Long-term follow-up of a trial comparing post-remission treatment with autologous or allogeneic bone marrow transplantation or intensive chemotherapy in younger acute myeloid leukemia patients

Even though the optimal post-remission therapy for younger acute myeloid leukemia (AML) patients has remained controversial[1] only a few prospective trials have been comparing intensive chemotherapy to autologous (auto-) or allogeneic (allo-) bone marrow transplantation (BMT). In addition, most of these studies have been published with a relatively short follow-up.[2] Therefore, we herein report a very long-term follow-up evaluation of AML patients previously enrolled in the pivotal EORTC/GIMEMA AML-8A trial.[3]

From November 1986 to April 1993, 990 patients were registered in the EORTC/GIMEMA AML-8A trial which prospectively compared the impact of three post-remission treatments on disease-free (DFS) and overall (OS) survival in younger (10-45 years of age) AML patients who reached a complete remission (CR) after induction chemotherapy (*Online Supplementary Figure 1*). Main inclusion criteria included previously untreated AML according to the French-American-British (FAB) classification system and 10 to 59 years of age at diagnosis (*NB*: some centers accepted to enter patients aged 46-59 years of age). Main exclusion criteria included AML occurring after a myeloproliferative disorder, and a prior history of myelodysplastic syndrome for more than six months. Thirty-six of the 990 patients were deemed ineligible because of inadequate diagnosis or because they met exclusion criteria. Further 13 patients could not be evaluated because of missing data. Thus, data from 941 patients were evaluated. The results were first reported in 1995 with a median follow-up of 3.3 years after registration.[3] All patients received a remission-induction con-

Table 1. Patient characteristics, treatment applicability and outcomes according to the three treatments planned at the evaluation of ICT1.

	Allo-BMT (n=168)	Auto-BMT (n=128)	ICT2 (n=126)	*P*
Age at registration				
Median (range)	32 (13-45)	32.5 (15-59)	32 (15-59)	0.80*
11-25, n (%)	42 (25)	42 (33)	45 (36)	
26-45, n (%)	126 (75)	77 (60)	72 (57)	
46-59, n (%)	0	9 (7)	9 (7)	
White-cell count at registration x109/L				
Median (range)	14.8 (0.4-294)	14.7 (0.5-288)	13.8 (0.2-376)	0.98*
< 5, n (%)	37 (22)	39 (31)	33 (26)	
5-49, n (%)	98 (58)	54 (42)	59 (47)	
≥ 50, n (%)	33 (20)	35 (27)	34 (27)	
Cytogenetic risk, n (%)*	n=73	n=59	n=56	0.45**
Good	18 (25)	11 (19)	7 (13)	
Intermediate	25 (34)	24 (41)	17 (30)	
Poor	14 (19)	12 (20)	11 (20)	
Inconclusive	16 (22)	12 (20)	21 (38)	
# of cycles needed to reach a CR, n (%)				0.052*
1	132 (79)	111 (87)	111 (88)	
2	36 (21)	17 (13)	15 (12)	
Treatment given in CR1, n (%)				
Allo-BMT	144 (86)	2 (2)	1(1)	
Auto-BMT	0	95 (74)	5 (4)	
ICT2	1 (1)	5 (4)	104 (83)	
Other	0	3 (2)	1 (1)	
None	23 (14)	23 (18)	15 (12)	
Median length of time between CR achievement and last treatment step (weeks)	15	14	10	<0.001*
Disease free-survival status, n (%)				
CR1	87 (52)	52 (41)	39 (31)	
Relapse	47 (28)	60 (47)	76 (60)	
Death without relapse	34 (20)	16 (13)	11 (9)	
Patients given a salvage auto-BMT, n (%)	0	2 (2)	13 (10)	
Patients given a salvage allo-BMT, n (%)	2 (1)	1 (1)	2 (2)	

*Kruskal-Wallis test ; **:Yates' χ^2 test. ICT: intensive consolidation chemotherapy; allo-BMT: autologous bone marrow transplantation; auto-BMT:allogeneic bone marrow transplantation; CR:complete remission; CR1: first complete remission. ICT: intensive consolidation chemotherapy.

