

(CY) ($n = 1$), busulfan (BU)/CY ($n = 3$), BU/melphalan ($n = 1$) or BU/etoposide/cytarabine ($n = 1$). Allografted patients received a myeloablative regimen using TBI/CY ($n = 11$), TBI/BU/CY ($n = 2$), BU/CY ($n = 6$) or a non-myeloablative fludarabine-based regimen ($n = 2$).

Non-HSCT group. Patients in this group received various consolidation and/or maintenance regimens with chemotherapy and/or ATRA (Table 1). Reasons for not undergoing HSCT in CR2 included age >60 years ($n = 6$), relatively poor condition ($n = 4$), patient refusal ($n = 5$), lack of an appropriate donor ($n = 1$), medical decision ($n = 13$) and unknown reasons ($n = 1$). Among patients in the non-HSCT group, 10 received allo-HSCT ($n = 8$) or auto-HSCT ($n = 2$) during the third CR (CR3) or more. After achievement of CR2, patients were treated with a variety of consolidation regimens, including chemotherapy, ATO, gemtuzumab ozogamycin and observation alone (Table S1).

Definitions. Hematological CR was defined as the presence of all of the following: $<5\%$ blasts in bone marrow; no leukemic blasts in peripheral blood or extramedullary sites; and recovery of peripheral blood counts. Relapse was defined as the presence of at least one of the following: two consecutive positive RT-PCR obtained 1 month apart after achieving molecular remission; recurrence of $>10\%$ leukemic cells in bone marrow; recurrence of any leukemic cells in peripheral blood; or development of extramedullary disease.⁽¹⁵⁾

Statistical analysis. Overall survival (OS) was calculated from the date of CR2 to the date of death or last follow up. Event-free survival (EFS) was calculated from the date of CR2 to an event (relapse or death) or to the date of last follow up. Cumulative incidence of relapse (CIR) was calculated from the date of CR2 to the date of second relapse or last follow up for patients alive in CR2. Results were analyzed as of 31 March 2010, allowing for median follow ups of 84 months (range, 16–120 months) and 87 months (range, 2–136 months) from the date of CR2 for the HSCT and non-HSCT groups, respectively. Differences in categorical factors between the HSCT and non-HSCT groups were compared using the χ^2 test. Age at CR2 was dichotomized using a cut-off point of 40 years to create a younger group (<40 years) and an older group (≥ 40 years) by taking the transplantation risk of age in the risk score of the European Group for Blood and Marrow Transplantation into consideration.⁽¹⁶⁾ Continuous data were compared using the Mann–Whitney test. The OS and EFS were estimated using the Kaplan–Meier method and compared using the log-rank test. To adjust for effects of the timing of HSCT in the survival analysis, HSCT was treated as a time-dependent covariate in the Kaplan–Meier estimates of OS and EFS. The CIR was estimated using the cumulative incidence method, where death in CR2 was considered as a competing risk and compared using Gray's test. All tests were two tailed and a value of $P < 0.05$ was considered statistically significant. All analyses were performed using STATISTICA version 6.0 software (Statsoft Inc., Tulsa, OK, USA) and STATA 11 software (STATA Corp LP, College Station, TX, USA).

Results

The characteristics and prognosis of patients with APL who achieved CR2 by salvage treatment with HSCT ($n = 27$) or non-HSCT ($n = 30$) are summarized in Table 2.

Clinical consequences for the HSCT group. In the 27 patients (six auto-HSCT and 21 allo-HSCT) with a median duration of first CR at 22 months (range, 6–81 months), six patients relapsed and seven patients died, including four patients with TRM (Table 2).

Among the six patients who received auto-HSCT, the median duration of first CR was 22 months (range, 10–81 months),

Table 2. Clinical consequences of APL patients in CR2 according to treatment with HSCT or non-HSCT after CR2

	HSCT group ($n = 27$)	Non-HSCT group ($n = 30$)	<i>P</i> -value
Male sex, n (%)	19 (70)	18 (60)	0.579
WBC counts at diagnosis, median (range) ($\times 10^9/L$)	3.9 (0.4–46.1)	1.9 (0.1–63.7)	0.129
Duration of first CR, median (range) (months)	22 (6–81)	18 (6–91)	0.415
Age at CR2, median (range) (years)	36 (22–59)	53 (16–72)	0.006
Relapses after CR2, n (%)	6 (22)	16 (53)	0.016
TRM, n (%)	4 (15)	N/A	N/A
Total deaths, n (%)	7 (26)	11 (37)	0.384
5-year EFS, % (95% CI) [†]	56.4 (32.1–74.9)	50.8 (30.4–68.0)	0.852
5-year OS, % (95% CI) [†]	70.4 (44.6–85.8)	77.4 (57.8–88.7)	0.860
5-year CIR, % (95% CI)	19.7 (7.1–36.8)	51.0 (31.0–67.9)	0.018

[†]Analyses were performed using a time-dependent covariate approach. APL, acute promyelocytic leukemia; CI, confidence interval; CIR, cumulative incidence of relapse; CR, complete remission; CR2, second complete remission; EFS, event-free survival; HSCT, hematopoietic stem cell transplantation; N/A, not available; OS, overall survival; TRM, transplantation-related mortality; WBC, white blood cell.

the median time from achievement of CR2 to HSCT was 6 months (range, 4–20 months), no TRM was seen and four patients (67%) relapsed at 9, 29, 46 and 84 months after auto-HSCT. Among those who relapsed, one died from APL progression 12 months after auto-HSCT. Another three patients achieved CR3 through treatment with ATO, Am80 or high-dose cytarabine and remained in CR3 at 7, 22, and 54 months after CR3, respectively. Of those who received auto-HSCT in CR2, four relapsed and one died, and the remaining two patients were alive in CR2.

