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Analysis of prognostic factors in newly diagnosed patients with acute promyelocytic leukemia: the APL92 study of the Japan Adult Leukemia Study Group (JALSG)

Abstract All-*trans*-retinoic acid (ATRA) has been incorporated in front-line therapy for newly diagnosed acute promyelocytic leukemia (APL). We conducted a multicenter study of differentiation therapy with ATRA alone or in combination with chemotherapy followed by intensive postremission chemotherapy in patients with

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APL (the JALSG APL92 study), and analyzed prognostic factors to increase the cure rate in our subsequent trial. From 1992 to 1997, adult patients with newly diagnosed APL received oral ATRA 45 mg/m^2 daily alone until complete remission (CR) if initial leukocyte counts were $< 3.0\times10^9$/l, and ATRA daily plus daunorubicin (DNR) 40 mg/m$^2\times$3 days plus enocitabine (BHAC) 200 mg/m$^2\times$5 days if leukocyte counts were $\geq 3.0 \times 10^9$/l. If peripheral blasts exceeded 1.0×10^9/l during therapy, DNR×3 days plus BHAC×5 days was added. After CR was achieved, three courses of consolidation and six courses of maintenance/intensification chemotherapy were administered. Of 376 patients enrolled, 369 were evaluable (median age 46 years, range 15–86 years; median leukocyte counts 2.0×10^9/l), and 333 (90%) achieved CR (94% of patients treated with ATRA alone, 88% with ATRA plus later chemotherapy, 89% with ATRA plus initial chemotherapy, and 86% with ATRA plus initial and later chemotherapy). At a median follow-up of 45 months, the predicted 6-year overall and event-free survival (EFS) rates for all patients were 65% and 52%, respectively. Favorable prognostic factors for CR were younger age, no or mild purpura, high serum total protein level, low lactate dehydrogenase level, and no or mild disseminated intravascular coagulation (DIC). Favorable prognostic factors for EFS were leukocyte counts $< 10.0\times10^9$/l, mild DIC, and no sepsis during induction therapy. In the JALSG APL97 study, we intensified chemotherapy for patients with leukocyte counts $\geq 3.0\times10^9$/l, and are randomly testing whether further chemotherapy is required for APL patients with negative PCR for PML/retinoic acid receptor α in the maintenance phase.

Keywords Acute promyelocytic leukemia · All-*trans*-retinoic acid · Differentiation therapy · PML/RARα · Disseminated intravascular coagulation

Introduction

Differentiation therapy for acute promyelocytic leukemia (APL) with all-*trans*-retinoic acid (ATRA) has markedly modified the therapeutic approach to APL [4, 14, 19, 24]. APL is a distinctive subtype of acute myeloid leukemia (AML), characterized by unique morphological features, by the t(15;17) translocation that fuses the PML gene to the retinoic acid receptor (RAR) α gene, and by coagulopathy associated with disseminated intravascular coagulation (DIC) and primary fibrinolysis [3, 4, 22, 24]. Intensive chemotherapy alone has achieved long-term survival in approximately 25% to 50% of patients with APL [6, 13, 16]. However, APL typically presents with a bleeding diathesis that is often exacerbated by cytotoxic chemotherapy, leading to a relatively high early mortality rate, primarily from intracranial hemorrhage [22, 24]. ATRA can induce a high rate of complete remission (CR) in patients with APL [4, 14, 19]. APL cells are eliminated by the differentiating effect of ATRA, resulting in a low incidence of life-threatening coagulopathy and infections [5, 24]. During ATRA therapy, however, a rapid increase in leukocyte number is often seen, accompanied by retinoic acid (RA) syndrome [11]. The second drawback of ATRA therapy is the development of resistance, and the duration of remission is relatively short in patients treated with ATRA alone after achievement of CR [19].

Several groups, including ours, have reported improved treatment outcomes with ATRA alone or in combination with chemotherapy during remission induction therapy followed by intensive postremission chemotherapy in patients with newly diagnosed APL, compared with chemotherapy alone [9, 15, 18, 23, 25]. However, more than 25% of patients who receive ATRA followed by chemotherapy relapse [2, 18, 23]. To increase the cure rate in our subsequent study, we analyzed prognostic factors in numerous patients with newly diagnosed APL in the JALSG APL92 study.

