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RESEARCH ARTICLE

Impact of the type of anthracycline and of stem cell transplantation in younger patients with acute myeloid leukaemia: Long-term follow up of a phase III study

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Abstract

We provide a long-term evaluation of patients enrolled in the EORTC/GIMEMA AML-10 trial which included a total of 2157 patients, 15-60 years old, randomized to receive either daunorubicin (DNR, 50 mg/m^2), mitoxantrone (MXR, 12 mg/m^2), or idarubicin (IDA, 10 mg/m^2) in addition to standard-dose cytarabine and etoposide for induction chemotherapy and intermediate dose cytarabine for

Frédéric Baron and Fabio Efficace contributed equally to the work.

consolidation. Younger patients who reached complete remission with complete (CR) or incomplete (CRi) recovery were then scheduled to receive an allogeneic hematopoietic stem cell transplantation (HSCT). That was if they had a HLA-identical sibling donor; in all other cases, an autologous HSCT had to be administered. At an 11-year median follow-up, the 5-year, 10-year and 15-year overall survival (OS) rates were 33.2%, 30.1% and 28.0%, respectively. No significant difference between the three randomized groups regarding OS was observed (P = .38). In young patients, 15-45 years old, no treatment difference (P = .89) regarding OS was observed, while in patients 46-60 years old, MXR and IDA groups had a trend for a longer OS as compared to the DNR group (P = .029). Among younger patients without a favorable MRC cytogenetic risk subgroup who achieved a CR/CRi after induction chemotherapy, those with a HLA-identical sibling donor had higher 10-year and 15-year OS rates than those without. In older patients who reached CR/CRi, the long-term outcomes of those with or without a donor was similar. In conclusion, long-term outcomes of the study confirmed similar OS in the three randomized groups in the whole cohort of patients.

1 | INTRODUCTION

Sixty to 80% of 15-60 years old patients with acute myeloid leukemia (AML) achieve a complete remission (CR) after a combination of cytarabine and an anthracycline such as daunorubicin (DNR), mitoxantrone (MXR), or idarubicin (IDA).[1] In order to compare the relative efficacy of these three anthracyclines, the EORTC and GIMEMA groups conducted a large international phase III randomized controlled trial (RCT) which started to enroll patients in 1993.[2] With a median follow-up of 5.6 years, main observations were that the use of different anthracyclines had no impact on outcomes in patients with a HLA-identical sibling donor. However, disease-free survival (DFS) and survival from CR were each longer in the MXR and IDA arms than in the DNR arm in the subgroup of patients without a donor.[2]

Still, the best post-remission treatment for younger AML patients remains debated.[1,3-5] Most prospective studies assessing the impact of having a HLA-identical sibling donor on AML outcomes ("genetic randomization") according to cytogenetic risk have been reported with a relatively short (≈5-6 years) median follow-up.[6-8] This is a significant gap in our knowledge as nonrelapse mortality (NRM) due to complications of chronic graft-vs-host disease may occur well beyond 5 years post transplantation[9] while late relapses are not infrequent in patients not offered an allogeneic transplantation.[10]

We herein provide results of the very long-term follow-up of patients included in the large EORTC/GIMEMA AML-10 trial.[2] The primary objective was to assess the long-term impact of the type of anthracycline given in the induction chemotherapy. The secondary objective was to evaluate, in patients who reached a CR/CRi, the difference in the long-term outcome of those who a HLA-identical donor vs those without such a donor. Subgroup analyses by age and cytogenetic features were investigated.

2 | METHODS

2.1 | Study design

Details of the EORTC/GIMEMA AML-10 trial design have been reported in the initial publication.[2] Briefly, inclusion criteria comprised age 15 to 60 years; diagnosis of primary or secondary AML (including AML occurring after myelodysplastic syndrome) other than French-American-British M3; no evidence of severe concurrent cardiac, pulmonary, neurologic, and metabolic diseases or uncontrolled infections; and adequate liver (serum bilirubin level <2× upper normal limit) and renal (serum creatinine <2× upper normal limit) function tests. Exclusion criteria included blast crisis of chronic myeloid leukemia and AML supervening after other chronic myeloproliferative diseases and other progressive malignant diseases.

Eligile patients were randomized to receive either DNR (50 mg/m^2), MXR (12 mg/m^2), or IDA (10 mg/m^2) on days 1, 3 and 5 in addition to standard-dose cytarabine (25 mg/m^2 bolus followed by 100 mg/m^2 given as a continuous infusion daily for 10 days), and etoposide (100 mg/m^2 on days 1-5) for induction chemotherapy. Randomization was stratified according to centre, age (15 to 45 years vs 46 to 60 years), white blood cell count (<50 vs 50 to 249 vs ≥250 × 10^9/L), and WHO performance status (0 to 2 vs 3 to 4) using a minimization technique.

