

Retinoic Acid and Arsenic Trioxide for Acute Promyelocytic Leukemia

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ABSTRACT

BACKGROUND

All-*trans* retinoic acid (ATRA) with chemotherapy is the standard of care for acute promyelocytic leukemia (APL), resulting in cure rates exceeding 80%. Pilot studies of treatment with arsenic trioxide with or without ATRA have shown high efficacy and reduced hematologic toxicity.

METHODS

We conducted a phase 3, multicenter trial comparing ATRA plus chemotherapy with ATRA plus arsenic trioxide in patients with APL classified as low-to-intermediate risk (white-cell count, $\leq 10 \times 10^9$ per liter). Patients were randomly assigned to receive either ATRA plus arsenic trioxide for induction and consolidation therapy or standard ATRA–idarubicin induction therapy followed by three cycles of consolidation therapy with ATRA plus chemotherapy and maintenance therapy with low-dose chemotherapy and ATRA. The study was designed as a noninferiority trial to show that the difference between the rates of event-free survival at 2 years in the two groups was not greater than 5%.

RESULTS

Complete remission was achieved in all 77 patients in the ATRA–arsenic trioxide group who could be evaluated (100%) and in 75 of 79 patients in the ATRA–chemotherapy group (95%) ($P=0.12$). The median follow-up was 34.4 months. Two-year event-free survival rates were 97% in the ATRA–arsenic trioxide group and 86% in the ATRA–chemotherapy group (95% confidence interval for the difference, 2 to 22 percentage points; $P<0.001$ for noninferiority and $P=0.02$ for superiority of ATRA–arsenic trioxide). Overall survival was also better with ATRA–arsenic trioxide ($P=0.02$). As compared with ATRA–chemotherapy, ATRA–arsenic trioxide was associated with less hematologic toxicity and fewer infections but with more hepatic toxicity.

CONCLUSIONS

ATRA plus arsenic trioxide is at least not inferior and may be superior to ATRA plus chemotherapy in the treatment of patients with low-to-intermediate-risk APL. (Funded by Associazione Italiana contro le Leucemie and others; ClinicalTrials.gov number, NCT00482833.)

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ACUTE PROMYELOCYTIC LEUKEMIA (APL) has become a highly curable disease with contemporary treatment, which consists of all-*trans* retinoic acid (ATRA) and anthracycline-based chemotherapy.^{1,2} As reported in several large multicenter trials, this combination results in overall remission rates of up to 95% and cure rates now exceeding 80%.³⁻¹¹ Thus, the combination of ATRA and chemotherapy is currently considered the standard of care for newly diagnosed APL.¹²

Arsenic trioxide is also highly effective in the treatment of APL. Early studies conducted in China and the United States showed that this agent can induce sustained molecular remission when used as a single agent in patients who have a relapse after treatment with ATRA-containing regimens,¹³⁻¹⁵ and other studies confirmed these findings.¹⁶ Arsenic trioxide acts through specific binding of the promyelocytic leukemia protein (PML) moiety of the disease-specific PML-retinoic acid receptor alpha (RARA) oncoprotein, leading to its degradation and resulting in partial differentiation and induction of apoptosis of leukemic promyelocytes. Synergy of arsenic trioxide and ATRA, which binds the RARA moiety of PML-RARA, has been shown at both the biologic and clinical levels.¹⁷⁻²¹

Arsenic trioxide with or without ATRA has proved highly effective in pilot studies involving patients with newly diagnosed APL.²²⁻²⁵ These studies also showed reduced hematologic toxicity as compared with ATRA and chemotherapy. However, studies using such arsenic-based approaches have mainly consisted of single-center assessments with relatively limited follow-up. In addition, outcomes were significantly poorer in patients with high-risk disease, commonly defined as those with an initial white-cell count greater than 10×10^9 per liter.²⁶

In this randomized study, we compared the efficacy and toxicity of standard ATRA plus chemotherapy with ATRA plus arsenic trioxide in patients with newly diagnosed, low-to-intermediate-risk APL.

METHODS

ELIGIBILITY CRITERIA

Eligible patients were 18 to 71 years of age with newly diagnosed APL classified as low-to-intermediate risk (white-cell count at diagnosis, $\leq 10 \times 10^9$ per liter). Initial enrollment and randomization