Patients and methods

Patients

A total of 376 consecutive adult patients with newly diagnosed APL were enrolled in the JALSG APL92 study between January 1992 and May 1997. Treatment outcomes of the first 110 and 198 patients have been reported previously [2, 15]. The diagnosis of APL was based on the French-American-British classification [3], and bone marrow smears were centrally reviewed by the JALSG Pathology Committee. The diagnosis was confirmed in the majority of patients by the presence of t(15;17) and/or the PML/RARα fusion transcript [12]. Written, informed consent was obtained from patients or their families before study entry, and the study protocol was approved by the institutional review boards in all participating centers.

Treatment regimens

As remission induction therapy, patients with leukocyte counts $< 3\times10^9$/l received ATRA 45 mg/m^2 three times daily (kindly provided by Hoffman La Roche, Basel, Switzerland, through the Japanese Ministry of Health and Welfare Leukemia Study Group) orally after meals until achievement of CR. ATRA at the same dosage combined with daunorubicin (DNR) 40 mg/m^2 per day (as a 30-min infusion) for 3 days and enocitabine (BHAC) 200 mg/m^2 per day (as a 30-min infusion) for 5 days was administered to patients who had initial leukocyte counts $\geq 3\times10^9$/l. Patients who had blast and promyelocyte counts in the peripheral blood $> 1\times10^9$/l during treatment with ATRA were scheduled to receive DNR 40 mg/m^2 for 3 days and BHAC 200 mg/m^2 for 5 days in addition to ATRA. Heparin and/or other antifibrinolytic agents (dalteparin, gabexate mesilate, or nafamostat mesilate), fresh frozen plasma, and platelet transfusions were administered if considered necessary by the primary attending physician.

After achieving CR, patients received three different courses of consolidation chemotherapy. The first consolidation regimen consisted of mitoxantrone (MIT) 7 mg/m^2 (as a 30-min infusion) on 3 days and cytarabine (ara-C) 200 mg/m^2 (as a continuous infusion) on 5 days. The second consolidation regimen consisted of BHAC 200 mg/m^2 as a 3-h infusion on 7 days, etoposide (VP-16) 100 mg/m^2 (as a 1-h infusion) on 5 days, DNR 50 mg/m^2 as a 3-h infusion on 3 days, and 6-mercaptopurine (6-MP) 70 mg/m^2 orally for 7 days. The third consolidation regimen consisted of BHAC 200 mg/m^2 as a 3-h infusion on 7 days and aclarubicin (ACR) 14 mg/m^2 (as a 30-min infusion) on 7 days.

After completion of consolidation therapy, patients received six courses of maintenance/intensification therapy every 6 weeks. The maintenance/intensification therapy was administered based on the results of the JALSG AML87 study [20], in which patients receiving a longer duration of maintenance/intensification therapy showed significantly better disease-free survival (DFS) rates. The first course consisted of BHAC 170 mg/m^2 (as a 2-h infusion on days 1 through 5), DNR 30 mg/m^2 (as a 30-min infusion on days 1 and 4), and 6-MP 70 mg/m^2 (orally on days 1 through 7). The second course consisted of BHAC 170 mg/m^2 (as a 2-h infusion on days 1–5), MIT 5 mg/m^2 (as a 30-min infusion on days 1 and 2). The third course was BHAC 170 mg/m^2 (as a 2-h infusion on days 1–5) and VP-16 80 mg/m^2 (as a 1-h infusion on days 1, 3, and 5), and vindesine (VDS) 2 mg/m^2 (as a bolus infusion on days 1 and 8). The fourth course consisted of BHAC 170 mg/m^2 (as a 2-h infusion on days 1–5) and ACR 14 mg/m^2 (as a 30-min infusion on days 1 through 4), and 6-MP 70 mg/m^2 orally on days 1–7. The fifth and sixth courses were the same as the first and third, respectively.