A second cycle of induction was administered in patients who achieved a partial response (PR). Patients who achieved a CR or a CR with incomplete blood cell counts recovery (CRi) after one or two courses of induction chemotherapy received a consolidation course

with the same anthracycline as in the induction course. They also received intermediate dose cytarabine (500 mg/m^2 every 12 hours as a 2-hour IV infusion on days 1-6). Younger patients, 15 to 45 (or 55, according to centre policy) years old were then scheduled to undergo an allogeneic hematopoietic stem cell transplantation (allo-HSCT) in first CR/CRi if they had a HLA-identical sibling donor. Younger patients without a HLA-identical sibling donor as well as older patients who reached a CR/CRi had to receive an autologous HSCT (auto-HSCT) after consolidation chemotherapy.

Criteria for response and relapse followed the Report of the National Cancer Institute-Sponsored Workshop.[11] The primary end point was overall survival (OS). Secondary end points included CR/CRi rate after induction, the DFS and OS from CR/CRi and the rate of completion of auto- and allo-HSCT.

2.2 | Ethic statement

The study was approved by the ethics committees of the participating institutions and was conducted in accordance with the Declaration of Helsinki. All participants gave their informed consent.

2.3 | Cytogenetic assessment

Cytogenetic examinations were performed at diagnosis. Cytogenetic data were centrally reported according to International System for Cytogenetic Nomenclature (ISCN) and centrally reviewed.[2] For the current analysis, cytogenetics were centrally re-reviewed, described according to International System for Cytogenetic Nomenclature (ISCN),[12] and classified using the refined UK Medical Research Council (MRC) classification[13] as previously reported.[14]

2.4 | Statistical analyses

The duration of OS was calculated from the date of randomization until death, of any cause. The DFS was calculated as the time from CR/CRi until the first relapse or death, whichever occurred first. OS from CR/CRi was calculated as the time from CR/CRi until death.

The Kaplan-Meier method was used to estimate these time-to-event distributions and the Greenwood formula to compute SEs and confidence intervals (CI) for the 10-year OS, OS and DFS from CR/CRi rates.[15] Logrank test was used to compare these time-to-event distributions between groups and the Cox proportional hazards model to compute the hazard ratio (HR) and its corresponding CI.[15]

The estimates of the cumulative incidences of relapse and of death without relapse from the date of CR/CRi, along with their SEs, were based on competing risk methods.[16,17] For the comparisons of cumulative incidences between groups, and for producing forest plots, the Fine-Gray model was used.[18]

The comparison of the three randomized groups regarding OS was performed at a two-sided significance level of 0.05, and the two pairwise comparisons (MXR vs DNR and IDA vs DNR) were performed at the 0.025 alpha level. In patients who reached CR/CRi, the time-to-event outcome comparisons of the randomized groups for donor vs no donor, and for subgroup analyses, the tests were performed at a two-sided significance level of 0.01. For these comparisons, the 99% CIs of the HRs were provided. Same was done when we combined the two experimental arms (IDA and MXR) - unplanned analyses in the protocol - in order to produce forest plots for OS and OS from CR/CRi. In this setting, a test of interaction between some variables (eg, cytogenetic group or age) and the treatment group (IDA/MXR vs DNR) or donor availability in a Cox model was undertaken. Note, SAS 9.4 (SAS Institute Inc. Cary, NC) was used for all statistical analyses.

3 | RESULTS

3.1 | Patients

Between November 1993 and December 1999, a total of 2157 patients were randomly assigned in the trial (Figure S1).[2] Median age was 44 years (range, 15-60 years). Majority of patients had *de novo* AML (n = 2064), the remaining secondary AML (n = 46) or therapy related AML (n = 47). The characteristics of the patients were well balanced between the three randomized treatment groups (Table S1). Results were initially published with a median follow-up of 5.6 years. In the current report, median follow-up was 11 years.

3.2 | Impact of the type of anthracycline in the induction/consolidation chemotherapy

3.2.1 | Overall survival

The overall 5-, 10- and 15-year OS rates were 33.2%, 30.1% and 28.0% respectively. No significant difference between the three randomized groups regarding OS was observed (P = .38; Figure 1A).

