demethylation that has therapeutic effects; indeed, we observed relatively little demethylation during the course of treatment (Figs. 1, 4, 5, 6). Our observations are in stark contrast to those of Figueroa et al. [7], who observed extensive global DNA demethylation 15 days after AZA treatment. This difference is probably due to our sampling of cells after several rounds of treatment or measuring methylation in the CD34+ subset, whereas Figueroa et al. made use of the whole BM MNC fraction. Although they demonstrated near-identical methylation in CD34+ and CD34$^-$ cells, this was done only before treatment. The CD34+ fraction represents an undifferentiated tumor cell population that can differentiate to a variety of lineages [39] and that contains the cancer stem cell compartment of MDS [40]. One of the therapeutic effects of AZA treatment is the decrease in the largely CD34+ blast cell population, and this can occur as a result of either differentiation or death of CD34+ cells. In MDS3 and MDS4 samples, we observed a rapid drop in blast cell counts but only a minor decrease in methylation in CD34+ cells following AZA treatment. This suggests that the demethylation observed by Figueroa et al. resulted in differentiation from the CD34+ compartment or by the direct death of tumorigenic cells, resulting in a lower proportion of tumor-derived BM MNCs. This is consistent with the persistence of karyotypically abnormal HSCs after AZA treatment otherwise resulting in morphologically complete remission [41].

It is clear from the data (both array and bisulfite sequencing at *WT1*) that DNA methylation can be maintained or increased despite AZA treatment (Figs. 1A, 5A) within the CD34+ compartment. AZA is an inhibitor of *DNMT1*, which recognizes hemimethylated DNA generated during DNA synthesis; hence, DNA demethylation is passive and depends on proliferation. This implies that AZA treatment will result in a range of methylation levels across cells and that the cells we assayed maintained sufficient methylation to remain CD34+. This may be why we do not observe an obvious correlation between DNA methylation and AZA treatment, although the treatment has clear therapeutic effects. Similarly, the inability of AZA to drive demethylation within the CD34+ population provides an explanation for disease relapse after otherwise complete remission. This observation also suggests that combining AZA treatment with agents (e.g., granulocyte colony-stimulating factor [42], interferon-α [IFN-α] [43], IFN-γ [44]) that activate proliferation of quiescent HSCs may allow demethylation throughout the CD34+ population and prevent relapse.

Although we observed MDS-associated hypermethylation primarily in genes not expressed within the hematopoietic system, AZA treatment has beneficial effects, and these are likely to arise through DNA demethylation. Presumably, demethylation can have an effect only if it occurs within regulatory regions of genes that would otherwise either be expressed in the tumor cells or be activated on differentiation. This reasoning led us to concentrate on genes differentially methylated between RAEB-2 and RCMD and to incorporate data from our previous analysis of long-term AZA treatment in the SKM-1 cell line. We found a small number of genes (*TRIB2*, *NR4A2*, *POU4F1*, *HDC*, and *OTP*) that are hypermethylated in RAEB-2 and that have expression that appears repressed in RAEB-2 samples but is activated after in vitro AZA treatment. Both *TRIB2* [45] and *POU4F1* [46] have been implicated in the development of AML, although both are thought to act as oncogenes and are associated with progression of disease. Interestingly, *Pou4f1* is thought to regulate transcription of *Nr4a2* during mouse habenula development [47], suggesting that their expression may also be linked in the hematopoietic system.

NR4A2 stands out from the rest (Fig. 6B), having both strong differential methylation and being clearly activated by AZA treatment. In addition, *NR4A2* is highly expressed in MDS2 samples but is repressed in the MDS3 and MDS4 samples (supplemental online Fig. 11). The *NR4A* family (types 1, 2, and 3) has previously been implicated in AML and MDS due to the phenotypes of their mouse mutants [48]. The combined loss of both *Nr4a1* (*Nur77*) and *Nr4a3* (*Nor1*) results in rapid development of an AML-like phenotype in mice, whereas mice lacking a single allele of both genes develop a disease more similar to MDS. The complete loss of *Nr4a2* expression in the hematopoietic system has not been assessed due to an embryonic lethality arising from the neural function of *Nr4a2*, but the loss of a single allele results in hyperproliferation of HSCs, whereas overexpression drives HSCs to quiescence [49]. Furthermore, the *NR4A2* DMR was one of the few TT-DMRs (2 of the top 200) to also be strongly differentially methylated in normal hematopoietic cells, and the loss of *Dnmt3a* in mouse HSCs leads to upregulation of *Nr4a2* expression [50]. Both of these observations suggest that *NR4A2* is normally regulated by DNA methylation through the identified DMR. In combination, these lines of evidence strongly suggest the involvement of the suppression of *NR4A2* in the development of MDS.

