Arsenic Trioxide and All-Trans Retinoic Acid Combination Therapy for the Treatment of High-Risk Acute Promyelocytic Leukemia: Results From the APOLLO Trial

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ABSTRACT

PURPOSE The phase III APOLLO trial prospectively compared the efficacy of arsenic trioxide (ATO) in combination with all-trans retinoic acid (ATRA) regimen (ATRA and ATO [ATRA-ATO]) plus low-dose idarubicin versus standard ATRA plus anthracycline-based chemotherapy (ATRA-CHT) regimen (ie, ATRA and idarubicin regimen) in patients with high-risk acute promyelocytic leukemia (APL; EudraCT 2015-01151-68; ClinicalTrials.gov identifier: NCT02688140).

METHODS Adult patients with newly diagnosed high-risk APL in the ATRA-ATO arm received ATO 0.15 mg/kg once daily and ATRA 45 mg/m² twice daily until complete remission (CR), with two doses of idarubicin 12 mg/m² on days 1 and 3, followed by consolidation therapy (four ATRA-ATO cycles). Patients in the ATRA-CHT arm received induction with ATRA 45 mg/m² twice daily and idarubicin 12 mg/m² once daily on days 1, 3, 5, and 7, followed by three cycles of chemotherapy-based consolidation and 2 years of maintenance therapy. The primary study end point was event-free survival (EFS) at 2 years.

RESULTS As of July 2022, 133 eligible patients had received either ATRA-ATO (n = 68) or ATRA-CHT (n = 65). The study was discontinued prematurely because of slow accrual during the COVID-19 pandemic. After a median follow-up of 37 months (range, 1.7-88.6 months), 2-year EFS was 88% in the ATRA-ATO arm and 71% in the ATRA-CHT arm (HR, 0.4 [95% CI, 0.17 to 0.92]; log-rank test $P = .02$). At a median of 7.8 and 12.1 months from achievement of CR, molecular relapse occurred in one (1.5%) ATRA-ATO patient versus eight (12.3%) ATRA-CHT patients ($P = .014$). Overall, 32% and 68% of patients receiving ATRA-ATO and ATRA-CHT, respectively, reported serious treatment-emergent adverse events ($P < .01$).

CONCLUSION The results of the APOLLO trial support the use of ATO and ATRA for the treatment of newly diagnosed patients with high-risk APL.

ACCOMPANYING CONTENT

Editorial, p. 3144

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

Acute promyelocytic leukemia (APL) is a rare and aggressive subtype of AML, occurring in approximately 5%-15% of patients with AML.[1,2]

All-trans retinoic acid (ATRA) plus anthracycline-based chemotherapy (ATRA-CHT) had previously been considered the standard treatment for patients with APL, but despite the increased survival and complete remission (CR) rates associated with ATRA-CHT, relapse (frequently accompanied

CONTEXT

Key Objective

To determine the efficacy of an all-trans retinoic acid and arsenic trioxide (ATRA-ATO) regimen versus a standard ATRA plus anthracycline-based chemotherapy (ATRA-CHT) regimen for the treatment of patients with newly diagnosed high-risk acute promyelocytic leukemia (APL).

Knowledge Generated

Two-year event-free survival was significantly higher among patients treated with ATRA-ATO when compared with patients treated with ATRA-CHT, and rates of molecular relapse were significantly lower among patients receiving ATRA-ATO when compared with patients receiving ATRA-CHT.

Relevance *(C. Craddock)*

This important randomized trial confirms the use of ATRA-ATO combination therapy as standard of care in newly diagnosed high-risk APL.*

*Relevance section written by *JCO* Associate Editor Charles Craddock, MD.

by ATRA resistance) occurs in approximately 15%-30% of patients.[3,4] Long-term anthracycline use has also been associated with secondary malignancies, in particular myeloid neoplasms, and cardiotoxicity.[5,6]

Randomized clinical trials have explored the use of arsenic trioxide (ATO) in the treatment of APL.[7,8] The randomized phase III clinical APL0406 trial demonstrated that a combination of ATRA and ATO (ATRA-ATO) is associated with improved survival and lower rates of relapse versus the standard ATRA-CHT therapy among patients with newly diagnosed non–high-risk APL (defined as a WBC count, WBC, at diagnosis ≤10 × 10^9/L).[9]

Both the European Medicines Agency and the US Food and Drug Administration have approved ATO in combination with ATRA for the treatment of patients with non–high-risk APL.[10-12] However, few studies have examined the potential use of the chemo-free combination in the treatment of high-risk APL, which accounts for about 25% of all newly diagnosed APL cases.[13]

Here, we present results of the phase III APOLLO trial, a pan-European academic randomized study of ATRA-ATO versus standard ATRA-CHT regimens for patients with high-risk APL, with the experimental arm consisting of an induction regimen including ATRA, ATO, and two doses of idarubicin (ie, half the total dose used in the standard ATRA-CHT regimen, intended to control hyperleukocytosis and achieve long-term disease control), followed by four cycles of ATRA-ATO consolidation therapy.

METHODS

Study Design

The APOLLO study is a prospective, open-label, multicenter, randomized phase III clinical trial (EudraCT 2015-01151-68; ClinicalTrials.gov identifier: NCT02688140) and was conducted as a European intergroup study with the PETHEMA (Spain), GIMEMA (Italy), GFM (France), HOVON (Belgium and the Netherlands), and OSHO, AML-SG, and SAL/AMLCG (Germany) study groups. The study was designed to compare event-free survival (EFS) for patients treated with ATRA-ATO and idarubicin versus patients treated with standard ATRA-CHT treatment. The APOLLO study was conducted according to the Declaration of Helsinki and approved by an independent ethics committee and national authorities. Figure 1 shows the CONSORT study design.

Eligibility Criteria

Eligible patients were age between 18 and 65 years with newly diagnosed APL (diagnosed by cytomorphology and confirmed by molecular analysis), had an Eastern Cooperative Oncology Group score of 0-3, and WBC at diagnosis >10 × 10^9/L. All patients provided informed consent.