We first studied whether there was an impact of age on the association between the type of induction treatment and OS (as mentioned in the material and method section randomization was stratified for patient age: < 46 vs ≥46 years) insuring the integrity of this analysis. Age impacted (test for interaction: P = .13) the treatment difference regarding OS (Figure S2A). In young (< 46 years) patients, the OS was comparable in the three treatment groups (P = .89; Figure 1B). While OS was shorter in patients ≥46 than <46 years old, in older patients OS was prolonged in the MXR and IDA groups, as compared to the DNR group (P = .07 for the three-arm comparison, Figure 1C, and P = .029, for the comparison between MXR and IDA vs DNR patients combined, HR 0.84, 99% CI 0.69-1.03), Figure S2A). Results remained unchanged by further adjustments by age and MRC cytogenetic risk group (data not shown).

As expected, the initial MRC cytogenetic risk group had an important impact on OS. The 10-year OS rates were 56.5%,

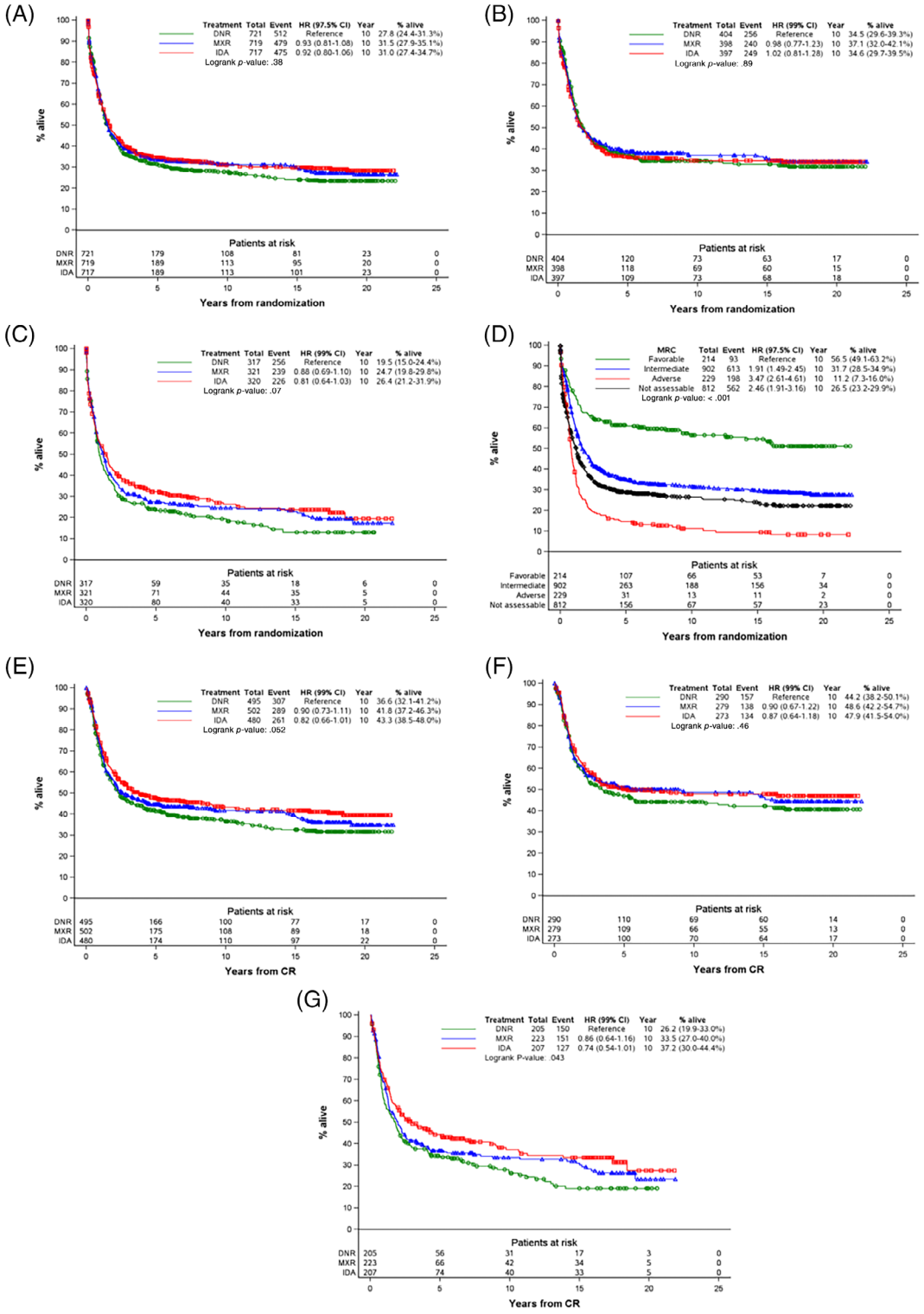

FIGURE 1 Kaplan–Meier plots for A, overall survival (OS) according to the randomized arm in the whole cohort. B, OS according to the randomized arm in patients 15-45 years old. C, OS according to randomized arm in patients 46-60 years old. D, OS according to MRC cytogenetic risk classification. E, OS from CR/CRi in the whole study population. F, OS from CR/CRi according to the randomized arm in patients 15-45 years old. G, OS from CR/CRi according to the randomized arm in patients 46-60 years old