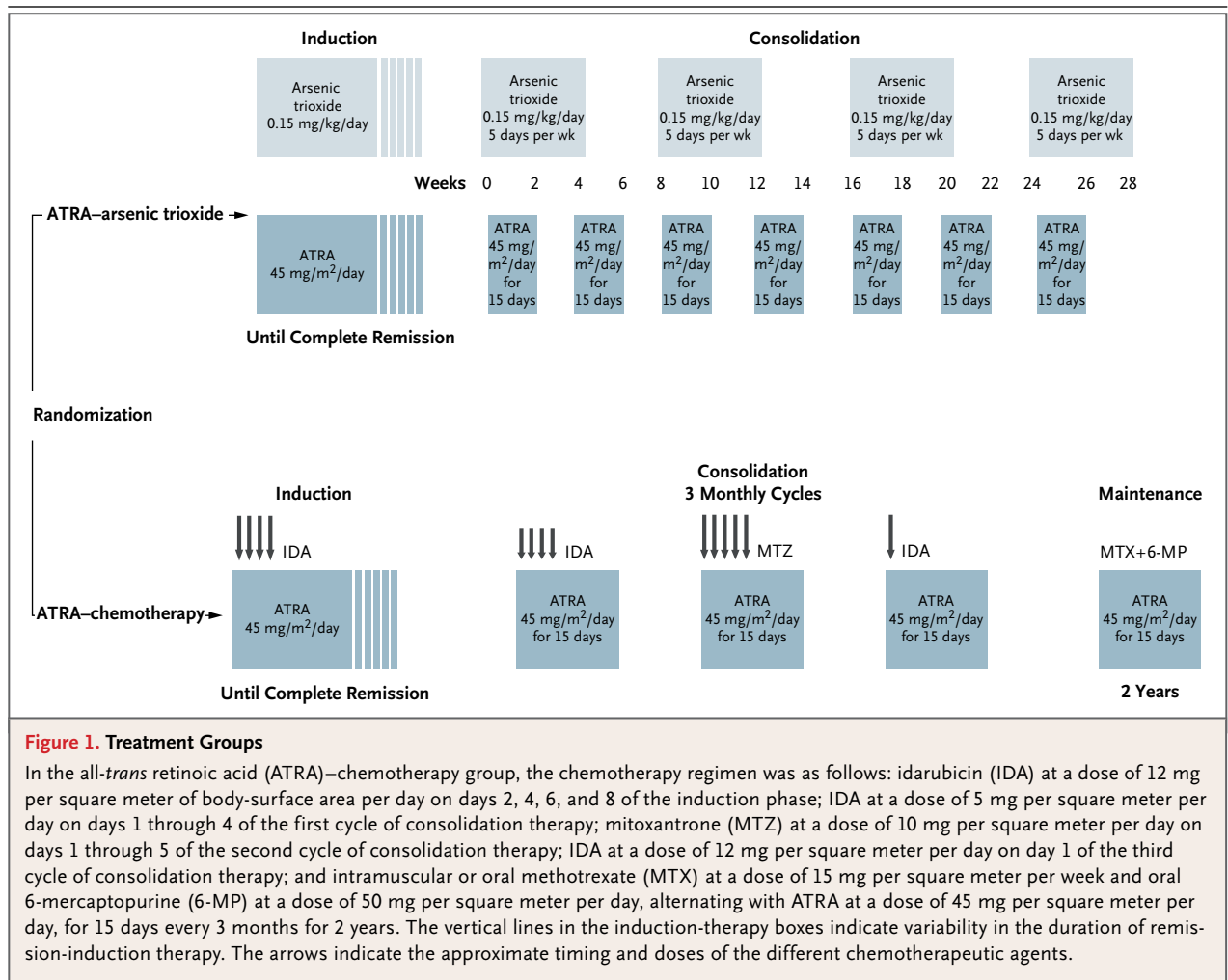
were performed solely on the basis of morphologic features.²⁷ Genetic confirmation of the diagnosis was required for subsequent eligibility and was carried out by reference laboratories. A genetic diagnosis could be established by detection of the PML-RARA fusion gene by means of reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay,^{28,29} demonstration of the t(15;17) translocation by means of conventional karyotyping or fluorescence in situ hybridization (FISH),³⁰ or evidence of a microspeckled PML pattern with the use of an indirect immunofluorescence assay.³¹ Other inclusion criteria were a World Health Organization (WHO) performance status score of 2 or lower (on a scale of 0 to 5, with lower numbers indicating better performance status), a creatinine level of 3.0 mg per deciliter or lower ($\leq 265 \mu\text{mol}$ per liter), and a bilirubin level of 3.0 mg per deciliter or lower ($\leq 51 \mu\text{mol}$ per liter). Written informed consent was obtained from all patients before study entry.

A total of 40 centers from Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) and 27 centers from the German-Austrian Acute Myeloid Leukemia Study Group and Study Alliance Leukemia participated in the study by enrolling at least one patient. The institutional review board at each participating center reviewed and approved the study. The trial was conducted in accordance with the Declaration of Helsinki.

STUDY DESIGN AND TREATMENT GROUPS

The study was a prospective, randomized, multicenter, open-label, phase 3 noninferiority trial. It was designed to show that ATRA-arsenic trioxide was not inferior to ATRA-chemotherapy with respect to the event-free survival rate at 2 years. Patients were randomly assigned to receive ATRA plus arsenic trioxide for induction and consolidation therapy or standard ATRA-idarubicin induction therapy followed by three cycles of consolidation therapy with ATRA plus chemotherapy and maintenance therapy with low-dose chemotherapy and ATRA. The two regimens have been described previously^{8,23} and are shown in Figure 1; detailed descriptions are available in the Supplementary Appendix (available with the full text of this article at NEJM.org). Randomization was centralized and stratified according to institution. The protocol, including the statistical analysis plan, is available at NEJM.org.

