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ORIGINAL ARTICLE

High numbers of mobilized CD34+ cells collected in AML in first remission are associated with high relapse risk irrespective of treatment with autologous peripheral blood SCT or autologous BMT

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The faster hematopoietic recovery after autologous peripheral blood SCT (APBSCT) in patients with AML may be offset by an increased relapse risk as compared with autologous BMT (ABMT). The EORTC and GIMEMA Leukemia Groups conducted a trial (AML-10) in which they compared, as second randomization, APBSCT and ABMT in first CR patients without an HLA compatible donor. A total of 292 patients were randomized. The 5-year DFS rate was 41% in the APBSCT arm and 46% in the ABMT arm with a hazard ratio (HR) of 1.17; 95% confidence interval = 0.85–1.59; $P = 0.34$. The 5-year cumulative relapse incidence was 56% vs 49% ($P = 0.26$), and the 5-year OS 50% and 55% ($P = 0.6$) in the APBSCT and ABMT groups, respectively. APBSCT was associated with significantly faster recovery of neutrophils and platelets, shorter duration of hospitalization, reduced need of transfusion packed RBC and less days of intravenous antibiotics. In both treatment groups, higher numbers of mobilized CD34+ cells were associated with a significantly higher relapse risk irrespective of the treatment given after the mobilization. Randomization between APBSCT and ABMT did not result in significantly different outcomes in terms of DFS, OS and relapse incidence.

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INTRODUCTION

Patients with AML in first CR (CR-1) usually receive post-remission therapy to prevent relapse. Three treatment modalities are generally applied: intensive consolidation chemotherapy, hematopoietic SCT or maintenance chemotherapy.[1,2] Auto-SCT (ASCT) resulted in a better outcome in terms of disease-free survival (DFS) and relapse rate when compared with intensive consolidation chemotherapy, but usually OS was not significantly different, partly due to a better response to second line therapy after relapse.[1–3] Nevertheless, several study groups consider ASCT as the treatment of choice for intermediate and high-risk AML patients if allo-SCT is not applicable.[1,4–9] BM is the traditional stem cell source for ASCT, but BM stem cells have been associated with insufficient harvests and prolonged hematopoietic hypoplasias in a substantial number of patients with AML leading to low compliance with this treatment modality.[1,2] In most studies comparing ASCT with chemotherapy autologous BM has been used as the source of stem cells.[10] Twenty-five years ago,[11] G-CSF-mobilized blood stem cells were introduced for autologous peripheral blood SCT (APBSCT) leading to faster hematopoietic recovery presumably due to higher numbers of infused CD34+ cells. A high relapse rate after ASCT using high numbers of PBSC has been reported in single arm studies.[12,13] A retrospective study by the European Group for Blood and Marrow Transplantation (EBMT) showed a higher relapse rate after using mobilized blood stem cells compared with BM stem cells.[14] A subsequent retrospective registry study by the EBMT showed an association between a high number of infused peripheral blood CD34+ cells and an increased relapse rate and lower leukemia-free survival.[15] The question is whether the increased relapse risk was because of higher numbers of infused leukemic stem cells in these patients or whether the number of collected stem cells just reflected the sensitivity of the patient to chemotherapy resulting from genetic polymorphisms to metabolize the administered cytotoxic drugs.[16]

The outcome after ASCT using peripheral blood rather than BM stem cells has not been compared prospectively before. To address the issue of a potentially increased relapse rate risk after APBSCT, we amended the AML-10 trial[4] for patients who were candidates for ASCT in 1994. Patients in CR after remission-induction chemotherapy were randomized between APBSCT and autologous BMT (ABMT).

SUBJECTS AND METHODS

In the randomized phase III AML-10 trial of the EORTC and GIMEMA Leukemia Groups,[4] patients achieving CR after one or two induction

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courses with either DNR, mitoxantrone or idarubicin in combination with cytarabine and etoposide in a 3+10+5 regimen, were treated subsequently by one consolidation course. The consolidation course consisted of intermediate dose cytarabine (500 mg/m^2, twice daily for 6 days) and 3 days of the randomized intercalating agent. Mobilization and collection of autologous PBSC was scheduled during the recovery phase of the consolidation course. Lenograstim (150 μg/m^2) was given by daily s.c. injections from day 20 of the consolidation course until completion of the blood stem cell collections. Collections took place on 1 to 5 consecutive days as soon as the leukocyte counts exceeded 2×10^9/L or the CD34+ cells in the blood exceeded 2×10^7/L. The total blood stem cell harvest should contain at least 2×10^6/kg body weight CD34+ cells. Patients who were randomized for ABMT underwent subsequently a BM harvesting procedure. The randomization between APBSCT and ABMT took place 28 days after the start of the consolidation course irrespective of the outcome of the mobilization. The study was approved by the ethics committees of the participating institutions and was conducted in accordance with the Declaration of Helsinki.

