

# An Effective and Chemotherapy-free Strategy of All-trans Retinoic Acid and Arsenic Trioxide for Acute Promyelocytic Leukemia in All Risk Groups

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# Abstract

The combination of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) has been demonstrated to be at least equally effective to ATRA and chemotherapy (CHT) in non-high-risk acute promyelocytic leukemia (APL). However, the efficacy of ATRA-ATO compared to ATRA-ATO plus CHT in high-risk APL remains unknown. Here we performed a multi-center non-inferiority phase III study to compare the efficacy of ATRA-ATO and ATRA-ATO plus CHT in newly diagnosed all-risk APL to address this question. Patients were assigned to receive ATRA-ATO for induction, consolidation and maintenance or ATRA-ATO plus CHT for induction followed by three cycles of consolidation therapy, and maintenance therapy with ATRA-ATO. In the non-CHT group, hydroxyurea was used to control leukocytosis. A total of 128 patients were treated. The complete remission rate was 97% in both groups. The 2-year disease-free, event-free survival rates were 98% v 97% and 95% v 92% in the non-CHT group and CHT group in all-risk patients ( $P=0.62$  and  $P=0.39$ , respectively). And they were 94% v 87% and 85% v 78% in the high-risk patients ( $P=0.52$  and  $P=0.44$ , respectively). This study demonstrated that ATRA-ATO had the same efficacy as the ATRA-ATO plus CHT in the treatment of patients with all-risk APL.

## Key Points

- The combination of ATRA and ATO, without CHT, is effective and safe for all newly diagnosed APL patients.
- The application of hydroxyurea may improve the outcomes of high-risk APL.

## Introduction

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) characterized by the t(15;17)(q22;q12) translocation, resulting in the fusion of the promyelocytic leukemia (PML) gene and retinoic acid receptor alpha (RAR $\alpha$ ) gene (*PML-RAR $\alpha$* ) [1]. Historically, APL was the leukemia subtype with the highest mortality due to serious coagulopathies in these patients [2]. The use of daunorubicin markedly improved the complete remission rate of APL patients from approximately 13% to 55% [3]. In contrast, the combination of all-trans retinoic acid (ATRA) and chemotherapy (CHT) resulted in complete remission rate of up to 90% [4]. This remarkable improvement has led to the combination of ATRA and CHT becoming the standard treatment for APL for a long time [5,6]. However, anthracycline-based CHT has several disadvantages, including severe bone marrow suppression, subsequent fatal infections and therapy-related neoplasms, which encourage scientists to explore CHT-free or CHT-reducing strategy to cure APL [7-9].

In addition to ATRA, arsenic trioxide (ATO) and gemtuzumab ozogamicin (GO) have been found to be highly effective in the treatment of APL [10-14]. A study from the MD Anderson Cancer Center and the AML17 trial from UK MRC demonstrated that ATRA-ATO plus GO was effective and safe, especially in high-risk APL [7,15]. However, GO is not yet commercially available in China and many developing countries, and its high price limits its wide application.

Compared with ATRA-CHT, the CHT-free Strategy of ATRA and ATO resulted in higher event-free survival in non-high risk APL in the APL0406 trial [8,16,17]. However, this study did not include high-risk patients, who account for roughly 25% of APL patients. Moreover, the control group in this study was ATRA-CHT rather than ATRA-CHT plus ATO, which was demonstrated to be superior to ATRA-CHT in all-risk APL patients in C9710 and APML4 study [18-20]. Therefore, we performed a randomized, multi-center non-inferiority clinical trial to directly compare the efficacy of ATRA-ATO and ATRA-ATO plus CHT in all newly diagnosed APL, to explore the necessity of chemotherapy, especially for high-risk patients.