Treatment Groups

Patients were randomly assigned in a 1:1 ratio to receive either ATRA-ATO in the experimental arm or the standard ATRA-CHT regimen.[10] Randomization was stratified by the country in which the patient was treated and by patient age

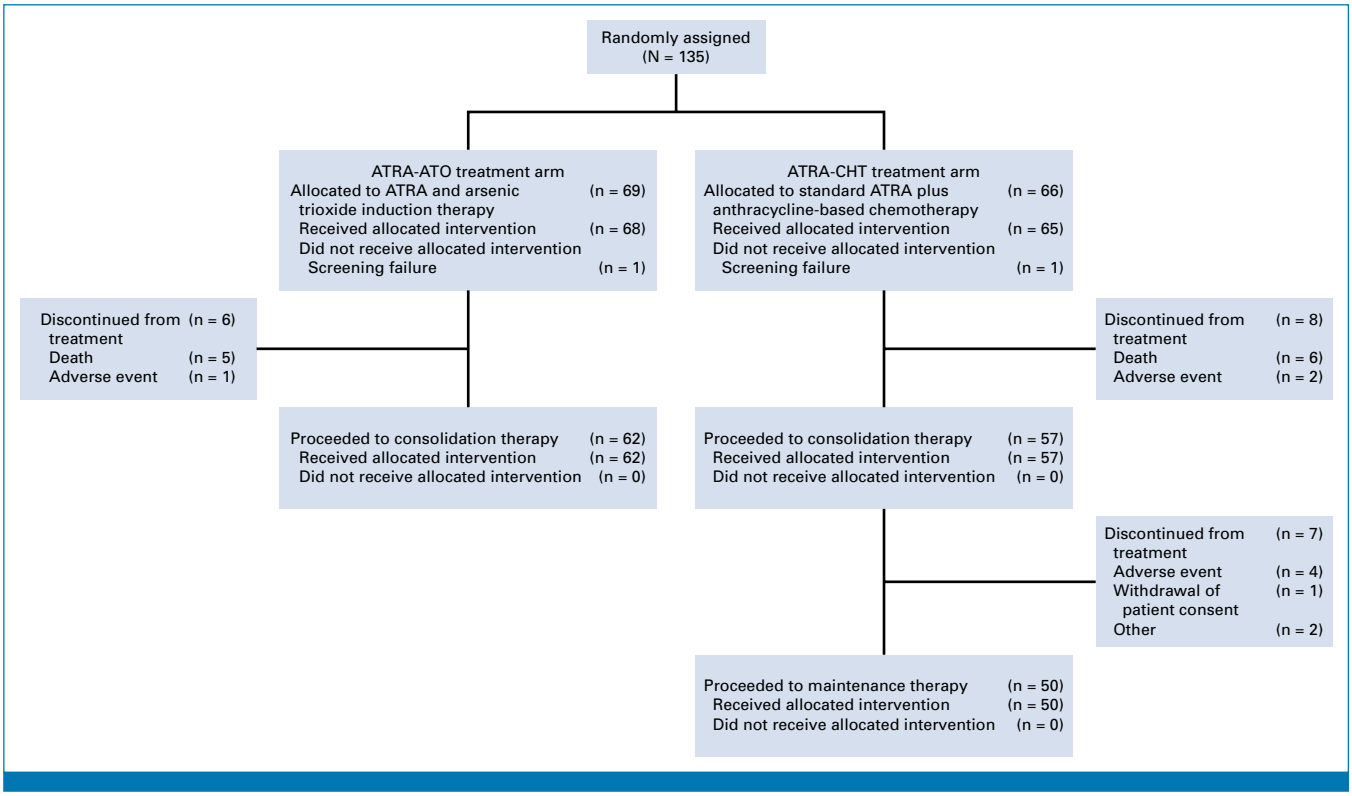

FIG 1. CONSORT study design and patient disposition. ATRA, all-trans retinoic acid; ATRA-ATO, ATRA and arsenic trioxide; ATRA-CHT, ATRA plus anthracycline-based chemotherapy.

(≤40 years *v* >40 years). More information on randomization can be found in Appendix 1 (online only).

An overview of the treatment regimens is shown in Figure 2. Full details can be found in Appendix 1. In brief, patients in the ATRA-ATO arm received induction therapy (45 mg/m² oral ATRA in two single doses with 12 mg/m² intravenous idarubicin on days 1 and 3, and 0.15 mg/kg intravenous ATO over 2 hours daily starting on day 5 after the start of idarubicin). Induction therapy was continued until achievement of either CR (defined as <5% blasts without atypical promyelocytes in the bone marrow, neutrophils ≥1.0 Gpt/L, and platelets ≥100 Gpt/L) or CR with incomplete recovery (CRi; defined as <5% blasts without atypical promyelocytes in the bone marrow, and neutrophils >1.0 Gpt/L or platelets M 100 Gpt/L). Induction therapy was followed by four 8-week courses of consolidation therapy (0.15 mg/kg ATO administered intravenously over 2 hours daily for 5 days a week, with a treatment break on days 6 and 7 for the first 4 weeks of each 8-week cycle, and 45 mg/m² ATRA administered orally in two doses daily for the first and third 14 days of each 8-week cycle).

Patients randomly assigned to the ATRA-CHT arm received induction therapy (12 mg/m² intravenous idarubicin on days 1, 3, 5, and 7 and 45 mg/m² oral ATRA in two single doses daily for up to 60 days).[9] Induction therapy was continued until achievement of CR or CRi. Induction therapy was followed by three 15-day cycles of consolidation therapy with 45 mg/m² ATRA orally in two single doses daily on days 1-15 of each consolidation cycle. In the first consolidation cycle, patients received 5 mg/m² idarubicin intravenously and 1,000 mg/m² cytarabine (Ara-C) administered intravenously over 3 hours on days 1-4. In the second consolidation cycle, patients received 10 mg/m² mitoxantrone intravenously on days 1, 2, 3, 4, and 5. In the third consolidation cycle, patients received 12 mg/m² idarubicin intravenously on day 1 and 150 mg/m² Ara-C intravenously every 8 hours on days 1-5. Patients who achieved CR or CRi and who were in molecular remission received maintenance therapy (50 mg/m² oral 6-mercaptopurine on days 1-91, 15 mg/m² methotrexate administered intramuscularly or orally once per week until day 91, and 45 mg/m² ATRA administered orally in two single doses on days 92-106 of cycles 1-6 only) for seven 106-day cycles. Differentiation syndrome (DS) prophylaxis was performed as described in Appendix 1.

