

Improved Outcomes With Retinoic Acid and Arsenic Trioxide Compared With Retinoic Acid and Chemotherapy in Non-High-Risk Acute Promyelocytic Leukemia: Final Results of the Randomized Italian-German APL0406 Trial

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A B S T R A C T

Purpose

The initial results of the APL0406 trial showed that the combination of all-*trans*-retinoic acid (ATRA) and arsenic trioxide (ATO) is at least not inferior to standard ATRA and chemotherapy (CHT) in first-line therapy of low- or intermediate-risk acute promyelocytic leukemia (APL). We herein report the final analysis on the complete series of patients enrolled onto this trial.

Patients and Methods

The APL0406 study was a prospective, randomized, multicenter, open-label, phase III noninferiority trial. Eligible patients were adults between 18 and 71 years of age with newly diagnosed, low- or intermediate-risk APL (WBC at diagnosis $\leq 10 \times 10^9/L$). Overall, 276 patients were randomly assigned to receive ATRA-ATO or ATRA-CHT between October 2007 and January 2013.

Results

Of 263 patients evaluable for response to induction, 127 (100%) of 127 patients and 132 (97%) of 136 patients achieved complete remission (CR) in the ATRA-ATO and ATRA-CHT arms, respectively ($P = .12$). After a median follow-up of 40.6 months, the event-free survival, cumulative incidence of relapse, and overall survival at 50 months for patients in the ATRA-ATO versus ATRA-CHT arms were 97.3% v 80%, 1.9% v 13.9%, and 99.2% v 92.6%, respectively ($P < .001$, $P = .0013$, and $P = .0073$, respectively). Postinduction events included two relapses and one death in CR in the ATRA-ATO arm and two instances of molecular resistance after third consolidation, 15 relapses, and five deaths in CR in the ATRA-CHT arm. Two patients in the ATRA-CHT arm developed a therapy-related myeloid neoplasm.

Conclusion

These results show that the advantages of ATRA-ATO over ATRA-CHT increase over time and that there is significantly greater and more sustained antileukemic efficacy of ATO-ATRA compared with ATRA-CHT in low- and intermediate-risk APL.

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INTRODUCTION

Standard therapy of acute promyelocytic leukemia (APL) has long since relied on the combination of all-*trans*-retinoic acid (ATRA) and chemotherapy (CHT). Despite providing high cure rates, this approach is associated with frequent severe hematologic toxicity and

development of secondary myeloid neoplasms in approximately 2% of patients.¹⁻¹¹ The introduction of arsenic trioxide (ATO) in APL treatment has resulted in similarly high remission and survival rates coupled with significantly reduced myelosuppression. ATO is currently regarded as the most effective single agent in APL and is licensed for the treatment of relapsed and refractory APL.¹²⁻¹⁵

Recently, CHT-free regimens based on ATO with or without ATRA have proven highly effective in newly diagnosed APL.¹⁶⁻¹⁹ After pilot studies suggesting that ATRA plus ATO could substitute the standard approach in the treatment of newly diagnosed disease,^{18,19} two large independent randomized trials reported significantly improved outcomes for patients treated with ATRA-ATO compared with those receiving ATRA-CHT.^{20,21} On the basis of these data, expert panels from the United States and Canada have indicated ATRA-ATO as the favored option in first-line therapy of non-high-risk APL.^{22,23}

The APL0406 randomized trial reported by the Gruppo Italiano per le Malattie Ematologiche dell'Adulto (GIMEMA), Acute Myeloid Leukemia Study Group (AMLSG), and Study Alliance Leukemia (SAL) showed in the initial series of 156 patients that ATO-ATRA is at least not inferior, and probably superior, to standard ATRA-CHT for patients with newly diagnosed, non-high-risk APL.²⁰ We herein report the results of this study after a more prolonged follow-up and including the extended and final series of patients who were randomly assigned to receive ATRA-ATO or ATRA-CHT.

PATIENTS AND METHODS

Study Design and Patients

The APL0406 study was a prospective, randomized, multicenter, open-label, phase III noninferiority trial. The study was designed by GIMEMA in April 2006 (APL0406); it was started in Italy in October 2007 and was joined in 2008 by the German SAL and AMLSG groups. The study was designed to show that the ATRA-ATO regimen is not inferior to the ATRA-CHT regimen in terms of event-free survival (EFS) rate at 2 years. The full trial design and the results obtained in the initial series of 156 patients were reported in 2013.²⁰ Briefly, eligible patients were adults age 18 to 71 years with newly diagnosed, low- or intermediate-risk APL (WBC at diagnosis $\leq 10 \times 10^9/L$). Initial patient enrollment and random assignment were based on the sole morphologic diagnosis of APL according to the French-American-British criteria. Random assignment was stratified by institutions; random block size was four.

Genetic diagnostic confirmation was mandatory for eligibility and was carried out through centralized reference laboratories in Italy and Germany (E.L.-C., Università Tor Vergata in Rome, Italy, for GIMEMA and C.T., Carl Gustav Carus Universitätsklinikum in Dresden, Germany, for SAL and AMLSG). The trial was conducted in accordance with the Declaration of Helsinki, received institutional review board approval by all participating centers, and was registered at ClinicalTrials.gov (identifier: NCT00482833).

In September 2010, the study reached the initially programmed accrual of 162 patients and enrollment was suspended. At the time of inclusion of the last patient, however, compliance with quality-of-life (QoL) questionnaires was lower than initially anticipated. Therefore, considering QoL was a key secondary objective of the trial, the study was amended and restarted in March 2011 in an effort to maximize information obtained regarding burden of disease and treatment effects over time from patients themselves. The new target accrual to meet the QoL objective was set to 276 patients. The amendment was approved by all ethical committees of participating centers, and all patients provided written informed consent. A list of authors and centers that contributed to the APL0406 trial can be found in the Appendix (online only).