Randomization was performed centrally (EORTC Data Center, Brussels, Belgium) using the minimization technique. Stratification factors were: institution, age (15–45 vs 46–60 years), treatment arm of first randomization, number of induction courses to reach a CR, cytogenetic groups at diagnosis (Table 1).

All the patients were transplanted with unpurged stem cells after BM ablative conditioning consisting of CY/TBI or CY/BU (Table 1). No prophylactic hematopoietic growth factors were allowed after stem cell infusion.

Primary endpoint was DFS. Secondary endpoints were time to relapse, death without relapse, OS and hematologic recovery in terms of recovery of neutrophils and platelets, duration of hospitalization, the need of i.v. antibiotics or packed RBC.

Criteria for evaluation

CALGB criteria of response and of relapse were used.

RESULTS

A total of 292 patients, registered by 43 institutions, were included in this study: 146 in each arm. The two treatment groups were well balanced regarding all characteristics, as indicated in Table 1. The median age was 44 years, ranging from 15–60 years.

Stem cell harvest of the randomized stem cell source was successful in 105 patients (72%) of the APBSCT arm and in 86 patients (59%) of the ABMT arm. In the APBSCT arm, 103 patients received APBSCT (72%), six patients received ABMT (4%), one patient received APBSCT combined with matched unrelated donor allograft rescue (1%) and 29 patients (20%) received no further treatment, including 23 patients with no stem cell harvest. In the ABMT arm, 71 patients received ABMT only (49%), 22 patients received ABMT followed by APBSCT rescue (15%) according to protocol, 17 patients received APBSCT (12%) and 28 patients (19%) received no further treatment, including 12 patients with no stem cell harvest (Figure 1). The mean (± s.d.) interval between start of the consolidation course and the date of ASCT was longer in the ABMT arm (103 ±50 days) than in the APBSCT arm (89 ± 43 days). This may explain why only two patients relapsed before the planned APBSCT and 12 patients before the planned ABMT (Figure 1).

At the time of evaluation, 130 patients were still alive and in CR-1, 150 patients have relapsed (79 in the APBSCT arm vs 71 in the ABMT arm) and 12 patients have died in CR-1 (5 in the APBSCT arm vs 7 in the ABMT arm). The DFS showed no significant difference between the two treatment arms (Figure 2); hazard ratio (HR) of APBSCT vs ABMT was 1.16, 95% confidence interval (CI) = 0.85–1.58 (Table 2). Results remained unchanged by adjusting the treatment comparison by factors, which appeared to be of independent prognostic importance (cytogenetic features, performance status at first randomization, number of cycles to reach CR) and other factors, used as stratification of randomization (WBC and initial randomized treatment). Model 3 (see Supplementary Table 1) which took into consideration all the independent factors, except the number of mobilized CD34+ cells, showed for DFS HR of 1.17; 95% CI = 0.85–1.59 ($P = 0.34$) and for OS a HR of 1.11; 95% CI = 0.79–1.56 ($P = 0.55$). The 5-year cumulative relapse incidence was 56% in the APBSCT arm vs 49% in the ABMT arm, and the relapse risk HR of APBSCT vs ABMT was 1.20 (log-rank $P = 0.26$). The 5-year cumulative death in CR incidence was 4% (APBSCT arm) vs 5% (ABMT arm) and the death in CR rate HR was 0.72.

A total of 135 patients died: 69 in the APBSCT arm and 66 in the ABMT arm. The OS was similar between the two arms (Figure 2); HR 1.09, 95% CI = 0.78–1.53 (Table 2). Results remained unchanged by adjusting the analysis by cytogenetic features and number of cycles to reach CR, which were of prognostic importance, and also by performance status, WBC and initial randomized treatment (see Supplementary Table 1).