An end-of-study visit was performed 30 months after random assignment and subsequent follow-up visits were performed every 6 months thereafter. Survival status and treatment change were assessed every 6 months until the end of the trial. Patients in either arm who experienced significant and sustained myelosuppression during consolidation therapy (defined as neutrophils $<1.0 \times 10^9$/L and/or platelets $<50 \times 10^9$/L) could have their treatment reduced; treatment was stopped until symptoms resolved to <grade 2, at which point treatment resumed at 50% of the previous dose for 7 days with treatment at full dosage resumed thereafter.

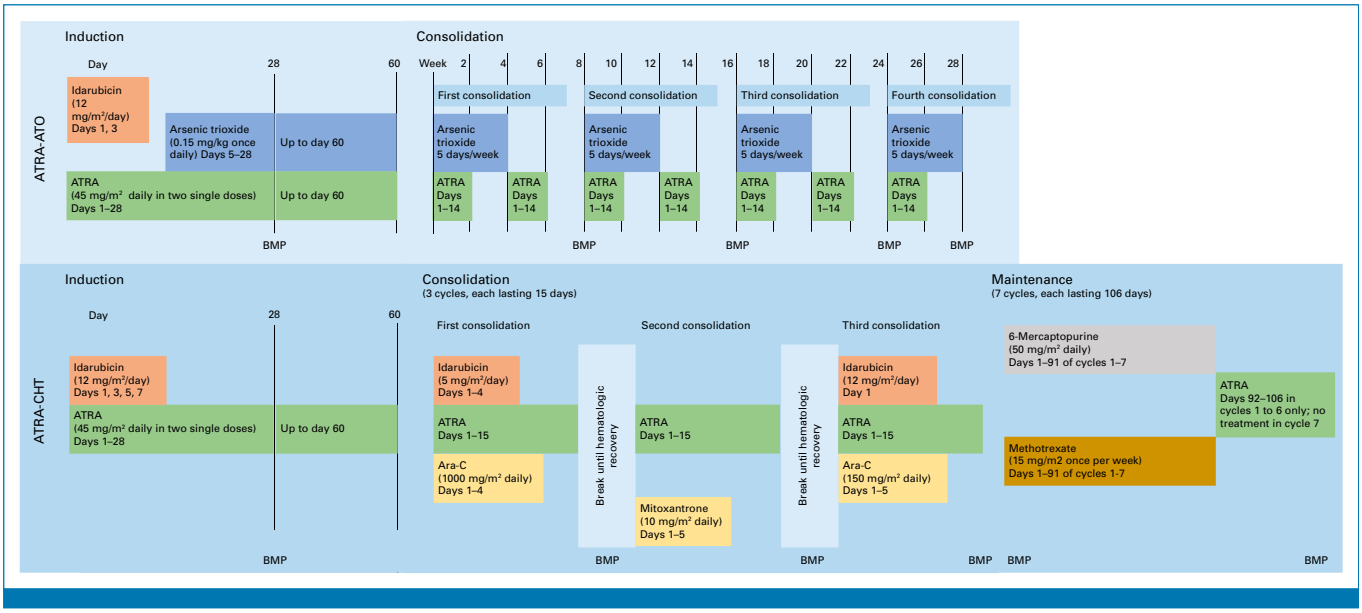

FIG 2. Treatment regimens. Ara-C, cytarabine; ATRA, all-trans retinoic acid; ATRA-ATO, ATRA and arsenic trioxide; ATRA-CHT, ATRA plus anthracycline-based chemotherapy; BMP, bone marrow puncture.

Patients were able to withdraw from the study at any time for any reason. Any patient who discontinued and who had received at least one dose of either ATRA or idarubicin underwent an end-of-study visit to evaluate treatment response within 2 weeks of withdrawal.

Measurable residual disease (MRD) studies in the bone marrow were recommended; peripheral blood was used only in case of dry tap. Further details of MRD studies can be found in Appendix 1.

End Points

The primary end point of the study was 2-year EFS, a cumulative end point comprising the following events (whichever occurred first): failure to achieve hematologic CR or CRi within 60 days after induction therapy, failure to achieve molecular remission after the last consolidation course (molecular resistance), hematologic relapse, molecular relapse, death, or development of secondary myelodysplasia or leukemia. Secondary end points included the rate of hematologic CR after induction, rate of early death (ED) after induction, overall survival at 2 years, toxicity, MRD status, and quality of life.

Statistical Analysis

Analysis of the primary end point (2-year EFS) was performed using a stratified log-rank test, assuming a constant hazard ratio over time. A total recruitment of 280 patients with a minimum follow-up period of 30 months was planned to observe a sufficient number of events to evaluate the primary end point. Patients who withdrew from the trial for any reason were followed until death or the end of the follow-up period; only patients who withdrew consent for further data collection were censored at the time of withdrawal. Median times to event and survival rates at 2 years were estimated using the Kaplan-Meier method for each arm and two-sided 95% CIs were calculated. Because of the different treatment durations in each arm, time to assessment of molecular resistance was approximately 120 days later among patients treated with ATRA-ATO versus patients receiving ATRA-CHT. To address this imbalance, event times of patients with molecular resistance in the ATRA-ATO arm were corrected by subtracting 120 days. A two-sided 95% Agresti-Coull CI was calculated for rate of CR, with differences between arms analyzed using the Mantel-Haenszel test for stratified binary data. Median follow-up time was calculated by using reverse Kaplan-Meier.