No pharmaceutical company was involved in the design of the study, data collection or analysis,



or the writing of the manuscript. Arsenic trioxide was donated for this investigation by Cephalon Europe and, since 2011, by Teva Pharmaceutical Industries. All authors vouch for the completeness and accuracy of the data and the fidelity of the study to the protocol.

CRITERIA FOR RESPONSE AND END POINTS

The primary study end point was event-free survival at 2 years after diagnosis, with treatment failure defined as any of the following: no achievement of hematologic complete remission after induction therapy, no achievement of molecular complete remission after three consolidation courses, molecular relapse, hematologic relapse, or death. Hematologic complete remission and hematologic (morphologic) relapse were defined according to the National Cancer Institute (NCI) workshop definitions.³² Molecular complete remission and molecular relapse were defined as reported else-

where.²⁸ Secondary end points included the rate of hematologic complete remission after induction, the probability of overall survival, the cumulative incidence of relapse, toxic effects (graded according to the NCI Common Terminology Criteria for Adverse Events, version 3 [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf]), and the kinetics of minimal residual disease. Disease-free survival was defined as the time from achievement of hematologic complete remission to relapse (either molecular or hematologic), persistence of PCR positivity after consolidation therapy, or death, whichever occurred first; data on patients who were still alive and in first molecular complete remission were censored at the time of the most recent follow-up visit. Overall survival and cumulative incidence of relapse were defined according to the NCI workshop definitions (see the Supplementary Appendix).³²

SUPPORTIVE MEASURES AND MANAGEMENT OF COMPLICATIONS

Guidelines for the prevention and management of coagulopathy, hyperleukocytosis, prolongation of the corrected QT (QTc) interval,³³ and hematologic and nonhematologic toxic effects were predefined in the protocol and are available in the Supplementary Appendix. As prophylaxis for the differentiation syndrome (see the Supplementary Appendix for definitions),³⁴ prednisone at a dose of 0.5 mg per kilogram of body weight per day was administered from day 1 until the end of induction therapy. At the earliest manifestations of suspected differentiation syndrome, ATRA, arsenic trioxide, or both were temporarily discontinued and intravenous dexamethasone was administered at a dose of 10 mg every 12 hours until the disappearance of signs and symptoms for a minimum of 3 days.

LABORATORY STUDIES

With very few exceptions, all genetic tests were carried out on bone marrow samples. Standardized protocols were used for FISH,³⁰ RT-PCR assay for PML-RARA^{28,29} (sensitivity, 10^{-4} [i.e., 1 leukemic cell in 10,000 normal cells]), and immunofluorescence staining for PML.³¹ Prospective monitoring for minimal residual disease was performed by means of RT-PCR assay after induction (for investigational purposes only) and after the third consolidation cycle. Real-time quantitative PCR (RQ-PCR) assays were performed in parallel for patients enrolled in Italy, with the use of previously published methods.^{35,36} The analysis of FMS-like tyrosine kinase 3 (*FLT3*)-internal tandem duplication (ITD) mutations was carried out according to the protocol reported previously.³⁷

STATISTICAL ANALYSIS

The expected event-free survival rates in the reference and experimental groups were 85% and 95%, respectively.^{8,25} According to the Farrington and Manning formulas (see the Supplementary Appendix), evaluation of 73 patients per group would allow a determination that ATRA–arsenic trioxide was not more than 5% inferior to ATRA–chemotherapy with a type I error probability of 5% and a power of 92%. The target sample was increased to 162 patients to allow for an expected rate of loss of 10%.

All efficacy analyses were based on the intention-to-treat principle, comparing groups according to the randomly assigned treatment. For the

primary efficacy analysis for noninferiority, we also carried out a per-protocol analysis, which included patients who received protocol treatments as scheduled. Noninferiority was assessed by estimating the two-sided 95% confidence interval for the between-group difference in crude rates of 2-year event-free survival and checking that the lower bound was not lower than –5%. The robustness of the results was confirmed by means of a sensitivity analysis that addressed all relevant scenarios for the patients who could not be evaluated, with the assumption of a poor outcome for all patients, a favorable outcome for all patients, or a poor outcome for patients in the ATRA–arsenic trioxide group and a favorable outcome for those in the ATRA–chemotherapy group. We completed the analysis of event-free survival by comparing Kaplan–Meier curves, to take into account the time to treatment failure and the loss to follow-up. The log reduction of PML-RARA transcript levels was assessed with the use of the Mann–Whitney test.

Survival distributions were estimated with the use of the Kaplan–Meier product-limit estimator and were compared between groups with the use of the log-rank test. The cumulative incidence of relapse was estimated with the use of the proper nonparametric estimator, and between-group comparisons were performed with Gray's K-sample test. SAS statistical software, version 9.1.3, was used for all analyses.

