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CORRESPONDENCE

Similar efficacy outcomes with peripheral blood stem cell versus bone marrow for autologous stem cell transplantation in acute myeloid leukemia: Long-term follow-up of the EORTC-GIMEMA randomized AML-10 trial

To the Editor:

Autologous hematopoietic stem cell transplantation (auto-HSCT) has remained a therapeutic option for selected patients with acute myeloid leukemia (AML) in first remission (CR). In the last survey of the European Society for Blood and Marrow Transplantation (EBMT), 183 auto-HSCTs were performed for AML in first CR in 2021 in EBMT-affiliated centers.[1] Among them, only one used bone marrow (BM) as the sole stem cell source while the remaining cases used peripheral blood stem cells (PBSC) alone or in addition to BM.

In 2009, Gorin et al. reported an important EBMT registry study challenging the preferential use of PBSC as stem cell source for auto-HSCT in AML.[2] In their large study, the use of PBSC instead of BM was associated with higher risk of relapse translating to lower disease-free-survival (DFS), particularly in the subgroup of PBSC recipients who were transplanted within 80 days after CR achievement.

In an attempt at demonstrating whether the use of PBSC versus BM improved DFS after auto-HSCT, the AML-10 EORTC/GIMEMA randomized trial[3] was amended in order to include a second randomization between auto-HSCT with PBSC (APBSCT) versus auto-HSCT with BM (ABMT) in AML patients in CR after one (or two) induction and one consolidation course of chemotherapy, who did not have a fit HLA-identical sibling donor. Detailed study design as well as results after 5 years have been previously reported.[4] However, for the current evaluation, cytogenetics were centrally rereviewed and classified using the refined UK Medical Research Council (MRC) classification.[5] Briefly, a total of 292 patients were randomized: 146 in each treatment arm. The two groups of patients had comparable characteristics (Supplementary Table 1). The median age was 44 years (range, 15–60 years) and the proportions of patients with not assessable, favorable, intermediate, and adverse MRC cytogenetic risks were 22.3%, 19.9%, 51.4%, and 6.5%, respectively. Among patients randomized in the APBSC arm, 104 (71%) patients received an APBSCT while six patients received an ABMT. Among patients randomized in the BM arm, 71 (49%) received an ABMT, 17 patients received an APBSCT, and 22 patients received an ABMT followed by APBSCT rescue (15%) according to the protocol (Supplemental Figure 1).

Here, we report a long-term follow-up analysis of this second randomization. For all efficacy endpoints (DFS, cumulative incidence of relapse and of death, overall survival [OS] from randomization), the intent-to-treat (ITT) principle was used. The median (interquartile range) follow-up was 15.7 (5.2–17.7) years for APBSCT group and 16.0 (7.1–18.1) years for the ABMT group.

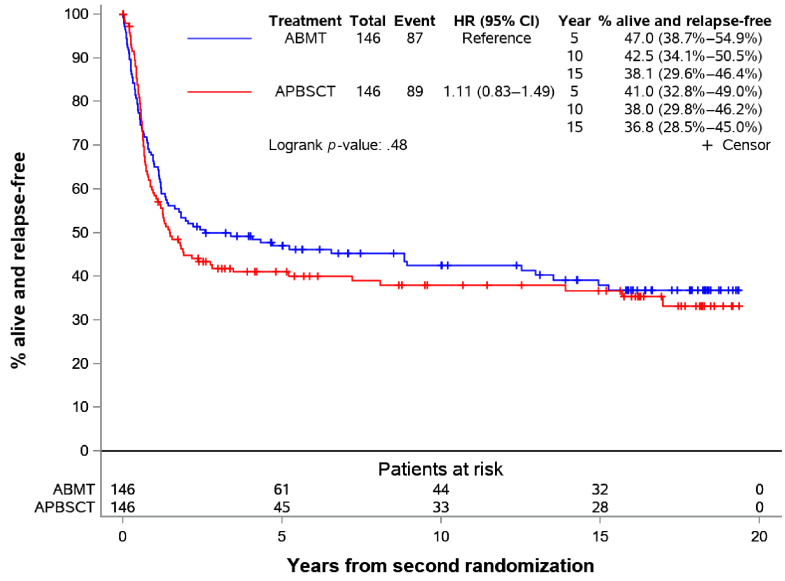
The 5-, 10-, and 15-year DFS rates from second randomization (primary endpoint of the study) were 41.0% (95% confidence interval [CI]: 32.8%–49.0%), 38% (95% CI: 29.8%–46.2%), and 36.8% (95% CI 28.5%–45.0%), respectively, in the APBSCT group versus 47.0% (95% CI: 38.7%–54.9%), 42.5% (95% CI: 34.1%–50.5%), and 38.1% (95% CI: 29.6%–46.4%), respectively, in the ABMT group (hazard ratio [HR], 1.11 [95% CI: 0.83–1.49]; Logrank $p = .48$) (Figure 1A). Therefore, among patients alive and still in first CR 5 years after randomization, the 15-year DFS rate was approximately 90% in APBSCT group ($N = 45$) and 81% in ABMT group ($N = 61$).