sisting of one or two (in case of partial response after the first course) courses of chemotherapy combining cytarabine (200 mg/m^2 given as a continuous intravenous (iv) infusion on days 1 through day 7) and daunorubicine (45 mg/m^2 given iv on days 1, 2 and 3). CR was reached by 623 patients (66%) after one or two courses of induction and 576 of these patients received the first course of intensive consolidation chemotherapy (ICT1) combining intermediate-dose cytarabine (1000 mg/m^2 during the first year of the study and then 500 mg/m^2, given iv in two hours every 12 hours on day 1 through day 6), and amsacrine (given iv at a dose of 120 mg/m^2 on days 5, 6, and 7). After ICT1, patients alive in first complete remission (CR1) who had an human leukocyte antigen (HLA)-compatible donor, and considered suitable to receive an allo-BMT, were included in the allo-BMT arm. Patients alive in CR1 without a HLA-compatible donor, and considered eligible to receive an auto-BMT, were randomized between auto-BMT and a second course of intensive consolidation chemotherapy (ICT2). The distributions of OS, DFS from CR and OS from CR1 were estimated using the Kaplan-Meier method and the treatment groups were compared using the log-rank test. The Cox model was used to estimate the treatment hazard ratios along with the 95% confidence interval (CI). The relapse incidence as well as the incidence of death in CR were calculated using cumulative incidence functions and the groups were compared using the Gray test.