In the 21 patients who received allo-HSCT in CR2, the median duration of first CR was 22 months (range, 6–63 months) and the median time from achievement of CR2 to HSCT was 6 months (range, 1–13 months). Of the 21 patients, four patients (19%) died of TRM (two patients died due to graft-versus-host disease [GVHD] and two patients died due to multiple organ failure) and two patients (9.5%) relapsed at 4 and 34 months after salvage HSCT and died. No significant difference in 5-year OS, EFS rates and CIR in seven patients with MRD before allo-HSCT was observed compared with eight patients negative for MRD (data not shown). Among those who received allo-HSCT in CR2, four died of TRM, two relapsed and died and the remaining 15 patients were alive in CR2.

Clinical consequences for the non-HSCT group. In the 30 patients in CR2 who did not receive any HSCT as post-remission therapy, the median duration of first CR was 18 months (range, 6–91 months) (Table 2). In CR2, these patients received consolidation treatment with various chemotherapy regimens, sometimes followed by maintenance treatment with ATRA. Of the 30 patients, 14 (47%) remained in CR2 after a median of 69 months (range, 2–133 months), but 16 (53%) experienced a second relapse after a median of 14 months (range, 1–113 months). One of the 14 patients who remained in CR2 died from secondary acute lymphoblastic leukemia.⁽¹⁷⁾ Among the 16 patients who experienced a second relapse, eight received allo-HSCT (three in CR3, one in CR4, two in the second relapse and two in the third relapse) and two received auto-HSCT in CR3. Of these eight patients who

received allo-HSCT, four died from TRM (GVHD in two patients, pneumonia in one patient and multiple organ failure in one patient), two died from APL progression with further relapse after HSCT and two survived in a disease-free state. Of the two patients who received auto-HSCT, both remained in CR3. Of the six patients who experienced a second relapse and did not receive HSCT, one failed to obtain CR and died from APL progression and five patients achieved CR3 (two died of APL progression after the third relapse, one died of myocardial infarction and two remained in CR3 as of 22 and 23 months). Of those who received no HSCT in CR2, 13 patients were alive in CR2 and one patient died in CR2. Of the remaining 16 patients who relapsed, 10 patients died and six were alive in CR3 or more.

Comparisons between the HSCT and non-HSCT groups. Median age at CR2 was significantly younger in the HSCT group than in the non-HSCT group ($P = 0.006$) (Table 2). No significant differences were observed between these two groups in the frequency of male sex, white blood cell count at diagnosis or duration of first CR. The frequency of relapse after CR2 was significantly higher in the non-HSCT group (22% vs 53%; $P = 0.016$) (Table 2). However, the frequency of death did not differ between the two groups.

Although no significant differences in the 5-year OS rate (Table 2, Fig. 1a) or 5-year EFS rate (Table 2, Fig. 1b) were evident between the two groups, the CIR was significantly lower in the HSCT group than in the non-HSCT group (5-year CIR, 19.7% vs 51.0%; $P = 0.018$) (Table 2, Fig. 1c).

When we analyzed the data by dividing each group into two age subgroups of younger patients (age <40 years) and older patients (age ≥ 40 years), younger patients showed no significant difference in 5-year OS rate between the HSCT group (100%) and non-HSCT group (82.5%; $P = 0.10$), but did show a tendency in favor of allo-HSCT (Fig. 2a). Conversely, among the older patients, the OS rate was significantly higher in the non-HSCT group than in the HSCT group (5-year OS, 78.0% vs 40.5%; $P = 0.04$) (Fig. 2b). In the HSCT group, OS rate was significantly better in younger patients (age <40 years, $n = 15$; 5-year OS, 100%) than in older patients (age ≥ 40 years, $n = 12$; 5-year OS, 50.0%; $P = 0.006$) (Fig. 2c).

Comparisons among auto-HSCT, allo-HSCT and non-HSCT groups. We compared several outcomes among auto-HSCT, allo-HSCT and non-HSCT groups. No significant differences were seen in the 5-year EFS rate (auto-HSCT, 41.7%; allo-HSCT, 71.1%; non-HSCT, 45.4%) (Fig. 3a) or 5-year OS rate (auto-HSCT, 83.3%; allo-HSCT, 76.2%; non-HSCT, 75.3%) (Fig. 3b). However, 5-year CIR differed significantly between patients who underwent auto-HSCT (58.3%) and allo-HSCT (9.8%; $P = 0.007$) and between patients who underwent non-HSCT (51.0%) and allo-HSCT (9.8%; $P = 0.009$), while no significant difference was evident between the auto-HSCT and non-HSCT groups ($P = 0.603$) (Fig. 3c).

Discussion

The main results of the present study indicate that the 5-year CIR was significantly better in patients who underwent allo-HSCT than in those who did not and the 5-year OS rate was significantly better in the non-HSCT group than in the HSCT group among older patients (age ≥ 40 years).

Several studies have demonstrated that auto-HSCT for APL in CR2 yields favorable results with a relatively low relapse rate.^(6,9) In an Italian study, it was reported that of 15 patients receiving auto-HSCT for APL in CR2 only two of eight patients who were negative for *PML-RARA* transcript by RT-PCR in bone marrow before auto-HSCT relapsed, whereas all seven patients with positive findings from the RT-PCR