Role of the Funding Source

The APOLLO trial was funded by the German Federal Ministry of Education and Research. The funders of the study had no involvement in the study design, data collection, data analysis, data interpretation, or writing of this report. Teva Pharmaceuticals Europe B.V. provided financial support for the Clinical Research Organizations involved and provided the investigational product free of charge. M.T.V. received support from AIRC Foundation for Cancer Research in Italy 5 × 1,000 call "Metastatic disease: the key unmet need in oncology" to MYNERVA project (21267) for MRD and translational studies.

RESULTS

Enrollment and Patient Characteristics

Enrollment started in June 2016 and was discontinued prematurely in August 2022 because of slow recruitment

during the COVID-19 pandemic. As of July 2022, a total of 135 patients had been randomly assigned; 69 were allocated to the ATRA-ATO treatment arm and 66 were allocated to the ATRA-CHT treatment arm. Two patients (one in each treatment arm) did not receive allocated therapy because of screening failures; the remaining 133 eligible patients received the allocated therapy: 68 patients received ATRA-ATO and 65 patients received ATRA-CHT. Last patient last visit for the whole trial was performed in January 2025.

Patient baseline characteristics are presented in Table 1. Among patients evaluable for the primary end point (N = 133), median age was 46 years (IQR, 37-51), 64 (48%) patients were female, and 69 (52%) were male. Median WBC was 36 × 10^9/L (range, 10.1-339.0 × 10^9/L) and 38% of patients had a WBC >50 × 10^9/L, with no significant differences between treatment arms.

A diagnostic lumbar puncture before consolidation cycle 1, according to national guidelines, was carried out in 22 (36%) patients in the ATRA-ATO arm and in 19 (33%) patients in the standard ATRA-CHT arm.

Treatment Exposure

Median treatment duration from induction to end of consolidation therapy was 35 weeks (IQR, 34-36) in patients receiving ATRA-ATO, and 21 weeks (IQR, 19-23) in patients receiving ATRA-CHT. A total of seven (19%) patients receiving ATRA-ATO and 24 (37%) patients receiving ATRA-CHT had discontinued the study. Patient disposition throughout the study is shown in Figure 1.

Induction Therapy

A total of 133 patients (68 patients receiving ATRA-ATO and 65 patients receiving ATRA-CHT) were evaluable for response to induction therapy. Sixty-three (93%) patients receiving ATRA-ATO achieved CR or CRi, compared with 59 (91%) patients receiving ATRA-CHT (P = .69). The median time to CR/CRi was 28 days (range, 22-45) among patients in the ATRA-ATO arm, and 28 days (range, 24-60) among patients in the ATRA-CHT arm. The rate of ED before CR was similar across treatment arms; five patients (7.4%) receiving ATRA-ATO and six patients (9.2%) receiving ATRA-CHT died prematurely at a median of 3 days from enrollment (range, 1-26 days). In patients receiving ATRA-ATO, EDs occurred due to bleeding (n = 3), thrombosis (n = 1), and pulmonary failure due to leukostasis related to APL (n = 1). In patients receiving ATRA-CHT, EDs occurred due to bleeding (n = 4), sepsis (n = 1), and thrombosis (n = 1). Severe DS ≥grade 3 occurred in 13 (19.1%) and 22 (33.8%) patients in arms A and B, respectively (P = .05), and was fatal in none of those patients. MRD-negativity for promyelocytic leukemia/retinoic acid receptor alpha was achieved after induction in 11 (17%) patients treated with ATRA-ATO versus 14 (23%) patients treated ATRA-CHT (P = .26).

Consolidation and Maintenance Therapy

A total of 119 of 133 patients, of whom 62 (47%) received ATRA-ATO and 57 (43%) received ATRA-CHT, proceeded to consolidation therapy. Six (8%) patients receiving ATRA-ATO did not receive consolidation therapy due to ED (n = 5, 83%) and withdrawal of therapy because of (serious) adverse

TABLE 1. Baseline Demographics and Disease Characteristics

Characteristic	ATRA-ATO (n = 68)	ATRA-CHT (n = 65)	Overall (N = 133)
Age, years, median (range)	46.5 (18-65)	44.0 (18-65)	46 (18-65)
Sex, No. (%)			
Male	34 (50)	35 (54)	69 (52)
Female	34 (50)	30 (46)	64 (48)
BMI, median (range)	26.7 (17.5-41.1)	27.2 (18.8-42.8)	26.9 (17.5-42.8)
Time from original diagnosis until random assignment, days, median (range)	1 (0-5)	1 (0-5)	1 (0-5)
WBC count at diagnosis, ×10^9/L, median (range)	33.5 (10.4-217.4)	35.0 (10.1-339)	34.7 (10.1-339)
WBC count at diagnosis, No. (%)			
≤50 × 10^9/L	44 (65.7)	38 (58.5)	82 (62.1)
>50 × 10^9/L	23 (34.3)	27 (41.5)	50 (37.9)
Platelet count at diagnosis, ×10^9/L, median (range)	36.0 (5.0-128)	35.5 (7.0-99)	36.0 (5.0-128)
PML-RARA BCR type, No. (%)			
BCR1	23 (34.3)	15 (23.1)	38 (28.8)
BCR2	2 (3.0)	3 (4.6)	5 (3.8)
BCR3	30 (44.8)	38 (58.5)	68 (51.5)
FLT3-ITD mutation, No. (%)	25 (37.3)	21 (32.3)	46 (34.8)

Abbreviations: ATRA, all-trans retinoic acid; ATRA-ATO, ATRA and arsenic trioxide; ATRA-CHT, ATRA plus anthracycline-based chemotherapy; BCR, breakpoint cluster region; PML-RARA, promyelocytic leukemia/retinoic acid receptor alpha.

events (n = 1, 17%). Eight (12%) patients receiving ATRA-CHT did not receive consolidation therapy due to ED (n = 6, 75%) and withdrawal of therapy because of (serious) adverse events (n = 2, 25%). No (0%) patients receiving ATRA-ATO and 43 (66%) patients receiving ATRA-CHT experienced thrombocytopenia ≥grade 1. Three (4.4%) patients receiving ATRA-ATO and 36 (55%) patients receiving ATRA-CHT experienced neutropenia ≥grade 3 (Fig 3). Central nervous system recurrence was diagnosed in one patient undergoing ATRA-CHT. No patients in either arm died during consolidation treatment.