Treatment Arms, Supportive Measures, and Management of Complications

The treatment schedules for the ATRA-ATO and ATRA-CHT regimens, the recommended supportive measures to prevent and treat the APL-

associated coagulopathy and differentiation syndrome (DS), and the management of major expected therapy-related complications (QTc prolongation, hyperleukocytosis, and hepatotoxicity) have been reported in detail.²⁰ In particular, prednisone prophylaxis (0.5 mg/kg daily) was administered during the entire remission induction phase to prevent DS. Hydroxyurea was the only cytotoxic agent allowed to control hyperleukocytosis. Finally, temporary discontinuation and dose adjustments were recommended to manage ATO nonhematologic toxicity, as detailed elsewhere.²⁰

Laboratory Studies

Genetic studies, including reverse transcriptase polymerase chain reaction (RT-PCR) amplification of the *PML-RARA* hybrid using standardized protocols, were mandatory at diagnosis and after the third consolidation for all patients enrolled onto the study. Furthermore, longitudinal prospective monitoring of minimal residual disease was assessed by nested RT-PCR and quantitative RT-PCR in marrow samples for patients in both arms after induction therapy (for investigational purposes only) and during follow-up. Molecular studies also included *fms*-like tyrosine kinase 3 (*FLT3*) mutational status for the presence of the internal tandem duplication.

Outcomes

The primary study objective was to compare EFS at 2 years from diagnosis between the two treatment arms. Treatment failure was defined as any of the following events: no achievement of hematologic complete remission (HCR) after induction therapy, no achievement of molecular complete remission (CR) after three consolidation courses, relapse (molecular or hematologic, whichever was detected first), and death.

Secondary end points included rate of HCR after induction, overall survival (OS) at 2 years, disease-free survival (DFS), cumulative incidence of relapse (CIR, defined as the time from HCR achievement to either molecular or hematologic relapse, whichever was detected first), incidence and severity of hematologic and nonhematologic toxic episodes during treatment (graded according to National Cancer Institute Common Terminology Criteria for Adverse Events), kinetics of minimal residual disease, and self-assessed QoL.

OS was defined as the time from diagnosis to death from any cause. DFS was defined as the time from HCR achievement to relapse (either molecular or hematologic), persistence of polymerase chain reaction (PCR) positivity after consolidation, death, or date of last follow-up for patients alive in first molecular CR. Induction death was defined as death occurring at any time during induction therapy, before the achievement of HCR. CIR was calculated from the date of HCR until first relapse (either molecular or hematologic relapse) considering death in CR as a competing risk.

Statistical Analysis

All patients enrolled onto the study were analyzed following an intent-to-treat principle. Characteristics of patients were summarized by cross-tabulations (categorical variables) and quantiles (eg, median; for continuous variables). Nonparametric tests were applied for comparisons between groups (χ^2 and Fisher's exact test for categorical variables; Mann-Whitney *U* test and Kruskal-Wallis test for continuous variables). Survival distributions (OS, EFS, and DFS) were estimated using the Kaplan-Meier method. CIR was calculated using the proper nonparametric method. Differences in terms of OS, EFS, and DFS were evaluated using the log-rank test. The Gray test was applied to compare cumulative incidence curves. All tests were two-sided.

RESULTS

Enrollment and Patient Characteristics

The enrollment period was from October 2007 to January 2013. A total of 276 patients with low- or intermediate-risk APL were randomly assigned. Genetic tests excluded *PML-RARA*-positive APL in six patients (five patients randomly assigned to

ATRA-ATO and one randomly assigned to ATRA-CHT). Of the remaining 270 patients, four patients did not start allocated treatment (two treatment refusals, both in the ATRA-CHT arm, and two major violations, both in the ATRA-ATO arm). Therefore, 266 patients (129 randomly assigned to ATRA-ATO and 137 randomly assigned to ATRA-CHT) were included in the intent-to-treat analysis. The disposition of the patients and reasons for exclusion are shown in Figure 1.

The main demographic, clinical, and laboratory features of the 266 patients eligible for analysis are listed in Table 1. There were no significant differences in the baseline characteristics between the two cohorts. The present analysis was performed in December 2015 with a median follow-up time of 40.6 months (range, 0.1 to 83.6 months).

Induction Therapy

Four patients died during induction in the ATRA-CHT group. The causes of death were DS (n = 2), ischemic stroke (n = 1), and

bronchopneumonia (n = 1). All deaths were recorded in the initial series,²⁰ and no further deaths occurred in the second cohort of 110 patients enrolled in the postamentment period from March 2011 to January 2013. One hundred twenty-seven patients in the ATRA-ATO arm and 136 patients in the ATRA-CHT arm were evaluable for induction response. HCR was documented in 127 patients (100%) and 132 patients (97%) in the ATRA-ATO and ATRA-CHT arms, respectively (P = .12). For two patients who started induction in the ATRA-ATO arm, the assigned treatment was terminated early. For one of these patients, a protocol violation occurred (early evaluation of bone marrow aspirate at day +13 with inappropriate diagnosis of resistant disease). This patient was alive at 2 years from diagnosis. In the other patient, treatment was permanently withdrawn by the treating physician as a result of toxicity (QTc prolongation and electrolyte abnormalities at day +3), and the patient was lost to follow-up. In one patient in the ATRA-CHT arm, treatment was discontinued as a result of an unknown reason, and the patient was lost to follow-up.