Response criteria and statistical analyses

Response was evaluated by standard criteria generally used for chemotherapy [15, 17, 20]. CR was defined as less than 5% blasts and promyelocytes with normal erythropoiesis, thrombopoiesis, and granulopoiesis in the bone marrow, neutrophil counts $>1.5\times10^9$/l, and platelet counts $>100\times10^9$/l in the peripheral blood. To test factors predicting the achievement of CR, the χ-squared test was used for univariate analysis and the logistic progression model for multivariate analysis. Survival was calculated from the first day of therapy until death. The event-free survival (EFS) rate was measured from the first day of therapy until relapse or death, and the EFS rate of patients who did not achieve CR was defined as 0. The DFS rate for patients who achieved CR was measured from the date of CR until relapse or death. Patients who underwent bone marrow transplantation (BMT) were reviewed at the date of BMT. EFS and DFS were determined according to the Kaplan-Meier method, and compared using the generalized Wilcoxon test, log-rank test for univariate analysis, and Cox regression model for multivariate analysis. SAS software (SAS Institute, Cary, N.C.) was used for these analyses.

Results

Of 376 consecutively enrolled patients, 3 died before the start of therapy and there were misdiagnoses in 4. Thus 369 patients were evaluated for treatment outcome. Patients experiencing early death were not excluded from analysis, and 12 patients died of hemorrhage within 7 days. Patient characteristics are summarized in Table 1. There were 173 men and 196 women; their age ranged from 15 to 86 years (median 46 years). The median leukocyte count was 2.0×10^9/l (range 0.2–356.0×10^9/l) at study entry. Of the 369 patients, 223 started treatment with ATRA alone, and in 97 of these chemotherapy was subsequently added to ATRA due to an increase in blasts and promyelocytes. The other 146 patients initially received both ATRA and chemotherapy, and in 36 an additional cycle of chemotherapy was subsequently added to ATRA due to an increase in blasts plus promyelocytes. Of the 369 evaluable patients, 333 (90%) achieved CR at a median of 40 days (range 8–84 days) after the start of therapy. Table 1 shows the breakdown of those who achieved CR by treatment regimen, age group, and initial leukocyte count.

During induction therapy, 28 patients (8%) showed signs of RA syndrome, primarily fever and respiratory distress, as previously described [11]. Only one patient died of RA syndrome. During the first 28 days from the start of therapy 28 patients (8%) died. Failure to achieve CR was mainly due to fatal hemorrhage.

Univariate analysis showed that factors with significance for achieving CR were no or minor purpura, no or mild DIC, age <30 years, age <70 years, leukocyte count $<10.0\times10^9$/l, leukocyte count $<20.0\times10^9$/l, lactate dehydrogenase (LDH) level <1000 U/l, LDH level <700 U/l, serum protein level of ≥7.0 g/dl, and performance status (PS) 0 or 1 (Table 2). Multivariate analysis showed that no or minor purpura ($P=0.0024$), serum protein level ≥7.0 g/dl ($P=0.0136$), LDH level <1000 U/l ($P=0.0265$), age <30 years ($P=0.0308$), and no or mild DIC during induction therapy ($P=0.0373$) were independent significant prognostic factors for achieving CR (Table 2). We tentatively

Table 1 Patient characteristics and clinical outcomes in induction therapy

	No. of patients	No. (%) achieving CR
Enrolled	376	
Nonevaluable	7[a]	–
Evaluable	369	333 (90)
Age groups (years)[b]		
15–29	72	71 (99)
30–49	140	125 (89)
50–69	138	124 (90)
70–86	19	13 (68)
Leukocyte count ($\times10^9$/l)[c]		
<3.0	218	203 (93)
3.0–9.9	58	53 (91)
≥10.0	93	77 (83)
Induction therapy		
ATRA alone	126	119 (94)
ATRA + later chemotherapy	97	85 (88)
ATRA + initial chemotherapy	110	98 (89)
ATRA + initial and later chemotherapy	36	31 (86)

[a]Three untreated, four misdiagnosed
[b]Age range 15–86 years (median 46 years)
[c]Leukocyte count range 0.2–356.0×10^9/l (median 2.0×10^9/l)