Because *NR4A2* can be reactivated by AZA treatment, it is possible that at least part of the effect of AZA treatment results from the reactivation of *NR4A2*, and given that a partial loss of *Nr4a2* expression is sufficient to contribute to excessive HSC proliferation, it is possible that chemical agents [51] that can activate *NR4A2* may have therapeutic potential for MDS, possibly in combination with conventional AZA therapy.

Conclusion

Our results demonstrate that both MDS-associated hypermethylation and AZA-induced demethylation occur at restricted genomic loci. Our observations not only suggest a mechanism for MDS progression and a means of overcoming its recalcitrance but also pinpoint genes that may be responsible for both disease progression and the AZA response. Our findings suggest new avenues for both basic research in stem cell biology and clinical therapy for MDS patients.

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Author Contributions

Y.-F.W.: conception and design, provision of study material or patients, collection and/or assembly of data, data analysis and interpretation, manuscript writing, final approval of

manuscript; C.N.M.: data analysis and interpretation; M.T.: provision of study material or patients, collection and/or assembly of data, data analysis and interpretation; H.I., Y.S., and D.I.: provision of study material or patients; S.N.: conception and design, financial support, provision of study material or patients; Y.M.: conception and design, financial support, provision of study material or patients; L.M.J.: conception and design, data analysis and interpretation, manuscript writing, final approval of manuscript.

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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ORIGINAL REPORT

Tamibarotene As Maintenance Therapy for Acute Promyelocytic Leukemia: Results From a Randomized Controlled Trial

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ABSTRACT

Purpose
The introduction of all-*trans*-retinoic acid (ATRA) has significantly improved outcomes for acute promyelocytic leukemia (APL), although a subset of patients still suffer relapse. The purpose of this study was to evaluate the role of maintenance therapy with the synthetic retinoid tamibarotene in APL.

Patients and Methods
Patients with newly diagnosed APL in molecular remission at the end of consolidation therapy were randomly assigned to receive ATRA or tamibarotene, both orally, for 14 days every 3 months for up to 2 years.

Results
A total of 347 patients were enrolled. Of the 344 eligible patients, 319 (93%) achieved complete remission. After completing three courses of consolidation therapy, 269 patients underwent maintenance random assignment. The relapse-free survival (RFS) rate at 4 years was 84% for the ATRA arm and 91% for the tamibarotene arm (hazard ratio [HR], 0.54; 95% CI, 0.26 to 1.13). When the analysis was restricted to 52 high-risk patients with an initial WBC count $\geq 10.0 \times 10^9$/L, the intergroup difference was statistically significant, with 4-year RFS rates of 58% for the ATRA arm and 87% for the tamibarotene arm (HR, 0.26; 95% CI, 0.07 to 0.95). For patients with non–high-risk disease, the HR was 0.82 (95% CI, 0.32 to 2.01). The test for interaction between treatment effects and these subgroups resulted in $P = .075$. Both treatments were generally well tolerated.

Conclusion
In this trial, no difference was detected between ATRA and tamibarotene for maintenance therapy. In an exploratory analysis, there was a suggestion of improved efficacy of tamibarotene in high-risk patients, but this requires further study.

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INTRODUCTION

Front-line therapy combining all-*trans*-retinoic acid (ATRA) and chemotherapy has significantly improved outcomes for patients with acute promyelocytic leukemia (APL).[1-14] Nevertheless, up to 30% of patients still experience relapse and die of the disease.