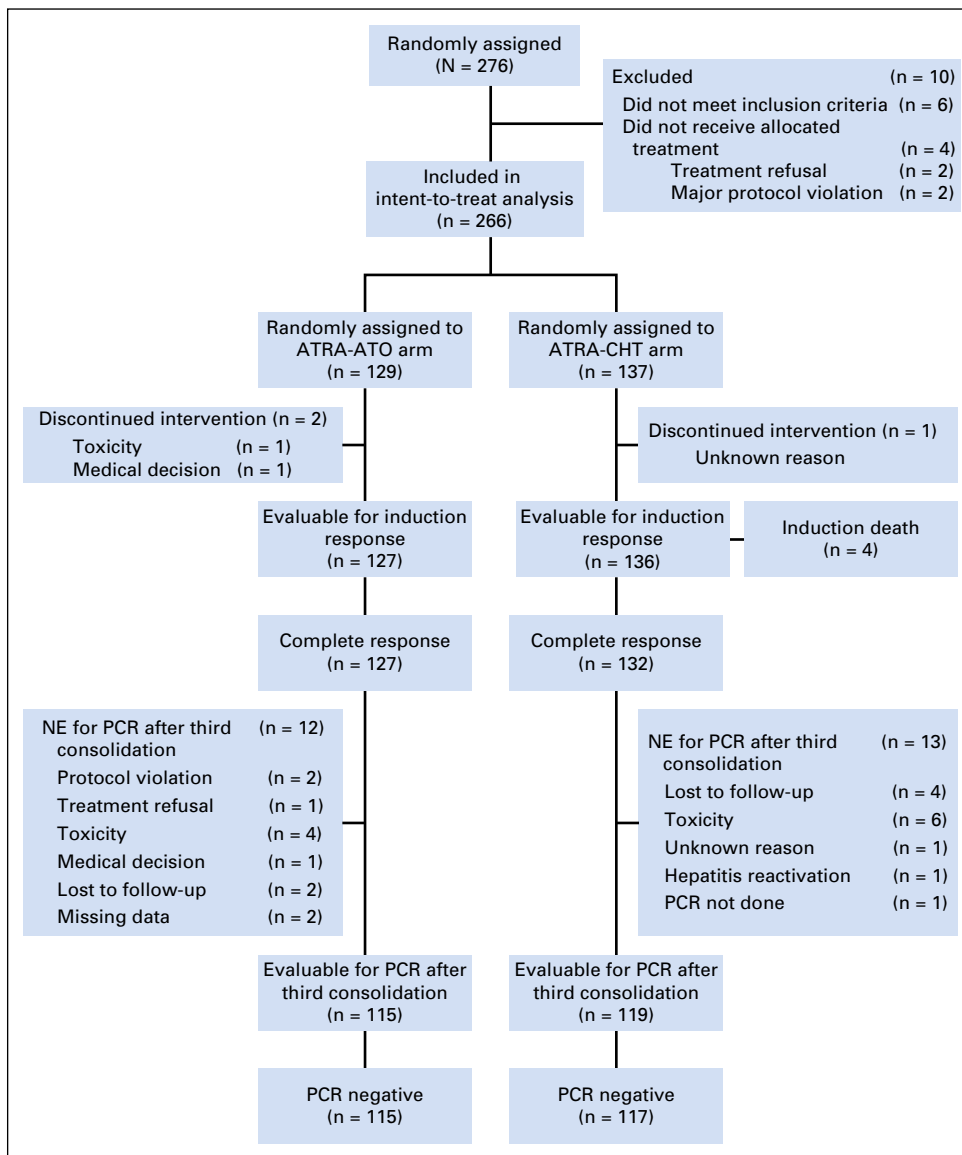


Fig 1. Study enrollment, random assignment, and retention. ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CHT, chemotherapy; NE, not evaluable; PCR, polymerase chain reaction.

Table 1. Demographic, Clinical, and Laboratory Characteristics of the Eligible Patients

Characteristic	ATRA-ATO (n = 129)	ATRA-CHT (n = 137)	P
Median age, years (range)	46.6 (18.8-70.2)	46.6 (18-70.3)	.84
Sex, No. (%)			.45
Male	60 (46.5)	70 (51.1)	
Female	69 (53.5)	67 (48.9)	
Median WBC, × 10 ⁹ /L (range)	1.4 (0.32-10)	1.5 (0.3-9.61)	.83
Median platelets, × 10 ⁹ /L (range)	36.5 (3-224)	31.5 (3-236)	.19
Sanz risk, No. (%)			.52
Low	57 (45.2)	55 (41.3)	
Intermediate	69 (54.7)	78 (58.6)	
<i>PML-RARA</i> isoform, No. (%)			.35
Long	83 (68.6)	78 (62.9)	
Short	38 (31.4)	46 (37.1)	
Missing	8 (7)	13 (10)	
<i>FLT3</i> ITD, No. (%)			.59
Mutated	26 (25.5)	22 (22.2)	
Unmutated	76 (74.5)	77 (77.8)	
Missing	27 (21)	38 (28)	

Abbreviations: ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CHT, chemotherapy; ITD, internal tandem duplication.

Leukocytosis greater than $10 \times 10^9/L$ developed during induction in 56 patients (43%) receiving ATRA-ATO and was successfully managed in all patients with hydroxyurea as per protocol recommendation. Moderate and severe DS (defined as in Montesinos et al²⁴) occurred during induction in 16 patients (13%) and five patients (4%) in the ATRA-ATO arm and in nine patients (7%) and eight patients (6%) in the ATRA-CHT arm, respectively ($P = .38$), and was fatal in two patients in the ATRA-CHT arm. In eight patients (four patients in each arm), indeterminate DS (defined according to Frankel et al²⁵) was reported.

Consolidation Therapy

Of 259 patients who proceeded to consolidation therapy, 234 patients (115 in the ATRA-ATO arm and 119 in the ATRA-CHT arm) were evaluable for molecular response after the third consolidation cycle. Twelve of 127 patients in the ATRA-ATO arm went off protocol before the bone marrow assessment after third consolidation as a result of major protocol violation ($n = 2$), consent withdrawal ($n = 1$), medical decision ($n = 1$), loss to follow-up ($n = 2$), toxicity ($n = 4$), or missing data ($n = 2$). In the

ATRA-CHT arm, 13 of 132 patients did not undergo bone marrow evaluation after third consolidation because of major protocol violation (PCR not performed, $n = 1$), loss to follow-up ($n = 4$), toxicity ($n = 6$), hepatitis reactivation ($n = 1$), or missing data ($n = 1$). Six patients (one in the ATRA-ATO arm and five in the ATRA-CHT arm) died in CR. The patient in the ATRA-ATO group died of bronchopneumonia driven by H1N1 virus. Of the five deaths in the ATRA-CHT group, one was caused by hemorrhagic shock, one by pulmonary embolism, two by bronchopneumonia, and one by secondary myelodysplastic syndrome.

Molecular evaluation of *PML-RARA* by RT-PCR after third consolidation showed PCR negativity in all patients in the ATRA-ATO arm, whereas two (1.7%) of 119 patients in the ATRA-CHT arm tested positive by PCR and were considered as having molecular resistance. Of these, one patient was treated with ATO salvage therapy followed by allogeneic stem-cell transplantation and remained in second CR 14 months after transplantation. In the other patient, a second PCR test after the end of consolidation did not confirm PCR positivity. The patient was continued on ATRA and low-dose CHT maintenance and remained in remission for greater than 24 months.