Table 1. Patient characteristics of 292 randomized patients by treatment group

	Treatment group	
	APBSCT	*ABMT*
	No. (%)	*No. (%)*
Total	146 (100)	*N* = 146 (100)
Age at diagnosis, years		
15–25	20 (13.7)	16 (11.0)
26–45	59 (40.4)	60 (41.4)
46–60	67 (45.9)	70 (47.9)
Sex		
Male	69 (47.3)	76 (52.1)
Female	76 (52.0)	70 (47.9)
Missing	1 (0.7)	—
Performance status at 1st randomization		
0	61 (41.8)	54 (37.0)
1	68 (46.6)	74 (50.7)
2	15 (10.3)	16 (11.0)
3–4	1 (0.7)	1 (0.7)
Missing	1 (0.7)	1 (0.7)
White cell count $\times 10^9$*/L at diagnosis*		
<25	91 (62.3)	86 (58.9)
25 to <100	46 (31.5)	49 (33.6)
$\geqslant 100$	9 (6.2)	11 (7.5)
Cytogenetic group[a]		
Good	26 (17.8)	32 (21.9)
Intermediate	44 (30.1)	42 (28.8)
Poor	11 (7.5)	15 (10.3)
Other	18 (12.3)	16 (10.6)
Inconclusive	47 (32.2)	41 (28.1)
Numbers of cycles to reach CR		
1	135 (92.5)	132 (90.4)
>1	7 (4.8)	9 (6.1)
Successful stem cell harvest[b]	105 (71.9)	86 (58.9)
Type of conditioning[c]	103	93
TBI based	65	55
Chemotherapy only	38	36

Abbreviations: ABMT = autologous BMT; APBSCT = autologous peripheral blood SCT. [a]Good prognosis: *t*(8;21), inv(16), del(16), *t*(16;16); intermediate prognosis: NN, -Y or -X only; poor prognosis:-7/7q-, − 5/5q-, complex, +8, Ph +; others: other cytogenetic characteristics; inconclusive: technical failure or not performed [b]Successful harvest of stem cell source in the randomized arm. [c]Only autografted patients with sufficient data.

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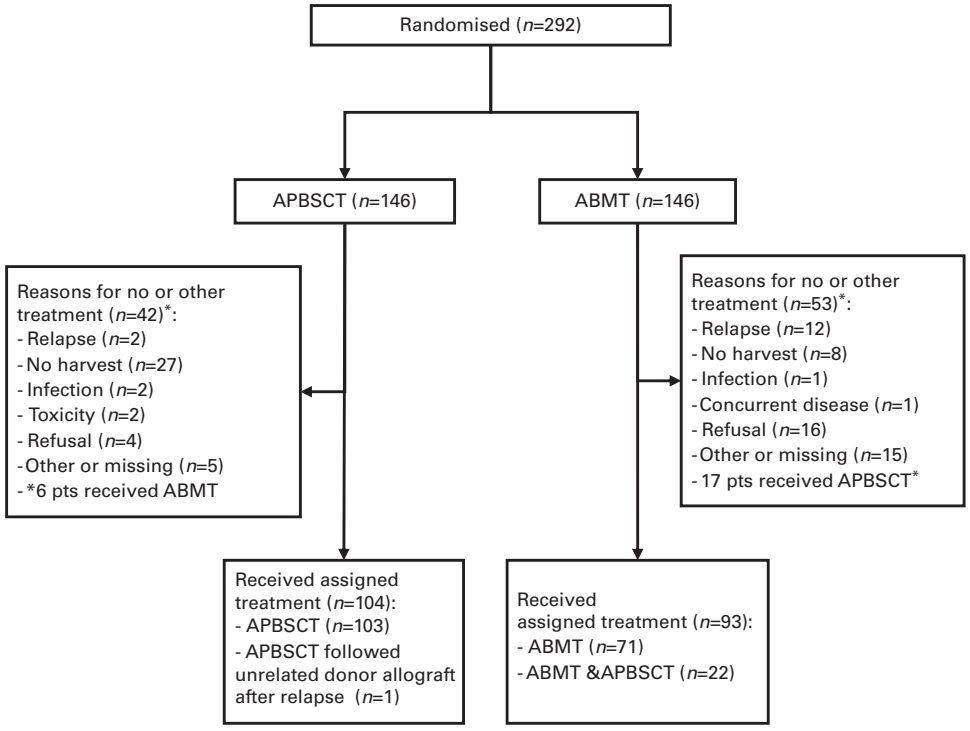

Figure 1. Flow diagram of actual treatment given. Details of the treatment are given in the Subjects and Methods section.