Table 2 Favorable factors for achievement of CR in the JALSG APL92 study

Favorable variable		% of patients	CR rate (%)	*P*-value
Univariate (chi-square)				
Age	< 30 years	20	98 vs 88	0.008
Age	< 70 years	95	91 vs 68	0.001
Leukocyte count	$< 10.0\times10^9$/l	75	93 vs 83	0.005
Leukocyte count	$< 20.0\times10^9$/l	83	92 vs 80	0.003
LDH level	< 1000 U/l	86	93 vs 75	0.000
LDH level	< 700 U/l	74	93 vs 84	0.009
Serum protein	≥7.0 g/dl	56	95 vs 85	0.001
Purpura at diagnosis	None to mild	86	93 vs 73	0.000
DIC during induction	None or mild	50	96 vs 85	0.000
PS	0 or 1	71	92 vs 85	0.028
Multivariate (logistic model)				
Purpura at diagnosis	None to mild	86	93 vs 73	0.0024
Serum protein	≥7.0 g/dl	56	95 vs 85	0.0136
LDH level	< 1000 U/l	86	93 vs 75	0.0265
Age	< 30 years	20	98 vs 88	0.0308
DIC during induction	None or mild	50	96 vs 85	0.0373

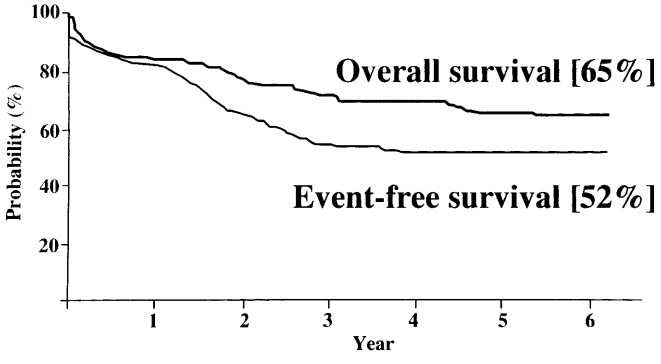

Fig. 1 Kaplan-Meier estimates of overall survival and EFS probability in evaluable patients in the APL92 study

defined purpura as minor if localized petechiae were present with no or a few small ecchymoses.

At a median follow-up of 45 months (range 24–52 months), the predicted 6-year overall survival and EFS rates of the 369 evaluable patients were 65% and 52%, respectively (Fig. 1). The predicted 6-year DFS rate in those achieving CR was 59%. Univariate analysis showed that significant favorable prognostic factors for EFS were initial leukocyte counts $< 10\times10^9$/l, LDH level < 1000 U/L, no or minor purpura at presentation, no or mild DIC during induction therapy, no sepsis during induction therapy, PS 0 or 1, and age < 70 years (Table 3). Multivariate analysis showed that initial leukocyte counts $< 10\times10^9$/l ($P = 0.0001$), no or mild DIC during induction therapy ($P = 0.0014$), and no sepsis during induction therapy ($P = 0.0059$) were independent significant favorable prognostic factors for EFS (Table 3). The predicted 6-year EFS rate in patients with initial leukocyte counts $< 10\times10^9$/l was 57%, which is significantly higher than the predicted 38% EFS rate in those with an initial leukocyte count $\geq 10\times10^9$/l ($P = 0.0001$) (Fig. 2).

In studies AML87 and AML89, which included standard intensive chemotherapy for newly diagnosed APL patients [1, 17, 20], 36 (80%) of 45 evaluable patients, and 45 (70%) of 64 evaluable patients achieved CR, respectively. The DFS rates in studies AML87 and AML89 were 40% and 45%, respectively, while the EFS rate in both studies was 32%. In combination with these two studies, 81 (74%) of 109 patients with APL who were treated with chemotherapy alone achieved CR. The combined DFS and EFS rates in studies AML87 and AML89 were 43% and 32%, respectively. There was a significant difference in the predicted 6-year DFS rate between APL92 and AML87/89 ($P = 0.0306$) (Fig. 3). Significant differences were also observed in the 6-year EFS rate between the two studies ($P = 0.0001$).

