.36 | 0.56 |
| Patient sex, *n* (%) | | | | 0.56 | 0.11 |
| Male | 40 (49) | 99 (53) | 81 (60) | | |
| Female | 41 (51) | 87 (47) | 53 (40) | | |
| Karnofsky score, *n* (%) | | | | 0.67 | 1 |
| ≤80 | 1 (1) | 5 (3) | 2 (2) | | |
| >80 | 75 (99) | 157 (97) | 124 (98) | | |
| Missing | 5 | 24 | 8 | | |
| Diagnosis to transplant (in months), median (IQR) | 5.3 (4.3–6.5) | 4.5 (3.8–5.5) | 5 (3.9–6.3) | <0.001 | 0.12 |
| Year of transplantation, median (range) | 2006 (2000–2018) | 2011 (2000–2018) | 2015 (2003–2018) | <0.001 | <0.001 |
| NPM1 | | | | 0.18 | 0.19 |
| Non-mutated | 35 (76) | 92 (85) | 80 (85) | | |
| Mutated | 11 (24) | 16 (15) | 14 (15) | | |
| Missing | 35 | 78 | 40 | | |
| FLT3-ITD, *n* (%) | | | | 0.9 | 0.16 |
| No | 37 (77) | 87 (76) | 67 (66) | | |
| Yes | 11 (23) | 27 (24) | 35 (34) | | |
| Missing | 33 | 72 | 32 | | |
| Female to male, *n* (%) | | | | | |
| No | 81 (100) | 145 (78) | 113 (84) | | |
| Yes | 0 | 40 (22) | 21 (16) | | |
| Missing | 0 | 1 | 0 | | |
| Cell sources, *n* (%) | | | | <0.001 | 0.06 |
| Bone marrow | 5 (6) | 44 (24) | 20 (15) | | |
| PBSC | 75 (94) | 142 (76) | 114 (85) | | |
| Missing | 1 | 0 | 0 | | |
| Conditioning, *n* (%) | | | | | |
| BuCy | 25 (36) | 53 (28) | 18 (13) | | |
| BuFlu | 1 (1) | 53 (28) | 63 (47) | | |
| FluMel | 0 | 18 (10) | 6 (4) | | |
| BuMel | 13 (19) | 0 | 0 | | |
| BuVP16 | 9 (13) | 0 | 0 | | |
| CyTBI | 4 (6) | 17 (9) | 6 (4) | | |
| FluTBI | 0 | 13 (7) | 13 (10) | | |
| Other | 18 (26) | 32 (17) | 28 (21) | | |
| Missing | 11 | 0 | 0 | | |
| Conditioning type, *n* (%) | | | | | |
| Myeloablative | | 96 (52) | 56 (42) | | |
| Reduced intensity [4] | | 90 (48) | 78 (58) | | |
| In vivo TCD, *n* (%) | | | | | |
| No | 81 (100) | 130 (70) | 33 (25) | | |
| Yes | 0 | 55 (30) | 101 (75) | | |
| ATG | | 37 | 94 | | |
| Alemtuzumab | | 18 | 7 | | |
| Missing | 0 | 1 | 0 | | |

*HCT* hematopoietic stem cell transplantation, *Auto-HCT* autologous HCT, *Allo-HCT* allogeneic HCT, *MSD* HLA-matched sibling donor, *UD* 10/10 HLA-matched unrelated donor, *IQR* interquartile range, *PBSC* peripheral blood stem cells, *Bu* busulfan, *Cy*, cyclophosphamide, *Flu* fludarabine, *Mel* melphalan, *TBI* total body irradiation.

