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ALL-TRANS-RETINOIC ACID IN ACUTE PROMYELOCYTIC LEUKEMIA

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ABSTRACT

Background All-*trans*-retinoic acid induces complete remission in acute promyelocytic leukemia. However, it is not clear whether induction therapy with all-*trans*-retinoic acid is superior to chemotherapy alone or whether maintenance treatment with all-*trans*-retinoic acid improves outcome.

Methods Three hundred forty-six patients with previously untreated acute promyelocytic leukemia were randomly assigned to receive all-*trans*-retinoic acid or daunorubicin plus cytarabine as induction treatment. Patients who had a complete remission received consolidation therapy consisting of one cycle of treatment identical to the induction chemotherapy, then high-dose cytarabine plus daunorubicin. Patients still in complete remission after two cycles of consolidation therapy were then randomly assigned to maintenance treatment with all-*trans*-retinoic acid or to observation.

Results Of the 174 patients treated with chemotherapy, 120 (69 percent) had a complete remission, as did 124 of the 172 (72 percent) given all-*trans*-retinoic acid ($P=0.56$). When both induction and maintenance treatments were taken into account, the estimated rates of disease-free survival at one, two, and three years were 77, 61, and 55 percent, respectively, for patients assigned to chemotherapy then all-*trans*-retinoic acid; 86, 75, and 75 percent for all-*trans*-retinoic acid then all-*trans*-retinoic acid; 75, 60, and 60 percent for all-*trans*-retinoic acid then observation; and 29, 18, and 18 percent for chemotherapy then observation. By intention-to-treat analysis, the rates of overall survival at one, two, and three years after entry into the study were 75, 57, and 50 percent, respectively, among patients assigned to chemotherapy, and 82, 72, and 67 percent among those assigned to all-*trans*-retinoic acid ($P=0.003$).

Conclusions All-*trans*-retinoic acid as induction or maintenance treatment improves disease-free and overall survival as compared with chemotherapy alone and should be included in the treatment of acute promyelocytic leukemia. (N Engl J Med 1997; 337:1021-8.)

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ACUTE promyelocytic leukemia is a distinct subtype of acute myeloid leukemia¹ in which a balanced reciprocal translocation between chromosomes 15 and 17 results in the union of portions of the promyelocytic leukemia gene with the gene for retinoic acid receptor alpha.² This chimeric gene encodes the promyelocytic leukemia-retinoic acid receptor alpha fusion protein.³⁻⁶ Although 65 to 80 percent of patients with acute promyelocytic leukemia have a complete remission with standard chemotherapy,^{7,8} approximately 10 to 20 percent die either before or during chemotherapy of bleeding attributable to disseminated intravascular coagulation, fibrinolysis, and proteolysis.⁹ All-*trans*-retinoic acid differentiates leukemic promyelocytes into mature cells.^{10,11} Phase 2 clinical trials have demonstrated that all-*trans*-retinoic acid induces complete remission in most patients, with rapid resolution of the coagulopathy and few deaths during induction therapy.¹²⁻¹⁹ The duration of complete remission with all-*trans*-retinoic acid alone is usually brief, and postremission chemotherapy is required to diminish the likelihood of relapse.¹²⁻¹⁹ This study was designed to compare the rates of complete remission, disease-free survival,

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overall survival, and toxic effects associated with all-*trans*-retinoic acid therapy with those associated with conventional chemotherapy in patients with previously untreated acute promyelocytic leukemia and to determine the value of maintenance therapy with all-*trans*-retinoic acid.

METHODS

Eligibility Criteria

The eligibility criteria were a diagnosis of acute promyelocytic leukemia established on the basis of bone marrow morphology, no prior chemotherapy except hydroxyurea, normal hepatic and renal function, and an Eastern Cooperative Oncology Group performance status of 0 (normal activity) to 3 (in bed more than 50 percent of the time). Cytogenetic evaluation for t(15;17) was mandatory; however, the results did not affect eligibility. The diagnostic bone marrow findings were centrally reviewed within each cooperative group. The immunophenotypic and molecular analyses were performed according to the guidelines of each participating cooperative group and are not described here.