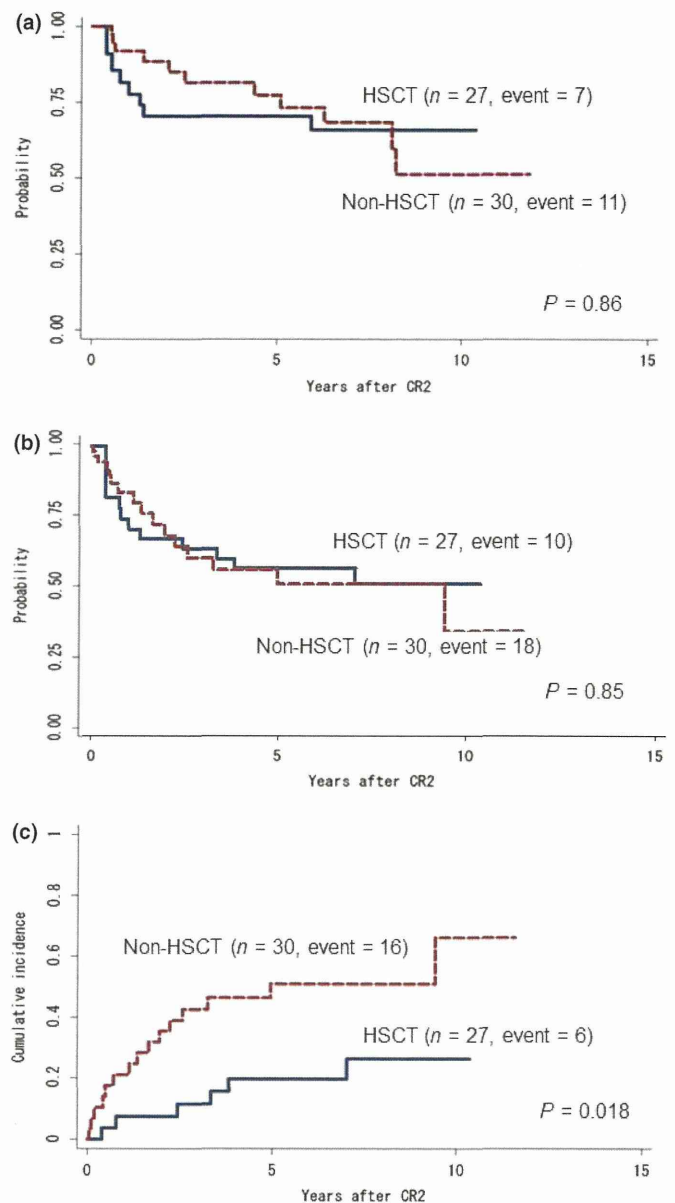


Fig. 1. Outcomes according to transplantation status. (a) Overall survival (OS). (b) Event-free survival (EFS). (c) Cumulative incidence of relapse. Probabilities of OS and EFS were assessed using a time-dependent covariate approach. CR2, second complete remission; HSCT, hematopoietic stem cell transplantation.

relapsed.⁽⁶⁾ In a study from the European Acute Promyelocytic Leukemia Group reported, among 28 auto-grafted patients who were in molecular remission at the time of stem cell harvest, only three relapsed (7-year EFS rate, 76.5%).⁽⁹⁾ A recent prospective study of our JALSG also observed a relatively low relapse rate, in which there were only three relapses among 23 auto-grafted patients with molecular remission at the time of stem cell harvest (5-year EFS rate, 65%).⁽¹⁴⁾ These studies show a prognostic importance of MRD negativity using molecular analysis before HSCT on the outcome. However, the results of the present study differ from previous report in that the MRD negativity is well associated with the low relapse rates in auto-HSCT. Contrary to our expectation, both the 5-year EFS rate (41.7%) and the 5-year CIR (58.3%) were worse for the auto-HSCT group than for the allo-HSCT group

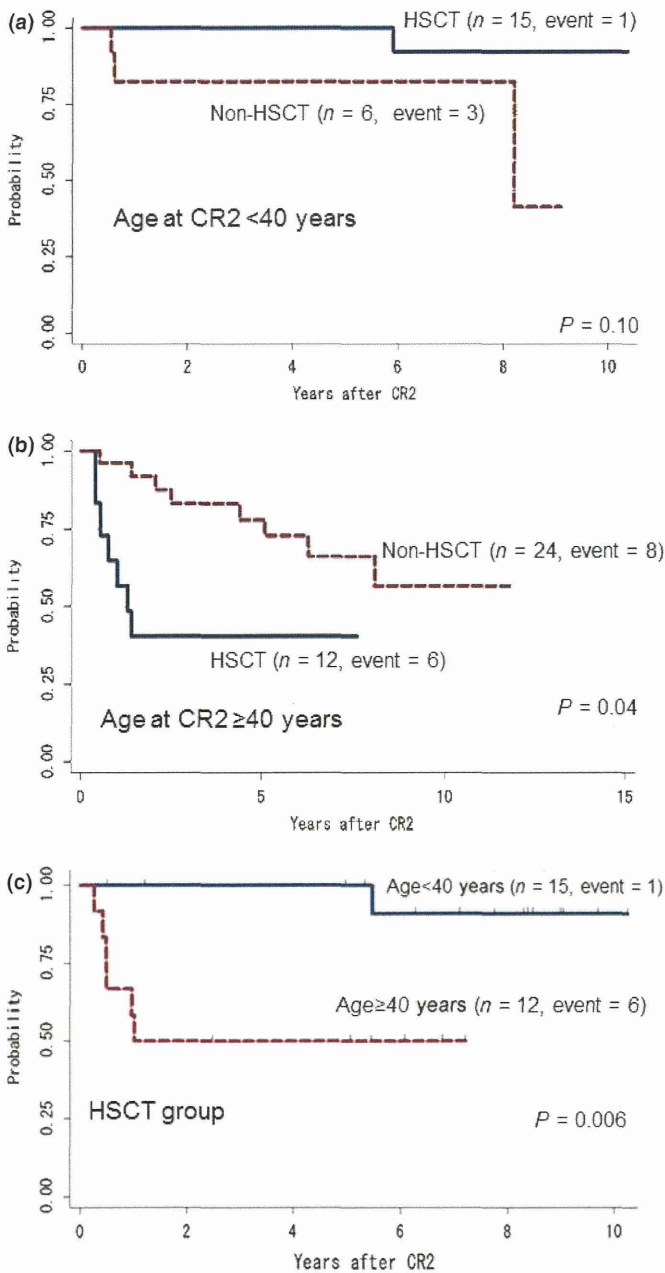


Fig. 2. Overall survival (OS) as a function of transplantation status in younger patients (a; age at second complete remission [CR2] <40 years) and older patients (b; age at CR2 ≥ 40 years) and as a function of age at CR2 in the hematopoietic stem cell transplantation (HSCT) group (c). A and B were assessed using a time-dependent covariate approach.