31.7% and 11.2% in the favorable, intermediate and adverse risk group, respectively (Figure 1D). However, MRC cytogenetic risk group had a limited impact on the treatment difference (test for interaction: $P = .26$; Figure 2A), so within each cytogenetic risk subgroup, treatment outcomes were quite homogeneous (Figure S3A-D).

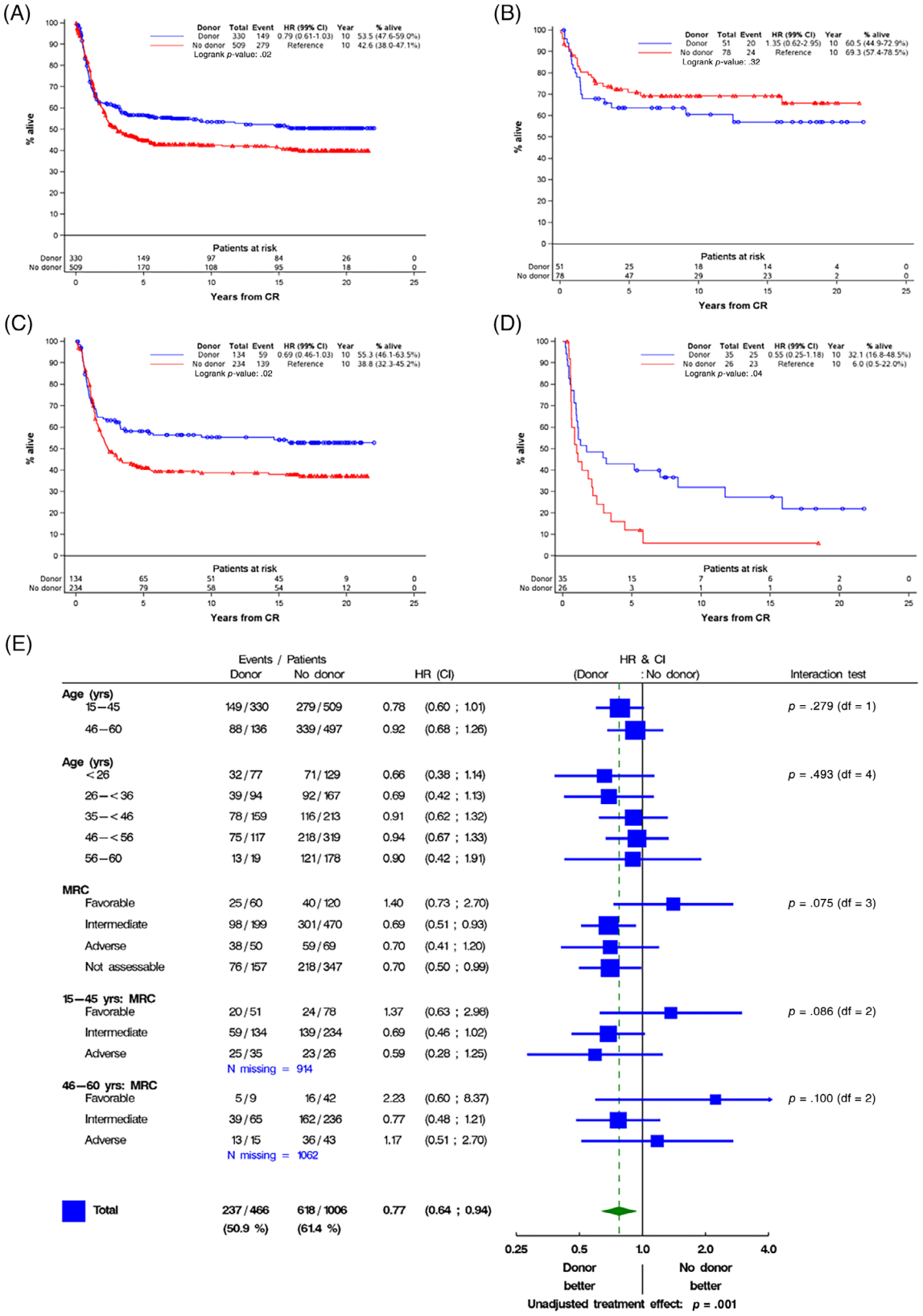

FIGURE 2 Kaplan-Meier plots for overall survival (OS) from CR/CRi according to HLA-identical sibling donor availability A, in patients 15-45 years old. B, in patients 46-60 years old. C, in patients 15-45 years old and MRC favorable cytogenetic risk group; D, in patients 15-45 years old and MRC intermediate cytogenetic risk group; E, Forest plot for OS from CR/CRi according to donor availability: subgroup analysis by MRC cytogenetic risk and age in patients 15-45 years old

3.2.2 | Outcomes in patients who reached a CR/CRi

A CR/CRi after one or two courses of induction chemotherapy was achieved in 69% of DNR patients, 70% of MXR patients, and 67% of IDA patients (Table S2). As expected, patients in the favorable cytogenetic risk group had a higher probability of achieving a CR/CRi (85%) than those in the intermediate (74%) or adverse (52%) MRC cytogenetic risk group.

A HLA-matched sibling donor was found in 466 (32%) of 1472 typed patients who reached a CR/CRi (n = 1477; five patients were not typed). An allo-HSCT was performed in 317 of these 466 patients with a donor (68%). The allo-HSCT rate in patients with a donor was similar in the three randomized groups. As expected, the allo-HSCT rate was higher in patients ≤45 years (71%) than in those 46-60 years old (60%), Tables 1 and 2. Among 1006 patients without a donor, an auto-HSCT was performed less frequently in patients from the MXR (41%) or IDA (44%) arm than in those from the DNR arm (53%) ($P < .01$). This was due to higher rate of withdrawals from toxicity and/or lower success rate of sufficient stem cell collection in the MXR and IDA arms in comparison to the DNR arm.[2] As expected, the auto-HSCT rate was higher in patients ≤45 years (53%) than in those 46-60 years old (40%), Tables 1 and 2. In the latter group, the auto-HSCT rate was 37%, 33% and 49% in the MXR, IDA and DNR groups, respectively.