RESULTS

ENROLLMENT AND CHARACTERISTICS OF THE PATIENTS

Enrollment of the prespecified 162 patients was started in October 2007 and was completed in September 2010. The present analysis was performed in November 2012, with a median follow-up of 34.4 months (range, 0.5 to 55.8). Genetic tests ruled out a diagnosis of PML-RARA–positive APL in 3 patients. Three of 159 patients with genetically confirmed APL did not start the assigned treatment (1 withdrew consent, and 2 had major protocol violations). The intention-to-treat analysis included all 156 patients who received at least one dose of the assigned therapy after randomization. The main demographic, clinical, and biologic characteristics of these 156 patients are shown in Table 1. There were no significant differences in the baseline characteristics between the two cohorts. The disposition of the

patients, including reasons for exclusion, is illustrated in Figure 2.

INDUCTION THERAPY

A total of 77 patients in the ATRA–arsenic trioxide group and 79 patients in the ATRA–chemotherapy group could be evaluated for a response to induction therapy. Hematologic complete remission was achieved in all 77 patients in the ATRA–arsenic trioxide group (100%) and in 75 of the 79 patients in the ATRA–chemotherapy group (95%) ($P=0.12$). The median time to hematologic complete remission was 32 days (range, 22 to 68) in the ATRA–arsenic trioxide group and 35 days (range, 26 to 63) in the ATRA–chemotherapy group ($P=0.61$). Four patients in the ATRA–chemotherapy group died during induction therapy: 2 from the differentiation syndrome, 1 from ischemic stroke, and 1 from bronchopneumonia. Induction therapy was terminated early in 2 patients in the ATRA–arsenic trioxide group: in 1 because of a major protocol violation, and in the other because of severe prolongation of the QTc interval and electrolyte abnormalities on day 3. Both these patients could be evaluated for a molecular response after consolidation therapy was given off protocol; thus, they were included in the intention-to-treat analysis (see below).

The differentiation syndrome, including moderate and severe forms,³⁴ developed in 15 patients in the ATRA–arsenic trioxide group (19%) and in 13 patients in the ATRA–chemotherapy group (16%) ($P=0.62$). Severe differentiation syndrome occurred in 10 patients (5 [6%] in each group, $P=0.99$) and was fatal in 2 patients assigned to ATRA–chemotherapy.

Leukocytosis, defined as a white-cell count of more than 10×10^9 per liter, developed during induction therapy in 35 of 74 patients in the ATRA–arsenic trioxide group (47%) and in 19 of 79 patients in the ATRA–chemotherapy group (24%) ($P=0.007$). All cases were successfully managed with hydroxyurea therapy as recommended in the protocol.

CONSOLIDATION THERAPY

A total of 146 of 152 patients in hematologic complete remission proceeded to consolidation therapy. Two patients in the ATRA–chemotherapy group did not receive consolidation therapy because of a cardiac toxic effect and loss to follow-up. Besides the 2 patients who went off pro-

Table 1. Demographic, Clinical, and Biologic Characteristics of the Patients at Diagnosis.*

Characteristic	ATRA–Arsenic Trioxide (N=77)	ATRA–Chemotherapy (N=79)
Age — yr		
Median	44.6	46.6
Range	19.1–70.2	18.7–70.2
Sex — no. (%)		
Male	40 (52)	36 (46)
Female	37 (48)	43 (54)
White-cell count — $\times 10^9$ /liter		
Median	1.49	1.60
Range	0.32–10.00	0.30–9.61
Platelet count — $\times 10^9$ /liter		
Median	31	27
Range	3–224	3–236
Risk level — no. (%)†		
Low	33 (43)	27 (34)
Intermediate	44 (57)	52 (66)
PML-RARA isoform — no. (%)		
Long	45 (58)	48 (61)
Short	31 (40)	29 (37)
Data missing	1 (1)	2 (3)
FLT3-ITD mutation — no./total no. (%)	14/65 (22)	16/63 (25)

* There were no significant differences in the baseline characteristics between the two study groups. ATRA denotes all-*trans* retinoic acid, and FLT3 the gene encoding FMS-like tyrosine kinase 3.

† A low risk level was defined as a white-cell count of no more than 10×10^9 per liter and a platelet count of more than 40×10^9 per liter at presentation, and an intermediate risk level as a white-cell count of no more than 10×10^9 per liter and a platelet count of no more than 40×10^9 per liter at presentation.

tol during induction therapy, 2 additional patients in the ATRA–arsenic trioxide group were taken off protocol after induction therapy owing to a toxic effect (repetitive tachycardia) and a major protocol violation. However, the patient with the protocol violation could be evaluated for the primary end point.