Study Design

Induction Therapy

Patients were randomly assigned to receive either 45 mg of daunorubicin per square meter of body-surface area per day by intravenous bolus on days 1 through 3, plus 100 mg of cytarabine per square meter per day by continuous intravenous infusion on days 1 through 7; or 45 mg of all-*trans*-retinoic acid (Vesanoid, Hoffmann-LaRoche, Nutley, N.J.) per square meter per day orally, divided into two doses given every 12 hours. Patients less than three years of age received either all-*trans*-retinoic acid, as described, or 1.5 mg of daunorubicin per kilogram of body weight per day by intravenous infusion on days 1 through 3, plus 3.3 mg of cytarabine per kilogram per day by continuous intravenous infusion on days 1 through 7. For patients assigned to cytotoxic chemotherapy, a second induction cycle with identical doses and schedules was given if disseminated intravascular coagulation recurred or the fibrinogen level declined and 50 percent or more of the promyelocytes in the bone marrow were abnormal after the first cycle. If the white-cell count was more than 10,000 per cubic millimeter, hydroxyurea was given before all-*trans*-retinoic acid. Patients received all-*trans*-retinoic acid until complete remission occurred, or for a maximum of 90 days. When serious toxic effects occurred, all-*trans*-retinoic acid was withheld until the effects diminished to a mild level and was then resumed at 75 percent of the initial dose. Patients who had unacceptable levels of toxic effects while taking all-*trans*-retinoic acid or who did not have a complete remission after a maximum of 90 days crossed over to chemotherapy. All-*trans*-retinoic acid was supplied by the National Cancer Institute. Patients who did not have a complete remission with chemotherapy received no further protocol therapy and were treated at the physician's discretion.

Consolidation Therapy

Patients who had a complete remission with chemotherapy or all-*trans*-retinoic acid received two cycles of consolidation therapy. The first cycle was identical to the induction chemotherapy. The second cycle consisted of high-dose cytarabine (2 g per square meter) as a 1-hour intravenous infusion every 12 hours for four consecutive days, with 45 mg of daunorubicin per square meter per day by intravenous infusion on days 1 and 2. For patients less than three years of age, the second cycle consisted of 67 mg of cytarabine per kilogram as a 1-hour intravenous infusion every 12 hours for four consecutive days, with 1.5 mg of daunorubicin per kilogram per day by intravenous infusion on days 1 and 2.

Maintenance Therapy

Patients in complete remission after both cycles of consolidation chemotherapy, irrespective of which induction therapy they had received, were randomly assigned either to a maintenance regimen of 45 mg of all-*trans*-retinoic acid per square meter per day given orally in divided doses every 12 hours for one year or to observation. Patients who were intolerant of induction therapy with all-*trans*-retinoic acid were directly assigned to observation.

Definition of Outcome

Toxic effects were graded according to the Common Toxicity Criteria of the National Cancer Institute. Complete remission and relapse were defined according to National Cancer Institute criteria.²⁰ Patients who were in clinical complete remission that was not confirmed by bone marrow findings were considered not to have had a response. Disease-free survival was defined as the time from the beginning of complete remission to relapse, death from any cause, or censoring of the data on the patient.

Supportive Care

Coagulopathy was treated at the physician's discretion. If the white-cell count rose during therapy to more than 30,000 per cubic millimeter, all-*trans*-retinoic acid was stopped, hydroxyurea was given until the white-cell count decreased to 10,000 per cubic millimeter, and then all-*trans*-retinoic acid was resumed.

Management of Retinoic Acid Syndrome

Retinoic acid syndrome was diagnosed in patients with unexplained fever, weight gain, respiratory distress, interstitial pulmonary infiltrates, and pleural or pericardial effusions.²¹ All-*trans*-retinoic acid was discontinued at the earliest signs of the syndrome, and dexamethasone was instituted (10 mg twice daily) for at least three days. After resolution of the symptoms, all-*trans*-retinoic acid was resumed at 75 percent of the initial dose. If there was no recurrence, the dose of all-*trans*-retinoic acid was increased to the initial dose after three to five days.