## Methods

### Study design and patients

This study is a prospective, multicenter, phase III non-inferiority trial done at three hospitals in China. The initial full trial design was published in 2018 [21]. Briefly, eligible patients were 15 to 80 years old with newly diagnosed, low- or high-risk APL. Initial patient enrollment was solely based on cytomorphologic features according to the French-American-British (FAB) criteria [22]. Genetic diagnosis of APL was confirmed by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) for the presence of the *PML-RARα* fusion transcript [23,24] or the presence of t(15;17) via standard karyotyping or fluorescence in-situ hybridisation (FISH) [25]. Additional inclusion criteria were a serum total bilirubin concentration of up to three times the maximum institutional upper limit of normal (ULN) and a serum creatinine concentration of up to 2.5 times the maximum ULN. Exclusion criteria were pregnancy, lactation, concomitant severe psychiatric disorder, significant arrhythmias, and other active malignancies.

This study was approved by the Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University in Xi'an, China (Approval no. 2015-012). The patients were enrolled from July 2015 to January 2021. Written informed consent was obtained from all patients before study entry. The trial was registered with the Chinese Clinical Trial Registry (ChiCTR-IPR-15006821) and conducted in accordance with the Declaration of Helsinki.

### Treatment regimen

The treatment schedules for the ATRA-ATO and ATRA-ATO plus CHT regimens have been published in detail [21,26]. All patients were assigned to receive ATRA-ATO for induction, consolidation and maintenance or ATRA-ATO plus CHT induction therapy followed by three cycles of consolidation therapy with ATRA-ATO plus CHT, and maintenance therapy with ATRA-ATO. Synchronous administration of mannitol and ATO was to increase the permeability of the BBB, thereby improving the ATO concentration in the CSF and preventing CNSL in ATRA-ATO treated high-risk patients [21,26]. In induction therapy, a bone marrow examination to assess the response was performed when the absolute neutrophil count was more than  $1.0 \times 10^9/L$  and the platelet count was more than  $100 \times 10^9/L$ . Once in CR, the disease monitoring and management of minimal residual disease were performed as previously reported [21].

In this study, ATRA (Shandong Longfine Pharmaceutical Co., Ltd, China) was given at 60 mg/d (20-45 mg/m<sup>2</sup>/d) in divided doses since previous studies from the Hospital Saint Louis (French) [27] and the Shanghai Institute of Hematology (China) [28] reported that the lower ATRA dose had the same therapeutic effects as the conventional dose of 45 mg/m<sup>2</sup>/d. In previous trials, ATRA was used for 2 weeks every 4 weeks, and ATO was used for 4 weeks every 8 weeks in post-remission treatment [8,29]. To simplify the treatment strategy, both ATRA and ATO were administered for 2 weeks every 4 weeks in this study.

### **Supportive measures and management of complications**

All patients received blood product transfusions to maintain platelet counts above 30 × 10<sup>9</sup>/L and serum fibrinogen above 1.5 g/L. Hydroxyurea was the only cytotoxic agent allowed to control hyperleukocytosis in the non-CHT group. Patients received hydroxyurea at 1-4 g/d according to the initial study design, but after 2018, hydroxyurea was given at 4 g/d when WBC count > 10 × 10<sup>9</sup>/L [21]. The maximum hydroxyurea dose could be up to 0.1 g/kg/d in high-risk patients if WBC count consistently increased.

No prophylaxis for differentiation syndrome (DS) was recommended, but dexamethasone was administered at a dose of 10 mg every 12 h intravenously at the earliest manifestations of suspected DS until the disappearance of signs and symptoms. Temporary discontinuation and dose adjustments were recommended to manage drug-related hematologic and nonhematologic toxicities.

### **Definitions and study end points**

Patients were risk stratified based on the WBC count at diagnosis using a modified classification into a non-high-risk group (WBC < 10 × 10<sup>9</sup>/L) and a high-risk group (WBC ≥ 10 × 10<sup>9</sup>/L) [21]. Leukocytosis was defined as a WBC count of more than 10 × 10<sup>9</sup>/L during induction therapy.

The primary end point was event-free survival (EFS) and disease-free survival (DFS) at 2 years. EFS was defined as the time from diagnosis to first event, including death during inducing therapy, failure to achieve remission, relapse at any site, death during remission, or the development of second malignant neoplasm. DFS was defined as the time from Hematological complete remission to either hematological or molecular relapse or death from APL. The secondary end points included complete remission (CR), and overall survival (OS) at 2 years. Hematological complete remission (HCR) and relapse were defined according to criteria described by the National Cancer Institute (NCI) workshop [21]. Molecular complete remission (MCR) was defined as the absence of detectable transcripts, and molecular relapse was defined as the reversion to positivity in two consecutive bone marrow samples performed at least 2 weeks apart [23]. OS was defined as the time from diagnosis to death. Treatment-related toxicities were graded according to the NCI Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE4). The monitoring of hematological and nonhematological adverse events details was performed as previously reported [21].