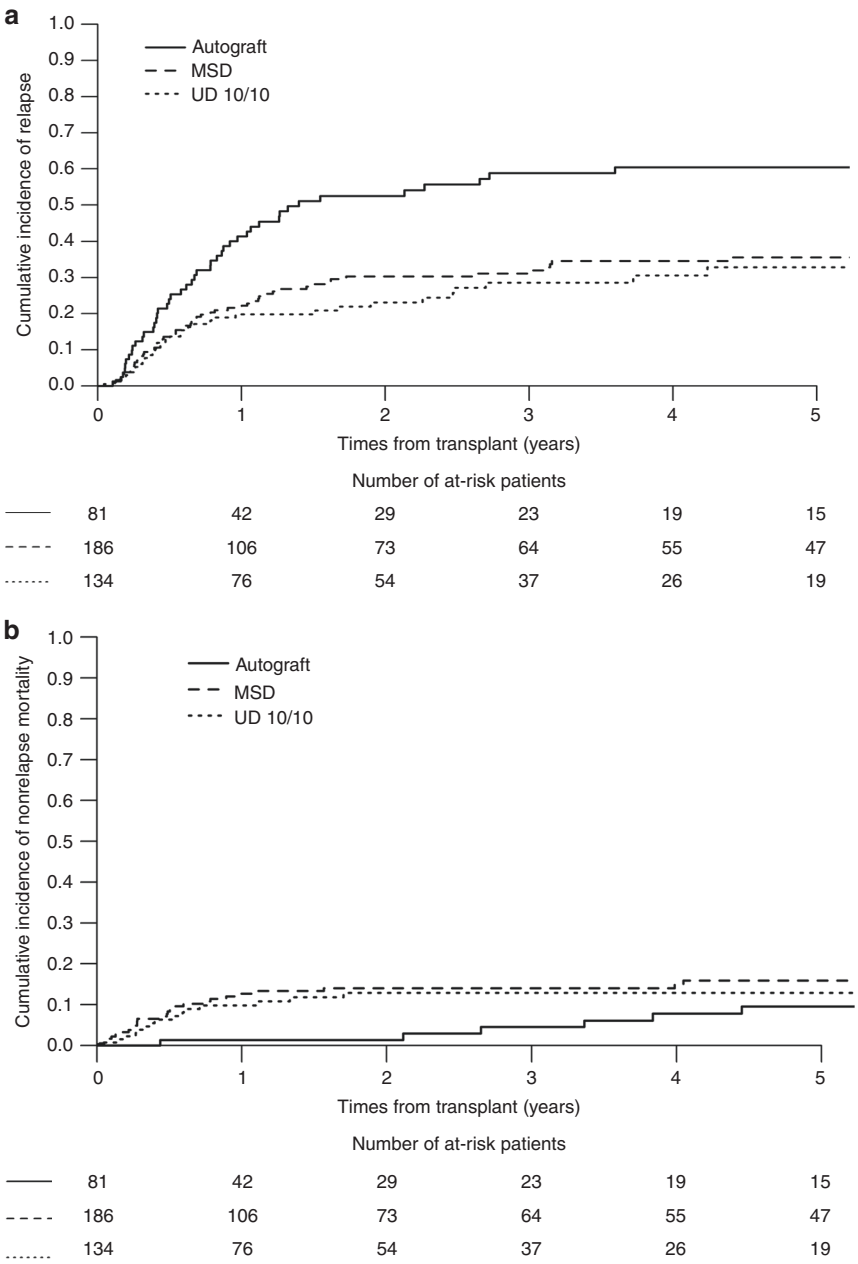


**Fig. 1 Relapse and nonrelapse mortality.** Cumulative incidence of relapse (**a**) and of nonrelapse mortality (**b**) according to the type of transplantation.

## Second transplantation after relapse

A total of 36 patients received a further allo-HCT after relapse. This include 17 out of 46 relapses (37%) in the auto-HCT group, 13 out of 57 relapses (22.8%) in the MSD group, and 6 out of 33 relapses (18.2%) in the UD 10/10 group.

## Discussion

Recent studies have demonstrated that AML blasts from patients with trisomy 8 AML have a specific signature marked in part by an overexpression of genes located in chromosome 8 [11]. Interestingly, several genes involved in the apoptosis pathway are downregulated in trisomy 8 AML blasts [11]. Since apoptosis is important for AML blast killing by both chemotherapy and immune cells [16], there is a strong rationale for comparing auto-HCT versus allo-HCT specifically in patients with trisomy 8 AML.

Given that patients with isolated trisomy 8 AML are classified in the European LeukemiaNet intermediate-risk group, an allo-HCT for fit AML patients with trisomy 8 in first CR with an appropriate donor has been recommended. However, as mentioned above, this recommendation has not yet been clearly supported by data. In the current study, we

**Table 2** Multivariate analysis of transplantation outcomes.

| | Relapse | | NRM | | LFS | | OS | |
|---|---|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Auto-HCT (reference) | 1 | | 1 | | 1 | | | |
| Allo-HCT MSD | 0.47 (0.31–0.72) | **0.0006** | 2.67 (1–6.9) | **0.043** | 0.69 (0.48–0.99) | **0.044** | 0.73 (0.5–1.1) | 0.12 |
| Allo-HCT UD 10/10 | 0.40 (0.24–0.67) | **0.0005** | 2.55 (0.86–7.5) | 0.09 | 0.60 (0.39–0.94) | **0.027** | 0.65 (0.4–1.1) | 0.08 |
| Time diag to HCT (mo) | 0.96 (0.87–1) | 0.35 | 0.97 (0.83–1.1) | 0.74 | 0.96 (0.89–1) | 0.30 | 0.98 (0.9–1.1) | 0.60 |
| Patient age (per 10 y.) | 0.95 (0.84–1.1) | 0.48 | 1.39 (1.1–1.8) | **0.014** | 1.04 (0.93–1.2) | 0.49 | 1.09 (0.96–1.2) | 0.17 |
| Y. of HCT | 1.01 (0.97–1) | 0.74 | 0.92 (0.86–0.99) | **0.022** | 0.98 (0.95–1) | 0.34 | 0.98 (0.94–1) | 0.25 |
| Center (frailty) | | 0.36 | | 0.26 | | 0.36 | | 0.26 |

*NRM* nonrelapse mortality, *LFS* leukemia-free survival, *OS* overall survival, *HCT* hematopoietic stem cell transplantation, *Auto-HCT* autologous HCT, *Allo-HCT* allogeneic HCT, *MSD* HLA-matched sibling donor, *UD* 10/10 HLA-matched unrelated donor, *Y* year.