Statistical Analysis

Univariate associations between dichotomous variables were evaluated with Fisher's exact test. Associations involving ordered categorical variables were evaluated with the Wilcoxon rank-sum test.²² Analyses of the joint association of multiple variables with response were performed with logistic regression. Univariate and multivariate analyses of disease-free survival and overall survival were performed with proportional-hazards regression. Survival distributions were estimated with the methods of Kaplan and Meier.²³

This study was designed with formal interim monitoring involving three planned analyses with an O'Brien-Fleming boundary. The study was unblinded by the Eastern Cooperative Oncology Group Data Monitoring Committee at the second analysis with 50 percent of the data available because of conclusive differences in disease-free survival between the two induction-therapy groups. The following groups of patients were excluded from the analyses of toxic effects and response to induction and maintenance therapy: patients who were removed from the study after randomization but before initiation of any study medication, because of their medical condition; patients who were found not to meet entry criteria on review; patients who were found not to have acute promyelocytic leukemia on review of bone marrow morphology; and patients on whom too little information was provided after the initiation of therapy. All patients with a confirmed complete remission who were enrolled in the study were considered in the analyses of maintenance therapy, although patients assigned directly to observation were omitted from analyses comparing the randomized treatment groups. To avoid bias, patients who had a complete remission after crossing over to chemotherapy were omitted from the primary analyses of induction

and maintenance therapy, since crossover to all-*trans*-retinoic acid was not available to patients assigned to induction chemotherapy who did not have a complete remission.

RESULTS

Accrual

Four hundred one patients from six cooperative oncology groups were enrolled in the study between April 1992 and February 1995. The data were analyzed as of February 1997. Of these 401 patients, 55 were excluded from detailed analysis: 23 because they did not have acute promyelocytic leukemia according to morphologic criteria, 14 because of their medical condition before any study treatment was given, 7 because they did not meet the entry criteria, and 11 because data on them were inadequate. Thus, 346 patients who could be evaluated were included in the analyses of the toxic effects and the outcome of the induction treatment, and 378 were included in the intention-to-treat analysis of survival. The characteristics of the 346 patients who could be evaluated are shown in Table 1.

Induction Therapy

Complete Remission

Of the 174 patients who could be evaluated and who received chemotherapy, 120 (69 percent) had a complete remission, and of the 172 patients who could be evaluated and who were treated with all-*trans*-retinoic acid, 124 (72 percent) had a complete remission ($P=0.56$). The rates of complete remission in patients with and without the microgranular variant (M3v) of acute promyelocytic leukemia were essentially the same (70 and 75 percent, respectively). The rate of complete remission for the 221 patients with t(15;17), by standard karyotyping, was 72 percent: 81 of 117 patients given chemotherapy (69 percent) and 79 of 104 patients treated with all-*trans*-retinoic acid (76 percent, $P=0.29$). The rate of complete remission for the 22 patients lacking t(15;17) was 61 percent: 7 of 10 patients receiving chemotherapy (70 percent) and 6 of 12 patients receiving all-*trans*-retinoic acid (50 percent, $P=0.67$). Four of the six patients receiving all-*trans*-retinoic acid who lacked t(15;17) and who had a complete remission tested positive for the promyelocytic leukemia-retinoic acid receptor alpha fusion transcript. The molecular analyses for the promyelocytic leukemia-retinoic acid receptor alpha fusion transcript have been described elsewhere.²⁴

Crossover Patients

Fifteen patients assigned to induction therapy with all-*trans*-retinoic acid discontinued the drug because of resistant disease (4 patients) or toxic effects (11 patients) and crossed over to chemotherapy. The toxic effects in these 11 patients included

TABLE 1. BASE-LINE CHARACTERISTICS OF 346 PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA.