Discussion

In this prospective multicenter study a high CR rate and superior survival rate were achieved in newly diagnosed patients with APL who were initially treated with ATRA alone or in combination with chemotherapy followed by intensive postremission chemotherapy, compared with those who received chemotherapy alone. As we have previously reported [1, 15], compared with the AML87 and AML89 studies [17, 20] in which intensive chemotherapy was administered, there was a significant improvement in EFS in APL92. A European trial (APL91) and US Intergroup study comparing chemotherapy alone and ATRA followed by the same chemotherapy in newly diagnosed APL patients showed that the EFS rate was significantly higher in the ATRA groups [9, 23]. Moreover, since ATRA therapy is associated with fewer complications than myelosuppressive chemotherapy, the medical costs incurred during remission induction therapy are lower with ATRA than with chemotherapy [21]. Thus ATRA has been incorporated in front-line therapy for newly diagnosed APL worldwide [10, 14, 15, 18, 23].

In the present study, 90% of the patients achieved CR, confirming the high CR rates reported by other groups [9, 18]. However, only 74% of patients achieved

Table 3 Favorable factors for EFS in the JALSG APL92 study

Favorable variable		% of patients	6-year EFS (%)	*P*-value
Univariate (generalized Wilcoxon)				
Leukocyte count	$<10\times10^9$/l	75	57 vs 38	0.0001
LDH level	<1,000 U/l	86	56 vs 33	0.0001
Purpura at diagnosis	None or mild	86	54 vs 44	0.0006
DIC during induction	None or mild	50	63 vs 42	0.0001
Sepsis during induction	None	91	54 vs 29	0.0005
PS	0 or 1	71	61 vs 47	0.0113
Age	<70 years	95	53 vs 36	0.0147
Gender	Female	53	51 vs 36	0.0634
Multivariate (Cox's model)				
Leukocyte count	$<10.0\times10^9$/l	75	57 vs 38	0.0001
DIC during induction	None or mild	50	63 vs 42	0.0014
Sepsis during induction	None	91	54 vs 29	0.0059
Gender	Female	53	51 vs 36	0.0763

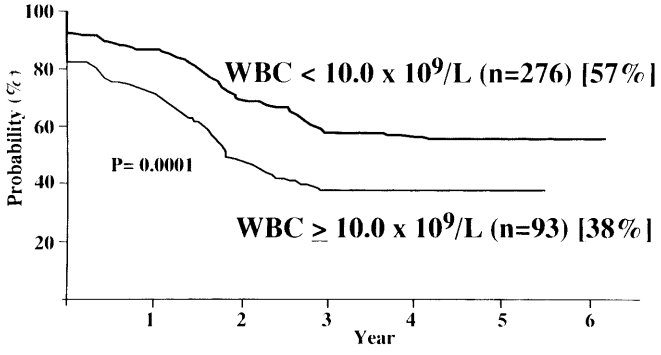

Fig. 2 Kaplan-Meier estimates of EFS probability based on initial leukocyte count in all evaluable patients in the APL92 study. A significant difference was observed between patients with initial leukocyte counts $<10.0\times10^9$/l ($n=276$) and those with higher counts ($n=93$) ($P=0.0001$)

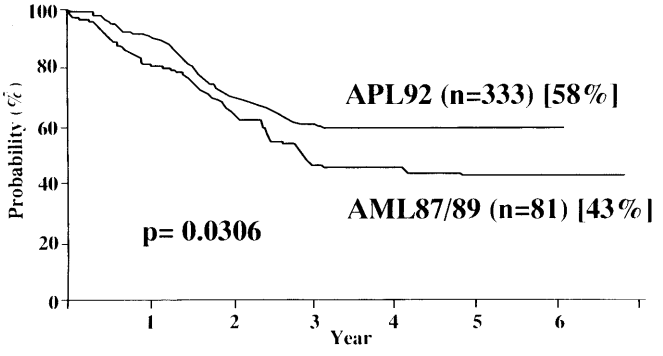

Fig. 3 Kaplan-Meier estimates of DFS probability in patients who achieved CR in the AML87/89 ($n=81$) and APL92 ($n=333$) studies. DFS in the APL92 study was significantly higher than that in the AML87/89 studies ($P=0.0306$)

CR in studies AML87 and AML89 [15, 17, 19]. The trend in favor of ATRA therapy may be attributed to the absence of resistant leukemia [9] and to the low incidence of early death [15]. ATRA can eliminate leukemia cells by virtue of its differentiating effect [5, 14, 19], which can rapidly resolve life-threatening coagulopathy during treatment. However, hemorrhage remained the major cause of death during remission induction therapy even in the present study. No or minor purpura at diagnosis ($P=0.0323$) and no or mild DIC during induction therapy ($P=0.0024$) were independent prognostic factors for achieving CR. This suggests that manifestations of hemorrhagic diatheses are important signs for achieving CR even in patients receiving ATRA therapy.