The 10-year DFS rates from CR/CRi were similar in the three treatment groups: 31.6% in DNR patients, 36.9% in MXR patients, and 36.9% in IDA patients, respectively ($P = .15$)(Table S2). There was no significant impact of randomization arm on the relapse incidence or on the incidence of NRM (Table S2), either. Ten-year OS rate from

TABLE 1 Patient characteristics, treatment applicability and outcomes according to HLA-identical sibling donor availability in patients <46 years of age[a]

	No donor n = 509	Donor n = 330		
Age (years), n (%)				
15- < 26	129 (25)	77 (23)		
26-45	380 (75)	273 (77)		
Assigned HSCT administered, n (%)	267 (53)	235 (71)		
All patients (n = 839)			**HR (99% CI)**	***P* value**
10-year DFS from CR/CRi rate, % (SE%)	36.6 (2.2)	47.7 (2.9)	0.76 (0.59-0.97)	.003*
10-year incidence of relapse, % (SE)	54.4 (2.3)	33.8 (2.7)	0.55 (0.41–0.74)	<.001**
10-year incidence of nonrelapse mortality, % (SE%)	9.0 (1.3)	18.6 (2.2)	1.92 (1.18–3.12)	<.001**
10-year OS from CR/CRi rate, % (SE%)	42.6 (2.3)	53.5 (2.9)	0.79 (0.61–1.03)	.02*
Outcome according to the refined MRC cytogenetic risk group[13]				
10-year DFS from CR/CRi rate, % (SE%)			**HR (99% CI)**	***P* value**
Not assessable (n = 281)	32.1 (4.2)	50.6 (4.9)	0.69 (0.45-1.07)	.03*
Favorable (n = 129)	63.2 (5.5)	54.6 (7.3)	1.20 (0.59-2.45)	.52*
Intermediate (n = 368)	33.2 (3.1)	49.5 (4.5)	0.66 (0.45-0.96)	.004*
Adverse (n = 61)	8.1 (5.5)	25.4 (7.4)	0.62 (0.30-1.31)	.096*
10-year cumulative incidence of relapse, % (SE%)				
Not assessable (n = 281)	57.1 (4.4)	33.3 (4.6)	0.58 (0.34-0.99)	.005**
Favorable (n = 129)	29.1 (5.2)	24.1 (6.1)	0.76 (0.31-1.90)	.45**
Intermediate (n = 368)	58.6 (3.3)	31.9 (4.1)	0.44 (0.27-0.70)	<.001**
Adverse (n = 61)	83.8 (7.4)	54.3 (8.4)	0.47 (0.21-1.05)	.016**
10-year OS from CR/CRi rate, % (SE%)				
Not assessable (n = 281)	41.0 (4.1)	56.3 (4.9)	0.71 (0.45-1.14)	.06*
Favorable (n = 129)	69.3 (5.4)	60.5 (7.2)	1.35 (0.62-2.95)	.32*
Intermediate (n = 368)	38.8 (3.3)	55.3 (4.5)	0.69 (0.46-1.03)	.016*
Adverse (n = 61)	6.0 (5.3)	32.1 (8.4)	0.55 (0.25-1.18)	.04*