Four patients died during consolidation therapy (three in the ATRA–chemotherapy group and one in the ATRA–arsenic trioxide group). The three patients in the ATRA–chemotherapy group died from hemorrhagic shock, pulmonary embolism, and bronchopneumonia. The patient in the ATRA–arsenic trioxide group died from

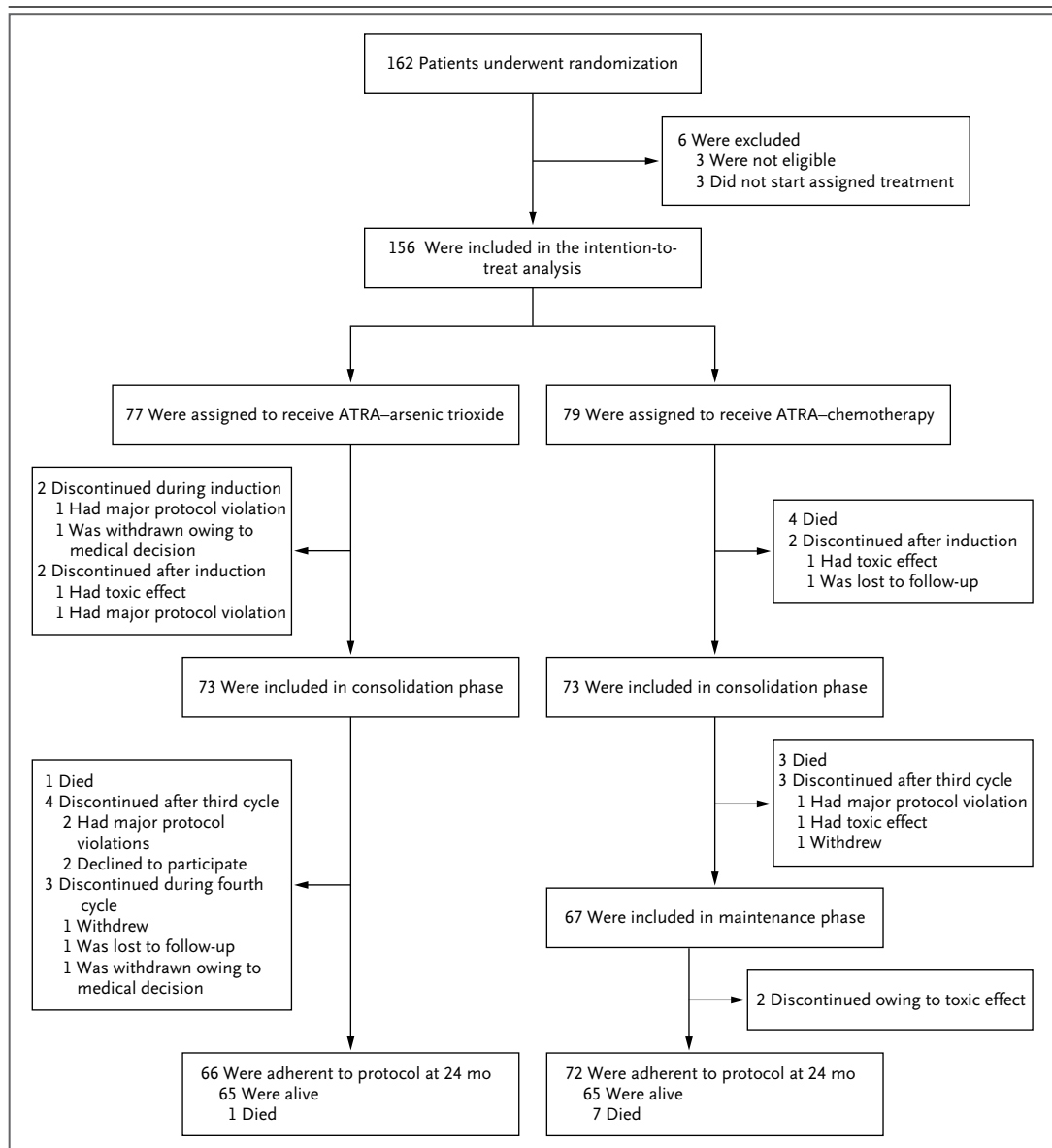


Figure 2. Study Enrollment, Randomization, and Retention.

In the ATRA–arsenic trioxide group, both the patients who did not complete induction therapy and the patient who discontinued treatment after induction therapy owing to a major protocol violation could be evaluated for postconsolidation polymerase-chain-reaction status and event-free survival at 2 years and thus were included in the intention-to-treat analysis. Two patients in the ATRA–arsenic trioxide group (one who withdrew from the study and one who was lost to follow-up during the fourth cycle of consolidation therapy) and one patient in the ATRA–chemotherapy group (who withdrew from the study after the third cycle of consolidation therapy) could not be evaluated for the primary end point owing to insufficient follow-up.

bronchopneumonia associated with H1N1 virus infection.