### **Statistical analysis**

This trial was designed to test non-inferiority of DFS in the non-CHT group compared with the CHT group at 2 years after start of induction therapy. We chose 10% as the non-inferiority margin, a type I error probability of 5%, and a power of 80%. All patients enrolled in the study were analyzed following an intent-to-treat principle. Patient characteristics were summarized by crosstab. Chi-square test or Fisher's exact test were used for comparison of categorical variables, and t test or Mann-Whitney U test for continuous variables. The survival distributions were estimated by the Kaplan-Meier method and compared with the use of log-rank test between the two groups. All statistical tests were two-sided with a significance level of 0.05, except the non-inferiority hypothesis. The data were analyzed using SPSS software (version 23.0) and R software (version 4.0.4).

## Results

### Patient characteristics

A total of 130 patients with newly diagnosed APL were enrolled from July 2015 to January 2021 and assigned to either the non-CHT group (n = 64) or CHT group (n = 67) (Fig. 1). Two patients (one in the non-CHT group and one in the CHT group) were excluded since they were tested negative for the *PML-RARα* fusion transcript. The remaining 128 patients were included in the intent-to-treat analysis, of which 40 were high-risk patients (21 in the non-CHT group and 19 in the CHT group). The median age of the participants was 40.5 years (15–69 years) and 13 were older than 60 years. The median WBC count at presentation was  $2.93 \times 10^9/L$  ( $0.31-163.42 \times 10^9/L$ ). The major clinical and biological characteristics of these 128 patients are shown in Table 1. There were no significant differences in the baseline characteristics between the two cohorts. The trial profile is provided in Fig. 1. The present analysis was performed in February 2022 with a median follow-up time of 45.22 months (0.1-78.27 months).

Table 1  
Patient characteristics at diagnosis

Characteristic	non-CHT group (n = 62)	CHT group (n = 66)	<i>P</i>
Median age, years(range)	41 (15–69)	40.5 (15–65)	0.82
Sex, No. (%)			0.87
Male	32 (51.6)	35 (53.0)	
Female	30 (48.4)	31 (47.0)	
Median WBC, ×10 <sup>9</sup> /L (range)	2.93 (0.34–84.80)	3.03 (0.31–91.19)	0.60
Median PLT, ×10 <sup>9</sup> /L (range)	28 (3-113)	24 (2-249)	0.31
Sanz risk, No. (%)			0.54
Low and intermediate	41 (66.1)	47 (71.2)	
High	21 (33.9)	19 (28.8)	
<i>PML/RARα</i> isoform, No. (%)			0.41
BCR1-2	36 (58.1)	43 (65.2)	
BCR3	26 (41.9)	23 (34.8)	
<i>FLT3</i> ITD, No. (%)			0.69
Mutated	17 (27.4)	22 (33.3)	
Unmutated	35 (56.5)	36 (54.5)	
Missing	10 (16.1)	8 (12.1)	
Abbreviations: ATRA, all-trans-retinoic acid; ATO, arsenic trioxide; CHT, chemotherapy; <i>PML/RARα</i> , promyelocytic leukemia/retinoic acid receptor alpha; BCR, breakpoint cluster regions; <i>FLT3</i> -ITD, Fms-like tyrosine kinase 3-internal tandem duplication.			