Note: Forest plots of the hazard ratio by donor availability, according to age and cytogenetic MRC risk group are provided in the supplemental Figures 4A-D (four endpoints: DFS, incidence of relapse, incidence of death without relapse, OS from CR/CRi).

Abbreviations: CI, confidence interval; CR, complete remission; CRi, CR with incomplete blood recovery; DFS, disease-free survival; HSCT, hematopoietic stem cell transplantation; MRC, UK Medical Research Council; N, number; OS, overall survival; SE, standard error; HR, hazard ratio.

[a]Information missing for three patients.

*P value provided by the logrank test.

**P value provided by the Gray test.

TABLE 2 Patient characteristics, treatment applicability and outcomes according to HLA-identical sibling donor availability in patients 46-60 years of age[a]

	No donor N = 497	Donor N = 136		
Age (years), n (%)				
46-50	163 (33)	71 (52)		
51-60	334 (67)	65 (48)		
Assigned HSCT administered, n (%)	197 (40)	82 (60)		
All CR/CRi patients (n = 635)			**HR (99% CI)**	***P* value**
10-year DFS from CR/CRi rate, % (SE%)	26.1 (2.1)	32.7 (4.2)	0.86 (0.63-1.15)	.18*
10-year incidence of relapse, % (SE)	59.0 (2.3)	42.7 (4.3)	0.66 (0.45–0.97)	.003**
10-year nonrelapse mortality, % (SE%)	15.3 (1.7)	24.7 (3.8)	1.66 (1.00-2.75)	.01**
10-year OS from CR/CRi rate, % (SE%)	31.0 (2.3)	37.0 (4.3)	0.92 (0.67-1.25)	.46*

Note: Forest plots of the hazard ratio by donor availability, according to age and cytogenetic MRC risk group are provided in the supplemental Figures 3A-D (four endpoints: DFS, incidence to relapse, incidence of death without relapse, OS from CR/CRi).

Abbreviations: CI, confidence interval; CR, complete remission; DFS, disease-free survival; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; N, number; OS, overall survival; SE, standard error.

[a]Information missing for two patients.

**P* value provided by the overall logrank test.

***P* value provided by the Gray test.

CR/CRi was 36.7% in DNR patients, 41.8% in MXR patients, and 43.3% in IDA patients, respectively (*P* = .052) (Table S2).

We also analyzed the impact of age, stratification factor for the randomization, on the association between the type of induction treatment and DFS and OS from CR/CRi. In young (≤ 45 years) patients, the DFS from CR/CRi (*P* = .50) as well as OS from CR/CRi (*P* = .46) were comparable in the three treatment groups (Table S2, Figure 1F). In contrast, in older patients, who had globally worse outcomes than younger patients, DFS from CR/CRi (*P* = .12) and OS from CR/CRi (*P* = .04) were prolonged in the MXR and IDA arms as compared to the DNR arm (Table S2, Figure S2B, Figure 1G).

Results were confirmed in multivariate analysis, where the treatment comparison was adjusted by age and MRC cytogenetic risk group (data not shown).

3.3 | Impact of having a HLA-identical sibling donor in patients who reached a CR/CRi