The 5-, 10-, and 15-year incidences of relapse from second randomization were 54.6% (95% CI: 46.0%–62.5%), 56.6% (95% CI: 47.8%–64.5%), and 56.6% (95% CI: 47.8%–64.5%), respectively, in the APBSCT group versus 48.2% (95% CI: 39.8%–56.1%), 51.8% (95% CI: 43.1%–59.7%) and 53.9% (95% CI: 45.0%–62.5%), respectively, in the ABMT group (HR, 1.23 [95% CI: 0.77–1.54]; Gray test $p = .45$) (Supplementary Figure 2A). Therefore, among patients alive and still in first CR 5 years after randomization, 15-year relapse incidence was 5% in APBSCT group and 12% in ABMT one. The 15-year cumulative incidence of death without relapse from second randomization was 6.7% (95% CI: 3.0%–12.3%) in the APBSCT group versus 8.0% (95% CI: 4.0%–13.9%) in the ABMT group (HR, 0.95 [95% CI 0.41–2.22]) (Supplementary Figure 2B).

In patients alive and in first CR 2 years after second randomization, the 10-year DFS rate was 84.8% in the APBSCT group ($N = 62$) and 80.5% in the ABMT group ($N = 77$), 10-year incidence of relapse was 11.1% and 16.4%, respectively, and 10-year incidence of death without relapse was 4.2% and 3.1%, respectively.

The 5-, 10-, and 15-year OS rates from second randomization were 49.6% (95% CI: 41.0%–57.6%), 42.5% (95% CI: 33.7%–50.9%), and 41.2% (95% CI: 32.4%–49.8%) in APBSCT patients versus 54.5% (95% CI: 46.1%–62.2%), 48.3% (95% CI: 39.7%–56.4%), and 43.7% (95% CI: 34.8%–52.2%) in the ABMT patients versus (HR, 1.11 [95% CI: 0.81–1.51]; Logrank $p = .52$) (Figure 1B). Therefore, among patients alive and still in first CR 5 years after randomization, 15-year OS rate was approximately 89% in APBSCT group versus 84% in the ABMT one.

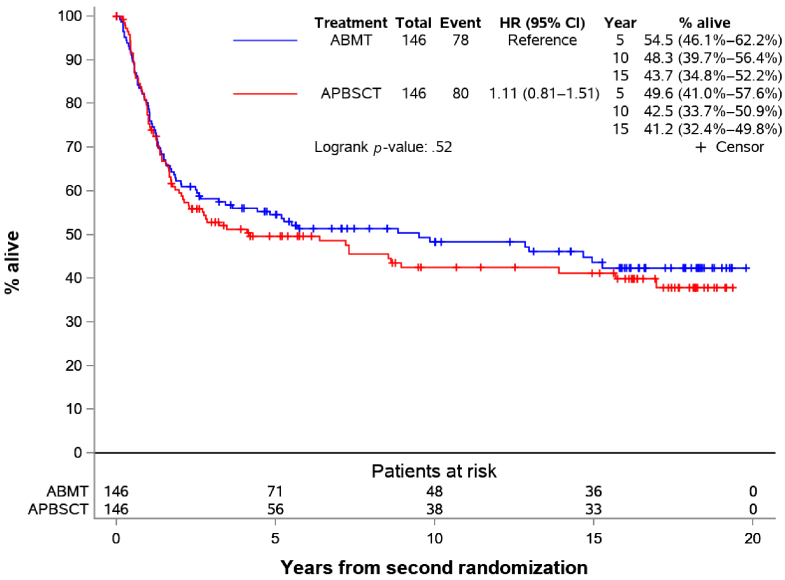
(A)



	Event/Total	Median (95% CI) [a]	Hazard Ratio (95% CI) [b]	Survival Estimates (95% CI) [a]	*p*-Value
Treatment					.48 [c]
ABMT	87/146	2.6 (1.3–12.5)	Reference	5: 47.0 (38.7%–54.9%) 10: 42.5 (34.1%–50.5%) 15: 38.1 (29.6%–46.4%)	
APBSCT	89/146	1.5 (1.0–2.8)	1.11 (0.83–1.49)	5: 41.0 (32.8%–49.0%) 10: 38.0 (29.8%–46.2%) 15: 36.8 (28.5%–45.0%)	

[a]Kaplan-Meier method. [b]Cox model. [c]Logrank test.