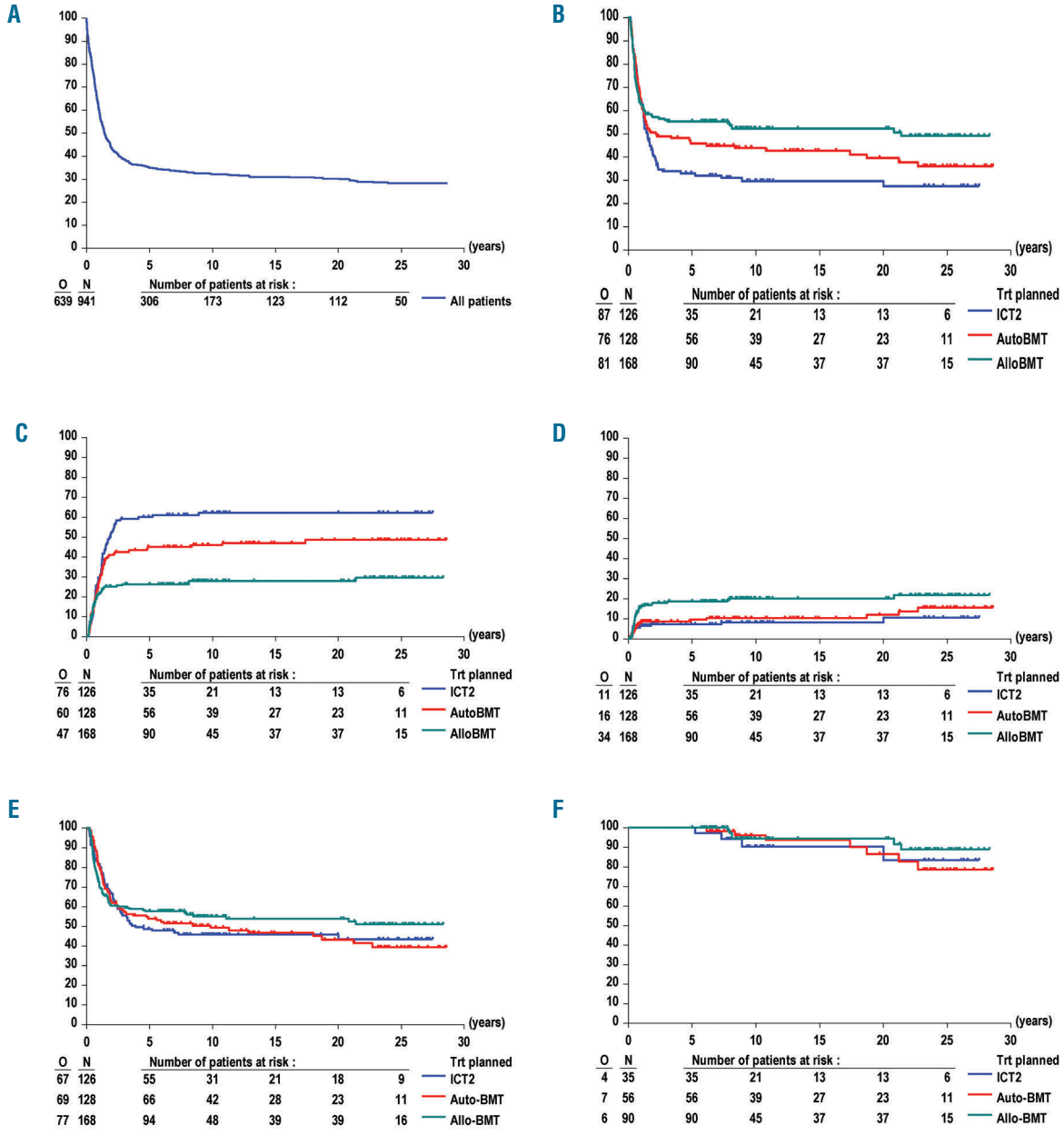

Figure 1. Outcomes based on intent-to-treatment analyses. (A) OS from inclusion in the whole population. (B) DFS from CR according to treatment group. (C) Cumulative incidence of relapse from CR according to treatment group. (D) Cumulative incidence death in CR from CR according to treatment group. (E) OS from CR according to treatment group. (F) DFS in patients alive in first CR 5 years after the achievement of CR, according to treatment group. OS: overall survival; DFS: disease-free survival; CR: complete remission.

In the current report, the median follow-up from inclusion was 11.1 years (95% CI 10-13 years; range 0-28 years). For the whole population (n=941), the 5-, 10- and 15-year OS rates from inclusion were 35%, 32% and 31%, respectively (Figure 1A). A total of 623 patients (66%) achieved a CR after one (n=508) or two (n=116) course(s) of induction chemotherapy. Out of 576 patients who completed ICT1, 168 were allocated to the allo-BMT arm, while 254 patients were randomized to auto-BMT (n=128) or ICT2 (n=126). The outcomes of these three treatment groups (n=422) are reported below.

As observed in the initial report,[3] DFS from CR was longer after allo-BMT than auto-BMT and was also longer after auto-BMT than after ICT2 (Figure 1B; *P*=0.015). Specifically, the five-year DFS from CR was 55% in the allo-BMT group, 46% in the auto-BMT group and 33% in the ICT2 group. At 10-year from inclusion, DFS from CR were 52%, 44% and 30% in the allo-BMT, auto-BMT and ICT2 patients, respectively. Restricting the analyses to patients < 46 years of age at registration (before the start of the induction treatment), the 10-year DFS from CR was 52%, 47% and 30% in the allo-BMT, auto-BMT and ICT2 patients, respectively (*P*=0.016) (*Online Supplementary Figure 2A*). Interestingly, subgroup analyses suggested that the advantage of allo-BMT was mainly observed in patients lacking good-risk cytogenetic features (*Online Supplementary Figure 2B*) and not in those with good-risk features (*Online Supplementary Figure 2C*).

In the 422 patient group, the 10-year relapse incidence from CR was lower in the allo-BMT group (28%) than in the auto-BMT (47%) and in the ICT2 group (62%) (Figure 1C; *P*=0.001), while the 10-year incidence of death in CR was higher in the allo-BMT (20%) than in the auto-BMT (10%) and in the ICT2 group (8%) (Figure 1D; *P*=0.019). In contrast to what was observed for DFS from CR, OS from CR was not significantly impacted by the treatment group (Figure 1E, *P*=0.61). Specifically, the 10-year OS from CR rate was 55% in the allo-BMT group, 49% in the auto-BMT group, and 46% in the ICT2 group. This might have been due to higher rates of salvage auto- or allo-BMT in the ICT2 group (12%) than in the auto-BMT (3%) and allo-BMT (1%) group (Table 1), given that both strategies proved to be effective in selected patients with relapsed AML.[4,5] As depicted in Figure 1F and the *Online Supplementary Figure 2D*, relatively few events occurred beyond five years after the study inclusion. Specifically, among the patients alive, still in first CR five years after the achievement of CR, the 10-year DFS rate and 10-year relapse incidence from CR1 were 94% and 3% in the allo-BMT group (n=90), 96% and 5% in the auto-BMT patients (n=56) and 90% and 7% in the ICT2 patients (n=36), respectively. Several deaths occurring approximately 20 years after the achievement of CR were not due to AML.