3.3.1 | Patients ≤45 years

The comparison of outcomes following auto- vs allo-HSCT was first assessed in a cohort of 839 patients ≤45 years of age who achieved a CR/CRi after induction chemotherapy, who were HLA-typed, and who mostly were given consolidation chemotherapy. A total of 330 patients had an HLA-identical sibling (donor group) while the remaining 509 patients had not (Table 1). As shown in Figure 2A and in Table 1, the 10-year DFS (HR 0.76, 99% CI 0.59-0.97), and OS from CR/CRi (HR 0.79, 99% CI 0.61-1.03) rates were approximately 10% higher in patients with a donor than in those without. This result was due to a lower incidence of relapse (HR 0.55, 99% CI 0.41-0.74), and despite an increased incidence of NRM (HR 1.92, 99% CI 1.18-3.12) in the donor group (Table 1, forest plots Figure S4). Assessing the impact of donor availability on the outcomes from CR/CRi according to cytogenetic risk group, we observed that patients with a donor had higher 10- and 15- year OS from CR/CRi rates in all but those in the favorable MRC cytogenetic subgroup (Figure 2B-E). Finally, sensitivity analyses using a Cox time-dependent model shows that patients who received allo-HSCT had a longer DFS (HR 0.67, 99% CI 0.47-0.95) and OS from HSCT (HR 0.77, 99% CI 0.54-1.11), compared to those who received auto-HSCT.

3.3.2 | Patients 46-60 years

The impact between allo-HSCT and auto-HSCT was then assessed in a cohort of 635 patients 46-60 years old, who achieved a CR/CRi after induction chemotherapy, and who generally received consolidation chemotherapy. A total of 136 patients had a HLA-identical sibling (donor group) while 497 patients had not (donor availability was unknown in two additional patients) (Table 2). Among patients aged 46-60 years, 635 reached CR/CRi. The outcomes (DFS and OS) of CR/CRi patients with a donor was only marginally prolonged as compared to those without a donor (Figure 2E). Indeed, the positive effect of decreased relapse incidence (HR 0.66, 99% CI 0.45-0.97; *P* = .003) was neutralized by an increased risk of death in CR/CRi (HR 1.66, 99% CI 1.0-2.75; *P* = .013) (Table 2; forest plots in Figure S5). Results remained practically unchanged by adjusting the comparison by age, randomized treatment and MRC cytogenetic risk group (data not shown). Finally, sensitivity analyses using a Cox time-dependent model indicated that similar DFS from HSCT (HR 0.85, 99% CI 0.54-1.33), and OS from HSCT (HR 0.95, 99% CI 0.60-1.51) were obtained in allo-HSCT compared to auto-HSCT recipients.

4 | DISCUSSION

Here we report the long-term follow-up of one of the largest phase III RCT comparing various anthracyclines in the remission induction and consolidation treatment of AML. Further, we assessed the long-term impact of allo-HSCT (in comparison to auto-HSCT) on outcomes in patients who achieved a CR/CRi, using a "genetic randomization" (ie, having a HLA-identical sibling donor or not).

First, with the long-term follow-up of the study, we confirmed that there was no significant difference between the three randomized groups regarding OS in the whole study population. However, we observed a trend for a higher 10-year OS rate in patients randomized to receive MXR or IDA in the induction and consolidation, as compared to those to receive DNR in the subgroup of patients 46 to 60 years of age. This was not the case in younger patients, possibly because a higher proportion of younger patients received an allo-HSCT, offsetting the insufficient efficacy of DNR in this subgroup of patients. Furthermore, in the entire study population, patients randomized in the MXR or IDA arms had also a trend for a higher 10-year OS from CR/CRi rate than those in the DNR arm; the corresponding increase was approximately 7% and 11%, respectively. These findings were not yet clear when the study was first evaluated at a median follow-up of 5.6 years, stressing the importance of reporting long-term follow up of large RCT. Even at long-term follow-up our study confirms the superiority of IDA over DNR regarding OS as reported by a Cochrane meta-analysis of RCTs reported in 2015 including data from 9549 patients.[19] The lower 10-year OS rate observed with DNR could be due to the fact that the dose of DNR used in the AML-10 trial (as well as in several trials included in the above-mentioned meta-analysis) was suboptimal (DNR/IDA ratio of 5). Note, a recent phase III trial observed similar outcomes in AML younger patients randomized to receive induction with cytarabine and high-dose DNR (90 mg/m^2 × 3 days) or IDA (12 mg/m^2 × 3 days).[20] In addition, superior outcomes with higher than standard doses of DNR (90 vs 45 mg/m^2) were reported by the ECOG.[21] Interestingly, a meta-analysis of RCT performed in children, and adults <60 years of age (n = 3382) reported in 2013 that the superiority of IDA for remission induction chemotherapy was restricted to RCT with a DNR/IDA ratio < 5.[22] More recently, the UK-NCRI group reported similar OS but higher 60-day mortality with DNR 90 mg/m^2 in comparison to DNR 60 mg/m^2.[23]

Another observation of our study was that the feasibility of performing an auto-HCT was higher in DNR than in IDA or MXR patients. Interestingly, this did not translate to lower relapse risk in DNR patients despite prior RCT from our group that demonstrated better outcomes with auto-HCT than with additional chemotherapy.[24]