## Induction therapy

A total of 62 patients in the non-CHT group and 66 patients in the CHT group were evaluable for induction response. HCR was achieved in 60 of 62 patients in the non-CHT group (97%) and 64 of 66 patients in the CHT group (97%) ( $P= 1.00$ ). Two patients in the non-CHT group died on day 3 and day 4, respectively, due to intracranial hemorrhage during the induction therapy. Two patients died in the CHT group: one died of bronchopneumonia on day 11 and another died of intracranial hemorrhage on day 17. All four patients that died were in high-risk group. HCR was 90% in the non-CHT group and 89% in the CHT group in high-risk patients ( $P= 1.00$ ). It was 100% in both groups in non-high-risk patients. Of the 124 patients, the

median time to HCR was 32.5 days (14–54 days) in the non-CHT group and 34 days (21–51 days) in the CHT group ( $P=0.64$ ). Ten patients in the non-CHT group (16%) and eleven patients in the CHT group (17%) developed the differentiation syndrome ( $P=0.87$ ), but none of the patients had severe differentiation syndrome. Leukocytosis developed during induction therapy in 32 of 41 non-high-risk patients in the non-CHT group (78%) and 42 of 47 non-high-risk patients in the CHT group (89%) ( $P=0.15$ ). All cases in the non-CHT group were successfully managed with hydroxyurea using the recommended doses in the protocol. In non-high-risk patients, the median WBC count peak was  $20.39 \times 10^9/L$  ( $1.49-96.10 \times 10^9/L$ ) in the non-CHT group and  $24.47 \times 10^9/L$  ( $4.48-96.15 \times 10^9/L$ ) in the CHT group ( $P=0.45$ ). No obvious side effects were observed from hydroxyurea during treatment.

## Consolidation therapy

A total of 118 of the 124 patients in HCR proceeded to consolidation therapy. In the non-CHT group, one high-risk patient did not receive any post-remission therapy and disease monitoring. Two patients (one with high-risk APL and one with non-high-risk APL) did not receive the assigned treatment, but received ATRA and realgar-Indigo naturalis formula (RIF) due to the patients' choice. In the CHT group, three patients only received ATRA-ATO in consolidation therapy because of patients' choice. However, all patients mentioned above were evaluated for the primary end point.

59 patients in the non-CHT group and 64 patients in the CHT group were evaluated for a molecular response and all achieved MCR. The median time to MCR was 55 days (35–85 days) in the non-CHT group and 62 days (41 to 127 days) in the CHT group ( $P=0.40$ ). All patients in the non-CHT group achieved MCR after 2 courses of consolidation therapy, whereas all patients achieved MCR after 3 courses of consolidation therapy in the CHT group.

## Maintenance therapy

A total of 118 patients completed the consolidation therapy described above, 115 of which proceeded to maintenance therapy. One non-high-risk patient in the non-CHT group did not receive maintenance therapy for unknown reasons. In the CHT group, one high-risk patient did not receive maintenance therapy for financial reasons and one non-high-risk patient violated the treatment protocol.

## Disease-free survival (DFS)

A total of 124 patients (60 and 64 in the non-CHT and CHT groups, respectively) were assessed for DFS according to the intent-to-treat analysis. In the non-CHT group, 2-year DFS were 98% and 97% in the non-CHT group and CHT group ( $P=0.62$ ). The percentage difference in DFS between the two groups was 1.4% (95% CI -3.8 to 6.8). The lower limit of the 95% CI for the percentage difference in DFS was greater than the -10% non-inferiority margin, confirming non-inferiority. For high-risk patients, the 2-year DFS was 94% and 87% in the non-CHT group and CHT group, respectively ( $P=0.52$ ). For non-high-risk patients, the 2-year DFS in both groups was 100%. Overall, three high-risk patients (one in the non-CHT group and two in the CHT group) experienced relapse during follow-up. Of note, the patient in the non-CHT group who did not proceed to post-remission therapy, relapsed at 17.4 months from diagnosis. The

patient discontinued the re-induction therapy on day 4 due to financial reasons, then died one month later. In the CHT group, the patient who did not complete maintenance therapy had CNSL at 11.2 months, and received intrathecal chemotherapy plus whole brain radiotherapy. However, the patient relapsed again in the CNS at 17.9 months and died as a result of disease progression. Another patient experienced hematological relapse at 24.1 months and remained alive after salvage therapy. In the per-protocol population, the 2-year DFS was 100% in the non-CHT group (56 of 56 patients) versus 98% in the CHT group (58 of 59) ( $P=0.34$ ) in all-risk patients. The percentage difference in the DFS between the two groups was 2% (95% CI -1.6 to 5.0), also confirming non-inferiority.