Maintenance Therapy (ATRA-CHT Arm)

All 117 patients in the ATRA-CHT arm who completed consolidation and tested RT-PCR negative for *PML-RARA* proceeded to maintenance. Excluding the nine patients who experienced relapse during maintenance, 20 patients did not complete maintenance as a result of toxicity ($n = 4$), treatment refusal ($n = 3$), major protocol violation ($n = 1$), or other reasons ($n = 12$).

Toxicities

Hematologic and nonhematologic toxicities are listed in Tables 2 and 3, respectively. A total of 95 serious adverse events (SAEs) were reported in 65 patients. Of these, 43 and 52 SAEs were reported in patients receiving ATRA-ATO and ATRA-CHT, respectively. The complete list of detailed SAEs is reported in Appendix Table A1 (online only).

Hematologic toxicity. As shown in Table 2, a significantly higher number of patients in the ATRA-CHT arm compared with the ATRA-ATO arm experienced grade 3 or 4 neutropenia and thrombocytopenia lasting more than 15 days ($P < .001$). Episodes of febrile neutropenia (including fever of unknown origin and

Table 2. Hematologic Toxicity

Toxicity and Treatment Arm	Induction		First Consolidation		Second Consolidation		Third Consolidation	
	No. (%)	P	No. (%)	P	No. (%)	P	No. (%)	P
Neutropenia (grade 3-4 lasting > 15 days)		< .001		< .001		< .001		< .001
ATRA-ATO	61 (35)		8 (16)		7 (7)		5 (15)	
ATRA-CHT	109 (64)		40 (67)		90 (92)		28 (85)	
Thrombocytopenia (grade 3-4 lasting > 15 days)		< .001		< .001		< .001		< .001
ATRA-ATO	74 (38)		6 (26)		6 (7)		8 (23)	
ATRA-CHT	120 (62)		17 (74)		77 (93)		26 (76)	
Infection and FUO		< .001		.54		< .001		1.0
ATRA-ATO	30 (23)		10 (8)		4 (3)		2 (1.6)	
ATRA-CHT	75 (55)		8 (6)		46 (38)		2 (1.7)	

Abbreviations: ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CHT, chemotherapy; FUO, fever of unknown origin.

Table 3. Nonhematologic Toxicity

Toxicity and Treatment Arm	Induction		First Consolidation		Second Consolidation		Third Consolidation	
	No. (%)	<i>P</i>	No. (%)	<i>P</i>	No. (%)	<i>P</i>	No. (%)	<i>P</i>
Hepatic toxicity (grade 3-4)		< .001		.11		.49		
ATRA-ATO	51 (40)		5 (4)		1 (0.8)		0	
ATRA-CHT	4 (3)		1 (0.7)		0		0	
QTc prolongation		.0022		.11		.11		.23
ATRA-ATO	11 (8.5)		3 (2)		3 (2)		2 (1.5)	
ATRA-CHT	1 (0.7)		0		0		0	
Cardiac function (grade 3-4)		.06						
ATRA-ATO	0		0		0		0	
ATRA-CHT	5 (3.7)		0		0		0	
Neurotoxicity (all grades)		.48		.02		.01		.006
ATRA-ATO	1 (0.7)		5 (4.2)		6 (5)		7 (5.9)	
ATRA-CHT	0		0		0		0	
GI toxicity (grade 3-4)		< .001		1.0		.03		1.0
ATRA-ATO	3 (2)		0		0		0	
ATRA-CHT	25 (18.2)		1 (0.8)		6 (4.9)		0	
Hypercholesterolemia		.55		.13		.14		.27
ATRA-ATO	14 (10)		19 (16)		19 (16)		16 (14)	
ATRA-CHT	12 (8.7)		12 (9.6)		12 (9.7)		11 (9)	
Hypertriglyceridemia		0.76		.49		.12		.5
ATRA-ATO	29 (22)		22 (18.4)		17 (14.4)		16 (14)	
ATRA-CHT	29 (22)		19 (15.2)		10 (8)		13 (11)	

Abbreviations: ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CHT, chemotherapy.

documented infections counted together) were also significantly more frequent in the ATRA-CHT arm than in the ATRA-ATO arm. In particular, in the ATRA-ATO and ATRA-CHT arms, 30 and 75 episodes were documented during the induction course ($P < .001$), 10 and eight occurred during the first consolidation cycle ($P = .54$), four and 46 occurred during the second consolidation cycle ($P < .001$), and two and two occurred during the third consolidation cycle ($P = 1.0$), respectively.

Other toxicities. Significant elevation of liver function tests (grade 3 or 4 according to National Cancer Institute Common Terminology Criteria for Adverse Events) was more frequent in the ATRA-ATO arm (44%) compared with the ATRA-CHT (3%) arm across all treatment cycles ($P < .001$). Toxicity resolved in all patients with temporary discontinuation of ATO and/or ATRA or of low-dose CHT during maintenance (for patients in the ATRA-CHT arm). QTc prolongation, defined as QTc greater than 450 milliseconds for men and greater than 460 milliseconds for women with correction calculated using the Framingham formula, was observed in 15 patients (11%) in the ATRA-ATO arm and one patient in the ATRA-CHT arm ($P < .001$) throughout the treatment cycles. There were no cases of life-threatening cardiac arrhythmias; however, ATO was permanently discontinued in one of the 15 patients, and the patient went off protocol. Neurotoxicity mainly consisting of reversible peripheral nerve neuropathy was observed in a greater proportion of patients in the ATRA-ATO arm and occurred during consolidation. Finally, GI toxicity and cardiac function abnormalities were significantly more frequent in the ATRA-CHT arm (Table 3).

Outcomes

All outcome estimates calculated at 24 and 50 months are listed in Table 4, whereas outcome curves are shown in Figure 2.