Maintenance therapy is a therapeutic component that potentially reduces the risk of APL relapse. Randomized controlled trials conducted by the North American Intergroup[6] and the European APL Group[11] both demonstrated the beneficial effects of maintenance therapy. In contrast to these studies, we showed that six courses of intensified maintenance chemotherapy did not reduce relapse, but rather worsened overall survival (OS) as a result of higher incidences of late relapse, therapy-related leukemia, and failure to respond to reinduction therapy.[8] More recently, the Gruppo Italiano Malattie Ematologiche dell'Adulto reported that maintenance therapy did not yield any clinical benefits.[14] In view of these conflicting findings, maintenance therapy for APL remains an issue in need of further investigation.[15]

Tamibarotene (formerly Am80) is a synthetic retinoid that induces differentiation of HL-60 and NB-4 cells, with in vitro activity approximately 10 times more potent than that of ATRA.[16,17] This drug has a low affinity for the cellular retinoic acid binding protein, the overexpression of which is known to be associated with ATRA resistance.[18] In addition, unlike ATRA, tamibarotene has a favorable pharmacokinetic profile because the plasma level does not decline after daily administration.[19] These properties suggest that tamibarotene could be superior to ATRA. We previously conducted a phase II study of tamibarotene in patients with APL who had experienced relapse after ATRA-containing therapy and demonstrated the efficacy and safety of this agent in a relapse setting.[19]

These findings prompted the Japan Adult Leukemia Study Group to test tamibarotene as maintenance therapy for APL. To this end, a phase III study, designated APL204, was initiated with the aim of comparing tamibarotene with ATRA as maintenance therapy for patients with newly diagnosed APL. We report here the results of this study.

PATIENTS AND METHODS

Patients

Patients enrolled onto this study had been newly diagnosed with APL with documented cytogenetic and/or molecular evidence of t(15;17)/*PML-RARA*. Other eligibility criteria included age between 15 and 70 years; an Eastern Cooperative Oncology Group performance status between 0 and 3; and adequate functioning of the liver (serum bilirubin level < 2.0 mg/L), kidneys (serum creatinine level < 2.0 mg/dL), lungs (partial pressure of oxygen in arterial blood ≥ 60 Torr or saturation of peripheral oxygen $\geq 93\%$), and heart (no severe abnormalities detected on ECG and/or echocardiograms). Written informed consent was obtained from all patients before registration. The protocol was reviewed and approved by the institutional review board of each of the participating centers and was conducted in accordance with the Declaration of Helsinki. This study is registered at the University Hospital Medical Information Network Clinical Trials Registry as C000000154.

Treatments

For remission induction therapy, ATRA was administered to all patients at a daily dose of 45 mg/m^2 until complete remission (CR) or for 60 days, whichever was shorter. The chemotherapy protocol depended on the initial WBC count and blast count in the peripheral blood. If the initial WBC count was less than 3.0×10^9/L and the blast count was less than 1.0×10^9/L (group A), simultaneous chemotherapy was withheld. If the initial WBC count was between 3.0×10^9/L and 10.0×10^9/L and/or the blast count exceeded 1.0×10^9/L (group B), idarubicin (IDA) 12 mg/m^2 was administered on days 1 and 2, and cytarabine (AraC) 100 mg/m^2 was administered on days 1 to 5. If the initial WBC count was 10.0×10^9/L or higher (group C), IDA 12 mg/m^2 was administered on days 1 to 3, and AraC 100 mg/m^2 was administered on days 1 to 7. Patients whose blast counts increased to 1.0×10^9/L during the induction course were given additional chemotherapy consisting of IDA 12 mg/m^2 for 3 days and AraC 100 mg/m^2 for 7 days for group A patients, IDA 12 mg/m^2 for 1 day and AraC 100 mg/m^2 for 2 days for group B patients, and IDA 12 mg/m^2 for 1 day for group C patients. All patients who received additional chemotherapy during the induction course were classified as group D.

Treatment of coagulopathy was risk adapted and stratified into levels 1, 2, and 3. Disseminated intravascular coagulation (DIC) was diagnosed in accordance with the Japanese Ministry of Health and Welfare scoring system.[20] Patients with a diagnosis of DIC were treated as level 1 if they met at least one of the following criteria: less than 7 days had elapsed since the start of chemotherapy; complication with retinoic acid syndrome, pneumonia, or severe hemorrhagic complications, or (3) documented increase of the Japanese Ministry of Health and Welfare DIC score. Otherwise, patients with a diagnosis of DIC were treated as level 2, and those without DIC were treated as level 3. Platelet transfusions were administered to maintain the platelet count greater than 50×10^9/L for level 1, 30×10^9/L for level 2, and 20×10^9/L for level 3. Fresh frozen plasma was transfused to maintain the plasma fibrinogen level greater than 1.5 g/L for level 1, 1.0 g/L for level 2, and as required for level 3. Anticoagulants were used for both levels 1 and 2. Retinoic acid syndrome was treated with high-dose dexamethasone or methylprednisolone along with immediate interruption of ATRA.