A total of 50 (77%) patients receiving ATRA-CHT who completed consolidation therapy proceeded to maintenance therapy; 14 (28%) patients did not complete maintenance therapy.

Outcomes

After a median follow-up of 37 months (range, 1.7-88.6 months), the 2-year EFS rate was 88% in patients receiving ATRA-ATO and 71% in patients receiving ATRA-CHT (HR, 0.4 [95% CI, 0.17 to 0.92]; log-rank test $P = .02$; Fig 4). After the fourth treatment cycle, molecular resistance was observed in one of 60 evaluable patients in the ATRA-ATO arm (1.7%), versus three of 55 in the ATRA-CHT arm (5.5%; $P = .268$). At a median of 7.8 and 12.1 months from achievement of MRD-negative CR, molecular relapse occurred in one (1.5%) patient receiving ATRA-ATO versus eight (12.3%) patients receiving ATRA-CHT ($P = .014$).

The 2-year overall survival rate was 93% in patients receiving ATRA-ATO and 87% in patients receiving ATRA-CHT (HR, 0.6 [95% CI, 0.2 to 1.8]; $P = .36$), and the 2-year cumulative incidence of relapse was 1.8% in patients receiving ATRA-ATO and 17% in patients receiving ATRA-CHT ($P = .008$; Fig 4).

Safety

Overall, 49 (72%) patients receiving ATRA-ATO and 60 (92%) patients receiving ATRA-CHT experienced at least one treatment-emergent adverse event (TEAE; Table 2). TEAEs were defined as adverse events that occurred after the start of trial medication until 28 days after last medication; this refers to the entire medication received per treatment arm. The duration of intervention and therefore time to monitor adverse events differed between both arms: 9 months for ATRA-ATO and 30 months for ATRA-CHT.

The most common TEAEs among patients receiving ATRA-ATO were DS (n = 13, 19%), neutropenia (n = 12, 18%), thrombocytopenia (n = 12, 18%), and hepatotoxicity (n = 10, 15%). The most common TEAEs among patients receiving ATRA-CHT were febrile neutropenia (n = 26, 40%), pyrexia (n = 23, 35%), DS (n = 22, 34%), and headache (n = 14, 22%). The incidence of treatment-related neutropenia grade ≥3 and thrombocytopenia grade ≥1 were higher in the ATRA-CHT arm compared with ATRA-ATO (Fig 3).

Serious TEAEs were reported in 22 (32%) patients receiving ATRA-ATO and 44 (68%) patients receiving ATRA-CHT ($P < .01$). The most common serious TEAEs among patients receiving ATRA-ATO were acute kidney injury, catheter site infection, cerebral hemorrhage, and epilepsy (all n = 2, 3%). The most common serious TEAEs among patients receiving

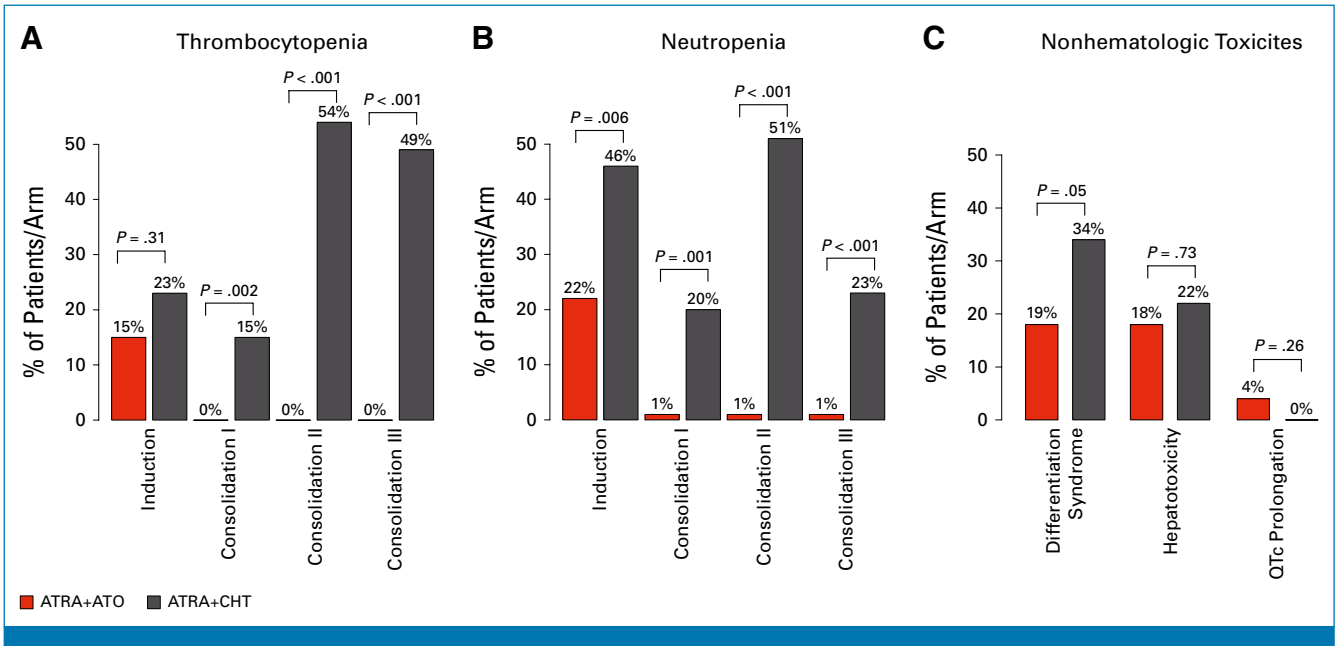

FIG 3. Hematologic and extrahematologic toxicity: (A) thrombocytopenia (grade 1-4) >15 days, (B) neutropenia (grade 3-4) >15 days, and (C) extrahematologic toxicity. QTc prolongation: QTc >500 ms both genders (using the Fridericia formula). ATRA, all-trans retinoic acid; ATRA-ATO, ATRA and arsenic trioxide; ATRA-CHT, ATRA plus anthracycline-based chemotherapy; QTc, QT interval corrected for heart rate.