Primary end point. A total of 263 patients (127 and 136 in the ATRA-ATO and ATRA-CHT arms, respectively) were evaluable for EFS according to the intent-to-treat analysis. In the ATRA-ATO group, 98.3% of patients (95% CI, 95.9% to 100%) were event free at 24 months from random assignment, compared with 86.8% in the ATRA-CHT group (95% CI, 81.1% to 92.8%; $P < .001$). At 50 months, EFS estimates were 97.3% (95% CI, 94.3% to 100%) and 80.0% (95% CI, 72.9% to 88.0%) in the ATRA-ATO and ATRA-CHT groups, respectively. Although 263 patients is not the full intent-to-treat complement for EFS evaluation, the number of unevaluable patients was small.

The noninferiority analysis was carried out in 229 patients with sufficient follow-up (beyond 24 months). Of these patients,

Table 4. Outcome Results

Outcome and Treatment Arm	Probability, % (95% CI)		<i>P</i>
	24 Months	50 Months	
Overall survival			.0073
ATRA-ATO	99.2 (97.7 to 100)	99.2 (97.7 to 100)	
ATRA-CHT	94.8 (91.1 to 98.6)	92.6 (87.9 to 97.5)	
Event-free survival			< .001
ATRA-ATO	98.3 (95.9 to 100)	97.3 (94.3 to 100)	
ATRA-CHT	86.8 (81.1 to 92.8)	80.0 (72.9 to 88.0)	
Disease-free survival			< .001
ATRA-ATO	98.3 (95.9 to 100)	97.3 (94.3 to 100)	
ATRA-CHT	89.4 (84.1 to 95.0)	82.6 (75.6 to 90.3)	
Cumulative incidence of relapse			.0013*
ATRA-ATO	0.9 (0 to 2.7)	1.9 (0.0 to 4.5)	
ATRA-CHT	8.2 (3.3 to 13.2)	13.9 (7.1 to 20.6)	

Abbreviations: ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CHT, chemotherapy.
*Gray test.

98.15% in the ATRA-ATO group (106 of 108 patients) were alive and event free at 24 months, compared with 85.95% of patients in the ATRA-CHT group (104 of 121 patients), with a difference in the EFS rates at 2 years of 12.2% (95% CI, 4.3% to 20.1%); because the lower bound of the 95% CI for this difference was $\geq 5\%$, the noninferiority of ATRA-ATO was confirmed ($P < .001$).

Seventeen patients experienced relapse during follow-up. Of these, two relapses occurred in the ATRA-ATO arm at 22 and 27 months, and 15 occurred in the ATRA-CHT arm at a median time of 14.0 months (range, 2.5 to 39.8 months). In four patients, relapse was detected at the molecular level before hematologic relapse, leading to administration of pre-emptive salvage therapy. Two patients in the ATRA-CHT arm and none in the ATRA-ATO arm developed a therapy-related myeloid neoplasm. Of these, one patient with therapy-related myelodysplastic syndrome died as a result of disease progression, whereas in the other patient, a therapy-related acute myeloid leukemia was diagnosed, and the patient remained alive in CR 14 months after undergoing allogeneic stem-cell transplantation.

Secondary end points. The 24- and 50-month OS, DFS, and CIR rates for patients in the two arms are listed in Table 4. The

results of the kinetics of molecular response and impact of *FLT3* status will be reported in a separate publication.

Regarding QoL, the results of the current extended series broadly confirm previously reported findings²⁶ on the benefits of ATRA-ATO versus ATRA-CHT after induction therapy. The previous main observation that fatigue severity (as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30) was significantly lower in the group treated with ATRA-ATO versus ATRA-CHT after induction therapy ($P = .034$)²⁶ was fully confirmed in this larger patient population ($P = .008$). A long-term QoL analysis has been planned, and full details will be reported separately.

DISCUSSION

This study shows that, compared with ATRA-CHT, the ATRA-ATO combination significantly improved both survival and relapse risk in patients with newly diagnosed, low- or intermediate-risk APL. Compared with our previous report in which no significant differences in DFS and CIR rates were found, we report here that the