## Overall Survival (Os) And Event-free Survival (Efs)

In the intent-to-treat analysis, the 2-year OS was 95% in the non-CHT group and 94% in the CHT group ( $P=0.80$ ). The 2-year EFS was 95% in the non-CHT group and 92% in the CHT group ( $P=0.39$ ). The EFS and OS at 2 years for high-risk patients in the non-CHT versus CHT arms were 85% *versus* 78% ( $P=0.44$ ) and 85% *versus* 83% ( $P=0.96$ ), respectively. Two patients in the CHT group but none in the non-CHT group developed a therapy-related malignancy. One high-risk patient was diagnosed with therapy-related acute myeloid leukemia at 29.7 months, and remained alive after intensive chemotherapy. One non-high-risk patient was diagnosed with small cell lung cancer at 16.1 months and died at 19.2 months. In the per-protocol analysis, the 2-year EFS was 97% in the non-CHT group (56 of 58 patients) versus 93% in the CHT group (56 of 61) ( $P=0.32$ ) in all-risk patients. For high-risk patients, the 2-year EFS was 89% in the non-CHT group (17 of 19 patients), and it was 81% in the CHT group (13 of 17) ( $P=0.39$ ). The 2-year OS was 97% in the non-CHT group (56 of 58 patients) versus 95% in the CHT group (58 of 61) ( $P=0.72$ ) in all-risk patients. For high-risk patients, the OS was 89% in the non-CHT group (17 of 19 patients), and it was 88% in the CHT group (15 of 17) ( $P=0.95$ ). All outcome estimates calculated at 2 years are listed in Table 2, whereas outcome curves are shown in Fig. 2 and Fig. 3.

Table 2  
Clinical outcomes

	All-risk			Low-risk (n = 88)			High-risk (n = 40)		
	non- CHT (n = 62)	CHT (n = 66)	<i>P</i>	non-CHT (n = 41)	CHT (n = 47)	<i>P</i>	non- CHT (n = 21)	CHT (n = 19)	<i>P</i>
<b>ITT analysis</b>									
CR	60 (97%)	64 (97%)	1.00	41 (100%)	47 (100%)	..	19 (90%)	17 (89%)	1.00
2-year EFS	59 (95%)	60 (92%)	0.39	41 (100%)	46 (98%)	0.36	18 (85%)	14 (78%)	0.44
2-year DFS	59/60 (98%)	62/64 (97%)	0.62	41 (100%)	47 (100%)	..	18/19 (94%)	15/17 (87%)	0.52
2-year OS	59 (95%)	62 (94%)	0.80	41 (100%)	46 (98%)	0.36	18 (85%)	16 (83%)	0.96
<b>PP analysis</b>									
2-year EFS	56/58 (97%)	56/61 (93%)	0.32	39/39 (100%)	43/44 (98%)	0.36	17/19 (89%)	13/17 (81%)	0.39
2-year DFS	56/56 (100%)	58/59 (98%)	0.34	39/39 (100%)	44/44 (100%)	..	17/17 (100%)	14/15 (93%)	0.30
2-year OS	56/58 (97%)	58/61 (95%)	0.72	39/39 (100%)	43/44 (98%)	0.37	17/19 (89%)	15/17 (88%)	0.95
ATRA, all-trans-retinoic acid; ATO, arsenic trioxide; CHT, chemotherapy; CR, complete remission; EFS, event-free survival; OS, overall survival; DFS, disease-free survival									