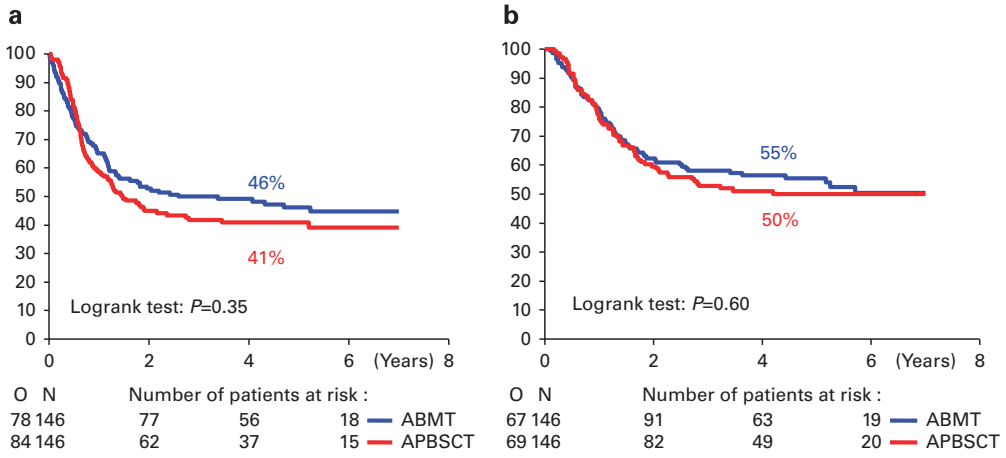

Figure 2. Duration of disease-free survival (**a**) and survival (**b**) from randomization in patients randomized to receiving mobilized autologous PBSC (red curve) or autologous BM stem cells (blue curve). N = number of patients; O = observed number of events (relapse or death in CR-1); *P*-value given by the log-rank test.

Hematopoietic recovery and associated variables

The hematopoietic recovery was faster in the APBSCT arm: the median number of days to reach $\geqslant 20\times10^9$/L platelets was 23 days in the APBSCT arm vs 77 days in the ABMT arm ($P < 0.0001$; see also Supplementary Table 2). The median number of days to reach $\geqslant 0.5\times10^9$/L neutrophils was 22 days vs 42 days, respectively ($P < 0.0001$). The short hypoplasia after PB CD34+ cell reinfusion resulted in a significantly lower median number of transfusions: three vs eight packs of RBC and 5 vs 34 packs of platelets, and shorter median number of 11 days on intravenous antibiotics in the APBSCT arm vs 19 days in the ABMT arm ($P < 0.0001$). The median duration of hospitalization was 24 days vs 41 days, respectively ($P < 0.0001$).

Impact of numbers of mobilized CD34+ cells on outcome

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 (Table 2). The total number of CD34+ cells collected during all subsequent mobilization rounds could not be used for this purpose as this was influenced by the predetermined target of 2×10^6 CD34+ cells/kg (Table 3).

Previously,[17] we analyzed the DFS according to the number of collected CD34+ cells, irrespective of the treatment administered to the patient. In the present study, we compared the outcome (DFS and DFI) in both treatment arms: APBSCT vs ABMT on an intention-to-treat basis after adjustment for the number of CD34+

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Table 2. The distribution of first randomization (type of anthracycline) and the harvests, defined by highest count of CD34+ cells $\times 10^6$/kg, by randomized treatment group (APBSCT vs ABMT) and by treatment actually given in the two randomized groups

	Treatment group		*Treatment given*		*Treatment not given*	
	APBSCT	*ABMT*	*APBSCT*	*ABMT*	*APBSCT*	*ABMT*
Total, *n* (%)	146	146	104	93	42	53
First randomization						
DNR	51(35)	46 (31)	9 (21)	18 (34)	42 (40)	28 (30)
MTZ	51 (35)	52 (36)	19 (45)	16 (30)	32 (31)	36 (39)
IDA	44 (30)	48 (33)	14 (33)	19 (36)	30 (29)	29 (31)
N with harvests (%)	118	116	87	76	31	40
Harvests[a]						
No harvest	28 (23.7)	24 (20.7)	4 (15)	13 (17)	24 (77)	11 (28)
H < 1	15 (12.7)	18 (15.5)	11 (13)	15 (20)	4 (13)	3 (8)
1 ⩽ H < 7	42 (35.6)	46 (39.7)	39 (45)	33 (43)	3 (10)	13 (33)
H ⩾ 7	33 (28.0)	28 (24.1)	33 (38)	15 (20)	0	13 (33)
5-year DFS (%)	41	46	44	57	42	30
HR: APBSCT vs ABMT[b]	1.17 (0.85–1.59)		1.68 (1.07–2.62)		0.65 (0.88–1.11)	
5-year survival (%)	50	55	53	68	50	40
HR: APBSCT vs ABMT[b]	1.11 (0.79–1.56)		1.53 (0.94–2.49)		0.68 (0.39–1.10)	

Abbreviations: ABMT = autologous BMT; APBSCT = autologous peripheral blood SCT; DFS = disease-free survival; HR = hazard ratio; IDA = idarubicin; MTZ = mitoxantrone. [a]Highest (H) count of CD34+ cells $\times 10^6$/kg body weight during a single apheresis. [b]Hazard ratio adjusted for all relevant prognostic factors, including the drugs of the first randomization and the number of CD34+ cells in the harvests (95% confidence intervals).