(Fig. 3a,c), even though all six patients were confirmed to have achieved molecular CR in bone marrow by nested RT-PCR or RT-PCR just before peripheral hematopoietic stem cell collection. Therefore, auto-HSCT was less effective for relapse in APL in CR2 and pre-transplant MRD had no predictive significance with respect to relapse in the present study. This might be due primarily to the small number of patients ($n = 6$) who received auto-HSCT in our analyses, which was the major limitation in the present study. Another possible explanation is the difference in sensitivity for the detection of MRD. In the APL97 study,⁽¹⁵⁾ although all patients who received auto-HSCT were MRD negative before transplantation, the detection limit of the *PML-RARA* fusion transcript was 10^{-4} ,

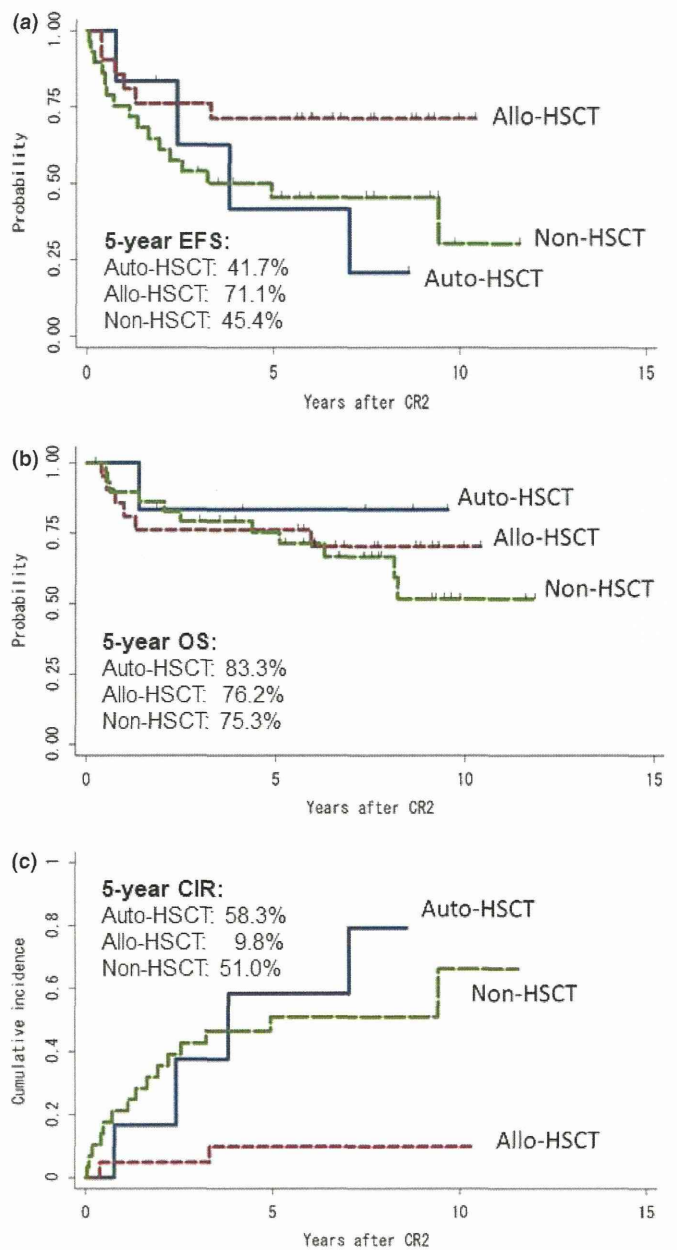


Fig. 3. Outcomes by type of hematopoietic stem cell transplantation (HSCT) (autologous [auto]-HSCT, allogeneic [allo]-HSCT or non-HSCT). (a) Event-free survival (EFS) rate. (b) Overall survival (OS) rate. (c) Cumulative incidence of relapse (CIR). CR2, second complete remission.

whereas in the report by de Botton *et al.*⁽⁹⁾, nested RT-PCR for *PML-RARA* amplification was used with a sensitivity of 10^{-5} to 10^{-6} . Although the 5-year EFS and 5-year CIR were worse in the auto-HSCT group in the present study, the 5-year OS rate (83.3%) was not inferior to that in the allo-HSCT and non-HSCT groups. No TRM was seen in the six patients who underwent auto-HSCT and all but one patient achieved CR3 by means of a range of post-relapse salvage treatments.

In the present study, none of the young patients (age <40 years) died within 5 years from the date of CR2. Taken together with our results that the 5-year OS rate tended to be better in the allo-HSCT group than in the non-HSCT group among younger patients (Fig. 2a), the 5-year EFS rate was better in allo-HSCT than in the auto-HSCT and non-HSCT groups

(Fig. 3a) and the 5-year CIR was lower in allo-HSCT than in the auto-HSCT and non-HSCT groups (Fig. 3c), we suggest that conventional allo-HSCT represents an effective option for young APL patients who achieve CR2. The reason for this is that allo-HSCT is originally aimed at producing a graft-versus-leukemia effect in addition to direct antitumor effects of conditioning and is also regarded as an acceptable method of treatment in patients who are positive for pre-transplant MRD.

It is to be expected that patients in the non-HSCT group (those who did not undergo transplantation during CR2) would be older and those with complications, so the outcomes would be poorer than those of the transplant groups. However, counter to our expectations, survival outcomes in the non-HSCT group were relatively high (5-year EFS rate, 45.4%; 5-year OS rate, 75.3%) and not inferior to those in the HSCT groups. A similar result was reported by the European Acute Promyelocytic Leukemia Group, in which a consistent proportion of relapsed APL patients in CR2 who did not undergo transplantation were almost completely cured (EFS rate, 30.4%; OS rate, 39.5%).⁽⁹⁾ Outcomes for the non-HSCT group were less favorable in the present study, but 13 of the 30 patients (43%) remained in CR2. The European APL study group also reported that 39% remained in CR2 in the non-HSCT group.⁽⁹⁾ Such findings suggest that HSCT might not always be necessary for all patients in CR2 to prevent further relapse, given the potential for unnecessary TRM.

