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ORIGINAL ARTICLE

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All-*trans* retinoic acid therapy for newly diagnosed acute promyelocytic leukemia: comparison with intensive chemotherapy

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Abstract We analyzed the results of treating patients with newly diagnosed acute promyelocytic leukemia (APL) with all-*trans* retinoic acid (ATRA) in the JALSG AML-92 study and compared them with those of the AML-87 and AML-89 studies, which consisted of standard chemotherapy. In the AML-92 study, patients were scheduled to receive 45 mg/m^2 oral ATRA daily until achievement of a complete remission (CR). If patients had initial leukocyte counts of $>3.0\times10^9$/l, they received 40 mg/m^2 daunorubicin (DNR) for 3 days and 200 mg/m^2 behenoyl cytarabine (BHAC) for 5 days in addition to ATRA. During remission induction therapy, if the patients showed peripheral blood myeloblast and promyelocyte counts of $>1.0\times10^9$/l, they received additional DNR and BHAC on the same schedule. After achievement of a CR, patients received three courses of consolidation and six courses of maintenance/intensification chemotherapy. Of 196 evaluable patients, 173 (88%) achieved a CR: 59 of 62 (95%) treated with ATRA alone, 41 of 49 (84%) treated with ATRA plus later chemotherapy, 63 of 73 (86%) treated with ATRA plus initial chemotherapy, and 10 of 12 (83%) treated with ATRA plus both initial and later chemotherapy. The CR rate in AML-92 was significantly higher than that in AML-89, but not than that achieved in AML-87. In addition, the early mortality and relapse rates in AML-92 were significantly lower than those in AML-89, but were not than those in AML-87. At a median follow-up of 36 months the predicted 4-year event-free survival (EFS) rate for 196 evaluable patients and the 4-year disease-free survival (DFS) rate for the CR cases were 54% and 62%, respectively. There was a significant difference in DFS between AML-92 and AML-87 (P = 0.0418) but not between AML-92 and AML-89 (P = 0.0687). In contrast, significant differences in EFS between AML-92 and both AML-87 (P = 0.0129) and AML-89 (P = 0.005) were observed. These results suggest that non-cross-resistant therapy combined with ATRA and intensive chemotherapy for APL contributes synergistically to the significant improvement in EFS.

Key words Acute promyelocytic leukemia · All-*trans* retinoic acid · Differentiation therapy · Chemotherapy

Introduction

It has been shown that all-*trans* retinoic acid (ATRA) can induce a high rate of complete remission (CR) in patients with acute promyelocytic leukemia (APL) due to its differentiating effect [4–6, 8, 15, 21, 23]. However, during ATRA therapy a rapid increase in leukocytes is commonly seen in APL patients; this is often accompanied by retinoic acid (RA) syndrome [4, 11]. The second drawback of ATRA therapy is the development of resistance, and the duration of remission after achievement of a CR with ATRA alone is relatively short [4, 8]. In contrast, intensive chemotherapy induces long-term survival in approximately 30–40% of patients [7, 14, 17].

We conducted a prospective multicenter trial of a combination of differentiation therapy with ATRA followed by intensive chemotherapy to obtain both a high CR rate and long-term survival in newly diagnosed APL patients [16]. Several groups have reported an improved treatment outcome with ATRA alone or in combination with chemotherapy during remission induction therapy followed by intensive postremission chemotherapy in such patients [9, 12, 16, 24]. However, as a considerable number of patients achieving a CR nonetheless relapse, the outcome of combination therapy consisting of ATRA and chemotherapy needs to be analyzed in detail. In this report we provide updated clinical results, analyze outcomes of treatment with ATRA combined with chemotherapy in newly diagnosed APL patients, and compare them with the results of our previous studies using standard intensive chemotherapy.

Patients and methods

A total of 45, 64, and 196 consecutive patients with newly diagnosed APL were registered in the AML-87 [20], AML-89 [19], and AML-92 studies, respectively, conducted by the Japan Adult Leukemia Study Group (JALSG). Eligibility criteria were morphological diagnosis and informed consent. Diagnosis of APL was made according to the French-American-British (FAB) classification [2, 3] and confirmed in part by the presence of t(15;17).