Table 3. Stem cell harvests in each treatment group

	Treatment group	
	APBSCT	*ABMT*
	No. (%)	*No. (%)*
Total	118 (100)	116 (100)
Number of BM harvests in first CR		
1	9 (7.6)	84 (72.4)
2	—	6 (5.2)
No BM harvest	109 (92.4)	26 (22.4)
Number of rounds of PBSC aphereses		
0	12 (10.2)	17 (14.7)
1	80 (67.8)	94 (81.0)
2	14 (11.9)	5 (4.3)
3	12 (10.2)	—

Abbreviations: ABMT = autologous BMT; APBSCT = autologous peripheral blood SCT.

cells, cytogenetics and number of courses to reach CR, age and treatment to remission-induction treatment (Table 4; for more details, see Supplementary Table 1). The number of CD34+ cells, cytogenetic risk group and number of courses to reach CR were independent prognostic factors. For exploratory purposes, we performed subgroup analyses regarding DFS according to the two first factors using forest plot technique. This subgroup analysis showed a consistent lack of treatment difference between APBSCT and ABMT (Figure 3). On the other hand, the magnitude of the CD34+ cell yield during the first apheresis was of prognostic importance in each randomized arm, and in each transplanted group (ABMT only, APBSCT only, ABMT ± APBSCT, APBSCT ± BMT), as those with a highest yield ($>7\times10^6$/kg) appeared to have the worst outcome (data not shown).

Impact of administered treatment on outcome

We analyzed the treatment outcome also according to the administered treatment, since an important proportion of patients did not receive the allocated treatment according to the randomization (Figure 1). More patients in the APBSCT arm received the allocated treatment compared with the ABMT arm: 104 and 93 patients, respectively. Twenty-two patients in the ABMT arm received an APBSCT rescue after a median of 35 days (range: 0–195 days) after the BM stem cell infusion. The OS was not significantly different ($P = 0.64$) when comparing the 71 patients who received BM alone vs the 22 patients who received APSC also as rescue with an HR of 1.2 (95% CI = 0.56–2.55).

The 5-year DFS of patients who received treatment according to randomization was 40% in the APBSCT arm compared with 55% in the ABMT arm with an HR of 1.68, 95% CI = 1.13–2.5 ($P = 0.009$). The HR decreased to 1.4, 95% CI = 0.94–2.14 ($P = 0.09$) after adjusting the treatment comparison by factors which appeared to be of independent prognostic importance, including harvest after mobilization and the drugs of the first randomization (Table 2). The corresponding 5-year survival was 50% and 65%, respectively (Figure 4a) with an HR of APBSCT vs ABMT of 1.50, 95% CI = 0.97–2.3 ($P = 0.065$). After adjusting the treatment outcome for all relevant factors, the HR remained stable with 1.53, 95% CI = 0.94–2.49 ($P = 0.086$).

In patients randomized for APBSCT (43 patients) and ABMT 53 (patients) and who did not receive their assigned stem cell source, the distribution of usual prognostic factors was quite similar (Table 1). However, patients in the APBSCT arm had received significantly less frequently DNR: 21% vs 40% in the patients group who received APBSCT according to randomization (Table 2). In addition, the percentage of patients with failed mobilization was significantly higher, 77% vs 4% in the group who did not receive APBSCT according to randomization compared with the group who did receive APBSCT as planned.

The 5-year DFS of the patients who did not receive treatment according to the randomization was 42% in the APBSCT arm compared with 30% in the ABMT arm with an estimated HR of 0.65, 95% CI = 0.88–1.11 ($P = 0.11$). After adjusting the treatment