After the third consolidation cycle, molecular complete remission was achieved in all 145 patients who could be evaluated for a molecular

response (75 in the ATRA–arsenic trioxide group and 70 in the ATRA–chemotherapy group). Four patients in the ATRA–arsenic trioxide group did not proceed to the fourth consolidation cycle (2 declined to continue treatment and 2 had major

protocol violations). Three patients in the ATRA–arsenic trioxide group did not complete the fourth consolidation course owing to withdrawal of consent, loss to follow-up, and the treating physician's decision.

MAINTENANCE THERAPY

A total of 67 of the 70 patients who completed consolidation therapy in the ATRA–chemotherapy group proceeded to maintenance therapy. Three patients went off protocol after consolidation therapy owing to withdrawal of consent, a major protocol violation, and a toxic effect. Two patients did not complete maintenance therapy because of prolonged myelosuppression (>50 days).

EVENT-FREE SURVIVAL

Seven patients had a relapse during follow-up (two in the ATRA–arsenic trioxide group, at 22 and 27 months after diagnosis, and five in the ATRA–chemotherapy group, at 8, 14, 16, 21, and 35 months). In two of the seven patients with disease recurrence, a relapse was detected at the molecular level before detection of the hematologic relapse, leading to early administration of salvage therapy.

Of 156 patients in the intention-to-treat population, 6 (4%) could not be evaluated at 24 months for the primary analysis because a molecular evaluation was not performed after the third consolidation cycle or follow-up was insufficient. Of the remaining 150 patients, 97% in the ATRA–arsenic trioxide group (72 of 74 patients) were alive and free of events at 24 months, as compared with 86% in the ATRA–chemotherapy group (65 of 76 patients) (difference, 11 percentage points; 95% confidence interval [CI], 2 to 22). Since the lower bound of the 95% confidence interval for the difference in event-free survival rates was not lower than –5%, the noninferiority of ATRA–arsenic trioxide was confirmed ($P<0.001$). Furthermore, the log-rank test for the difference in event-free survival curves indicated the superiority of ATRA–arsenic trioxide ($P=0.02$).

In the per-protocol population, the event-free survival rates were 97% in the ATRA–arsenic trioxide group (64 of 66 patients) versus 85% in the ATRA–chemotherapy group (61 of 72) (difference, 12 percentage points; 95% CI, 2 to 23; $P<0.001$ for noninferiority).

SECONDARY END POINTS

Overall Survival, Disease-free Survival, and Cumulative Incidence of Relapse

The 2-year overall survival probability was 99% (95% CI, 96 to 100) in the ATRA–arsenic trioxide group and 91% (95% CI, 85 to 97) in the ATRA–chemotherapy group ($P=0.02$). The 2-year disease-free survival rate was 97% (95% CI, 94 to 100) in the ATRA–arsenic trioxide group and 90% (95% CI, 84 to 97) in the ATRA–chemotherapy group ($P=0.11$). The 2-year cumulative incidence of relapse was 1% (95% CI, 0 to 4) in the ATRA–arsenic trioxide group and 6% (95% CI, 0 to 11) in the ATRA–chemotherapy group ($P=0.24$). Outcome estimates are shown in Figure 3.

Kinetics of Minimal Residual Disease

The kinetics of PML-RARA transcript reduction after induction and consolidation therapy were assessed in 63 unselected patients. There were no significant differences between the two groups (Table S2 in the Supplementary Appendix).