Statistically significant *p* values are in bold

report on the largest cohort of AML patients with isolated trisomy 8 who underwent either an auto-HCT or an allo-HCT in first CR. Our data clearly demonstrate better LFS with allo-HCT than with auto-HCT, due to a significantly lower risk of relapse. This was true irrespective of donor type (MSD or UD 10/10). There was a similar trend for OS that did not reach statistical significance perhaps because of insufficient statistical power for the OS outcome. In the other hand, more efficient salvage strategies could have been possible among auto-HCT patients. This is illustrated by the observation of a higher proportion of patients in the auto-HCT group than in the two allo-HCT groups receiving a further allo-HCT as treatment for AML relapse. Since quality of life is better after auto-HCT than after allo-HCT [17], further studies are needed to define the role of auto-HCT in subgroups of trisomy 8 AML patients with a lower risk of relapse (such as those without detectable minimal residual disease (MRD) at HCT) and a high risk of non-relapse mortality.

Obviously genetic randomization (i.e., HLA-identical sibling availability versus not) [18–21] or true randomization have remained the gold standard for assessing the role of allo-HCT in AML subtypes. However, since such studies are not likely to be performed in isolated trisomy 8 AML, we must rely on alternative methods for assessing the role of allo-HCT in that setting. Comparison of outcomes between auto-HCT and allo-HCT has been shown to produce valid observations. Furthermore, we were reassured by the fact that the three groups were relatively well balanced for the main AML characteristics (except median time from diagnosis to transplantation which was highest in the auto-HCT group, providing a possible bias in favor of auto-HCT). In order to reduce the risk of further bias as much as possible, we restricted the study to patients in first CR and we excluded patients receiving allo-HCT from alternative donors. Although we did not have MRD data for the patients included in this study, it is unlikely that this introduced a bias in our main observations (lower relapse incidence and better LFS in allo-HCT patients) since patients with detectable MRD at HCT would have been more likely to receive an allo-HCT than an auto-HCT. We however acknowledge that other factors that might have prompted patients to allo-HCT or auto-HCT are missing in the current analyses. These factors include HCT-CI [22] (the data was missing for 53% of the patients included in the current study) as well as extensive molecular data. Finally, there was no center effect identified in the Cox models for any of the outcomes.

Although trisomy 8 blasts have a specific signature, trisomy 8 AMLs are heterogeneous in terms of presence of additional molecular mutations [2]. Some of these molecular mutations might have a stronger prognostic impact than the trisomy 8 itself and might also influence the susceptibility of AML blasts to graft-versus-leukemia effects. Unfortunately, we do not have the full molecular profile for the patients in this study. However, we performed sensitivity analyses in the subgroup of patients with known NPM1 and FLT3-ITD status. Interestingly, although the results should be taken with some caution given the relatively low patient numbers, we observed that allo-HCT remained associated with lower relapse incidence as well as with better LFS than auto-HCT in the subgroup of patients with wild-type FLT3 status. The number of patients with mutated NPM1 or FLT3-ITD per group was unfortunately too low to allow assessing the impact of auto-HCT versus allo-HCT in these subgroups.

Interestingly, the transplantation outcomes of allo-HCT patients were not statistically impacted by the intensity of the conditioning regimen in univariate analyses. This in in contrast to what has been observed in the BMT-CTN 0901 trial [23]. This might indicate that graft-versus-leukemia effects are more important than conditioning intensity in