CHARACTERISTIC	CHEMOTHERAPY (N=174)	ALL-TRANS-RETINOIC ACID (N=172)
Sex — no. (%)		
Male	97 (56)	82 (48)
Female	77 (44)	90 (52)
Age — no. (%)		
<3 yr	3 (2)	2 (1)
3 to <15 yr	18 (10)	23 (13)
15 to 55 yr	116 (67)	115 (67)
>55 yr	37 (21)	32 (19)
Age — yr		
Median	38	37
Range	1-74	1-81
Performance status — no. (%)*		
0	68 (39)	73 (42)
1	70 (40)	70 (41)
2	30 (17)	15 (9)
3	6 (3)	13 (8)
White-cell count — no. (%)		
0 to 2000/mm ³	85 (49)	88 (51)
>2000 to 5000/mm ³	26 (15)	28 (16)
>5000 to 10,000/mm ³	22 (13)	25 (15)
>10,000/mm ³	41 (23)	31 (18)
White-cell count/mm ³		
Median	2200	2000
Range	200-16,200	300-5500
Morphology		
Classic M3	149 (86)	148 (86)
Microgranular variant (M3v)	25 (14)	24 (14)
Coagulopathy (bleeding)		
Yes	105 (60)	90 (52)
No or unknown	69 (40)	82 (48)
Karyotype		
t(15;17)	117 (67)	104 (60)
Not t(15;17)	10 (6)	12 (7)
Karyotype unavailable	47 (27)	55 (32)

*Data were not available for one patient treated with all-*trans*-retinoic acid.

acute thyroiditis, pulmonary hemorrhage, and vasculitis in 1 patient each and the retinoic acid syndrome in 8 patients. The four patients with resistant disease received all-*trans*-retinoic acid for 15, 24, 29, and 98 days. One of these four patients was positive for the promyelocytic leukemia-retinoic acid receptor alpha fusion transcript, and the others were negative. Ten of the 15 patients who discontinued all-*trans*-retinoic acid had a complete remission with chemotherapy. The cytogenetic findings in the 15 patients were as follows: t(15;17), 8 patients; trisomy 8, 1 patient; t(11;17), 1 patient; normal, 1 patient; and unknown, 4 patients.

Induction Failures and Toxic Effects

There were 43 deaths within 28 days among the 346 patients who could be evaluated (12.4 percent of patients; 95 percent confidence interval, 9.2 to 16.4 percent) (Table 2). There was no difference in mortality during induction treatment between the

TABLE 2. SEVERE, LIFE-THREATENING, AND LETHAL TOXIC EFFECTS DURING INDUCTION THERAPY.

TOXIC EFFECT	CHEMOTHERAPY (N = 174)			ALL-TRANS-RETINOIC ACID (N = 172)		
	SEVERE	LIFE-THREATENING	LETHAL	SEVERE	LIFE-THREATENING	LETHAL
	number of patients (percent)					
Hepatic effects	22 (13)	15 (9)	0	22 (13)	11 (6)	1 (1)
Infection	66 (38)	14 (8)	10 (6)	35 (20)	6 (3)	2 (1)
Hemorrhage	10 (6)	7 (4)	12 (7)	4 (2)	10 (6)	10 (6)
Pulmonary effects	4 (2)	4 (2)	2 (1)	13 (7)	20 (11)	3 (2)
Stomatitis	9 (5)	2 (1)	0	9 (5)	3 (2)	0
Cardiac effects	16 (9)	0	0	12 (7)	5 (3)	2 (1)
Nausea	15 (9)	0	0	11 (6)	0	0
Diarrhea	18 (10)	1 (1)	0	5 (3)	1 (1)	0
Dermatologic effects	9 (5)	1 (1)	0	4 (2)	1 (1)	0
Neurologic effects	13 (7)	2 (1)	0	15 (9)	1 (1)	0
Thrombosis	0	0	0	0	0	1 (1)

two groups, with 24 deaths among patients who received chemotherapy (14 percent) and 19 among those who received all-*trans*-retinoic acid (11 percent, $P=0.52$). Of the patients who received chemotherapy, 12 died of intracerebral hemorrhage, 10 of infection, 1 of pulmonary toxic effects, and 1 of cardiopulmonary arrest. Of the patients who received all-*trans*-retinoic acid, 10 died of hemorrhage, 2 of infection, 2 of acute myocardial infarction, 3 of pulmonary complications (including 2 patients with the retinoic acid syndrome), 1 of hepatic toxic effects, and 1 of thrombosis.