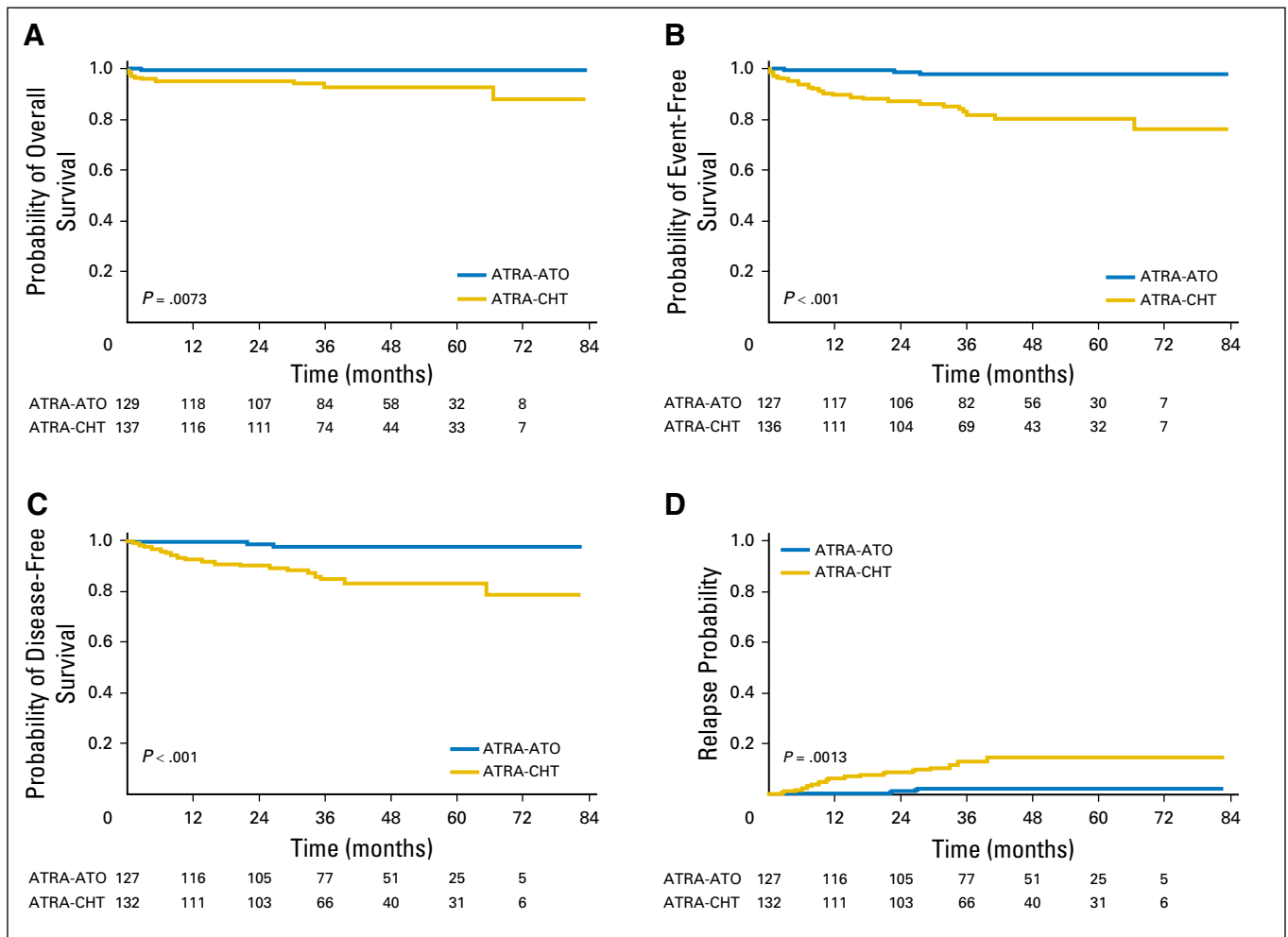


Fig 2. Outcome estimates. (A) Overall survival. (B) Event-free survival. (C) Disease-free survival. (D) Relapse. ATO, arsenic trioxide; ATRA, all-trans-retinoic acid; CHT, chemotherapy.

CHT-free approach based on ATRA-ATO resulted in higher antileukemic efficacy. In addition, the present analysis conducted in a substantially extended cohort of patients with prolonged follow-up revealed significantly improved differences in all other analyzed outcomes (EFS, OS, and DFS) compared with the initial report.²⁰ These data indicate that the advantage of ATRA-ATO over ATRA-CHT increases over time and that the inclusion of ATO in the treatment of low- or intermediate-risk APL not only reduces mortality and hematologic toxicity, but also results in improved and sustained antileukemic activity. Neither additional fatal events nor further relapses were recorded in patients randomly assigned to ATRA-ATO in this extended cohort. By contrast, new relapses, two instances of molecular resistance (ie, testing PCR positive after third consolidation), and two therapy-related myeloid neoplasms were observed in the group of patients receiving ATRA-CHT.

A recent study conducted in the United Kingdom by the National Cancer Research Institute (NCRI) reported similar results in terms of EFS and relapse rate, with patients treated with ATRA-ATO showing significantly better outcomes.²¹ At variance from our study, the NCRI trial used an ATO schedule consisting of two or three weekly administrations at increased doses and included no maintenance in the ATRA-CHT arm (which was otherwise derived from the same ATRA and idarubicin [AIDA] protocol used in our study). Furthermore, the study included patients with high-risk disease, for whom a provision was made to use one or two 6 mg/m² doses of gemtuzumab ozogamicin during the first 4 days of induction. This important study independently confirmed the advantage of including ATO in first-line management of APL, suggesting that the benefit is also observed in high-risk patients. In this respect, however, it should be noted that a total of 57 patients with high-risk disease were included in the comparison and that the efficacy of ATO in this patient subset may be difficult to analyze given the addition of a potent anti-APL agent such as gemtuzumab ozogamicin.²¹ A randomized trial comparing ATRA-ATO to the AIDA2000 protocol⁵ and involving several European cooperative groups will be started soon to further investigate this issue.

The toxicity profiles in the current study were comparable to those observed for the two cohorts in the original series. For patients receiving ATRA-ATO, adverse effects mainly consisted of frequent increase of liver enzymes, QTc prolongation, and hyperleukocytosis. In almost all patients, this toxicity was reversible and manageable with temporary drug interruption and dose adjustments as per protocol recommendations, including the addition of hydroxyurea (the only cytotoxic agent allowed for the control of hyperleukocytosis). The study from the United Kingdom²¹ reported similar toxicities for patients in the ATO group in

terms of DS and cardiac adverse effects, but a lower incidence of grade 3 or 4 hepatic toxicity, probably as a result of the different schedule. Regarding medium- and long-term toxicity, the absence of secondary therapy-related myeloid neoplasms at the extended follow-up in the ATRA-ATO cohort also represents a major improvement in the treatment of a disease where high cure rates are achieved.

In conclusion, in line with results of pilot studies^{18,19} and those of the recent randomized NCRI trial,²¹ our results support the use of ATRA-ATO in patients with newly diagnosed APL and point to this strategy as the new standard of care for low- or intermediate-risk patients. Studies exploring the role of ATRA-ATO are warranted in other APL subsets including high-risk, pediatric, and elderly patients.

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Disclosures provided by the authors are available with this article at www.jco.org.

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Improved Outcomes With Retinoic Acid and Arsenic Trioxide Compared With Retinoic Acid and Chemotherapy in Non-High-Risk Acute Promyelocytic Leukemia: Final Results of the Randomized Italian-German APL0406 Trial

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Table A1. Hematologic Toxicity