## Safety and toxicity

Most severe adverse events occurred during induction therapy. Hematologic and non-hematologic toxicities are listed in Table 3. Grade 3–4 thrombocytopenia (lasting more than 15 days) occurred in 20 patients (32.3%) in the ATRA-ATO group and 25 patients (36.8%) in the ATRA-ATO plus CHT group ( $P=0.59$ ). Grade 3–4 neutropenia lasting more than 15 days occurred in 5 patients in both groups ( $P=1.00$ ). Pneumonia and fever occurred in 31 patients (50.0%) in the ATRA-ATO group and 35 patients (51.5%) in the ATRA-ATO plus CHT group ( $P=0.87$ ). Five patients had grade 3–4 hepatic toxicities in each group ( $P=1.00$ ). Grade 3–4 renal toxicity occurred in one patient in the non-CHT group, while grade 3–4 QTc prolongation occurred in one patient in the CHT group. Grade 3–4 cardiac function was reported in one (1.6%) of 62 patients in the non-CHT group versus 7 (10.3%) of 68 patients in the CHT group ( $P=0.06$ ). Skin toxicity mainly occurred during consolidation and maintenance therapy. Grade 1–2 skin toxicities

occurred in 9 patients in the non-CHT group and 11 (16.2%) patients in the CHT group ( $P=0.74$ ). Grade 3–4 skin toxicity did not occur in either group.

Table 3  
Incidence of all non-hematological and hematological toxic effects

Characteristic	non-CHT group (n = 62)	CHT group (n = 68)	<i>P</i>
Neutropenia (grade 3–4 lasting > 15 days)	5 (8.1%)	5 (7.4%)	1.00
Thrombocytopenia (grade 3–4 lasting > 15 days)	20 (32.3%)	25 (36.8%)	0.59
Pneumonia and fever	31 (50.0%)	35 (51.5%)	0.87
Hepatic toxicity (grade 3–4)	5 (8.1%)	5 (7.4%)	1.00
Renal toxicity (grade 3–4)	1 (1.6%)	0	1.00
Cardiac function (grade 3–4)	1 (1.6%)	7 (10.3%)	0.06
QTc prolongation (grade 3–4)	0	1 (1.5%)	1.00
Skin toxicity (grade 1–3)	9 (14.5%)	11 (16.2)	0.79
ATRA, all-trans-retinoic acid; ATO, arsenic trioxide; CHT, chemotherapy.			
Skin toxicity occurred during consolidation and maintenance therapy, all of other toxic effects occurred during induction therapy.			

## Discussion

This trial demonstrates that the combination of ATRA and ATO is non-inferior to ATRA-ATO plus CHT not only in non-high-risk APL, but also in high-risk APL patients. The addition of chemotherapy to ATRA-ATO did not significantly improve the durable anti-leukemia efficacy in these patients. Therefore, a chemotherapy-free regimen of the ATRA plus ATO is a feasible approach to cure all-risk APL patients.

The common treatment of APL were the different drug combination strategies, including ATRA, ATO, anthracycline-based chemotherapy and GO for induction and post-remission therapy. The conventional treatment combined ATRA and anthracycline-based chemotherapy to induce remission, followed by consolidation chemotherapy and ATRA maintenance over ten years ago [6, 30–32]. Compared with this classical combination strategy, C9710 study showed that the addition of ATO as initial consolidation therapy for adult patients with all-risk newly diagnosed APL significantly improved EFS and DFS [18]. Later on, APML4 study introduced ATO to ATRA and anthracycline induction, and eliminated chemotherapy from consolidation, utilizing 2 cycles of ATRA-ATO followed by maintenance therapy with ATRA, 6-mercaptopurine, and methotrexate for 2 years [19]. The incorporation of ATO in initial therapy induction and consolidation for all APL patients reduced the relapse rate when compared with historical controls of APML3 study, which was the ATRA-CHT without ATO strategy [20]. APL2012 trial from China

demonstrated that ATRA-ATO in both chemotherapy-replacing and -reducing settings in consolidation is not inferior to ATRA-CHT [13]. In above study, ATO was also added in maintenance therapy. The results of C9710, APML4 and APL2012 strongly supported the application of ATO in all APL patients. AML17 trial, a randomized controlled phase 3 trial, explored the combination of ATO and ATO without chemotherapy for APL for all-risk patients. The results showed that, ATRA and ATO is effective in low-risk and high-risk patients, with a high cure rate, less relapse, and a low incidence of liver toxicity when compared with ATRA-CHT group [7, 33]. However, this study added GO to high-risk patients and low-risk patient with leukocytosis in the ATRA-ATO arm. In many countries where chemotherapy is much more affordable than GO, the combination of ATRA-ATO plus chemotherapy is the conventional treatment option. Therefore, we performed a controlled trial to test the possibility of ATRA-ATO without chemotherapy and GO for all-risk patients. The results showed that the cure rates and survival rates in the ATRA-ATO group are not different to the ATRA-ATO plus CHT group for all-risk patients. When compared with APML4 and AML17 trial, the outcomes in the ATRA-ATO group in our study were similar to those. This is the first study that reported all APL patients could be curable without chemotherapy or GO.