The toxic effects are listed in Table 2. The incidence of severe hemorrhage was the same in the two groups. There were fewer serious infections among the patients treated with all-*trans*-retinoic acid (25 percent) than among those receiving chemotherapy (52 percent). However, more patients treated with all-*trans*-retinoic acid had serious pulmonary toxic effects (21 percent) than did patients receiving chemotherapy (6 percent). Pseudotumor cerebri developed in at least four patients (two adults and two children) in the group receiving all-*trans*-retinoic acid.

Hyperleukocytosis

Seventy-four of the 172 patients assigned to all-*trans*-retinoic acid (43 percent) received hydroxyurea. Fifteen patients received hydroxyurea before receiving all-*trans*-retinoic acid to reduce the white-cell count to below 10,000 per cubic millimeter. The other 59 patients received hydroxyurea after starting all-*trans*-retinoic acid to maintain the white-cell count below 30,000 per cubic millimeter. Five of the 10 patients with fatal hemorrhage in the group receiving induction therapy with all-*trans*-retinoic acid had received hydroxyurea.

Retinoic Acid Syndrome

Retinoic acid syndrome developed in 45 of the 172 patients who could be evaluated (26 percent) in the group receiving induction therapy with all-*trans*-retinoic acid after a median of 12 days (range, 2 to 47). Forty-four of the 45 patients with the retinoic acid syndrome were treated with dexamethasone. Among the 45 patients, the syndrome resolved in 43 patients, and the other 2 died. Seven additional patients had signs or symptoms suggestive of the syndrome, but concurrent medical problems complicated the diagnosis.

Consolidation Therapy

Of 244 patients who could be evaluated and who had a complete remission, 229 received both cycles of consolidation chemotherapy. There were no lethal toxic effects during consolidation therapy. Fifteen patients received only one cycle. Nine of these patients discontinued treatment and received no further protocol therapy after cycle 1 of consolidation therapy; the other six did not receive cycle 2 of consolidation therapy because of toxic effects during cycle 1 and underwent random assignment to maintenance therapy directly. Daunorubicin was omitted in one or both consolidation cycles in 26 patients, in most cases because of decreased cardiac function. Twenty-two of these patients had been assigned to induction chemotherapy, and four had been assigned to induction therapy with all-*trans*-retinoic acid, with approximately equal numbers assigned to each maintenance treatment.

Maintenance Therapy

Of the 237 patients who entered the maintenance phase of the trial, 14 were excluded from the anal-

ysis of the induction phase, 14 did not have a complete remission confirmed by bone marrow findings (6 who received all-*trans*-retinoic acid and 8 who received chemotherapy), 4 who were intolerant of all-*trans*-retinoic acid were directly assigned to observation, and 6 who crossed over from all-*trans*-retinoic acid to chemotherapy during induction treatment were excluded from the analysis of the results of maintenance therapy. Thus, 199 patients were randomly assigned to either maintenance therapy with all-*trans*-retinoic acid (94 patients) or observation (105 patients) and were included in this portion of the analysis. Of the 94 patients who were assigned to all-*trans*-retinoic acid, 64 (68 percent) completed the full one year of all-*trans*-retinoic acid. The reasons for stopping early included relapse (12 patients), toxic effects (14 patients), withdrawal of consent (2 patients), complicating disease (1 patient), and withdrawal from the study (1 patient). The median duration of maintenance therapy with all-*trans*-retinoic acid for patients who stopped early was 5 months (range, 1 week to 11 months). Toxic effects among these patients included headache (three patients), depression (one patient), elevated aminotransferase levels (three patients), rash (two patients), cardiac effects (two patients), nausea (one patient), pseudotumor cerebri (one patient), and distal-digit vaso-occlusive syndrome (one patient).