(B)



	Event/Total	Median (95% CI) [a]	Hazard Ratio (95% CI) [b]	Survival Estimates (95% CI) [a]	*p*-Value
Treatment					.52 [c]
ABMT	78/146	9.5 (2.6–NE)	Reference	5: 54.5 (46.1%–62.2%) 10: 48.3 (39.7%–56.4%) 15: 43.7 (34.8%–52.2%)	
APBSCT	80/146	4.2 (2.1–13.9)	1.11 (0.81–1.51)	5: 49.6 (41.0%–57.6%) 10: 42.5 (33.7%–50.9%) 15: 41.2 (32.4%–49.8%)	

[a]Kaplan-Meier method. [b]Cox model. [c]Logrank test.

FIGURE 1 Disease-free survival (A) and overall survival (B) according to the randomized group. ABMT, autologous bone marrow transplantation; APBSCT, autologous peripheral blood stem cell transplantation; CI, confidence interval; HR, hazard ratio.

Forest plot analyses indicated that none of the initial characteristics, like age, sex, MRC cytogenetic risk group and white blood cell (WBC) had a clear impact on the treatment difference regarding DFS (Supplementary Figure 3A) and OS (Supplementary Figure 3B).

Multivariable analyses for DFS, cumulative incidence of relapse and OS (Table 1, Model 2), confirmed the results indicated above and are summarized in Table 1, Model 1: there was no significant differences between the two randomized treatment groups. Among 291 patients included in these analyses, the following features were significantly or marginally significantly associated with these three outcomes: cytogenetic adverse and intermediate risk as compared with favorable risk group, and male. On the other hand, the other initial characteristics (age, initial WBC), the number of cycles to reach CR, and the first randomized anthracycline group, were not significantly associated with these three outcomes. However, the group of patients with high WBC (≥25) and of those who required several cycles of chemotherapy to reach CR was very limited (Supplementary Table 1).

We have repeated the analyses in those 234 patients (APBSCT arm [$N = 118$] and ABMT arm [$N = 116$]), with information on mobilized stem cell harvests (supplementary Table 2). As a surrogate marker for the mobilizing capacity after consolidation treatment, we used the highest $CD34^+$ cell yield of a single apheresis procedure during the first mobilization round, which may consist of several apheresis procedures. The highest $CD34^+$ cell harvest remained a strong prognostic factor, as previously reported.[4] Indeed, the group of patients ($N = 61$) with the highest (H) yield ($\geq 7 \times 10^6$ $CD34^+$ cells/kg) had the worse outcome as compared with those patients ($N = 34$) with the lowest yield ($H < 1 \times 10^6$ $CD34^+$ cells/kg), regarding DFS (at 10 years: 20.1% vs. 64.6%, HR = 3.11, $p = .0005$), cumulative incidence of relapse (at 10 years: 78.3% vs. 29.5%, HR = 4.48, $p = .0001$), and OS (at 10 years: 24.3% vs. 64.4%, HR = 2.35, $p = .0086$) (Supplementary Table 3). Those with no harvest ($N = 52$) and those ($N = 88$) with an intermediate highest yield ($1 \leq H < 7 \times 10^6$ $CD34^+$ cells/kg), had an intermediate prognosis (Supplementary Figure 4). Similar results were observed by considering the total number of $CD34^+$ cells harvested during the first apheresis round (*data not shown*).

The long-term analysis of this prospective randomized trial, using the ITT principle, provided important observations. First, among patients in CR 5 years after randomization, approximately 10%–15% of the patients died in the following 10 years. Among patients in first CR 2 years after randomization, approximately 15% of the patients relapsed in the following 8 years and almost 5% died without relapse. This is consistent with a recent large study of the EBMT showing that

TABLE 1 Results of univariable model (model 1) and multivariable model (model 2) for three outcomes: Disease-free survival, cumulative incidence of relapse, overall survival.