Consolidation therapy consisted of three courses of intensive chemotherapy: mitoxantrone 7 mg/m^2 on days 1 to 3 and AraC 200 mg/m^2 on days 1 to 5 for the first course; daunorubicin 50 mg/m^2 on days 1 to 3 and AraC 200 mg/m^2 on days 1 to 5 for the second course; and IDA 12 mg/m^2 on days 1 to 3 and AraC 140 mg/m^2 on days 1 to 5 for the third course. Before the start of the third consolidation course, intrathecal injection of methotrexate, AraC, and prednisolone was used for CNS prophylaxis.

After completion of the third consolidation course, the *PML-RARA* transcript levels in the bone marrow were assessed. Patients in molecular remission at this time were then randomly assigned to oral administration of ATRA at a daily dose of 45 mg/m^2 or to tamibarotene at a daily dose of 6 mg/m^2, both for 14 days every 3 months. Random assignment was stratified according to induction treatment (ie, group A, B, C, or D). Maintenance therapy was continued for up to 2 years for a total of up to eight courses.

Assessments

CR was defined as the presence of all of the following: less than 5% of blasts in the bone marrow, no leukemic blasts in the peripheral blood or extramedullary sites, and recovery of peripheral-blood counts. Hematologic relapse was defined as the presence of at least one of the following: recurrence of more than 5% leukemic cells in the bone marrow, recurrence of any leukemic cells in the peripheral blood, or development of extramedullary

Table 1. Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	No. of Patients (N = 344)
Age, years	
Median	48
Range	15-70
Sex	
Male	183
Female	161
Performance status	
0	188
1	126
2	19
3	11
White blood cell count, $\times 10^9$/L	
Median	1.4
Range	0.1-127
Platelet count, $\times 10^9$/L	
Median	3.1
Range	0.1-47.0
Sanz's risk category	
Low	115
Intermediate	151
High	70
Unknown	8
Morphology	
M3	323
M3v	21
Induction therapy group	
A	133
B	56
C	69
D	86

Abbreviations: ATRA, all-*trans*-retinoic acid; M3v, M3 variant.

disease. Bone marrow was analyzed for *PML-RARA* levels after the end of consolidation therapy, after every two courses during maintenance therapy, and every 6 months thereafter. The *PML-RARA* levels were measured at a single independent laboratory using the real-time quantitative reverse transcription polymerase chain reaction assay as described elsewhere.[8] Levels less than 100 copies/μg RNA were defined as molecular remission for this study. If a patient lost molecular remission, an extra bone marrow examination was performed 1 month later to confirm the results. Molecular relapse was defined as loss of molecular remission confirmed in two consecutive bone marrow samples taken 1 month apart.

Statistical Analyses

The primary end point of this study was relapse-free survival (RFS), which was defined as the time from random assignment to hematologic or molecular relapse, death, or last visit, whichever came first. We aimed to include 240 patients in a maintenance random assignment procedure for the detection of an increase in the RFS probability by 17% in the tamibarotene arm compared with the ATRA arm. This sample size ensured two-tailed $\alpha = .05$, and $1\text{-}\beta = .83$. All the analyses for maintenance comparisons were intent-to-treat analyses.

Distributions of patient characteristics between groups were compared using the Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. The probabilities of RFS and OS were estimated using the Kaplan-Meier method, with differences between groups determined with the log-rank test. OS was defined as the time from registration to death or last visit. The Cox proportional hazards regression model was used for calculating the hazard ratio (HR) in conjunction with the 95% CI. The proportional hazards assumption was tested based on Schoenfeld residuals,[21] and the test for significance showed nonsignificance ($P = .491$), supporting that the proportional hazard assumption was not violated.

RESULTS

Patients

Between April 2004 and December 2010, 347 patients with newly diagnosed APL were enrolled onto this study. Three patients who had subsequently turned out to be negative for *PML-RARA* were excluded, leaving 344 patients eligible for analysis. Table 1 lists the baseline characteristics of the eligible patients.