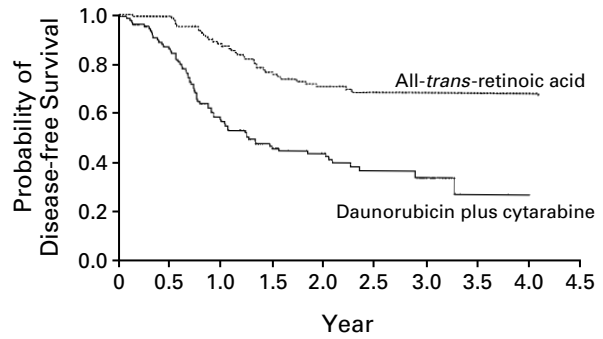
Toxic Effects of Maintenance Therapy

Of the 94 patients assigned to all-*trans*-retinoic acid, 34 (36 percent) had severe or life-threatening toxic effects. These effects included neurotoxicity in 11 patients, of whom 5 had headache, 3 (2 children and 1 adult) had pseudotumor cerebri, 2 had hearing loss, and 1 had depression; infections in 7 patients; and hepatotoxicity in 5 patients (hyperbilirubinemia or aminotransferase elevation). Four episodes of severe toxic effects (infection, hepatotoxicity, headache, and hypertriglyceridemia) occurred in 3 of the 105 patients assigned to observation.

Disease-free Survival

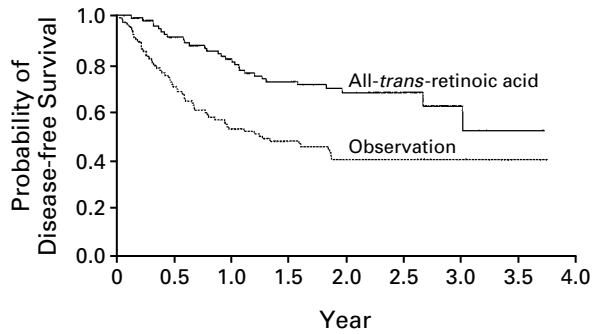
Effect of Induction Treatment

With a median follow-up of 30 months for surviving patients, the estimated 1-, 2-, and 3-year rates of disease-free survival from the time of entering complete remission were 57, 43, and 32 percent, respectively, for patients who could be evaluated and who received induction chemotherapy. There were 70 relapses among these 120 patients (Fig. 1). For patients who received induction therapy with all-*trans*-retinoic acid, the estimated one-, two-, and three-year rates of disease-free survival were 87, 70, and 67 percent, respectively. There were 36 relapses among these 124 patients ($P < 0.001$).



	1ST YR	2ND YR	3RD YR	4TH YR	5TH YR
	no. of events/no. at risk				
Daunorubicin plus cytarabine	49/120	14/61	6/35	1/8	0/0
All- <i>trans</i> -retinoic acid	15/124	18/98	2/67	0/21	1/3

Figure 1. Kaplan–Meier Product-Limit Estimate of Disease-free Survival from the Time of Complete Remission for Patients Randomly Assigned at Induction to Either Daunorubicin plus Cytarabine or All-*trans*-Retinoic Acid.

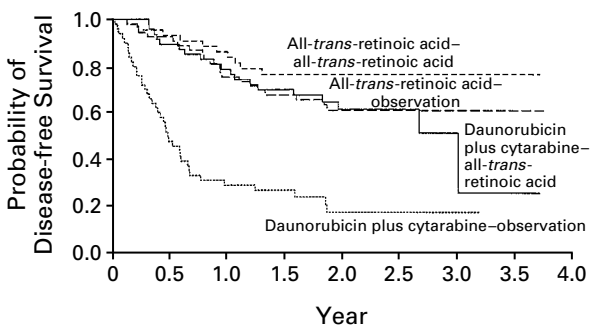


	1ST YR	2ND YR	3RD YR	4TH YR
	no. of events/no. at risk			
All- <i>trans</i> -retinoic acid	16/94	11/73	1/38	1/6
Observation	48/105	11/52	0/25	1/8

Figure 2. Kaplan–Meier Product-Limit Estimate of Disease-free Survival from the Time of Random Assignment to Maintenance with All-*trans*-Retinoic Acid or to Observation.