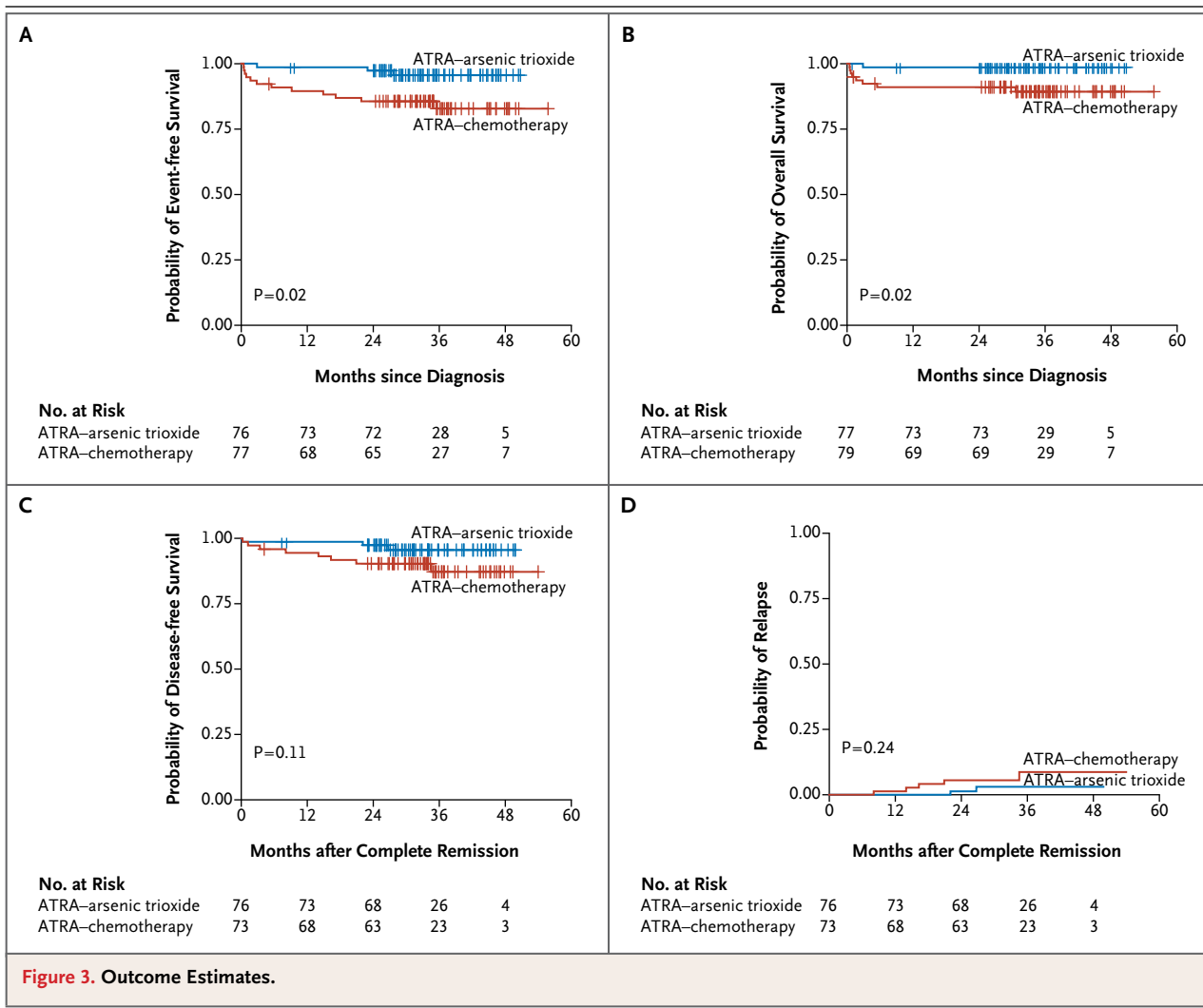
Hematologic Toxicity

Grade 3 or 4 neutropenia lasting more than 15 days and grade 3 or 4 thrombocytopenia lasting more than 15 days were significantly more frequent both during induction therapy and after each consolidation course in the ATRA–chemotherapy group than in the ATRA–arsenic trioxide group (Fig. 4). Counting together fever of unknown origin and documented infectious episodes occurring during either induction or consolidation therapy, we recorded 26 episodes in the ATRA–arsenic trioxide group and 59 episodes in the ATRA–chemotherapy group ($P<0.001$).

Nonhematologic Toxicity

A total of 43 of 68 patients in the ATRA–arsenic trioxide group (63%) and 4 of 69 patients in the ATRA–chemotherapy group (6%) had grade 3 or 4 hepatic toxic effects during induction or consolidation therapy (for patients in the two groups) or during maintenance therapy (for patients in the ATRA–chemotherapy group) ($P<0.001$). In all cases, the toxic effects resolved with temporary discontinuation of arsenic trioxide, ATRA, or both or with temporary discontinuation of chemotherapy during the maintenance phase (for patients in the ATRA–chemotherapy group).

Prolongation of the QTc interval occurred in 12 patients in the ATRA–arsenic trioxide group



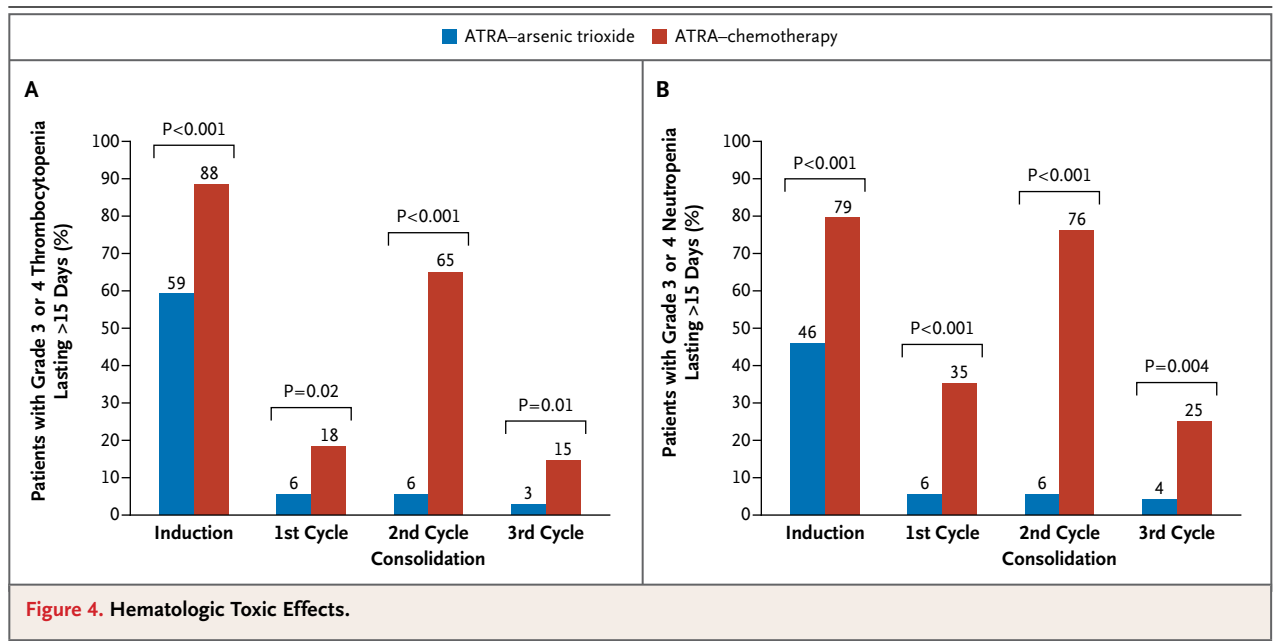
(16%) and in no patients in the ATRA-chemotherapy group ($P<0.001$). In 1 of the 12 patients with a prolonged QTc interval, arsenic trioxide was permanently discontinued, and the patient went off protocol. Information on nonhematologic toxic effects is shown in Table S3 in the Supplementary Appendix.