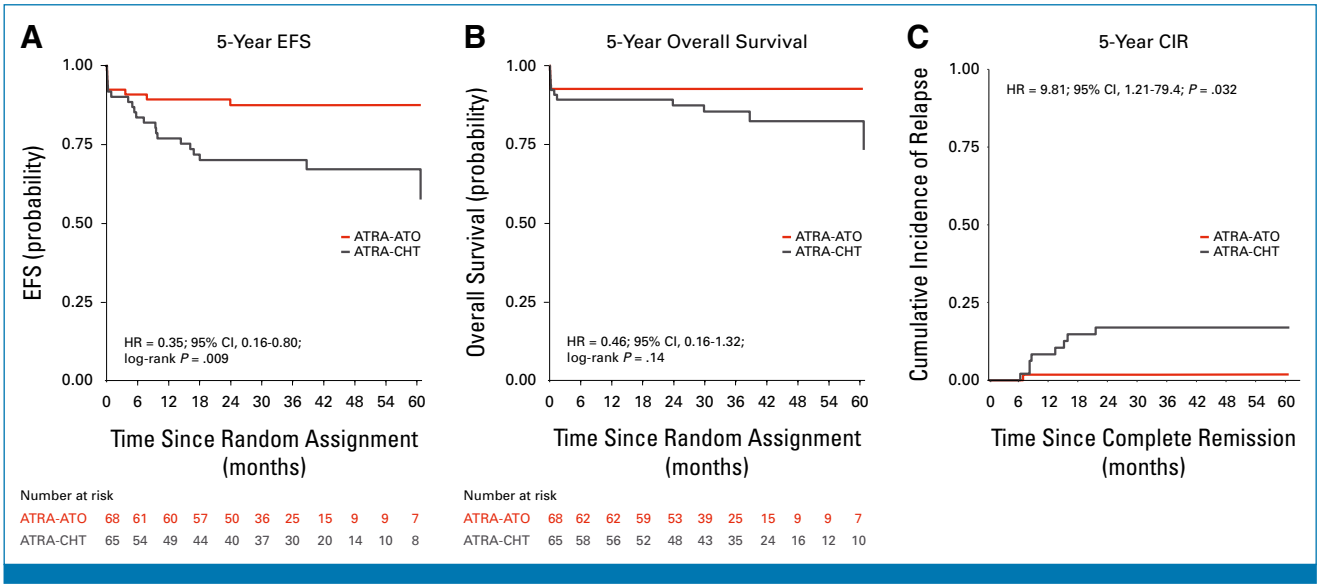

FIG 4. (A) EFS, (B) overall survival, and (C) cumulative incidence of relapse in patients treated with ATRA-ATO and patients treated with the standard ATRA and chemotherapy. ATRA, all-trans retinoic acid; ATRA-ATO, ATRA and arsenic trioxide; ATRA-CHT, ATRA plus anthracycline-based chemotherapy; CIR, cumulative incidence of relapse; EFS, event-free survival; HR, high risk.

ATRA-CHT were febrile neutropenia (n = 13, 20%), DS (n = 5, 8%), recurrent APL (n = 4, 6%), and cerebral hemorrhage (n = 4, 6%; Appendix Table A1).

Serious TEAEs that were suspected to be related to the trial medication were reported in seven (10%) patients receiving ATRA-ATO and 24 (37%) patients receiving ATRA-CHT ($P < .01$). The most common serious TEAEs that were suspected to be related to the trial medication among patients receiving ATRA-ATO were acute kidney injury, acute pulmonary edema, capillary leak syndrome, DS, herpes zoster, intercranial pressure increased, myocarditis, and pericardial effusion (all n = 1, 2%). The most common serious TEAEs that were suspected to be related to the trial medication among patients receiving ATRA-CHT were febrile neutropenia (n = 9, 14%), DS (n = 5, 8%), and sepsis (n = 2, 3%; Appendix Table A1).

Four (6%) patients receiving ATRA-CHT died after achieving CR/CRi due to recurrent APL, metastatic squamous cell carcinoma, heart failure, and unknown reason (all n = 1). No patients receiving ATRA-ATO died in CR/CRi.

DISCUSSION

The results of the APOLLO trial show that a near-chemo-free ATRA-ATO treatment significantly improves outcomes of patients with high-risk APL when compared with the standard ATRA-CHT regimen. Despite the challenges posed by slow recruitment and premature discontinuation due to the COVID-19 pandemic, we show that ATRA-ATO is associated at a median follow-up of 3 years with significantly higher EFS and lower cumulative incidence of relapse when compared with standard ATRA and idarubicin chemotherapy, underscoring its potential to sustain remission in the difficult-to-treat high-risk APL setting.

The results of this study extend the existing knowledge on the use of ATRA and ATO in the treatment of APL and corroborate previous findings, mostly obtained in standard-risk APL, emphasizing the potential of ATRA-ATO to also become standard first-line therapy for high-risk APL. The randomized phase III trials APL0406[7,9] and AML-17 (which included patients with high-risk disease)[8] and real-world data from the large HARMONY APL and the APL Asian consortium databases (also including patients with high-risk disease) have demonstrated that ATRA combined with ATO offers significant advantages over traditional chemotherapy regimens, including improved survival outcomes (independent of patient age, treatment scenario, or Sanz risk score in the case of the HARMONY APL study) and a favorable toxicity profile.[14,15] The APL15 trial also found that 2-year EFS was similar in patients treated with either ATRA-ATO or ATRA-ATO plus chemotherapy, including in all-risk and high-risk patients,[16] while the AAML1331 and ALLG APML4 studies found that ATRA-ATO was associated with non-inferior or improved outcomes, including survival, in patients with APL when compared with historical controls.[17,18]

ATRA-ATO's favorable safety profile is also consistent with previous studies.[8] The reduced incidence of DS in the ATRA-ATO versus ATRA-CHT arms is also noteworthy, as this complication is well documented in APL therapy and is associated with leukocytosis and EDs, particularly in high-risk disease.[19] In this setting, two doses of idarubicin were added on days 1 and 3 of induction to both the experimental