Randomly Assigned Treatment	UPN	System, Organ, Class	Preferred Term	Drug 1	Relationship 1	Drug 2	Relationship 2	Outcome
ATRA-ATO	1	Investigations	ECG QT prolonged	ATO	Related	ATRA	Related	Recovered
ATRA-ATO	2	Infections	Pneumonia	ATO	Related	ATRA	Related	Recovered
ATRA-ATO	2	Respiratory, thoracic, and mediastinal disorders	Respiratory failure	ATO	Related	ATRA	Related	Unchanged
ATRA-ATO	3	Investigations	ALT increased	ATO	Related	ATRA	Related	Recovered
ATRA-ATO	4	Respiratory, thoracic, and mediastinal disorders	APL differentiation syndrome	ATO	Related	ATRA	Related	Recovered
ATRA-ATO	5	Nervous system disorders	Cerebrovascular accident	ATO	Related	ATRA	Related	Recovered
ATRA-ATO	6	Respiratory, thoracic, and mediastinal disorders	Dyspnea	ATO	Unrelated	—	—	Recovered
ATRA-ATO	7	Respiratory, thoracic, and mediastinal disorders	Respiratory failure	ATO	Unrelated	—	—	Recovered
ATRA-ATO	8	Cardiac disorders	Pericarditis	ATO	Unrelated	ATRA	Unrelated	Recovered
ATRA-ATO	9	Injury poisoning and procedural complications	Maternal exposure before pregnancy	ATO	Unrelated	—	—	Recovered
ATRA-ATO	10	Hepatobiliary disorders	Hepatotoxicity	ATO	Related	ATRA	Related	Recovered
ATRA-ATO	11	Nervous system disorders	Cerebral hemorrhage	ATO	Related	ATRA	Related	—
ATRA-ATO	12	Vascular disorders	Intracranial aneurysm	ATO	Unrelated	ATRA	Unrelated	Unchanged
ATRA-ATO	13	Investigations	ALT increase	ATO	Related	ATRA	Related	Recovered
ATRA-ATO	13	Investigations	AST increase	ATO	Related	ATRA	Related	Recovered
ATRA-ATO	14	GI disorders	Dyspepsia	ATO	Related	—	—	Recovered
ATRA-ATO	14	Respiratory, thoracic, and mediastinal disorders	APL differentiation syndrome	ATO	Not assessable	—	—	Recovered
ATRA-ATO	15	Eye disorders	Diplopia	ATO	Not assessable	ATRA	Not assessable	Recovered
ATRA-ATO	16	Psychiatric disorders	Confusional state	ATO	Unrelated	—	—	Recovered
ATRA-ATO	17	Hepatobiliary disorders	Hypertransaminasemia	ATO	Related	ATRA	Related	Recovered
ATRA-ATO	18	Infections	Catheter site infection	ATO	Unrelated	—	—	Recovered
ATRA-ATO	19	Infections	Pneumonia	ATO	Unrelated	ATRA	Unrelated	Recovered
ATRA-ATO	20	General disorders and administration site conditions	Pyrexia	ATO	Unrelated	ATRA	Unrelated	—
ATRA-ATO	21	Hepatobiliary disorders	Hepatic failure	ATO	Related	ATRA	Related	Recovered
ATRA-ATO	21	Respiratory, thoracic, and mediastinal disorders	APL differentiation syndrome	ATO	Related	ATRA	Related	Recovered
ATRA-ATO	22	Infections	Herpes zoster	—	Related	—	Related	Recovered
ATRA-ATO	22	Nervous system disorders	Hydrocephalus	ATO	Related	ATRA	Related	Unchanged
ATRA-ATO	22	Skin and subcutaneous tissue disorders	Leukocytoclastic vasculitis	ATO	Unrelated	ATRA	Unrelated	Recovered
ATRA-ATO	23	Respiratory, thoracic, and mediastinal disorders	Pneumonia	ATO	Unrelated	ATRA	Unrelated	Fatal
ATRA-ATO	24	Respiratory, thoracic, and mediastinal disorders	Dyspnea	ATO	Unrelated	—	—	Recovered
ATRA-ATO	25	Nervous system disorders	Depression	—	—	—	—	Recovered
ATRA-ATO	26	Respiratory, thoracic, and mediastinal disorders	Retinoic acid syndrome	ATO	Related	ATRA	Related	Recovered
ATRA-ATO	27	Cardiac disorders	Syncope	ATO	Unrelated	ATRA	Unrelated	Recovered
ATRA-ATO	27	Hepatobiliary disorders	Cholelithiasis	ATO	Unrelated	ATRA	Related	Recovered
ATRA-ATO	27	Investigations	Hepatic enzyme increased	ATO	Related	ATRA	Related	Recovered
ATRA-ATO	27	Musculoskeletal and connective tissue disorders	Fracture	ATO	Unrelated	ATRA	Unrelated	Recovered
ATRA-ATO	28	Infections	Catheter site infection	ATO	Unrelated	—	—	Recovered

(continued on following page)

ATRA-ATO or ATRA-CHT in Low- or Intermediate-Risk APL

Table A1. Hematologic Toxicity (continued)