Figure 1 depicts patient flow in the CONSORT diagram. For remission induction, 133 patients (39%) were included in treatment group A, 56 (16%) in group B, 69 (20%) in group C, and 86 (25%) in group D. Group D consisted of 83 patients who had been initially

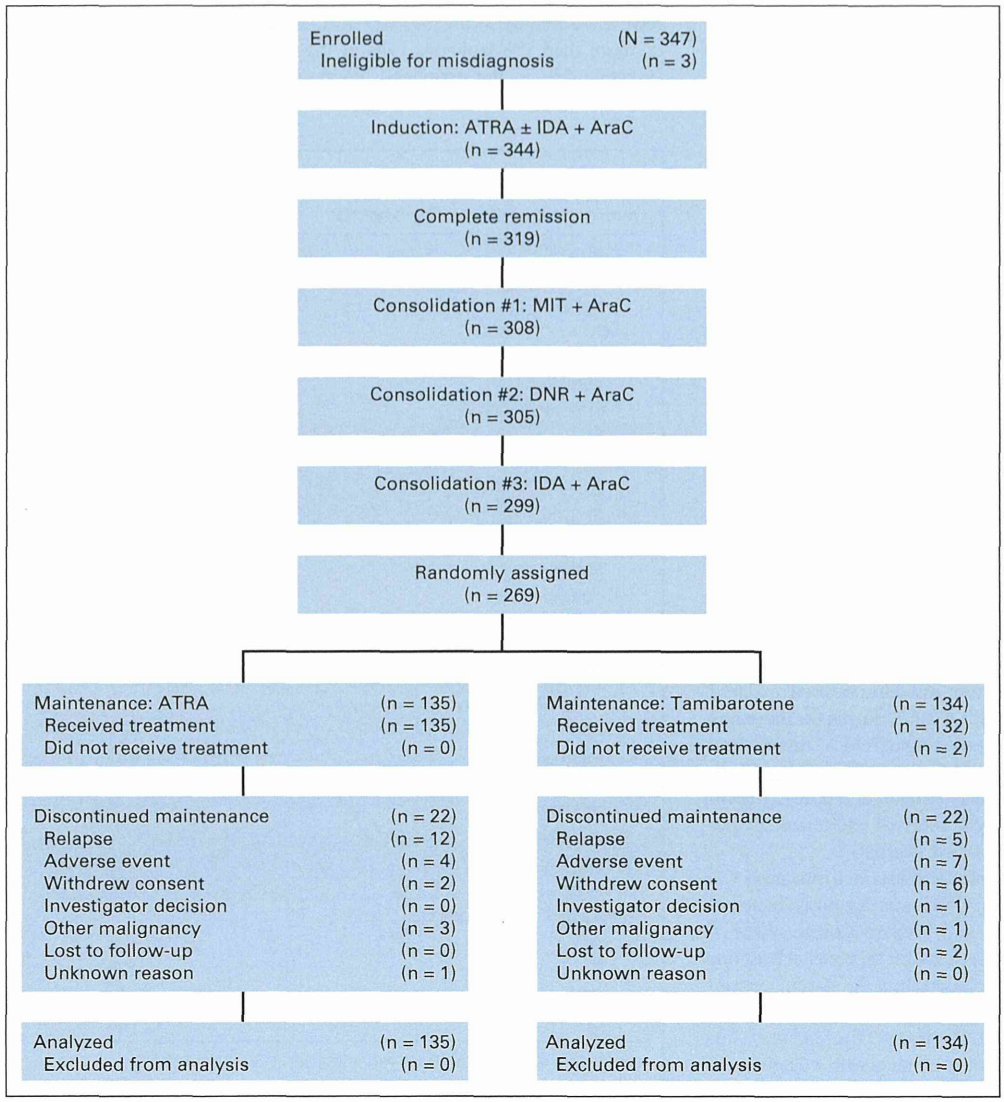

Fig 1. CONSORT diagram and treatment schema. AraC, cytarabine; ATRA, all-*trans*-retinoic acid; DNR, daunorubicin; IDA, idarubicin; MIT, mitoxantrone.

treated as group A, two patients who had been treated as group B, and one patient who had been treated as group C. CR was attained in 319 (93%) of the 344 eligible patients; CR rates by group were as follows: 92% for group A, 91% for group B, 87% for group C, and 99% for group D. Sixteen patients (4.7%) died within 30 days, and 14 of these deaths were associated with hemorrhagic complications. During the median follow-up of 4.3 years (range, 1.3 to 8.0 years), 39 relapses and 37 deaths were documented. The probability of OS for the entire cohort was 89% at 4 years.