TABLE 2. Summary of Adverse Events

Term	ATRA-ATO (n = 68), No. (%)	ATRA-CHT (n = 65), No. (%)	Overall (N = 133), No. (%)
Summary of TEAEs			
Patients with ≥one TEAE	49 (72.1)	60 (92.3)	109 (82.0)
Patients with grade 3-4 TEAEs	42 (61.8)	51 (78.5)	93 (69.9)
Grade 3-4 TEAEs	107 (55.4)	268 (75.9)	375 (68.7)
Most common TEAEs			
Differentiation syndrome	13 (19.1)	22 (33.8)	35 (26.3)
Neutropenia	12 (17.6)	7 (10.8)	19 (14.3)
Thrombocytopenia	12 (17.6)	8 (12.3)	20 (15.0)
Hepatotoxicity	10 (14.7)	10 (15.4)	20 (15.0)
Febrile neutropenia	4 (5.9)	26 (40.0)	30 (22.6)
Pyrexia	1 (1.5)	23 (35.4)	24 (18.0)
Headache	10 (14.7)	14 (21.5)	24 (18.0)
Patients with serious TEAEs	22 (32.4)	44 (67.7)	66 (49.6)
Patients with suspected-related serious TEAEs	7 (10.3)	24 (36.9)	31 (23.3)
Relapses			
Molecular	1 (1.5)	8 (12.3)	9 (6.8)
Hematologic	1 (1.5)	3 (4.6)	4 (3.0)
Total number of deaths	5 (7.4)	11 (16.9)	16 (12.0)
Deaths during the first 30 days of treatment	5 (7.4)	6 (9.2)	11 (8.3)

Abbreviations: ATRA, all-trans retinoic acid; ATRA-ATO, ATRA and arsenic trioxide; ATRA-CHT, ATRA plus anthracycline-based chemotherapy; TEAE, treatment-emergent adverse event.

and ATRA-CHT arms to control increasing WBC, and reduce complications during the first critical days after diagnosis of high-risk APL (which still represent a medical emergency), thereby also allowing safe completion of the randomization procedures for the protocol. Using this approach, we were able to manage DS, which was not fatal in any of our patients.

Although the lack of statistical significance for overall survival between the treatment arms may suggest that both treatments are comparable, this equivalence may be due to the lower number of patients recruited in the trial than originally planned, and longer follow-up may be needed to explore this issue. The use of ATRA-ATO rescue in patients previously treated with ATRA-CHT has also been shown to induce sustained remissions in these patients and may account for the similar rates of overall survival in the two patient groups.[10] In the short term, we report a similarly low prevalence of ED in the treatment arms, underlining the prominent role of the aggressive disease subtype in this complication, independent of treatment. These ED figures are indeed low when compared with population-based cohorts such as the Swedish and SEER registries,[20,21] while the primary causes of ED in our study were bleeding and thrombosis, a distribution similar to previous reports.[22,23] Despite advancements in prevention and management of adverse events, ED remains an unmet clinical need in APL.[24,25]

This study's long-term findings, including the lower rate of molecular relapse and the more durable response to ATRA-ATO, are consistent with findings from the GIMEMA and NCRI cooperative trials, which reported similar efficacy results for arsenic-based regimens in standard-risk APL,[7,9,26] and from real-world studies such as the large-scale HARMONY APL project.[14]

Finally, given the short treatment duration, our results contribute to the growing body of evidence supporting ATRA-ATO's role in improving both the toxicity and the long-term cure rate and health-related quality of life burden[9] in APL survivors. We believe that the regimen of the APOLLO trial should become the new standard of care for patients with newly diagnosed high-risk APL.

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Arsenic Trioxide and All-Trans Retinoic Acid Combination Therapy for the Treatment of High-Risk Acute Promyelocytic Leukemia: Results From the APOLLO Trial

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APPENDIX 1. SUPPLEMENTARY METHODS

Randomization

Patients were randomly assigned in a 1:1 ratio to receive either all-trans retinoic acid and arsenic trioxide (ATRA-ATO) in the experimental arm or the standard ATRA plus anthracycline-based chemotherapy (ATRA-CHT) regimen.[10] Randomization was stratified by the country where the patient was treated and by patient age (≤40 years *v* >40 years). Patients were randomly assigned using a block randomization scheme. Randomization of the first patient at each participating center was determined via an investigator study file provided to each study center by the Study Alliance Leukemia study office. The investigator study file included two randomization envelopes for the first patient at each participating center, which included the randomization result and details for online database activation. Subsequent patients were randomly assigned using the online database.

Treatment Regimens

Patients in the ATRA-ATO arm received induction therapy consisting of 45 mg/m^2 ATRA administered orally in two single doses, supplemented with 12 mg/m^2 idarubicin administered intravenously on days 1 and 3 and 0.15 mg/kg ATO administered intravenously over 2 hours daily starting on day 5 after the start of idarubicin. Bone marrow puncture was performed on day 28, and induction therapy was continued until achievement of either complete remission (CR) or CR with incomplete recovery (CRi). Patients who did not achieve CR or CRi within 60 days of starting induction therapy were discontinued from the study. Induction therapy was followed by four 8-week courses of consolidation therapy, which consisted of 0.15 mg/kg ATO administered intravenously over 2 hours daily for 5 days a week (with a treatment break on days 6 and 7) for the first 4 weeks of each 8-week cycle, and 45 mg/m^2 ATRA administered orally in two doses daily for the first and third 14 days of each 8-week cycle (no ATRA was administered during the second and fourth 14 days of each cycle). Each course of consolidation therapy was initiated upon hematologic recovery from the previous course. Bone marrow evaluation was performed at the start of cycles 2 and 3 and at the end of cycle 4 (an optional bone marrow puncture could be performed at the start of cycle 4 per national cooperative group guidelines). Patients who did not achieve molecular remission by the end of cycle 4 were considered molecularly resistant and discontinued from the study. Follow-up visits began 3 months after the bone marrow evaluation at the end of cycle 4 and were carried out quarterly until end of study (30 months after random assignment). Survival status and treatment change were assessed every 6 months after the end of the study. Patients in the ATRA-ATO arm did not receive maintenance therapy.