More recently, ATO has been used worldwide for the treatment of relapsed APL patients,^(7,13,18) and has been included in the design of several front-line studies, with the aim of reducing therapy-related toxicities and obtaining more profound molecular remission. However, the efficacy of ATO alone in relapsed APL patients remains contentious. A study from France that treated relapsed APL reported that OS in patients with an ATO-based regimen was superior to that in patients with conventional combination chemotherapy or allo-HSCT,⁽¹³⁾ but others have reported that an ATO-based regimen offered a high response rate but also a high relapse rate.^(8,19) Moreover, a recent study from India that treated relapsed APL patients who had achieved molecular CR with ATO reported that the EFS rate was significantly inferior in patients who

underwent continuous administration of ATO+ATRA without auto-HSCT (34%, $n = 19$) compared with that in patients treated with auto-HSCT after CR2 (83%, $n = 14$; $P = 0.001$).⁽²⁰⁾ The reason for such discrepancies in the effects of ATO-based regimen among different studies might be attributed to the small numbers of patients, selection bias and differences in economic constraints. Nevertheless, approximately 40% and 60% of patients receiving an ATO-based regimen relapsed in the French and Indian studies, respectively. In the present study, none of the relapsed patients were treated with ATO, because all relapsed before ATO gained approval for use in Japan. Only quite recently, our study group has reported better efficacy of a regimen of ATO followed by auto-HSCT for relapsed APL in the phase 2 study ($n = 23$; 5-year EFS, 65%).⁽¹⁴⁾

In conclusion, the present study suggests that allo-HSCT is favorably recommended for younger APL patients during CR2, but for older APL patients, safer and less toxic treatments such as non-myeloablative transplantation might be preferable. Nevertheless, given the small number of patients in the present study and the retrospective nature of the analysis, clear conclusions are difficult to reach. Further prospective studies with larger numbers of patients are required to confirm the role of HSCT both alone and in combination with ATO on the outcomes for patients with APL in CR2.

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Disclosure Statement

The authors have no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Actual treatment after CR2 in the non-HSCT group.

The Demarcation Between Younger and Older Acute Myeloid Leukemia Patients

A Pooled Analysis of 3 Prospective Studies

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BACKGROUND: Contemporary treatment protocols for adult acute myeloid leukemia (AML) are age-specific, and older patients are generally treated less intensively than younger patients. However, it remains uncertain whether older but fit patients with AML really need to have their treatment attenuated. **METHODS:** To evaluate the contribution of age to outcome for patients with AML receiving intensive chemotherapy, data were analyzed for 2276 patients aged less than 65 years who were treated uniformly, regardless of age, in 3 consecutive prospective studies conducted by the Japan Adult Leukemia Study Group. **RESULTS:** A substantial drop in overall survival (OS) between patients aged 40 to 49 years and 50 to 64 years led to a focus on 2 comparisons: 1) age <50 versus ≥50 years; and 2) age 50 to 54 versus 55 to 59 versus 60 to 64 years. OS was significantly better for patients aged <50 years than that for those aged ≥50 years (49.6% and 37.0% at 5 years; $P < .001$); older patients were more susceptible to relapse, but not to early death or nonrelapse mortality. The significant differences in OS between these 2 age groups were equally seen for patients with favorable, intermediate, and adverse cytogenetics ($P < .001$ each). Outcomes for those aged 50 to 54, 55 to 59, and 60 to 64 years were similar, with 5-year OS rates of 38.2%, 35.1%, and 38.0%, respectively ($P = .934$), and no differences in early death or nonrelapse mortality were observed among these age groups. **CONCLUSIONS:** These findings justify the use of intensive chemotherapy without dose attenuation toward older but fit patients with AML, at least up to the age of 64 years. *Cancer* 2013;119:3326-33. © 2013 American Cancer Society.

KEYWORDS: acute myeloid leukemia; age; overall survival; early death; relapse; nonrelapse mortality.

INTRODUCTION

Age is among the most important prognostic factors in acute myeloid leukemia (AML).¹⁻⁵ Increasing age in AML is associated with a higher frequency of unfavorable biological characteristics such as adverse cytogenetics, preceding myelodysplastic syndrome (MDS), and expression of the multidrug resistance phenotype, all of which are involved in intrinsic resistance to chemotherapy.⁶⁻⁹ In addition to the disease biology, patient-related factors such as poor general condition and significant comorbidities also contribute to inferior outcomes for older patients.^{8,10,11} Because of such distinct biological and clinical features, contemporary treatment protocols for adult AML are age-specific and are typically divided into those for younger and older patients, with older patients treated less intensively than younger patients. For this purpose, age 55 or 60 years is generally used as the demarcation between these 2 groups^{1,2}; however, this cutoff age is quite arbitrary, and it remains uncertain whether patients over such age limits really need to have their treatment attenuated.

For the recent prospective AML studies conducted by the Japan Adult Leukemia Study Group (JALSG), age less than 65 years was used as the eligibility criterion, with dose modifications not having been adopted according to age. This

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situation provides a welcome opportunity to evaluate the contribution of age to outcome for patients with AML treated with uniform intensive chemotherapy. For the study reported here, we integrated data for 2276 patients entered into 3 consecutive prospective studies between 1995 and 2005 for a comparison of patient characteristics and treatment outcomes among different age groups.

MATERIALS AND METHODS

Patients

All patients were subjects of one of the three phase 3 studies conducted by the JALSG, that is, the AML95 (from 1995-1997),¹² AML97 (from 1997-2001),^{13,14} and AML201 (from 2001-2005) studies.^{15,16} All of these studies adopted the same eligibility criteria: newly diagnosed AML (acute promyelocytic leukemia excluded), age 15 to 64, an Eastern Cooperative Oncology Group performance status 0 to 3, adequate functioning of the liver (serum bilirubin level < 2.0 mg/L), kidneys (serum creatinine level < 2.0 mg/dL), lungs ($\text{PaO}_2 \geq 60$ Torr or $\text{SpO}_2 \geq 93\%$), and heart (no significant abnormalities on electrocardiograms and echocardiograms). Patients with AML secondary to MDS or cytotoxic treatment were not eligible for enrollment. Written informed consent was obtained from all patients prior to registration. Each protocol was reviewed and approved by the institutional review boards of the participating centers, and was conducted in accordance with the Declaration of Helsinki.