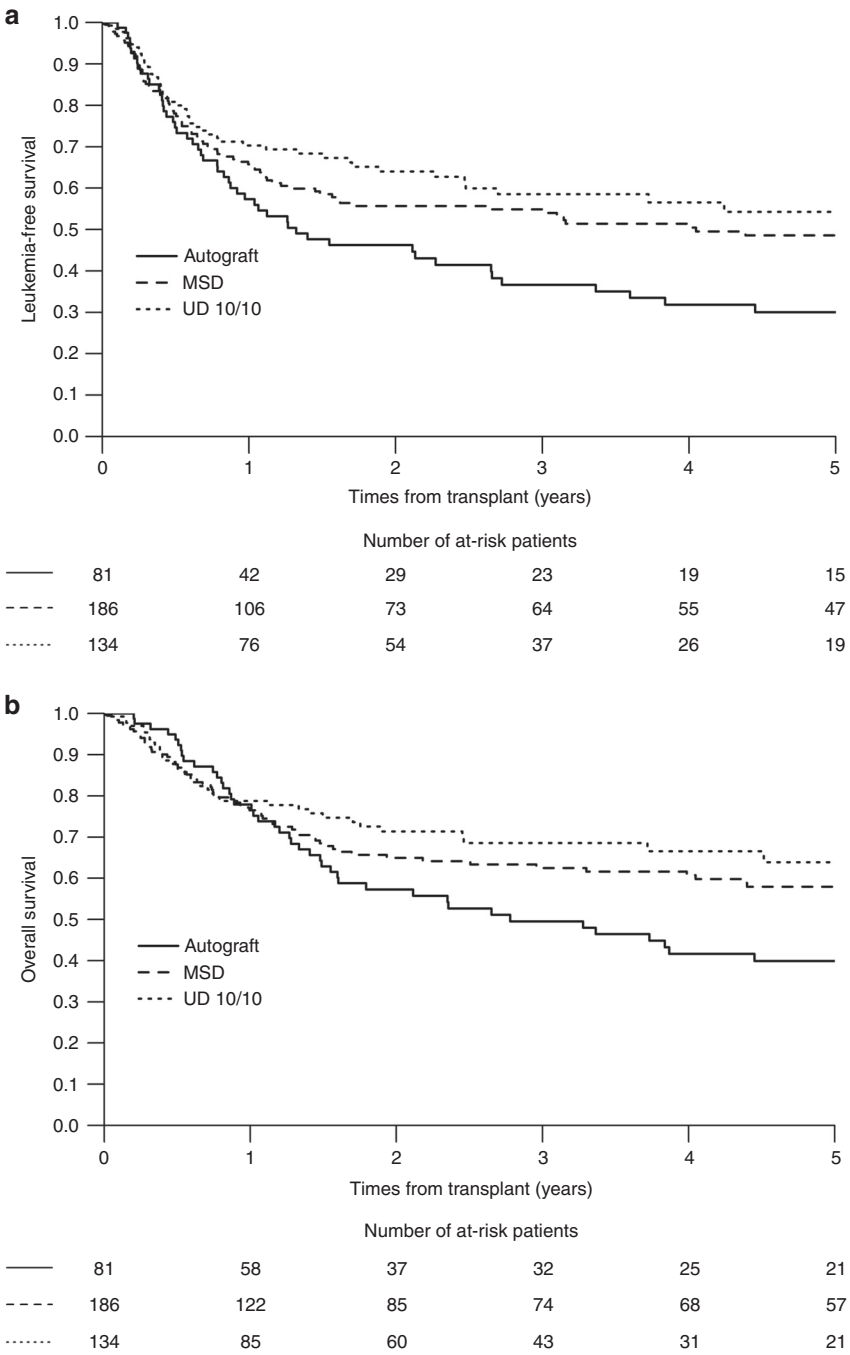


**Fig. 2** LFS and OS according to the type of transplantation.

trisomy 8 AML. However, this hypothesis should be taken with extreme caution given the relatively small number of patients (and thus little power to identify risk factors in subgroups) and the lack of data on molecular abnormalities, HCT-CI and on MRD status in a relatively high proportion of patients in the current study, precluding us to build a robust multivariate model assessing the impact of conditioning intensity in allo-HCT patients with trisomy 8 AML. In addition, there was a high heterogeneity in the conditioning regimens in both the RIC and the myeloablative arms with some regimens classified in the RIC group such as the fludarabine plus melphalan one having stronger anti-leukemic activity according to recent studies [24, 25].

In summary, we report here the largest study to date comparing auto-HCT with allo-HCT in AML patients with isolated trisomy 8 in first CR. We observed that allo-HCT in first CR with either a MSD or a UD 10/10 resulted in better LFS than auto-HCT, due to significantly lower risks of disease relapse.

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**Author contributions** FB wrote the paper, designed the study, and interpreted the data; ML designed the study, analyzed and interpreted the data, and edited the paper; AN and MM designed the study, interpreted the data and edited the paper; DB, MIR, GS, EF, IYA, NCG, and JE reviewed the paper and provided clinical data. All authors approved the final version of the paper.

## Compliance with ethical standards

**Conflict of interest** FB has received travel grants and/or speaker honoraria from Celgene, AbbVie, Novartis, Pfizer and Sanofi. The other authors declare that they have no relevant conflict of interest in relation with this study.

**Ethical approval** The scientific board of the ALWP of the EBMT approved this study

**Informed consent** All patients gave informed consent to participate in retrospective studies

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