In this study, 13 (68%) of 19 patients aged ≥70 years achieved CR. Thus ATRA therapy can improve survival in elderly patients with APL. On the other hand, 71 (99%) of 72 patients aged <30 years achieved CR, and age <30 years was an independent favorable prognostic factor for achieving CR ($P=0.0308$). Since failure to achieve CR was mainly due to fatal hemorrhage, the high CR rate in younger patients may depend on low incidence of hemorrhage.

Compared with standard chemotherapy, ATRA therapy followed by intensive chemotherapy resulted in a significant improvement in the EFS rate [9, 23]. This may be attributable to the high CR and low relapse rates. It is likely that the lack of cross-resistance between ATRA and chemotherapeutic drugs contributed to the significant improvement in EFS rate. Nevertheless, many patients who received intensive chemotherapy after achieving CR relapsed in this study. Multivariate analysis showed that severe DIC and sepsis during induction therapy were independent unfavorable factors for EFS. Although these factors were associated with the achievement of CR, patients who experienced severe DIC or sepsis during induction therapy might have received insufficient ATRA therapy or chemotherapy, resulting in a poorer EFS. It is interesting that RA syndrome was associated with a poorer EFS in the European APL93 study [7].

We demonstrated that an initial leukocyte count $\geq10.0\times10^9$/l was also an independently significant unfavorable prognostic factor for longer EFS ($P=0.0001$). In the European APL93 study, higher circulating blast counts were also a predictive factor for poorer EFS and overall survival [7, 10]. The predicted 6-year EFS rate of 57% in patients with initial leukocyte counts $<10\times10^9$/l is comparable to the results from the European APL91 study in which patients with leukocyte counts $>10\times10^9$/l were not enrolled [9]. On the other hand, the predicted

6-year EFS rate in the approximately 25% of patients with initial leukocyte counts $\geq 10.0\times10^9$/l was 38%. A high leukocyte count at presentation was reported to be a significantly unfavorable prognostic factor for DFS in patients with APL who were treated with conventional intensive chemotherapy [6, 13, 16]. This indicates that DFS in patients treated with ATRA plus chemotherapy may depend on the chemotherapy regimen, and suggests that more effective regimens than currently administered should be considered at the induction and/or at the postremission therapy stage in patients with leukocyte counts $> 10.0\times10^9$/l.

Recently, another European group has reported a study of ATRA and idarubicin (IDA) in induction therapy in 480 patients with APL [18]. They reported a CR rate of 93% and 4-year EFS rate of 68%, indicating that combination therapy with ATRA and IDA is effective in APL [18]. We are currently conducting the multicenter study APL97, which incorporates the results of APL92. To evaluate individualized therapy based on the initial leukocyte count, patients are treated with ATRA alone or in combination with IDA and ara-C in remission induction therapy, followed by intensive consolidation therapy. It will be useful to detect minimal residual disease (MRD) by RT-PCR using the PML/RARα fusion transcripts at the end of consolidation therapy because the results of this assay can evaluate the quality of CR and predict subsequent relapse in patients with APL [8, 12]. If MRD is detected, more intensive therapy including allogeneic stem cell transplantation should be administered.

In APL92, maintenance/intensification therapy was administered based on the results of AML87 [20], in which patients receiving longer maintenance/intensification therapy had significantly longer DFS. The European APL93 trial also showed that continuous chemotherapy consisting of low-dose 6-MP and methotrexate as well as intermittent maintenance with ATRA can reduce the incidence of relapse in APL [10]. If short-term therapy without maintenance/intensification shows identical DFS rates compared with long-term therapy, it could be beneficial to the quality of life of patients and lead to a reduction in medical costs. In our experience, APL is a subtype of AML in which short-term therapy is effective. We are therefore conducting a randomized trial comparing maintenance/intensification therapy and no treatment after intensive consolidation therapy in adult patients with APL.

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