Treatments

The treatment schedule for each study is described in detail elsewhere.¹²⁻¹⁶ The AML95 study compared a fixed schedule (ie, "3+7") and an individualized schedule (up to "4+10" depending on the bone marrow findings on day 8) for induction therapy with idarubicin and cytarabine.¹² Postremission therapy consisted of 3 courses of consolidation therapy including behenoyl cytarabine and 12 months of maintenance therapy. The AML97 study adopted the 3+7 induction therapy with idarubicin and cytarabine for all patients.^{13,14} After achieving complete remission (CR), patients were randomized to receive 3 or 4 consolidation courses that included standard-dose cytarabine, followed by 12 months of maintenance therapy only for the 3 courses. Those with a human leukocyte antigen (HLA)-identical sibling donor were assigned to allogeneic hematopoietic cell transplantation (HCT) if they were younger than 50 years and at intermediate or poor risk, as determined with a scoring system which took into account cytogenetics, white blood cell count, and other factors. The AML201 study compared idarubicin

(12 mg/m² for 3 days) and daunorubicin (50 mg/m² for 5 days) both combined with cytarabine for induction therapy.^{14,15} Patients in CR were randomly assigned to either 4 consolidation courses with standard-dose cytarabine or 3 courses with high-dose cytarabine. Allogeneic HCT was offered to patients aged 50 or younger if they presented with intermediate or adverse cytogenetics and had an HLA-identical sibling donor. In principle, doses were not modified according to age for any protocol. The single exception was for high-dose cytarabine in the AML201 study, in which reduction of the cytarabine dose from 2 g/m² to 1.5 g/m² was allowed for patients aged 60 years or older.

Definitions

Karyotypes were classified as favorable, intermediate, or adverse, in line with the revised UK Medical Research Council (MRC) criteria.¹⁷ Monosomal karyotype was defined according to the criteria developed by Breems et al.¹⁸

CR was defined as the presence of all of the following: < 5% of blasts in bone marrow, no leukemic blasts in peripheral blood or extramedullary sites, and recovery of peripheral blood counts. Early death was defined as death from any cause occurring within 30 days after the start of induction therapy.⁸ Overall survival (OS) was defined as the time from the start of treatment to death or last visit, and relapse-free survival as the time from CR to relapse, death or last visit. Patients undergoing allogeneic HCT were not censored at the time of transplantation unless indicated.

Statistical Analysis

Distributions of patient characteristics between and among groups were compared by using the chi-square test for categorical variables. Differences in continuous variables were compared by means of the Wilcoxon rank-sum test for distribution between 2 groups, and the Kruskal-Wallis test for distribution among 3 groups. The probabilities of OS and relapse-free survival were estimated by using the Kaplan-Meier method, with differences between groups qualified with the log-rank test. First, we examined OS by dividing patients into 4 age groups: 15-29, 30-39, 40-49, and 50-64 years. This provisional analysis disclosed a substantial drop in OS between patients aged 40-49 and 50-64 years (Fig. 1A). This finding led us to focus on 2 comparisons for subsequent analyses: 1) age < 50 versus ≥ 50 years; and 2) age 50 to 54 versus 55 to 59 versus 60 to 64 years. Relapse and nonrelapse mortality were considered as competing risk events for each other, and the probabilities of relapse

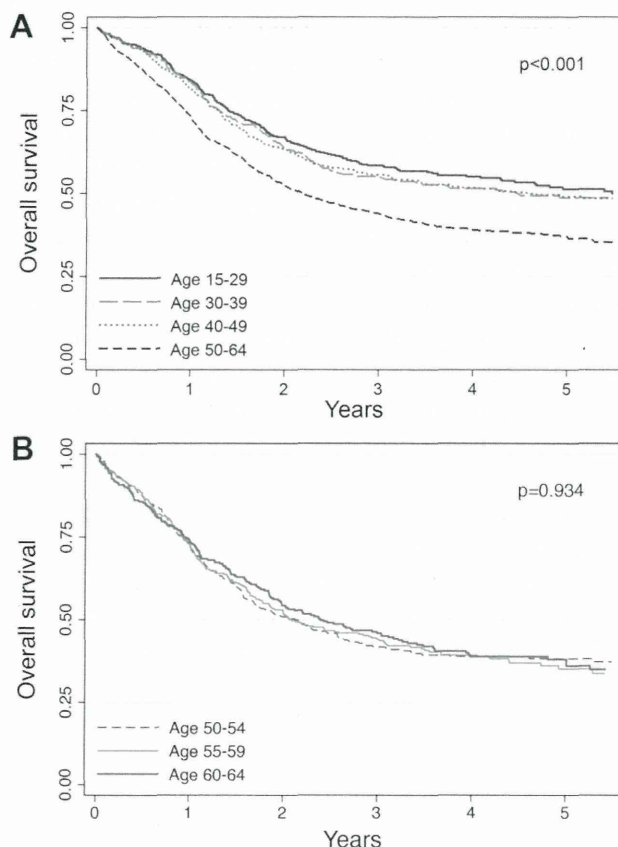


Figure 1. Overall survival for (A) the entire cohort and (B) for patients 50 to 64 years, is shown by age group. First, patients aged 15 to 29 (N = 438), 30 to 39 (N = 391), 40 to 49 (N = 510), and 50 to 64 (N = 937) are compared, and those aged 50 to 64 are then divided into 3 groups: 50 to 54 (N = 334), 55 to 59 (N = 322), and 60 to 64 (N = 281).

and nonrelapse mortality were estimated by using the cumulative incidence functions, with differences between groups qualified by the Gray test. The Cox proportional hazards regression model was used for multivariate analysis, and a hazard ratio (HR) was calculated in conjunction with a 95% confidence interval (CI). All statistical analyses were performed by using Stata version 12.0 software (StataCorp, College Station, Tex).