In the AML-92 study, patients received 45 mg/m^2 ATRA (kindly provided by Hoffman La Roche AG, Basel, Switzerland, through the Ministry of Health and Welfare Leukemia Study Group) orally after meals daily until achievement of a CR as remission induction therapy if they had leukocyte counts $<3\times10^9$/l at the start of therapy. ATRA given at the same dose together with daunorubicin (DNR) at 40 mg/m^2 per day for 3 days (30-min infusion) and behenoyl cytosine arabinoside (BHAC) at 200 mg/m^2 per day for 5 days (3-h infusion) were received by patients who had initial leukocyte counts of $>3\times10^9$/l. When the patients showed peripheral blood myeloblast and promyelocyte counts of $>1\times10^9$/l during treatment with ATRA, they were scheduled to receive DNR and BHAC at the same doses described above in addition to ATRA.

After achieving a CR, patients received three courses of consolidation chemotherapy. The first course consisted of 7 mg/m^2 mitoxantrone (MIT) given daily by 30-min infusion for 3 days and 200 mg/m^2 cytarabine (Ara-C) given daily by continuous infusion for 5 days. The second course consisted of 200 mg/m^2 BHAC for 7 days, 100 mg/m^2 etoposide (ETP) by 1-h infusion for 5 days, 50 mg/m^2 DNR for 3 days, and 70 mg/m^2 6-mercaptopurine (6-MP) p.o. for 7 days. The third course consisted of BHAC for 7 days and 14 mg/m^2 aclarubicin (ACR) by 30-min infusion for 7 days.

After the completion of consolidation therapy, patients received six courses of maintenance/intensification therapy given at 6-week intervals. The first course consisted of 170 mg/m^2 BHAC by 2-h infusion from day 1 to day 5, 30 mg/m^2 DNR by 30-min infusion on days 1 and 4, and 70 mg/m^2 6-MP given daily p.o. between days 1 and 7. The second course consisted of BHAC and 5 mg/m^2 MIT by 30-min infusion on days 1 and 2; the third course comprised BHAC, 80 mg/m^2 ETP by 1-h infusion on days 1, 3, and 5, and 2 mg/m^2 vindesine (VDS) by bolus infusion on days 1 and 8; and the fourth course consisted of BHAC, 14 mg/m^2 ACR by 30-min infusion on days 1–4, and 6-MP. The fifth and sixth courses were the same as the first and third courses, respectively.

In the AML-87 and AML-89 studies, remission induction therapy was response-oriented, individualized intensive chemotherapy as previously described elsewhere [20]. In the AML-87 study, patients were randomized to therapy with or without 0.35 mg/m^2 vincristine (VCR) given daily by 3-h infusion for 4 days [20]; induction therapy consisted of 200 mg/m^2 BHAC given daily by 3-h infusion, 70 mg/m^2 6MP given daily p.o. for 7 days, 40 mg/m^2 prednisolone (PSL) given daily by 3-h infusion for 4 days, and 50 mg/m^2 DNR given daily by bolus infusion for 5 days and for an additional 2 or 3 days if necessary. After achievement of a CR, patients received three courses of consolidation therapy consisting of BHAC for 7 days, DNR for 3 days, 6-MP for 7 days, and PSL for 4 days (first course); 6 mg/m^2 MIT by bolus infusion for 3 days, Ara-C for 5 days, and PSL for 4 days (second course); and BHAC for 7 days, ETP for 5 days, VDS on days 1 and 10, and PSL for 4 days (third course). After the completion of consolidation therapy, patients were randomized to either 4 or 12 courses of maintenance/intensification therapy using the regimens used for maintenance/intensification therapy courses 1–4 in the AML-92 study, except for the addition of PSL given for 4 days in each course. The 4 regimens were repeated 3 times in the groups receiving 12 courses.

In the AML-89 study, patients were randomized to receive either BHAC or Ara-C in induction therapy and the first and third courses of consolidation therapy [19]. The induction and consolidation therapies were the same as those used in the AML-87 protocol except that VDS was given on days 10 and 12 of the third consolidation course. Maintenance/intensification therapy was the same as that used in the AML-92 protocol, except for the addition of PSL.