The comparison of the results of the two randomized groups showed that the patients randomized to the auto-BMT arm had a longer DFS from randomization than the patients in the ICT2 group (HR=0.78; 95% CI: 0.57-1.07, *P*=0.12) due to a lower incidence of relapse (HR=0.71; 95% CI: 0.51-1.00, *P*=0.050). In contrast, OS from randomization was comparable in the auto-BMT and ICT2 groups (HR=0.97; 95% CI: 0.69-1.36, *P*=0.9). This also might be explained by the relatively high incidence of salvage auto-BMT in the ICT2 group (10% *versus* 2% in the auto-BMT patients) (Table 1).

Previous studies have noted that non relapse fatalities due in part to complications of chronic graft-*versus*-host disease (GvHD) may occur well beyond five years post transplantation,[6] while late relapses have been reported especially in patients not offered an allogeneic transplantation.[7] These observations prompted us to perform a long-term follow-up of the pivotal EORTC/GIMEMA AML-8A trial comparing three post-remission strategies.

A first novel finding was that our initial observations hold true after a long-term follow up, with a benefit in terms of DFS from CR in the allo-BMT patients in comparison to the auto-BMT and further to the ICT2 patients. These results are in concordance with those observed by Vallenga *et al*. who reported better five-year relapse free survival with autologous peripheral blood stem cell (PBSC) transplantation than with intensive chemotherapy in AML patients, in first CR after 2 cycles of intensive chemotherapy, who did not have a HLA-identical sibling donor.[8]

A second important result from the current analysis is that among AML patients in CR five years after the study inclusion, the probability to remain alive and disease free five years later was >90%, and was quite similar in the three post-remission treatment groups. The long-term analyses of the health related quality of life (HRQOL) of the patients is planned in a further study (the SPARTA platform).

It should be noted that, in the AML arena, many advances have been made in each group since the EORTC/GIMEMA AML-8A study was designed. These include, for example, GvHD prophylaxis (they had shorter OS than those receiving cyclosporine A plus methotrexate for GvHD prophylaxis), better conditioning regimens for each auto-BMT and allo-BMT[9], the demonstration of the importance of high-dose cytarabine-based consolidation chemotherapy in patients with core-binding factor leukemia and important advances in the supportive care.[10] Also the dose of the intercalating agent used in the remission induction chemotherapy (3 x 45 mg/m^2 of daunorubicin) was suboptimal according to more recent studies. Finally, autologous transplantation is nowadays performed with PBSC instead of with BM as a stem cell source although one large registry and one phase III study did not show better DFS with auto-PBSCT than with auto-BMT.[11,12]

In summary, this long-term follow-up of the EORTC/GIMEMA AML-8A study confirms a longer DFS with allo-BMT or auto-BMT when compared to ICT2 in younger AML patients in CR1. Further, this long-term follow-up study revealed that the vast majority of patients alive in CR1 at five years remain disease-free survivors five years later. Although indications of allogeneic hematopoietic stem cell transplantation are nowadays largely driven by the cytogenetic/molecular AML profile[10,13] and the presence or absence of minimal residual disease at transplantation,[14] long-term results of the AML-8A study demonstrate that auto-BMT remained superior to ICT2 in younger AML patients not candidate for an allo-HSCT. These results suggest that new prospective trials comparing autologous hematopoietic stem cell transplantation to additional intensive chemotherapy should be carried out. These studies could include patients with favorable European Leukemia Net classification risk with minimal residual disease (MRD) negative levels.[15]

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