Maintenance Comparisons

Among 299 patients who received the third consolidation course, 269 eventually underwent maintenance random assignment; 135 patients were randomly assigned to ATRA, and 134 patients were assigned to tamibarotene. All subsequent comparisons between the two arms were conducted by intention to treat. Table 2 lists the characteristics of randomly assigned patients. The main characteristics were equally distributed between the two arms.

Autologous hematopoietic cell transplantation was performed in 23 patients (16 patients in the ATRA arm and seven in the tamibarotene arm), all after relapse, and allogeneic hematopoietic cell transplantation was performed in two patients (one patient in each arm), both in first CR, for the treatment of secondary myelodysplastic syndrome (MDS). These two patients were censored at the time of transplantation. During the entire follow-up period, 30 patients (20 in the ATRA arm and 10 in the tamibarotene arm) suffered relapse, with the

Table 2. Demographics and Clinical Characteristics of Patients Randomly Assigned for Maintenance Therapy

Characteristic	No. of Patients		
	ATRA (n = 135)	Tamibarotene (n = 134)	
Age, years			.597
Median	48	46	
Range	15-70	16-69	
Sex			.807
Male	70	72	
Female	65	62	
Performance status			.840
0	72	78	
1	50	43	
2	8	8	
3	5	5	
White blood cell count, $\times 10^9$/L			.841
Median	1.3	1.4	
Range	0.2-111	0.2-88.5	
Platelet count, $\times 10^9$/L			.343
Median	2.8	3.3	
Range	0.2-20.8	0.1-47.0	
Sanz's risk category			.636
Low	46	44	
Intermediate	59	63	
High	26	26	
Unknown	4	1	
Morphology			.597
M3	126	128	
M3v	9	6	
Induction therapy group			.977
A	49	45	
B	21	22	
C	25	26	
D	40	41	

Abbreviations: ATRA, all-*trans*-retinoic acid; M3v, M3 variant.