RESULTS

Patient Characteristics

A total of 2276 patients (430 from AML95, 789 from AML97, and 1057 from AML201) were analyzed for this study, with a median follow-up of surviving patients of 4.2 years (range, 0.0-8.0 years). Table 1 shows baseline characteristics of the patients according to age groups (age < 50, 50-54, 55-59, and 60-64 years). There was no significant relationship between performance status and age. The distribution of cytogenetic risk differed modestly

but significantly for patients aged < 50 and ≥ 50 ($P < .001$), but the difference was not significant for those aged 50 to 54, 54 to 59, and 60 to 64 years ($P = .577$). Comparison of patients aged < 50 and ≥ 50 years showed that $t(8;21)$ and $inv(16)/t(16;16)$ occurred more frequently in younger patients ($P < .001$ and $P = .043$, respectively), whereas the frequencies of $add(5q)/del(5q)/-5$, $add(7q)/del(7q)/-7$, complex karyotype, and monosomal karyotype were higher for older patients ($P = .002$, $P = .021$, $P < .001$ and $P < .001$, respectively). None of these cytogenetic aberrations, however, showed significant differences in distribution among those aged 50 to 54, 54 to 59, and 60 to 64 years.

Complete Remission and Early Death

Rates of CR and early death are summarized in Table 2. Patients younger than 50 years tended to show higher CR rates than those aged 50 or older, but the difference failed to reach statistical significance ($P = .078$), whereas there was no difference in the CR rates among those aged 50 to 54, 54 to 59, and 60 to 64 years ($P = .829$). Early death within 30 days after the start of induction therapy occurred in 1.8%, 1.5%, 2.5%, and 3.2% of patients aged < 50, 50 to 54, 55 to 59, and 60 to 64 years, respectively, with no significant difference between those aged < 50 and ≥ 50 ($P = .367$), or among those aged 50 to 54, 54 to 59, and 60 to 64 ($P = .356$). The rates of death within 60 days were 2.7%, 5.1%, 5.0%, and 6.1% for the respective age groups ($P = .003$ for age < 50 and ≥ 50 , and $P = .813$ for age 50 to 54, 54 to 59, and 60 to 64 years).

Relapse and Nonrelapse Mortality

Cumulative incidences of relapse and nonrelapse mortality for the 1788 patients who attained CR are shown in Table 2. Patients 50 years of age or older were more likely to experience relapse than were those younger than 50 ($P = .008$), whereas there was no difference in relapse rates among those aged 50-54, 55-59, and 60-64 years ($P = .196$). The nonrelapse mortality rates did not differ significantly between patients aged < 50 and ≥ 50 years ($P = .695$), or among those aged 50 to 54, 54 to 59, and 60 to 64 years ($P = .388$).

Overall Survival

Figure 1A compares OS for patients divided into 4 age groups: 15 to 29, 30 to 39, 40 to 49, and 50 to 64 years. As mentioned above, this result prompted us to first postulate a distinction between patients younger and older than 50 years. OS was significantly better for patients aged < 50 years than that for those aged ≥ 50 years

TABLE 1. Patient Characteristics

Characteristic	Age <50 y N = 1339	Age 50-54 y N = 334	Age 55-59 y N = 322	Age 60-64 y N = 281
Protocol				
AML95	276 (21%)	53 (16%)	52 (16%)	49 (17%)
AML97	477 (36%)	112 (34%)	110 (34%)	90 (32%)
AML201	586 (44%)	169 (51%)	160 (50%)	142 (51%)
Sex				
Male	774 (58%)	220 (66%)	193 (60%)	161 (57%)
Female	565 (42%)	114 (34%)	129 (40%)	120 (43%)
Performance status				
0	668 (50%)	145 (43%)	162 (50%)	142 (51%)
1	504 (38%)	149 (45%)	107 (33%)	105 (37%)
2	100 (7%)	25 (7%)	32 (10%)	20 (7%)
3	55 (4%)	13 (4%)	16 (5%)	12 (4%)
Unknown	12 (1%)	2 (1%)	5 (2%)	2 (1%)
White blood cell count, $\times 10^9/L$				
Median	15.4	13.6	15.3	9.1
Range	0.1-450	0.3-247	0.5-367	0.5-709
Hemoglobin level, g/dL				
Median	8.5	8.4	8.4	8.6
Range	1.9-17.0	2.2-17.2	3.4-16.7	3.6-15.2
Platelet count, $\times 10^9/L$				
Median	48	46	50	54
Range	0-1150	1-736	0-468	0-999
Bone marrow blasts, %				
Median	71	68	66	66
Range	0-100	0-100	2-100	0-98
Peripheral blood blasts, %				
Median	59	49	45	44
Range	0-100	0-100	0-100	0-100
Cytogenetic risk				
Favorable	347 (26%)	69 (21%)	56 (17%)	43 (15%)
Intermediate	834 (62%)	220 (66%)	214 (66%)	193 (69%)
Adverse	124 (9%)	34 (10%)	36 (11%)	35 (12%)
Unevaluable	34 (3%)	11 (3%)	16 (5%)	10 (4%)
Specific cytogenetic aberrations				
t(8;21)	274 (20%)	54 (16%)	41 (13%)	39 (14%)
inv(16)/t(16;16)	73 (5%)	15 (4%)	15 (5%)	4 (1%)
add(5q)/del(5q)/-5	24 (2%)	8 (2%)	13 (4%)	16 (6%)
add(7q)/del(7q)/-7	44 (3%)	18 (5%)	16 (5%)	15 (5%)
t(11q23)	58 (4%)	12 (4%)	8 (2%)	6 (2%)
Complex karyotype	41 (3%)	18 (5%)	23 (7%)	20 (7%)
Monosomal karyotype	46 (3%)	21 (6%)	23 (7%)	19 (7%)

(49.6% and 37.0% at 5 years, $P < .001$). Among those aged ≥ 50 , however, increasing age did not seem to affect OS, because survival curves for patients aged 50 to 54, 55 to 59, and 60 to 64 years were superimposed, with 5-year OS rates of 38.2%, 35.1%, and 38.0%, respectively ($P = .934$; Fig. 1B).