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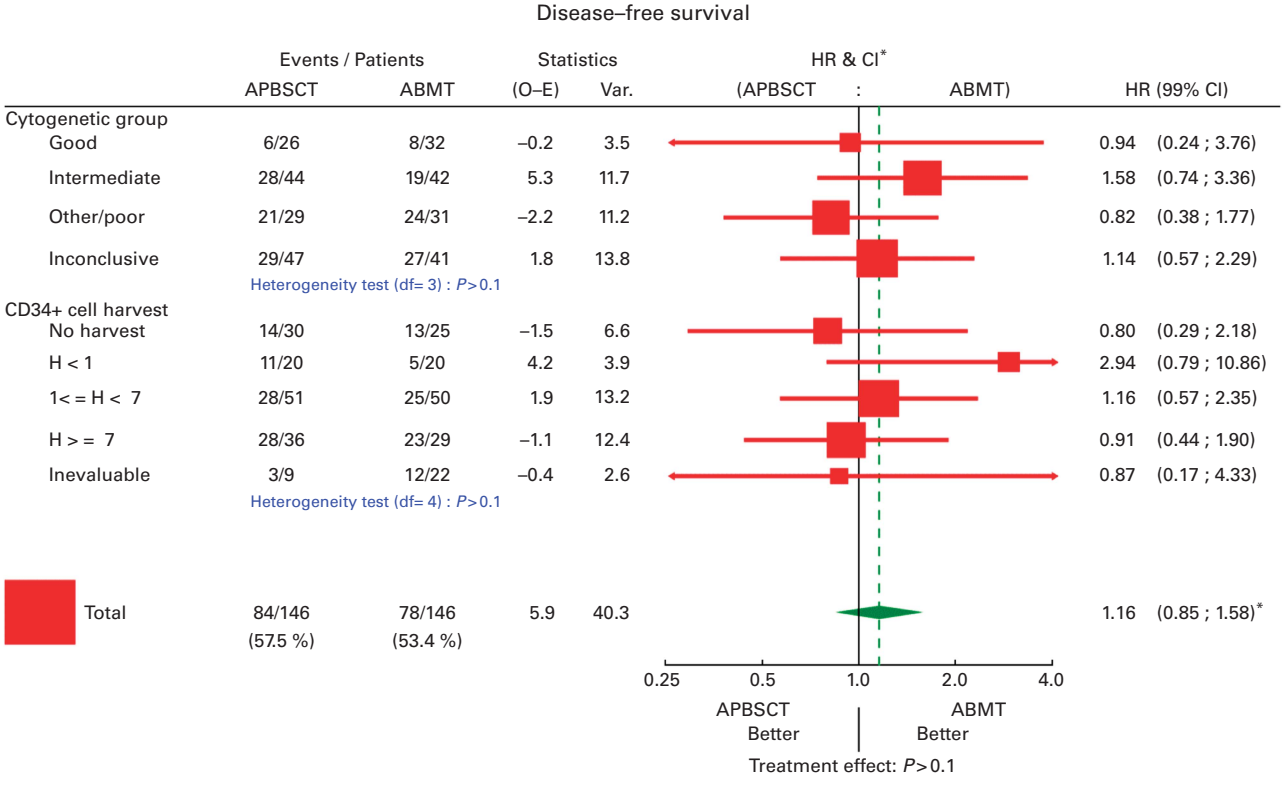
Table 4. Results of the multivariate Cox model regarding disease-free survival (DFS) and disease-free interval (DFI)

Parameter	*Endpoint*			
	DFS		*DFI*	
	HR (95% CI)	P-*value*	*HR (95% CI)*	P-*value*
Model 1				
Randomized group: APBSCT vs ABMT	1.07 (0.76–1.52)	0.69	1.08 (0.75–1.54)	0.68
Model 2				
Randomized group: APBSCT vs ABMT	0.94 (0.66–1.33)	0.72	0.92 (0.64–1.33)	0.66
CD34+ cell harvest: no harvest vs H < 1	1.82 (0.86–3.83)	0.12	2.06 (0.95–4.48)	0.07
CD34+ cell harvest: 1 ⩽ H < 7 vs H < 1	1.86 (0.94–3.69)	0.08	1.98 (0.96–4.06)	0.06
CD34+ cell harvest: H ⩾ 7 vs H < 1	3.62 (1.8–7.29)	0.0003	4.34 (2.09–9.01)	< 0.0001
Cytogenetics group: inconclusive[a] vs good	3.5 (1.77–6.92)	0.0003	2.969 (1.485–5.936)	0.0021
Cytogenetics group: intermediate vs good	3.01 (1.53–5.92)	0.001	2.963 (1.503–5.842)	0.0017
Cytogenetics group: other/poor vs good	4.29 (2.14–8.59)	< 0.0001	4.059 (2.01–8.195)	< 0.0001
Age (years): 26–45 vs < 26	0.66 (0.37–1.17)	0.16	0.63 (0.35–1.12)	0.12
Age (years): 46–60 vs < 26	0.89 (0.51–1.54)	0.68	0.75 (0.43–1.31)	0.32
Numbers of cycles to reach CR: 2 vs 1	2.46 (1.34–4.5)	0.004	2.41 (1.31–4.44)	0.005
First randomization: MTZ vs DNR	0.95 (0.6–1.5)	0.82	0.89 (0.55–1.43)	0.62
First randomization: IDA vs DNR	1.27 (0.83–1.96)	0.27	1.25 (0.81–1.95)	0.32

Abbreviations: ABMT = autologous BMT; APBSCT = autologous peripheral blood SCT; CI = confidence interval; HR = hazard ratio; IDA = idarubicin; MTZ = mitoxantrone. [a]Patients with unknown cytogenetic data were classified as 'inclusive' in a separate cytogenetic risk group. For preparatory models of Model 2, see models 1/3 in Supplementary Table 1. H: highest count of CD34+ cells × 10^6/kg body weight during a single apheresis. A total of 234 patients were included in these models restricted to patients with information on mobilized stem cell harvests (118 patients in the APBSCT arm and 116 patients in the ABMT arm).