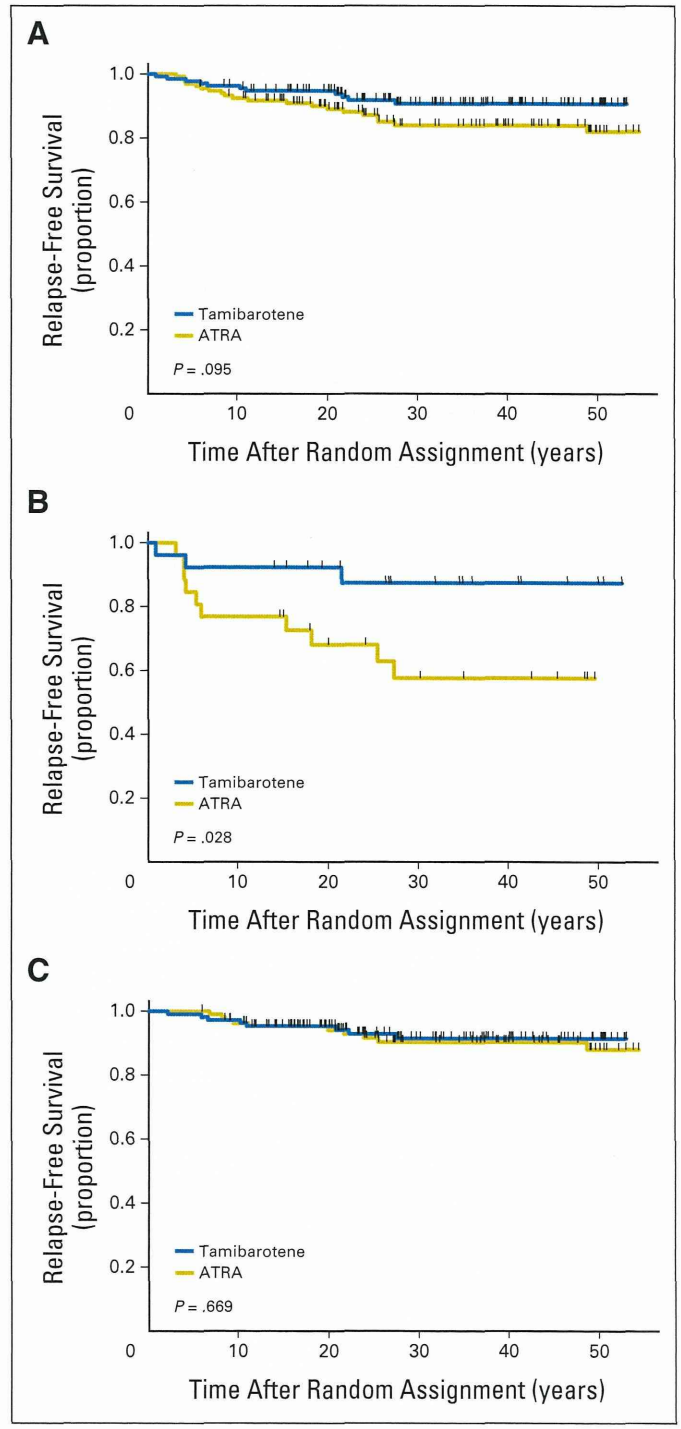

Fig 2. Kaplan-Meier curves for relapse-free survival in relation to maintenance therapy random assignment (A) for all patients (N = 269), (B) for patients with an initial WBC count of ≥ 10.0 × 10^9/L (n = 52), and (C) for patients with an initial WBC count less than 10.0 × 10^9/L (n = 217). ATRA, all-*trans*-retinoic acid.

median time from random assignment to relapse of 1.0 year for the ATRA arm and 0.8 year for the tamibarotene arm. Death occurred in two patients in the ATRA arm and four in the tamibarotene arm; the causes of death were transplant-related mortality (n = 2) in the ATRA arm and APL (n = 3) and secondary MDS (n = 1) in the tamibarotene arm. There was only one death during first CR of a patient in the tamibarotene arm 2.1 years after random assignment as a result of MDS.

Figure 2 compares the RFS curves of the two arms. RFS rates at 4 years were 84% in the ATRA arm and 91% in the tamibarotene arm, and this difference did not reach statistical significance ($P = .095$; HR, 0.54; 95% CI, 0.26 to 1.13; Fig 2A). However, when the analysis was restricted to high-risk patients with an initial WBC count of 10.0×10^9/L or higher, the intergroup difference was statistically significant ($P = .028$; HR, 0.26; 95% CI, 0.07 to 0.95), with 4-year RFS rates of 58% in the ATRA arm and 87% in the tamibarotene arm (Fig 2B). For patients whose initial WBC count was lower than 10.0×10^9/L, RFS was almost identical between the arms (90% for the ATRA arm *v* 92% for the tamibarotene arm; $P = .669$; HR, 0.82; 95% CI, 0.32 to 2.01; Fig 2C). The results of a test for interaction between treatment effects and subgroups suggest a possible difference in treatment effects between these two subgroups ($P = .075$).

Table 3 lists grade 2 or higher drug-related adverse events that were reported at a frequency of greater than 5% in either arm. Both treatments were generally well tolerated, and most of the adverse events were grade 2 or lower except for triglyceride increase. Hyperlipidemia was the most common adverse event in both arms, with a higher frequency in the tamibarotene arm. Skin rash was predominantly seen in the tamibarotene arm. Four patients in the ATRA arm and seven in the tamibarotene arm had to discontinue maintenance therapy because of adverse events. In the ATRA arm, nausea (n = 1), headache (n = 1), liver dysfunction (n = 1), and triglyceride increase (n = 1) resulted in discontinuation, whereas skin rash (n = 5), liver dysfunction (n = 1), and coagulopathy (n = 1) resulted in discontinuation in the tamibarotene arm.

DISCUSSION

To the best of our knowledge, this is the first study to evaluate tamibarotene as maintenance therapy for APL. The study results showed no statistical difference between ATRA and tamibarotene, although there was a suggestion of improved efficacy of tamibarotene in high-risk patients in an exploratory analysis.