Statistical analyses of the clinical data and CR rates were performed using the χ^2 test. Event-free survival (EFS) was measured from the 1st day of therapy to relapse or death; the EFS of patients who did not achieve a CR was defined as 0. Disease-free survival (DFS) for patients who achieved a CR was measured from the date of CR to relapse or death. Patients who underwent bone marrow transplantation (BMT) were censored at the date of BMT. EFS and DFS were determined according to the Kaplan-Meier method [18] and were compared using the generalized Wilcoxon test and the log-rank test. SAS programs (SAS Institute, Inc., Cary, N.C., USA) were used for the analysis.

Results

Patients' characteristics

The characteristics of patients enrolled in the AML-87, AML-89, and AML-92 studies are summarized in Table 1. Early death was not excluded, although two, one, and seven patients died of bleeding within 7 days in the respective studies. In the AML-92 study the median age was 46 years (range 15–86 years.) The median leukocyte count was 2.2×10^9/l (range 0.2–356.0×10^9/l) on admission; 110 patients had leukocyte counts of $<3.0\times10^9$/l, 35 had counts ranging between 3.0×10^9/l and 9.9×10^9/l, and 51 had counts of $>10.0\times10^9$/l. For remission induction therapy, 62 patients were treated with ATRA alone; chemotherapy

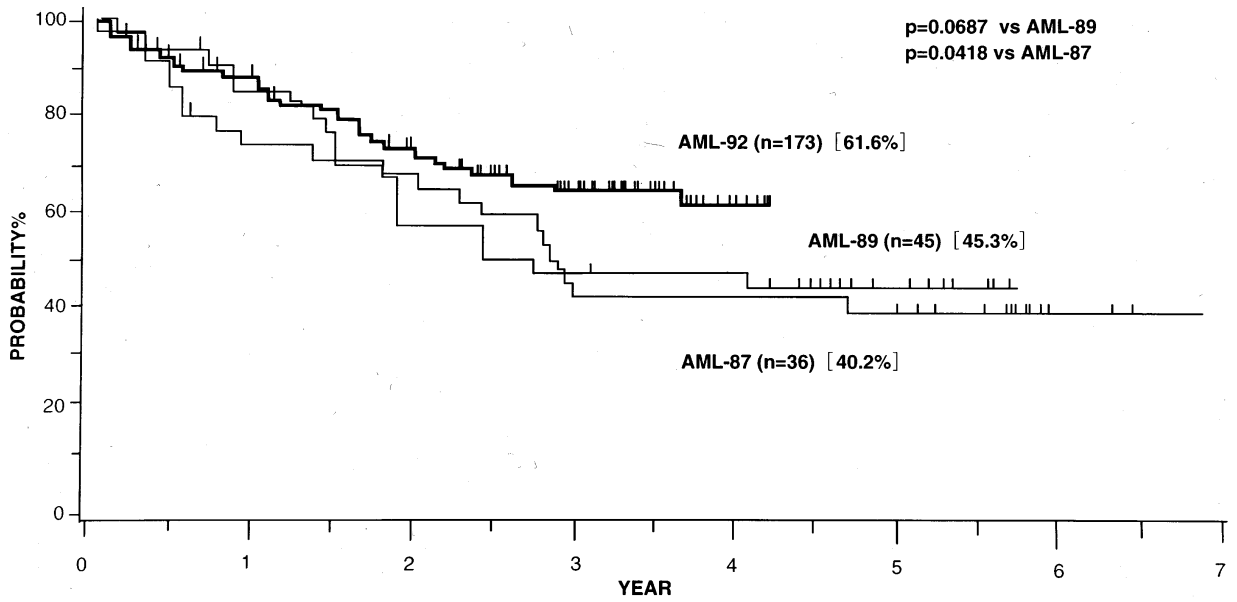

Fig. 1 DFS estimated by the Kaplan-Meier method in patients achieving CR in the AML-87 (n = 36), AML-89 (n = 45), and AML-92 (n = 173) studies. Significance of differences between AML-92 and AML-89 (P = 0.0687) and between AML-92 and AML-87 (P = 0.0418)

was added to ATRA later in the course of treatment due to increased peripheral blood blast and promyelocyte counts in 49 patients, 73 patients received both ATRA and chemotherapy from the beginning of therapy, and 12 received both initial and later chemotherapy together with ATRA.