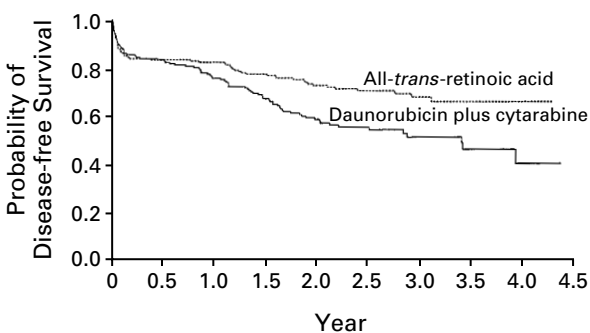
Effect of Maintenance Treatment

Of the 94 patients assigned to maintenance treatment with all-*trans*-retinoic acid, 29 relapsed, as compared with 60 of the 105 patients assigned to observation. The estimated one-, two-, and three-year rates of disease-free survival from the date of assignment to maintenance therapy or observation were 82, 68, and 65 percent, respectively, for patients assigned to all-*trans*-retinoic acid, and 53, 40, and 40 percent, respectively, for patients assigned to observation, regardless of the induction regimen



	1ST YR	2ND YR	3RD YR	4TH YR
	no. of events/no. at risk			
Daunorubicin plus cytarabine-all-trans-retinoic acid	10/48	7/36	1/19	1/2
Daunorubicin plus cytarabine-observation	35/51	4/13	0/3	0/1
All-trans-retinoic acid-all-trans-retinoic acid	6/46	4/37	0/19	0/4
All-trans-retinoic acid-observation	13/54	7/39	0/22	1/7

Figure 3. Kaplan–Meier Product-Limit Estimates of Disease-free Survival on the Basis of Both the Type of Induction Therapy and the Type of Maintenance Therapy.



	1ST YR	2ND YR	3RD YR	4TH YR	5TH YR
	no. of events/no. at risk				
Daunorubicin plus cytarabine	45/190	29/131	7/80	3/32	0/6
All-trans-retinoic acid	33/188	17/147	5/111	1/41	0/7

Figure 4. Kaplan–Meier Product-Limit Estimate of Overall Survival According to Intention-to-Treat Analysis for Patients Receiving Daunorubicin plus Cytarabine or All-trans-Retinoic Acid as Induction Therapy.

($P < 0.001$, with stratification according to induction regimen) (Fig. 2).

Combined Effects of Induction and Maintenance Treatments

There were 19 relapses among the 48 patients who received induction chemotherapy with daunorubicin plus cytarabine and maintenance therapy with all-trans-retinoic acid, 10 relapses among the 46 patients who received all-trans-retinoic acid for both induction and maintenance, and 21 relapses among the 54 patients who received all-trans-retinoic acid for induction and no maintenance therapy; all these numbers are significantly lower than the 39 relapses among the 51 patients who never received all-trans-retinoic acid ($P < 0.001$) (Fig. 3).

Overall Survival

The estimated rates of overall survival at one, two, and three years from entry into the study for the 346 patients who could be evaluated were 75, 57, and 50 percent, respectively, for patients who received induction chemotherapy, and 84, 74, and 71 percent, respectively, for patients who received induction therapy with all-trans-retinoic acid ($P < 0.001$). The overall survival rates in the intention-to-treat analysis of all patients at one, two, and three years were 75, 57, and 50 percent, respectively, among the 190 patients assigned to chemotherapy, and 82, 72, and 67 percent, respectively, among the 188 patients assigned to all-trans-retinoic acid ($P = 0.003$) (Fig. 4).

DISCUSSION

This study shows that all-trans-retinoic acid given as induction or maintenance therapy results in improved disease-free survival and overall survival, as compared with chemotherapy alone, in patients with newly diagnosed acute promyelocytic leukemia. All-trans-retinoic acid given during induction did not improve the rate of complete remission or decrease early mortality, but it reduced the likelihood of relapse. It is not clear whether the use of all-trans-retinoic acid for both induction and maintenance is superior to the use of the drug only during induction, or whether maintenance with all-trans-retinoic acid actually prevents, rather than delays, relapse.