Late NRMs (due in a large part to complications of chronic graft-vs-host disease) are not infrequent beyond 5 years post allo-HSCT,[9] while more late relapses can occur in patients not offered an allo-HSCT.[10,24] In fact, a recent study by the European Society for Blood and Marrow Transplantation has demonstrated that, among AML patients who were disease free at least for 2 years after an auto-HSCT, the 5- and 10-year incidences of relapse from auto-HSCT were 11% and 16%, respectively.[25] Consequently, long-term follow-up of studies assessing the impact of post-remission treatment with allo-HSCT are of major interest. In studies where information on the donor availability at the achievement of CR/CRi is not collected, the Mantel-Byar method[26] or Cox time-dependent model should be used. This is to avoid the guarantee time bias in the outcome comparison of patients who received allo-HSCT, vs the other CR/CRi patients. In order to eliminate the bias of such comparison due to patients' selection, which is stricter for patients allografted, a prospective collection of donor availability in CR/CRi patients is mandatory in well-conducted studies, like RCT. The comparison based on the availability HLA-match donor vs no donor ("genetic randomization") provides an unbiased assessment of the allo-HSCT outcome, so it became the gold standard statistical method in this setting.[27] Here, we observed that, in the group of patients <46 years of age, those with a HLA-identical sibling donor (71% of them received an allo-HSCT) had a lower risk of relapse translating to higher 10-year and 15- year DFS and OS rates from CR/CRi in all patients but those with favorable risk cytogenetics. This occurred despite a higher NRM in patients with a donor. Interestingly, the advantage of having a donor in the subgroup of patients with intermediate-risk cytogenetics was not apparent at the time of the initial report,[6] further stressing the importance of long-term follow-up studies.

While transplant-related mortality has dramatically decreased in the last decades, one could argue on the continued relevance of our donor vs no donor analyses. On the other hand, given the progresses in alternative donor transplantation, the vast majority of patients have nowadays a suitable donor. Consequently, studies comparing allo-HSCT to auto-HSCT and/or chemotherapy using a donor vs no donor genetic randomization are no longer feasible. Since reduction of NRM will result in a higher benefit of having a donor, the message of our paper that having a donor (and thus receiving an allo-HSCT) is beneficial to patients with intermediate and adverse cytogenetic remains true for transplanted patients. It should be however noted that the decision of allo-HCT or not in patients with intermediate-risk cytogenetic is mainly based on FLT3-ITD and NPM1 status of leukemia, as well as on persistence of not or measurable residual disease.

In patients 46 years of age or older, there was no overall benefit of having a donor because the reduction of relapse in this group of patients was offset by a higher NRM. Further, even within the subgroup of patients <46 years old, the advantage of having a donor was more pronounced in very younger patients (15 to 29 years) than in those 30 to 45 years old. These observations might be due to the fact that AML-10 trial was performed 20 years ago, before the development of modern reduced intensity/toxicity or truly nonmyeloablative conditioning regimen for transplantation.[28] Further studies are needed to assess the long-term impact of reduced intensity allo-HSCT in older AML patients with intermediate or poor risk cytogenetic features. Indeed, recent data have observed that post-remission treatment with a nonmyeloablative allo-HSCT might prolong OS in AML patients even above 60 years of age.[29]

In summary, to the best of our knowledge this study reports the first evidence-based data with regard to long-term impact of anthracycline-type and donor availability on outcomes in younger

AML patients. Specifically, long-term follow-up of the EORTC/GIMEMA AML-10 trial confirmed that, overall, similar outcomes were obtained by using either DNR, MXR or IDA (at the studied dosages) during induction and consolidation. In 46-60 years old patients who reached CR/CRi, having a donor or not yielded similar outcomes; however, MXR and IDA tended to provide better results than DNR given at 50 mg/m^2. In addition, in the group of younger patients without favorable cytogenetic features who reached CR/CRi, the long-term outcome was improved when an HLA-identical sibling donor was available.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

F.B, F.E and S.S wrote the manuscript. All authors (FB, FE, LC, PM, ST, C..J..M.H, P..F, M.V, J.P.M, P.C, WvdV, E.L, U.V, X.T, F.L, F.D.R, J.H..B, G..S, J.E.G, B.A, R.V, F.F, M.S.K, L.M, T.dW, R.W, S.A, S.S) participated in study conception and design, data analysis, collection and/or data interpretation and manuscript revising/editing. All authors approved the manuscript and agreed to be accountable for all aspect of the work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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