The median age of patients in the AML-87 and AML-89 studies was 46 years (range 15–68 years) and 42 years (range 15–74 years), respectively. Median leukocyte counts were 1.5×10^9/l (range 0.36–89.6×10^9/l) and 3.62×10^9/l (range 0.4–129.3×10^9/l), respectively, in these studies.

Table 1 Patients' characteristics in AML-87, AML-89, and AML-92

Characteristic	AML-87	AML-89	AML-92
Number of evaluable cases	45	64	196
M/F	22/23	34/30	87/109
Median age (range, years)	46 (15–68)	42 (15–74)	46 (15–86)
<30	7	16	37
30–59	34	36	125
≥60	4	12	34
Initial leukocyte count	1.5	3.62	2.2
	(0.36–89.6)	(0.4–129.3)	(0.2–356.0)
Median (range, $\times10^9$/l):			
$<3.0\times10^9$/l	29	30	110
$3.0-9.9\times10^9$/l	2	11	35
$\geq10.0\times10^9$/l	14	23	51

Table 2 Comparison of the results of chemotherapy and combination therapy consisting of ATRA and chemotherapy in APL patients

Event	AML-87	AML-89	AML-92
Number of evaluable cases	45	64	196
CR (%)	36 (80)	45 (70)[a]	173 (88)[a]
Early death (within 4 weeks)	2 (4)	13 (20)[a]	17 (9)[a]
Relapse (%)	12 (33)	21 (47)[a]	42 (24)[a]
Death in CR (%)	8 (22)[a]	1 (2)	13 (8)[a]
DFS (%)	40.2[a]	45.3	61.6[a]
EFS (%)	32.2[a]	31.9[a]	54.3[a]

[a] Significant difference (P <0.05) as compared to ATRA therapy followed by chemotherapy (AML-92)

Treatment outcome

In the AML-92 study, 173 (88%) of 196 evaluable patients achieved a CR at a median of 38 days (range 15-84) days after the initiation of therapy (Table 2): 59 (95%) of 62 patients achieved a CR with ATRA alone; 41 (84%) of 49 with ATRA plus later chemotherapy; 63 (86%) of 73 with ATRA plus initial chemotherapy; and 10 (83%) of 12 with ATRA plus both initial and later chemotherapy (P = 0.222). All of the 37 patients aged <30 years, 108 (86%) of 125 aged 30–59 years, and 28 (82%) of 34 aged ≥60 years achieved a CR. Of the 110 patients with initial leukocyte counts of $<3.0\times10^9$/l, 99 (90%) achieved a CR, as did 32 (91%) of 35 with leukocyte counts of $3.0-9.9\times10^9$/l and 42 (82%) of 51 with counts of $>10.0\times10^9$/l. No patient had resistant leukemia.

In the AML-87 study, 36/45 (80%) patients achieved a CR at a median of 36 (range 23–74) days after the initiation of therapy; the CR rates in the AML-92 and AML-87 studies were not significantly different (P = 0.141). As determined by age, 5/7 (71%) patients aged <30 years, 32/34 (94%) aged 30–59 years, and 2/4 (50%) aged ≥60 years achieved a CR. In the AML-89 study, 45/64 (70%) patients attained a CR at a median of 32 (range 27–86) days after the initiation of therapy; the CR rate was significantly lower in the AML-89 study than in the AML-92 study (P = 0.001). As determined by age, 12/16 (75%) patients aged <30 years, 25/36 (69%) aged 30–59 years , and 8/12 (67%) aged ≥60 years achieved a CR.