The role of maintenance therapy in APL has been a matter of controversy.[15] To date, several randomized controlled trials have attempted to address this issue, but with conflicting results. Earlier studies showed significant benefits of maintenance,[6,11] whereas more recent studies did not.[8,14] When discussing the role of maintenance, we should keep in mind that whether and to what extent maintenance therapy provides clinical benefits depends on the target patients. For instance, the addition of effective maintenance therapy may improve outcomes for patients with a certain amount of residual disease, whereas the same does not apply to patients without any residual disease at all when maintenance therapy is started. For this reason, inconsistent or even contradictory results reported by various studies could be explained by differences in types of patients enrolled onto each of these studies. In this regard, it is interesting to note that two studies reporting negative results mainly used IDA for anthracycline drugs,[8,14] whereas the two studies with positive results used only daunorubicin.[6,11] In addition, the negative studies used three consolidation courses,[8,14] but positive studies used only two.[6,11] These differences indicate that more intensive treatments were used in the former than in the latter studies, which raises the possibility that the more intensive antileukemic effect of the former may have diminished the proportion of patients who actually benefited from maintenance therapy. Also of interest is the fact that only patients with negative *PML-RARA* at the end of consolidation therapy underwent maintenance random assignment in the two negative studies,[8,14] whereas all patients with hematologic CR did so, irrespective of minimal residual disease status, in the two positive studies.[6,11] These conditions may have led to an increase in the percentage of patients in the negative studies who did not actually benefit from maintenance therapy. Therefore, it is not surprising that maintenance random assignment had no impact on outcomes in our non–high-risk patients, because a substantial fraction of these patients may have done well regardless of which maintenance arm they were assigned to, or even without maintenance in some cases, because our study used IDA as well as three courses of consolidation therapy, and only patients whose *PML-RARA* levels had considerably diminished proceeded to maintenance random assignment.

Our data indicate a possible relationship between the beneficial effects of tamibarotene and the initial WBC count. Patients with an initial WBC count of 10.0×10^9/L or higher are commonly defined as at high risk for relapse.[5,9] Although statistical significance was not reached, there was a trend for a greater effect size for these high-risk patients. Here we should bear in mind that this subgroup analysis

Table 3. Grade 2 or Higher Drug-Related Adverse Events Reported in More Than 5% of Patients in Either Maintenance Arm

	ATRA (n = 135)						Tamibarotene (n = 134)					
	Grade 2		Grade 3		Grade 4		Grade 2		Grade 3		Grade 4	
Adverse Event	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Triglyceride increased	25	19	17	13	6	4.4	28	21	28	21	6	4.5
Cholesterol increased	11	8.1	0	0	2	1.5	20	15	3	2.2	0	0
Rash	2	1.5	1	0.7	0	0	19	14	0	0	0	0
AST/ALT increased	6	4.4	1	0.7	0	0	8	6.0	3	2.2	0	0
Headache	6	4.4	2	1.5	0	0	4	3.0	0	0	0	0

Abbreviation: ATRA, all-*trans*-retinoic acid.

includes several merits and limitations. The result has some authenticity because patients with an initial WBC count of 10.0×10^9/L or higher constitute a clinically significant subgroup in APL[15]; random assignment was stratified in terms of induction therapy, which had been decided based on the initial WBC count; and there was a possible difference of treatment effects between the two subgroups. However, this subgroup analysis was not prespecified in the protocol, and the result therefore needs to be interpreted cautiously. Another issue to note is that RFS for high-risk patients in our control arm seems somewhat lower than the RFS rates reported in previous studies using ATRA in combination with continuous chemotherapy,[11,13,14] suggesting the possibility that maintenance therapy with ATRA alone might not be optimal for these patients. The advantage of tamibarotene over ATRA observed in this study thus may have disappeared if these drugs had been combined with continuous chemotherapy. While acknowledging these notions, our data suggest clinical activity of tamibarotene in APL. The fact that this benefit in terms of RFS did not translate into prolonged survival could be largely a result of availability of effective salvage therapy for relapsed APL, because we recently demonstrated the outstanding efficacy of a sequential treatment consisting of induction and consolidation with arsenic trioxide (ATO), peripheral-blood stem-cell harvest after high-dose AraC chemotherapy and autologous hematopoietic cell transplantation for patients with relapsed APL.[22]

With the accumulation of experience using ATO for relapsed APL, enthusiasm is currently growing for incorporating ATO into front-line therapy in APL clinical trials.[23-26] Some may argue that this development will irrevocably change the role of maintenance therapy, but prognosis for patients with an initial WBC count of 10.0×10^9/L or higher still seems to remain poor even if they are treated with ATO-containing therapy.[23,24] For this reason, tamibarotene may play an important role in the ATO era. Moreover, incorporation of tamibarotene along with ATO into front-line therapy for APL may contribute to a reduction in the use of cytotoxic chemotherapy without impairing outcome, which may constitute a major challenge for the future treatment of APL.

In summary, this randomized controlled trial showed no statistical difference between ATRA and tamibarotene for maintenance therapy, but there was a suggestion of improved efficacy of tamibarotene in high-risk patients. This needs to be confirmed in further studies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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