DISCUSSION

This study shows that a combination of ATRA and arsenic trioxide given for induction and consolidation therapy is at least not inferior and is possibly superior to standard ATRA and anthracycline-based chemotherapy for adults with low-to-intermediate-risk APL. The observed advantage in the 2-year event-free survival with

ATRA-arsenic trioxide appears to be due mainly to lower mortality from causes other than relapse, probably as a consequence of reduced severe hematologic toxicity together with similar antileukemic efficacy.

In light of the rarity of the disease, the exclusion from the study of patients with high-risk disease, and the very high cure rates for low-risk APL, we chose a noninferiority study as an investigation with more realistically achievable objectives than a superiority study would have allowed. The decision to exclude patients with high-risk disease was based on three main factors: the results of arsenic trioxide treatment with or without ATRA in these patients were reported to be significantly inferior to the results in low-to-intermediate-risk patients²²⁻²⁵;



prolonged event-free and overall survival was routinely achieved in high-risk patients with risk-adapted consolidation therapy that included cytarabine,^{7,8,38} and there was concern about a potential increase in cases of the differentiation syndrome. In this study, we did not observe an increase in the incidence or severity of the differentiation syndrome in patients receiving ATRA-arsenic trioxide. It is likely that prednisone prophylaxis and exclusion of high-risk patients contributed to these findings.

Earlier studies suggested that APL was curable without chemotherapy. Tsimberidou et al. reported that 38% of patients receiving liposomal ATRA as monotherapy were presumably cured of their disease.³⁹ Other studies showed an event-free survival rate of 95% at 1 year among low-to-intermediate-risk patients treated with the ATRA-arsenic trioxide combination selected for the present investigation.^{23,25} The excellent outcomes reported in these studies are confirmed by the outcomes with ATRA-arsenic trioxide in our multicenter study involving a larger series of patients. In addition, our results in patients receiving the standard ATRA-chemotherapy regimen are very similar to previous findings reported by GIMEMA,⁸ despite the use of this strategy at the multinational level.

Our findings also confirm the distinct side-effect profiles of ATRA combined with arsenic

trioxide and ATRA combined with chemotherapy. The latter combination results in more frequent prolongation of cytopenias, mucositis, and infections, whereas the ATRA-arsenic trioxide combination results in more frequent prolongation of the QTc interval and liver-function abnormalities. Hepatic toxic effects appeared to be manageable with temporary discontinuation of the study medication and subsequent dose adjustments; the use of hydroxyurea was sufficient to counteract hyperleukocytosis.

Pilot studies of arsenic trioxide as a single agent have shown encouraging results, which were particularly favorable for patients with low-to-intermediate-risk disease.^{22,24} Other trials have shown the benefit of incorporating arsenic trioxide with ATRA and chemotherapy as front-line treatment.^{10,21,40} A randomized study showed significantly improved outcomes in patients receiving ATRA combined with arsenic trioxide for induction therapy, as compared with those treated with either agent alone.²¹ This study also showed improved clearance of PML-RARA transcripts in patients receiving the combination therapy. Finally, an interesting study combining the three most effective agents for APL — ATRA, arsenic trioxide, and anthracyclines — suggested that it may be possible to substantially reduce the intensity of chemotherapy when the triple combination is used.¹⁰

The present study suggests that APL is curable without conventional chemotherapy. Although longer follow-up will be needed to draw firm conclusions, our results support previously reported clinical and experimental evidence indicating that ATRA and arsenic trioxide act synergistically to eradicate APL.¹⁷⁻²¹

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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