	Disease-free survival				Cumulative incidence of relapse				Overall survival			
Endpoint	**HR**	**95% CI**		***p*-Value**	**HR**	**95% CI**		***p*-Value**	**HR**	**95% CI**		***p*-Value**
Model 1												
Second randomization: APBSCT versus ABMT	1.11	0.82	1.49	.50	1.12	0.82	1.54	.47	1.10	0.81	1.51	.54
Model 2												
Second randomization: APBSCT versus ABMT	1.12	0.83	1.52	.46	1.16	0.84	1.60	.37	1.16	0.84	1.59	.37
MRC: Not assessable versus favorable	3.59	2.07	6.2	<.0001	3.62	1.99	6.59	<.0001	3.68	2.02	6.69	<.0001
MRC: Intermediate[a] versus favorable	2.69	1.63	4.45	.0001	2.63	1.53	4.53	.0005	2.66	1.55	4.58	.0004
MRC: Adverse versus favorable	5.90	2.94	11.80	<.0001	7.02	3.39	14.53	<.0001	6.98	3.37	14.5	<.0001
Age (years): 26–45 versus 15–25	0.82	0.50	1.35	.43	0.95	0.55	1.65	.86	0.95	0.55	1.64	.86
Age (years): 46–60 versus 15–25	1.21	0.75	1.95	.44	1.52	0.90	2.57	.12	1.50	0.89	2.54	.13
Sex: male versus female	1.41	1.04	1.91	.029	1.33	0.96	1.85	.085	1.36	0.98	1.88	.064
WBC ($\times 10^9$/L): ≥25 versus <25	1.24	0.92	1.69	.16	1.22	0.86	1.73	.26	1.29	0.93	1.78	.12
Number of cycles to reach CR: >1 versus 1	1.35	0.82	2.25	.24	1.62	0.91	2.89	.10	1.64	0.98	2.74	.060
First randomization: IDA versus DNR	0.85	0.58	1.24	.39	1.60	0.95	2.68	.075	0.78	0.52	1.16	.21
First randomization: MTZ versus DNR	0.72	0.50	1.04	.083	0.80	0.53	1.19	.26	0.76	0.52	1.12	.16

Note: For disease-free survival and overall survival, the Cox model was used, and for cumulative incidence of relapse, the Fine-Gray model was used. A total of 291 patients were these models; among the 292 patients randomized, one patient, in the APBSCT was excluded from the analyses as no information on sex (male or female) was reported in case report forms. There were 175 patients who reported a disease-free survival event (154 relapses and 21 deaths without proven relapse), and 157 patients who died.

Abbreviations: ABMT, autologous bone marrow transplantation; APBSCT, autologous peripheral blood stem cell transplantation; CI, confidence interval; CR, complete remission; DNR, daunorubicin; H, highest count of $CD34^+$ cells $\times 10^6$/kg body weight during a single apheresis; HR, hazard ratio; IDA, idarubicin; MRC, Medical Research Council; MTZ, mitoxantrone; WBC, white blood cell.

[a]Patients with unknown cytogenetic data were classified as "inclusive" in a separate cytogenetic risk group.

among AML patients who received auto-HSCT in first or second CR, and being still alive in CR 2-years after auto-HSCT, 16% of the patients experienced disease relapse and another 8% died without relapse in the following 8 years.[6]

A second important information was that comparable DFS, OS, and relapse incidence were observed among patients randomized in the APBSCT versus the ABMT arm. It should however be stressed that 15% of the patients randomized in the ABMT arm received APBSCT rescue as per protocol. Interestingly, long-term relapse incidence was not impacted either by the autologous stem cell source. These data are unique given that we report here the long-term follow-up of the only published study which randomized AML patients between ABMT versus APBSCT.

Thirdly, the current study confirmed the results of prior retrospective studies showing that higher counts of $CD34^{+}$ cells in the apheresis product, probably having a higher contamination of the product by residual AML cells, were associated with an increased relapse incidence.

Fourthly, a central rereview of the MRC cytogenetic risk group showed that it was of a major prognostic factor in our study.

In summary, we report here the long-term follow-up of the only prospective randomized trial of APBSCT versus ABMT in AML patients in first CR. We observed that among patients alive and still in CR 5 years after planned auto-HSCT, approximately 10%–15% of the patients died in the following 10 years. This stresses the need for long-term close surveillance of AML patients after auto-HSCT. Further, long-term follow-up of the trial confirms that APBSCT was comparable with ABMT in term of DFS and OS.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data request should be addressed via the link https://www.eortc.org/data-sharing/.

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SUPPORTING INFORMATION

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