The rate of complete remission we found with all-trans-retinoic acid (72 percent) is lower than the 91 percent reported in the only other randomized study of the drug in acute promyelocytic leukemia,²⁵ but the two studies are not directly comparable, since most patients assigned to all-trans-retinoic acid by Fenaux and colleagues also received standard chemotherapy along with all-trans-retinoic acid to control hyperleukocytosis. Single-institution and multi-institution phase 2 studies report rates of complete remission of 86 to 100 percent with all-trans-retinoic acid alone.¹³⁻¹⁹ The lower rate reported here is partly attributable to our requirement of rigorous

documentation of complete remission. If we included patients believed to be in complete remission by their treating physicians who had long survival but inadequately confirmed complete remissions, either because of lack of documentation (seven patients) or failure to be assigned to maintenance treatment (six patients), our rate of complete remission would be about 80 to 85 percent. Furthermore, if the crossover patients were included among the patients given all-*trans*-retinoic acid who had a complete remission, the rate of complete remission would be 78 percent (134 of 172 patients).

The disappointing outcome with chemotherapy alone (18 percent disease-free survival at three years) is not easily explained. Although our results are less favorable than those reported in earlier analyses of the effect of chemotherapy in acute promyelocytic leukemia,^{7,8,26,27} they are similar to the results of the randomized study by Fenaux et al.²⁵ The outcome of our patients who did not receive the full dose of daunorubicin during consolidation treatment did not differ from that of patients who received the full dose of the drug.

A number of questions remain. First, can retinoid toxicity, particularly the retinoic acid syndrome, be reduced? A major toxic effect of all-*trans*-retinoic acid is the retinoic acid syndrome; eight patients with the disorder discontinued all-*trans*-retinoic acid and crossed over to chemotherapy. The strategies of administering prophylactic corticosteroids²⁸ or using a lower dose of all-*trans*-retinoic acid²⁹ (15 to 20 mg per square meter per day) have not yet been evaluated in randomized trials.

Second, would concurrent induction treatment with all-*trans*-retinoic acid and chemotherapy improve the outcome over that with all-*trans*-retinoic acid alone? Avvisati and colleagues³⁰ had excellent results with all-*trans*-retinoic acid plus idarubicin. Their findings suggest that further investigation of the simultaneous administration of all-*trans*-retinoic acid and chemotherapy is warranted. The combination may prevent hyperleukocytosis, reduce the incidence of the retinoic acid syndrome, lead to a higher rate of complete remission, and improve the long-term outcome.

Third, what would be the best chemotherapy to administer with all-*trans*-retinoic acid for induction and consolidation therapy? In one study conducted before all-*trans*-retinoic acid was available, high-dose daunorubicin for induction resulted in an excellent outcome.³¹ It may even be possible to omit cytarabine from a regimen containing all-*trans*-retinoic acid.³²

Fourth, can a subgroup of patients at high risk for relapse be identified? The reverse-transcriptase-polymerase-chain-reaction (PCR) assay can successfully detect minimal residual disease,³³ and a positive PCR result after consolidation chemotherapy may predict relapse.^{34,35}

Finally, is there a role for bone marrow transplantation in patients who are PCR-positive but in clinical remission?

This study shows that all-*trans*-retinoic acid, when given during induction or maintenance therapy, improves disease-free survival and overall survival in patients with newly diagnosed acute promyelocytic leukemia over that obtained with chemotherapy alone. Given the decrease in the duration of hospitalization, the use of blood products, and the cost of care in patients treated with all-*trans*-retinoic acid,^{36,37} we recommend the use of all-*trans*-retinoic acid for induction therapy in all patients with acute promyelocytic leukemia. Further follow-up is needed to define its role as maintenance therapy more precisely.

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CORRECTION

All-*trans*-Retinoic Acid in Acute Promyelocytic Leukemia

All-*trans*-Retinoic Acid in Acute Promyelocytic Leukemia . On page 1026, in Figure 4, the y-axis label should have read, "Probability of Overall Survival," not "Probability of Disease-free Survival," as printed. We regret the error.