Randomly Assigned Treatment	UPN	System, Organ, Class	Preferred Term	Drug 1	Relationship 1	Drug 2	Relationship 2	Outcome
ATRA-ATO	29	Investigations	C-reactive protein increased	ATO	Related	—	—	Recovered
ATRA-ATO	29	Respiratory, thoracic, and mediastinal disorders	Dyspnea	ATO	Related	—	—	Recovered
ATRA-ATO	30	Infections	Febrile infection	ATO	Related	ATRA	Related	Recovered
ATRA-ATO	30	Reproductive system and breast disorders	Endometriosis	ATO	Unrelated	ATRA	Unrelated	Recovered
ATRA-ATO	31	Cardiac disorders	Acute myocardial infarction	ATO	Unrelated	ATRA	Unrelated	Recovered
ATRA-ATO	32	Investigations	ECG QT prolonged	ATO	Related	—	—	Recovered
ATRA-CHT	33	Respiratory, thoracic, and mediastinal disorders	Acute respiratory distress syndrome	IDA	Related	ATRA	Related	Fatal
ATRA-CHT	34	Cardiac disorders	Myocardial ischemia	IDA	Related	ATRA	Related	Recovered
ATRA-CHT	35	Respiratory, thoracic, and mediastinal disorders	Respiratory failure	IDA	Related	ATRA	Related	Fatal
ATRA-CHT	35	Respiratory, thoracic, and mediastinal disorders	Retinoic acid syndrome	IDA	Related	ATRA	Related	Fatal
ATRA-CHT	36	Cardiac disorders	Acute myocardial infarction	IDA	Unrelated	ATRA	Unrelated	Recovered
ATRA-CHT	37	Investigations	Aminotransferases increased	IDA	Unrelated	ATRA	Unrelated	Unchanged
ATRA-CHT	38	Blood and lymphatic system disorders	Febrile neutropenia	MTX	Related	ATRA	Related	Recovered
ATRA-CHT	39	GI disorders	Pancreatitis acute	ATRA	Unrelated	—	—	Recovered
ATRA-CHT	40	Nervous system disorders	Ischemic stroke	IDA	Related	ATRA	Related	Fatal
ATRA-CHT	41	Cardiac disorders	Pericarditis	IDA	Related	ATRA	Related	Improved
ATRA-CHT	42	Cardiac disorders	Cardiac failure	IDA	Related	ATRA	Related	Recovered
ATRA-CHT	43	General disorders and administration site conditions	Pyrexia	MTX	Related	ATRA	Related	Recovered
ATRA-CHT	44	Blood and lymphatic system disorders	Febrile neutropenia	MTX	Related	ATRA	Related	—
ATRA-CHT	45	Blood and lymphatic system disorders	Bone marrow failure	MTX	Related	ATRA	Related	Improved
ATRA-CHT	46	Respiratory, thoracic, and mediastinal disorders	Pulmonary embolism	—	—	—	Not assessable	Improved
ATRA-CHT	46	Respiratory, thoracic, and mediastinal disorders	Retinoic acid syndrome	—	—	ATRA	Related	Improved
ATRA-CHT	46	Vascular disorders	Shock hemorrhagic	IDA	Unrelated	ATRA	Unrelated	Fatal
ATRA-CHT	47	Infections	Bronchopneumonia	—	—	ATRA	Related	Fatal
ATRA-CHT	48	Vascular disorders	Thrombosis	IDA	Related	ATRA	Related	Recovered
ATRA-CHT	48	Infections	Bronchopneumonia	MTX	Related	—	—	Fatal
ATRA-CHT	49	Blood and lymphatic system disorders	Febrile neutropenia	IDA	Related	ATRA	Related	Recovered
ATRA-CHT	50	Blood and lymphatic system disorders	Neutropenia	MTX	Related	ATRA	Related	Recovered
ATRA-CHT	50	Infections	Pneumonia	MTX	Related	ATRA	Related	Recovered
ATRA-CHT	51	General disorders and administration site conditions	Mucosal inflammation	IDA	Related	ATRA	Related	Recovered
ATRA-CHT	51	Vascular disorders	Pulmonary embolism	—	Unrelated	—	—	Fatal
ATRA-CHT	52	GI disorders	Inguinal hernia	MP	Unrelated	MTX	Unrelated	Recovered
ATRA-CHT	53	Blood and lymphatic system disorders	Febrile neutropenia	MTX	Related	ATRA	Related	Improved
ATRA-CHT	53	GI disorders	Anal hemorrhage	MTX	Related	ATRA	Related	Recovered
ATRA-CHT	53	Injury poisoning and procedural complications	Maternal exposures before pregnancy	ATRA	Unrelated	MP	Unrelated	Recovered
ATRA-CHT	54	Blood and lymphatic system disorders	Febrile neutropenia	—	Related	—	—	Recovered

(continued on following page)

Table A1. Hematologic Toxicity (continued)

Randomly Assigned Treatment	UPN	System, Organ, Class	Preferred Term	Drug 1	Relationship 1	Drug 2	Relationship 2	Outcome
ATRA-CHT	54	Blood and lymphatic system disorders	Febrile neutropenia	IDA	—	ATRA	—	Recovered
ATRA-CHT	54	Vascular disorders	Extradural hematoma	IDA	Unrelated	ATRA	Unrelated	Improved
ATRA-CHT	55	Respiratory, thoracic, and mediastinal disorders	Retinoic acid syndrome	IDA	Related	ATRA	Related	Improved
ATRA-CHT	56	Infections	Urinary tract infection	IDA	Unrelated	ATRA	Unrelated	Recovered
ATRA-CHT	57	Blood and lymphatic system disorders	Febrile neutropenia	MTX	Related	ATRA	Related	Recovered
ATRA-CHT	58	General disorders and administration site conditions	Pyrexia	MP	Related	—	—	Recovered
ATRA-CHT	58	Infections	Bacteremia	IDA	Related	ATRA	Related	Recovered
ATRA-CHT	58	Infections	Infection	MP	Related	—	—	Recovered
ATRA-CHT	58	Infections	Infection	MTX	Related	ATRA	Related	Recovered
ATRA-CHT	59	Cardiac disorders	Ejection fraction decreased	MP + MTX	Unrelated	ATRA	Unrelated	Unchanged
ATRA-CHT	60	Infections	Sepsis	IDA	Related	ATRA	Related	Recovered
ATRA-CHT	61	Cardiac disorders	Pericarditis	IDA	Related	—	—	Unchanged
ATRA-CHT	61	General disorders and administration site conditions	Mucosal inflammation	MTX	Related	ATRA	Related	Recovered
ATRA-CHT	61	Respiratory, thoracic, and mediastinal disorders	Respiratory failure	—	—	—	—	Recovered
ATRA-CHT	62	GI disorders	Diarrhea	ATRA	Unrelated	—	—	Recovered
ATRA-CHT	62	GI disorders	Emesis	ATRA	Unrelated	—	—	Recovered
ATRA-CHT	63	General disorders and administration site conditions	Fever in aplasia	IDA + MTX	Related	ATRA	Related	Recovered
ATRA-CHT	64	Infections	Sepsis	IDA	Unrelated	ATRA	Unrelated	Recovered
ATRA-CHT	64	Investigations	Hyperglycemia	MTX, MP	Unrelated	ATRA	Unrelated	Recovered
ATRA-CHT	64	Blood and lymphatic system disorders	Febrile neutropenia	MTX	Related	ATRA	Related	Recovered
ATRA-CHT	65	Cardiac disorders	Tachyarrhythmia	Prednisone	Unrelated	ATRA	Unrelated	Recovered
ATRA-CHT	65	Infections	Pneumonia	Prednisone	Related	ATRA	Related	Recovered

Abbreviations: APL, acute promyelocytic leukemia; ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CHT, chemotherapy; IDA, idarubicin; MP, mercaptopurine; MTX, methotrexate; UPN, unique patient number.