Patients randomly assigned to the standard ATRA-CHT regimen received induction therapy consisting of 12 mg/m^2 idarubicin administered intravenously on days 1, 3, 5, and 7, and 45 mg/m^2 ATRA administered orally in two single doses daily for up to 60 days.[10] Bone marrow puncture was performed on day 28, and induction therapy was continued until achievement of CR or CRi; patients who did not achieve CR or CRi within 60 days of starting induction therapy were discontinued from the study. Induction therapy was followed by three 15-day cycles of consolidation therapy. Patients received 45 mg/m^2 ATRA orally in two single doses daily on days 1-15 of all three consolidation cycles. In the first consolidation cycle, patients received 5 mg/m^2 idarubicin intravenously and 1,000 mg/m^2 cytarabine (Ara-C) administered intravenously over 3 hours on days 1-4. In the second consolidation cycle, patients also received 10 mg/m^2 mitoxantrone intravenously on days 1, 2, 3, 4, and 5. In the third consolidation cycle, patients also received 12 mg/m^2 idarubicin intravenously on day 1 and 150 mg/m^2 Ara-C intravenously every 8 hours on days 1-5. Each course of consolidation therapy was initiated upon hematologic recovery from the previous course; patients who experienced a delay between courses of more than 60 days were discontinued from the study. Bone marrow evaluation was performed before the start of cycles 2 and 3 and after the final consolidation cycle. In the event of morphologic CR and hematologic recovery (defined as neutrophils ≥1.0 × 10^9/L and platelets ≥100 × 10^9/L), consolidation therapy was started within 2-4 weeks after documented CR. Patients who did not achieve molecular remission by the end of cycle 3 were considered molecularly resistant and discontinued from the study. Patients who experienced hematologic regeneration and who were in molecular remission (defined as the absence of the promyelocytic leukemia/retinoic acid receptor alpha [PML-RARA] hybrid transcript in bone marrow, as measured by reverse transcriptase polymerase chain reaction) received maintenance therapy between 1 month and 60 days after the bone marrow puncture at the end of consolidation cycle 3. Maintenance therapy consisted of seven 106-day cycles (for a total of 2 years). Each cycle consisted of 50 mg/m^2 6-mercaptopurine administered orally on days 1-91, 15 mg/m^2 methotrexate administered intramuscularly or orally once per week until day 91, and 45 mg/m^2 ATRA administered orally in two single doses on days 92-106 (cycles 1-6 only). Bone marrow samples were collected at the beginning of each maintenance cycle (beginning with cycle 2) and at the end of the last maintenance cycle for morphology testing. An end-of-study visit was carried out 30 months after random assignment, and subsequent follow-up visits were carried out every 6 months thereafter. Survival status and treatment change were also assessed every 6 months until the end of the trial. Patients in either arm who experienced significant and sustained myelosuppression during consolidation therapy (defined as neutrophils <1.0 × 10^9/L and/or platelets <50 × 10^9/L) could have their treatment reduced; this involved stopping treatment until symptoms resolved to <grade 2, at which point treatment resumed at 50% of the previous dose for 7 days with treatment at full dosage resumed thereafter.

Differentiation Syndrome Prophylaxis

Differentiation syndrome prophylaxis was performed with oral prednisone at a dose of 0.5 mg/kg/day, from day one of ATRA to the end of the third week of the induction therapy; hydroxyurea could also be administered to patients with sustained leukocytosis (WBC >10 GPt/L), with patients receiving either 500 mg four times daily (for patients with WBC 10-50 GPt/L) or 1,000 mg four times daily (for patients with WBC >50 GPt/L). Per protocol, intracranial prophylaxis was not recommended in general but allowed according to local standards.

Measurable Residual Disease Studies

Measurable residual disease (MRD) studies in the bone marrow were recommended; peripheral blood was used only in case of dry tap. MRD studies using quantitative PCR for PML-RARA were performed for both arms at the end of induction, at the beginning of consolidations 2-3 (arm B) or 4 (arm A), and at the end of consolidation. Later, MRD was assessed every 3 months for 2 years until end of study during maintenance treatment in the ATRA-CHT arm or during the observational period in the ATRA-ATO arm.

APPENDIX 2. MEMBERS OF SAL, AMCL-CG, AML-SG, OSHO, PETHEMA, HOVON, AND GIMEMA STUDY GROUPS

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TABLE A1. Patients With Serious TEAEs and Serious TEAEs Suspected to Be Related to Treatment

TEAE	ATRA-ATO (n = 68), No. (%)	ATRA-CHT (n = 65), No. (%)
Patients with serious TEAEs	22 (32.4)	44 (67.7)
Febrile neutropenia	0	13 (20.0)
DS	1 (1.5)	5 (7.7)
Cerebral hemorrhage	2 (2.9)	4 (6.2)
Recurrent AML	1 (1.5)	4 (6.2)
Cerebral hemorrhage	2 (2.9)	4 (6.2)
Acute kidney injury	2 (2.9)	1 (1.5)
Catheter site infection	2 (2.9)	1 (1.5)
Epilepsy	2 (2.9)	0
Patients with serious TEAEs suspected to be medication-related	7 (10.3)	24 (36.9)
Febrile neutropenia	0	9 (13.8)
DS	1 (1.5)	5 (7.7)
Sepsis	0	2 (3.1)
Acute kidney injury	1 (1.5)	0
Acute pulmonary edema	1 (1.5)	0
Capillary leak syndrome	1 (1.5)	0
Herpes zoster	1 (1.5)	0
Intracranial pressure increased	1 (1.5)	0
Myocarditis	1 (1.5)	0
Pericardial effusion	1 (1.5)	0

Abbreviations: ATRA, all-trans retinoic acid; ATRA-ATO, ATRA and arsenic trioxide; ATRA-CHT, ATRA plus anthracycline-based chemotherapy; DS, differentiation syndrome; TEAE, treatment-emergent adverse event.