*95% CI for totals and subtotals, 99% CI elsewhere

Figure 3. Subgroup analyses regarding disease-free survival comparing the APBSCT and ABMT arms according to cytogenetic and CD34+ cell yield using forest plot technique.

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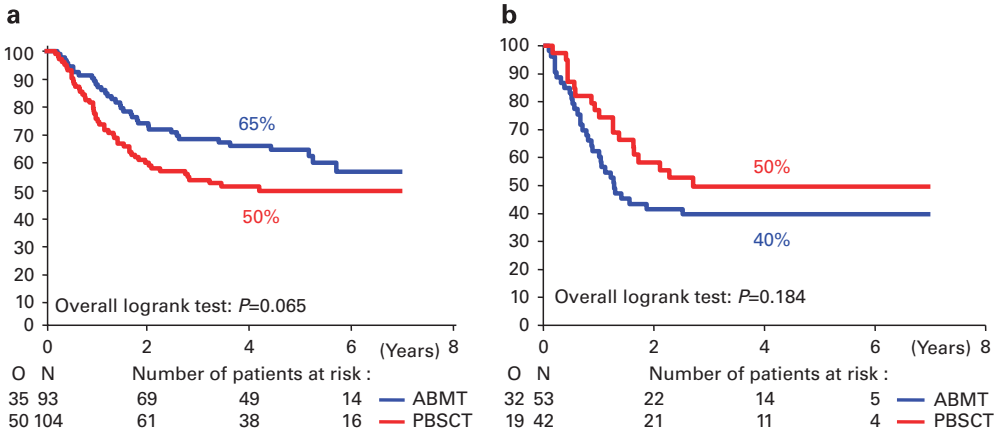

Figure 4. Duration of OS from randomization in patients randomized to receiving mobilized autologous PBSC (red curve) or autologous BM stem cells (blue curve): (**a**) patients who received treatment according to randomization; (**b**) patients who received other treatment or no treatment (see flow diagram in Figure 1). N = number of patients; O = observed number of events (death); *P*-value given by the log-rank test.

comparison by factors which appeared to be of independent prognostic importance, including harvest after mobilization and the drugs of the first randomization (Table 2), the HR was 0.52, 95% CI = 0.29–0.94 ($P = 0.028$). The corresponding 5-year survival was 50% and 40%, respectively (Figure 4b), with a hazard ratio of APBSCT vs ABMT of 0.68, 95% CI = 0.39–1.20 ($P = 0.18$). After adjusting the treatment outcome for all relevant factors, the HR decreased further to 0.58, 95% CI = 0.31–1.10 ($P = 0.09$).

DISCUSSION

APBSCT is an appealing alternative to ABMT in view of the faster hematopoietic recovery after APBSCT, but an increased relapse risk after APBSCT has remained a serious concern. Therefore, we amended the AML-10 trial to address this issue.[4] The two investigational drugs in this study had a significant ($P < 0.001$) impact on the application of ASCT. ASCT was performed in 54% of cases who received the first consolidation course in the DNR arm vs 41% and 47% in mitoxantrone and idarubicin, respectively. This difference was due to a lower success rate of stem cell collection in the mitoxantrone and idarubicin arms,[4,17] comparable to the 49% success rate in a recent study.[18] Studies with higher success rates have randomized patients at a later time point after recovery of the last consolidation course excluding patients with prolonged hypoplasias and early relapses.[3] The randomization of the present study occurred 28 days after the start of the consolidation course, leading to a successful ASCT rate of 69% and 61% in the APBSCT and ABMT arm, respectively.