During induction therapy with ATRA, 11 patients (6%) in the AML-92 study developed RA syndrome; 7 of these received ATRA plus later chemotherapy. Only one patient

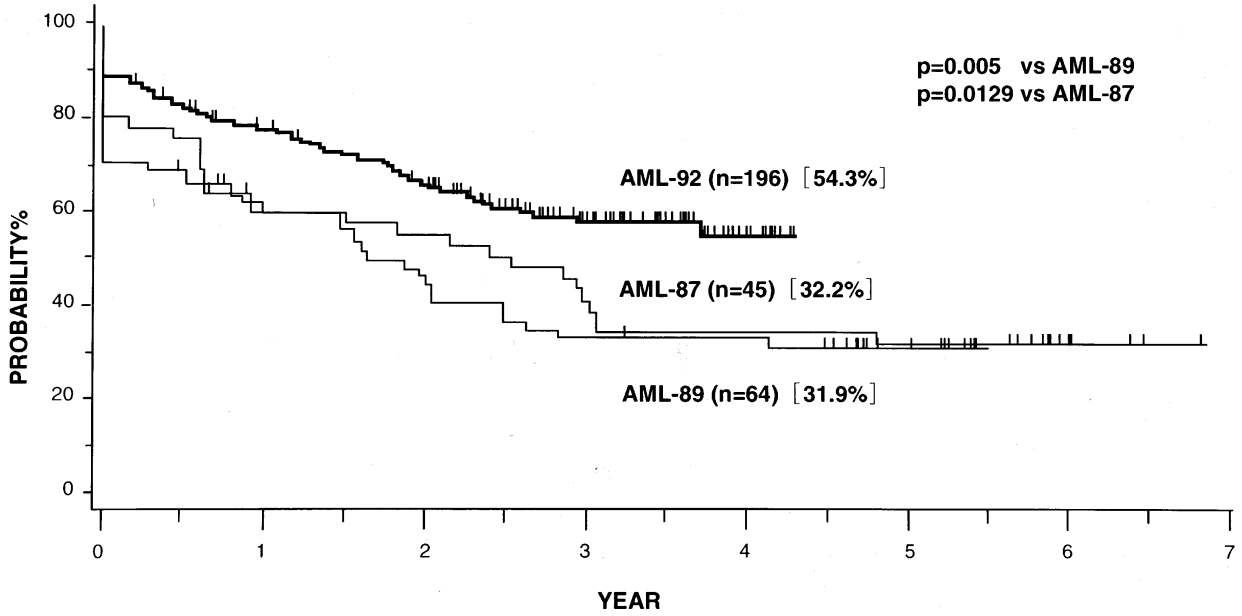

Fig. 2 EFS estimated by the Kaplan-Meier method in all evaluable patients in the AML-87 (n = 45), AML-89 (n = 64), and AML-92 (n = 196) studies. Significance of differences between AML-92 and both AML-89 (P = 0.005) and AML-87 (P = 0.0129)

died of RA syndrome. Early death within 4 weeks of the start of therapy was observed in 2 (4%), 13 (20%), and 17 (9%) patients in the AML-87, AML-89, and AML-92 studies, respectively. As compared with the AML-89 study, the early mortality rate in the AML-92 study was significantly different.

At a median follow-up of 36 (range 24-52) months, 42/173 (24%) patients had relapsed and 14 had died in the AML-92 study. Another 13 patients died in CR and 11 (6%) of them died of infection while undergoing consolidation therapy. In the AML-87 and AML-89 studies, respectively, 12 (33%) and 21 (47%) patients relapsed; in addition, 8 (22%) patients and 1 (2%) patient died in CR in the AML-87 and AML-89 studies, respectively. The predicted 4-year EFS of all 196 ATRA-treated patients was 54.3% [95% confidence limit (CL) 45–63%], and the DFS of those who achieved a CR was 61.6% (95% CL 52–71%). In the AML-87 study the predicted 4-year EFS and DFS were 32.2% and 40.2%, respectively; in the AML-89 study these values were 31.9% and 45.3%, respectively. There was a significant difference in DFS between the AML-92 and AML-87 studies (P = 0.0418), but not between the AML-92 and AML-89 studies (P = 0.0687; Fig. 1). In contrast, significant differences in EFS between the AML-92 and both the AML-87 (P = 0.0129) and AML-89 studies (P = 0.005) were observed (Fig. 2).