To evaluate whether the difference in OS between those aged < 50 and ≥ 50 years depends on cytogenetic risk, comparisons between these 2 groups were made within each cytogenetic risk group. This analysis showed that the intergroup difference was significant for favorable ($P < .001$; Fig. 2A), intermediate ($P < .001$; Fig. 2B), and adverse cytogenetic risk ($P < .001$, Fig. 2C). The effect of age on OS remained significant in a multivariate analysis adjusting for other covariates (Table 3). Allogeneic HCT

was performed for 687 (51%) of the patients aged < 50 years, 101 (30%) of those aged 50 to 54 years, 58 (18%) of those aged 55 to 59 years, and 19 (7%) of those aged 60 to 64 years. Censoring the findings for these patients at the time of allogeneic HCT did not alter the main results; Kaplan-Meier survival curves with censoring of patients undergoing allogeneic HCT are shown for those aged < 50 and ≥ 50 years in Fig. 3.

Finally, we examined whether lack of significant interaction between age and OS in patients aged 50 to 64 years remains after adjusting for other potentially confounding factors. When a multivariate analysis was undertaken for these older patients by including the covariates listed in Table 3, age group had no impact on OS (HR = 0.93; 95% CI = 0.76-1.13, for patients aged

TABLE 2. Remission Induction Results and Outcomes at 5 Years by Age Group

Outcome	Age <50 y N = 1339 (1069) ^a	Age 50-54 y N = 334 (260) ^a	Age 55-59 y N = 322 (246) ^a	Age 60-64 y N = 281 (213) ^a	<50 vs ≥50 y	50-54 vs 55-59 vs 60-64 y
Complete remission	79.8%	77.8%	76.4%	75.8%	<i>P</i> = .078	<i>P</i> = .829
95% CI	77.6%-82.0%	73.0%-82.2%	71.4%-80.9%	70.1%-80.9%		
Early death ^b	1.8%	1.5%	2.5%	3.2%	<i>P</i> = .367	<i>P</i> = .356
95% CI	1.2%-2.7%	0.5%-3.5%	1.1%-4.8%	1.5%-6.0%		
Overall survival	49.6%	38.2%	35.1%	38.0%	<i>P</i> < .001	<i>P</i> = .934
95% CI	46.7%-52.5%	32.7%-43.7%	29.2%-41.1%	31.9%-44.1%		
Relapse-free survival	40.6%	29.2%	30.8%	37.3%	<i>P</i> = .002	<i>P</i> = .126
95% CI	37.5%-43.6%	23.6%-35.1%	24.7%-37.1%	30.6%-43.9%		
Relapse	53.4%	62.6%	63.6%	57.1%	<i>P</i> = .008	<i>P</i> = .196
95% CI	50.3%-56.5%	56.2%-68.3%	56.8%-69.7%	50.0%-63.6%		
Nonrelapse mortality	6.0%	8.2%	5.6%	5.6%	<i>P</i> = .695	<i>P</i> = .388
95% CI	4.6%-7.5%	5.2%-12.0%	3.1%-9.2%	3.1%-9.3%		

Abbreviation: CI, confidence interval.

^a Figures in parentheses represent numbers of patients who achieved complete remission.

^b Death within 30 days after the start of induction therapy.

55-59 years; HR = 0.93; 95% CI = 0.76-1.14, for patients aged 60-64 years; both with reference to those aged 50-54 years).

DISCUSSION

To investigate how increasing age affects outcomes for patients with newly diagnosed AML, we analyzed data for 2276 patients 15 to 64 years of age who were treated uniformly, regardless of age, in 3 consecutive prospective AML studies by JALSG. This large-scale retrospective analysis yielded several relevant findings: 1) age 50 was a significant dividing point for outcomes; 2) patients aged 50 to 64 years were more susceptible to relapse, but not to early death or nonrelapse mortality than those younger than 50 years; and 3) outcomes did not differ among patients aged 50 to 54, 55 to 59, and 60 to 64 years.

Why were the survival rates for patients 50 years of age or older in our study significantly inferior to those of patients younger than 50? Our data indicate that worse outcomes for older patients resulted from higher relapse rates. In AML, it has been well established that cytogenetic findings at diagnosis are associated with the risk of relapse.¹⁷⁻²⁰ Comparison of the frequencies of distinct cytogenetic aberrations showed that younger patients were more likely to exhibit favorable cytogenetics such as t(8;21) and inv(16)/t(16;16), whereas older patients were more likely to show adverse cytogenetics such as abnormalities of chromosome 5 or 7, complex karyotype, and monosomal karyotype. However, such a difference in the distribution of cytogenetics alone could not have accounted for the difference in outcomes between patients aged < 50 and ≥ 50 years observed in this study, because the significant differences in OS

between these 2 age groups were seen for all cytogenetic risk groups.

Moreover, it could be expected that allogeneic HCT would result in more favorable outcomes for younger patients. However, although the proportion of patients who had undergone allogeneic HCT was indeed higher among younger than older patients, censoring the findings obtained at the time of allogeneic HCT produced no major changes in the study results. Therefore, it seems that neither cytogenetics nor allogeneic HCT can explain why older patients suffered relapse more frequently than younger patients. Secondary AML could not have been the reason, either, because our study cohort consisted of only patients with de novo AML. Other mechanisms that had not been studied here, such as molecular profiles, may play a significant role in differences in outcomes for younger and older patients.²¹⁻²⁴

The analytic results for data of patients 50 years of age or older in our study also provide insights into the treatment of older patients with AML. Patients aged 50 to 54, 55 to 59, and 60 to 64 years had similar long-term survival, and no differences in early death or nonrelapse mortality were observed among them. This finding calls into question whether older patients really need to be treated differently. Recently, Lowenberg et al compared the effect of a doubled dose of daunorubicin of 90 mg/m² with that of a conventional dose of 45 mg/m² in the context of the 3+7 regimen for patients aged 60 years or older.²⁵ Although no difference in outcome was observed overall, patients between 60 and 65 years of age significantly benefited from the doubled dose of daunorubicin. Taking these results into account, older and fit patients, especially those under the age of 65 years, may still benefit from intensified chemotherapy.