Our trial shows no significant differences in terms of DFS (main endpoint), OS and incidence of relapse between the APBSCT and ABMT arms, when analyzed on an intention-to-treat analysis. This lack of significant difference might be due to a true low treatment difference, to a low statistical power (for example, 50% for detecting an 11% increase in 5-year DFS rate), as only 162 DFS were reported in this study (see sample size calculations in Supplementary Data), and/or a relatively low rate of SCT performed according to randomization. However, duration of aplasia, transfusion need, days on i.v. antibiotics or duration of hospitalization were significantly favorable in APBSCT arm. The mortality incidence in first CR was low in both arms: 4% and 5% after APBSCT and ABMT, respectively. Other retrospective studies[13,14] showed higher relapse rates after APBSCT after reinfusion of higher numbers of leukemic CD34+ cells.[14] In a previous analysis,[17] we showed that high numbers of mobilized CD34+ cells were an important, independent poor prognostic factor. Our present study confirms the shorter DFS in the group with high numbers of mobilized CD34+ cells when compared with low numbers of mobilized CD34+ cells or a failed mobilization. The prognostic impact of the number of mobilized stem cells appeared independent from the cytogenetic risk groups which were the most powerful prognostic factor. The DFS in the APBSCT and ABMT arms was not different in the four groups defined by the number of mobilized CD34+ cells, confirming that the number of mobilized CD34+ cells is a poor prognostic factor independently from the treatment given after mobilization. These data confirm that high numbers of mobilized CD34+ cells have a negative impact of outcome even without infusing the mobilized stem cells, confirming the observations using flow cytometry to study leukemic stem cell contamination in the harvests by leukemia-associated phenotypes.[19]

Twenty-two patients, randomized to ABMT received APBSCT as rescue. The OS of these 22 patients was not different when compared with the 71 patients who received BM alone ($P = 0.64$). Moreover, we analyzed the outcome in patients who received treatment according to randomization vs patients who did not receive this treatment (Table 2 and Figure 3). The 5-year survival in the APBSCT arm did not change irrespective of whether patients received APSCT according to randomization or not. However, the 5-year survival of patients in the ABMT arm was 65% when patients were treated according to randomization vs 40% in patients who did not receive ABMT. This difference can be explained by the shorter interval between randomization and ASCT in the APBSCT arm leading to less relapses before ASCT in this arm (two relapses) compared with the ABMT arm (12 relapses) and by relatively high number of patients (33%) in this group (randomized to ABMT, but no ABMT administered) with $> 7 \times 10^6$ mobilized CD34+ cells/kg (Table 2).

The results of this study confirm the results of earlier retrospective studies showing that higher CD34+ cell counts in the mobilized stem cell harvests correlate with a high frequency of cells with an abnormal phenotype, a higher level of minimal residual disease, and a higher relapse risk.[19,20] In an earlier analysis, we showed that the duration of hypoplasia after the consolidation course was short in the group of patients with a high CD34+ cell harvest, probably reflecting an *in vitro* purging of the normal and leukemic stem cells.[17] A shorter duration of pancytopenia after the consolidation course, and especially the duration of neutropenia, was associated with a worse prognosis. Genetic polymorphisms in the ABCG2 transmembrane transporter protein may contribute to differential survival outcomes in AML patients by a decreased drug efflux and higher cytotoxicity in both normal progenitors and AML cells and a longer hypoplasia after the consolidation course.[16]

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Targeted therapy might be relevant for specific patient groups. However, addition of gemtuzumab ozogamicin to the remission-induction course conferred a significant survival benefit for patients with favorable cytogenetics, but no benefit for patients with poor-risk disease.[21] Similarly, addition of gemtuzumab ozogamicin to the consolidation course did not improve outcome after APBSCT.[18]

In conclusion, randomization between APBSCT and ABMT did not result in significantly different outcomes in terms DFS, OS and relapse incidence, but hematopoietic recovery after APBSCT was substantially faster. This resulted in lower requirement of transfusions and antibiotics and in a 2-week shorter hospitalization. High numbers of CD34+ cells obtained during the first round of mobilization was a strong adverse prognostic factor, independent of cytogenetic features and independent of the administered treatment. Patients with high numbers of 'mobilizable' CD34+ cells after the first consolidation course have a poor prognosis. These patients may benefit from allo-SCT or new alternative treatment approaches, similar to patients with adverse risk cytogenetic or molecular features.[22]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

SS, J-PM, PM, SA, BL, FM, AH, RW and TdW were involved in the conception and design of study. SS, PF and MV provided administrative support. YC, J-PM, PM, FL, FM, FP, SA, GF, BL, FB, JC, J-HB, GS, RW and TdW provided the study materials or patients. SS, PF and MV were involved in the collection and assembly of data. AH reviewed the cytogenetic data. MH, SS and TdW were involved in the data analysis and interpretation. MH, SS, J-PM, PM, SA, FB, MV, RW and TdW wrote the manuscript. All the authors gave final approval of the manuscript.

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