Discussion

Our prospective multicenter study revealed a higher CR rate and superior survival rate in newly diagnosed APL patients who were initially treated with ATRA alone or combined with chemotherapy followed by intensive consolidation and maintenance/intensification chemotherapy. These results confirm those reported by other groups [9, 12, 24].

The differences in CR and early mortality rates observed between the AML-92 and AML-89 studies, but not those seen between the AML-92 and AML-87 studies, were significant. However, as the numbers of patients in the AML-87 and AML-89 studies were relatively small, it is likely that the discrepancies between the AML-87 and AML-89 studies resulted from the patients' characteristics, including their age and initial leukocyte counts; the group of patients aged >60 years and/or showing high initial leukocyte counts was larger in the AML-89 study than in the AML-87 study. Nevertheless, the trend in favor of ATRA therapy may be attributed to the absence of resistant leukemia as reported by Fenaux et al. [10] because therapy-resistant leukemia was found in 3 (7%) and 5 (8%) patients in the AML-87 and AML-89 studies, respectively.

With conventional chemotherapy, failure to achieve a CR was partly due to fatal bleeding resulting from exacerbation of coagulopathy by rapid cell death [7, 17]. Through its differentiating effect, ATRA can eliminate leukemic cells; this could rapidly resolve the life-threatening complication of coagulopathy during the treatment of APL, resulting in a significantly shorter duration of coagulopathy. However, hemorrhage was a major cause of death during remission induction therapy with ATRA in AML-92. Warrell et al. [24] observed fatal hemorrhage in 6 of 87 patients (7%) treated with ATRA alone for induction therapy. These observations suggest that hemorrhagic diathesis at presentation is a critical sign and that adequate antihemorrhagic therapy, as well as early detection of leukemia and early initation of therapy, is of importance in achievment of a CR, even in ATRA therapy.

ATRA could also decrease the incidence of infections due to myelosuppression. We observed that 28/34 (82%) patients aged >60 years and 8/12 (67%) patients aged >70 years achieved a CR. Therefore ATRA might improve the CR and long-term survival rates in elderly APL patients.

ATRA is safe and well tolerated if RA syndrome can be prevented or managed. In this study, 11 of 196 patients (6%) developed RA syndrome, and only 1 died of it. This relatively low RA-syndrome incidence may be attributable to the combination of ATRA and relatively mild chemotherapy used in this study.

In comparison with the standard chemotherapy regimen used in the AML-87 and AML-89 studies, ATRA followed by intensive chemotherapy in newly diagnosed APL patients induces significant improvements in EFS as previously reported [16]. The predicted 4-year EFS for the AML-92 study indicates that $>50\%$ of adults with newly diagnosed APL will be cured by combination therapy consisting of ATRA and chemotherapy. A European trial comparing chemotherapy alone and ATRA followed by the same chemotherapy regimen in newly diagnosed APL patients was prematurely stopped after 18 months because the EFS was significantly better in the ATRA group [10]. This significant difference can be attributed to the high CR rate and low relapse rate obtained with the ATRA and chemotherapy combination. There is no cross-resistance between ATRA and chemotherapy, as ATRA has been effective in treating chemotherapy-resistant APL [4–6, 8, 21, 23]. Therefore, it is likely that non-cross-resistant therapy combined with ATRA and intensive chemotherapy contributes synergistically to the significant improvement in EFS.

High leukocyte counts at presentation are a significant prognostic factor for DFS in patients receiving conventional intensive chemotherapy [7, 14, 17], suggesting that more intensive chemotherapy, including allogeneic BMT, should be added to treatment regimens for such patients. It is also useful to detect minimal residual disease using the reverse transcriptase-polymerase chain reaction to detect PML/RARα fusion transcripts at the completion of consolidation therapy [1, 13]. Moreover, the medical costs incurred during the AML-92 study were significantly lower than those involved in either the AML-87 study or the AML-89 study [22].

The results of this and other studies suggest that ATRA followed by chemotherapy should be used as first-line therapy for newly diagnosed APL.

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