For low-risk patients, APL0406 trial showed that chemotherapy could be replaced by ATO. ATRA-ATO strategy became the standard of care for patients with low-risk APL. However, the frontline treatment was ATRA-ATO with CHT or GO for high-risk patients. In the single-arm study conducted by MD Anderson Cancer Center, induction with ATRA-ATO plus GO and followed with ATRA-ATO consolidation therapy, the 5-year event-free and overall survival rates were 81% and 86% for high-risk patients. While they were 83% and 87% in the APML4 with the ATRA-ATO plus CHT strategy. In our study, the 2-year event-free and overall survival were 85% and 85% in the non-CHT group. The outcomes were not inferior to CHT group in our study or historical study of ATRA-ATO plus GO treatment in MD Anderson Cancer Center or ATRA-ATO plus CHT strategy in APML4 trial. Therefore, we propose that chemotherapy can be removed from the induction and consolidation treatment for high-risk patients with APL. In addition to the combination of ATRA and intravenous arsenic, another study in China is exploring to use oral arsenic realgar-indigo naturalis to replace or reduce CHT in high-risk patients [9].

Hydroxyurea has been shown to significantly reduce WBC counts [34]. The APL0406 trial reported that non-high-risk patients with hyperleukocytosis were successfully treated with hydroxyurea [16]. In this trial, we increased the maximum dose to 0.1 g/kg/d, which has been shown to be safe in previous studies [35]. The administration of hydroxyurea may achieve the same treatment efficacy as chemotherapy or GO in reducing the WBC count and the mortality rate in high-risk patients with APL. Compared with anthracyclines-based chemotherapy, the hydroxyurea dose can be adjusted easily according to the WBC count. In terms of safety, no additional hematological or non-hematological toxicity from hydroxyurea was observed. High-risk APL patients have an increased risk of CNS relapse [36]. Because ATRA and ATO poorly penetrate the blood-brain barrier (BBB), intrathecal chemotherapy has been the major treatment for CNS prophylaxis. However, its use is still controversial due to the requirement for an invasive operation and insufficient long term follow-up outcome data [36]. Mannitol has been reported to allow arsenic to better penetrate the BBB and reach therapeutically effective levels in the CSF [26]. In this trial, mannitol was used in high-risk patients to prevent CNS relapse. There were no patients with CNS relapse in the

non-CHT group in our study. The use of mannitol in combination with arsenic as a noninvasive CNS prophylaxis strategy may be considered as a new prevention approach of CNS relapse in high-risk APL.

In conclusion, our results showed that ATRA and ATO without CHT or GO was effective and safe for all-risk APL, suggesting that chemotherapy might be unnecessary for high-risk patients. This work may lead to a new treatment strategy for APL patients, particularly for the high-risk patients. However, more research centers and participants are still needed to further verify this conclusion.

## Declarations

**The authors declare no competing interests.**

**Scientific category: Clinical Trials and Observations**

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## Authorship Contributions

Conception and design: H.-Y. W.; provision of study materials or patients: H.-Y.W., L.L., G.-H.L, Y.-Z.Y., Y.-S.Z., W.-W.Q., S.-H.W, J.-Y.X., M.-C.W., L.-M.C.; collection and assembly of data: S.G., H.-B.L., X.-X.Z., H.-Y.Z., C.-Y.Z.; data analysis and interpretation: S.G., X.-H.L., X.-X.Z.; manuscript writing: H.-Y.W., S.G., D.N.W.; C.-S.Z., and final approval of manuscript: H.-Y.W., D.W..

## Conflict-of-interest disclosure

The authors declare no competing financial interest.

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## Figures

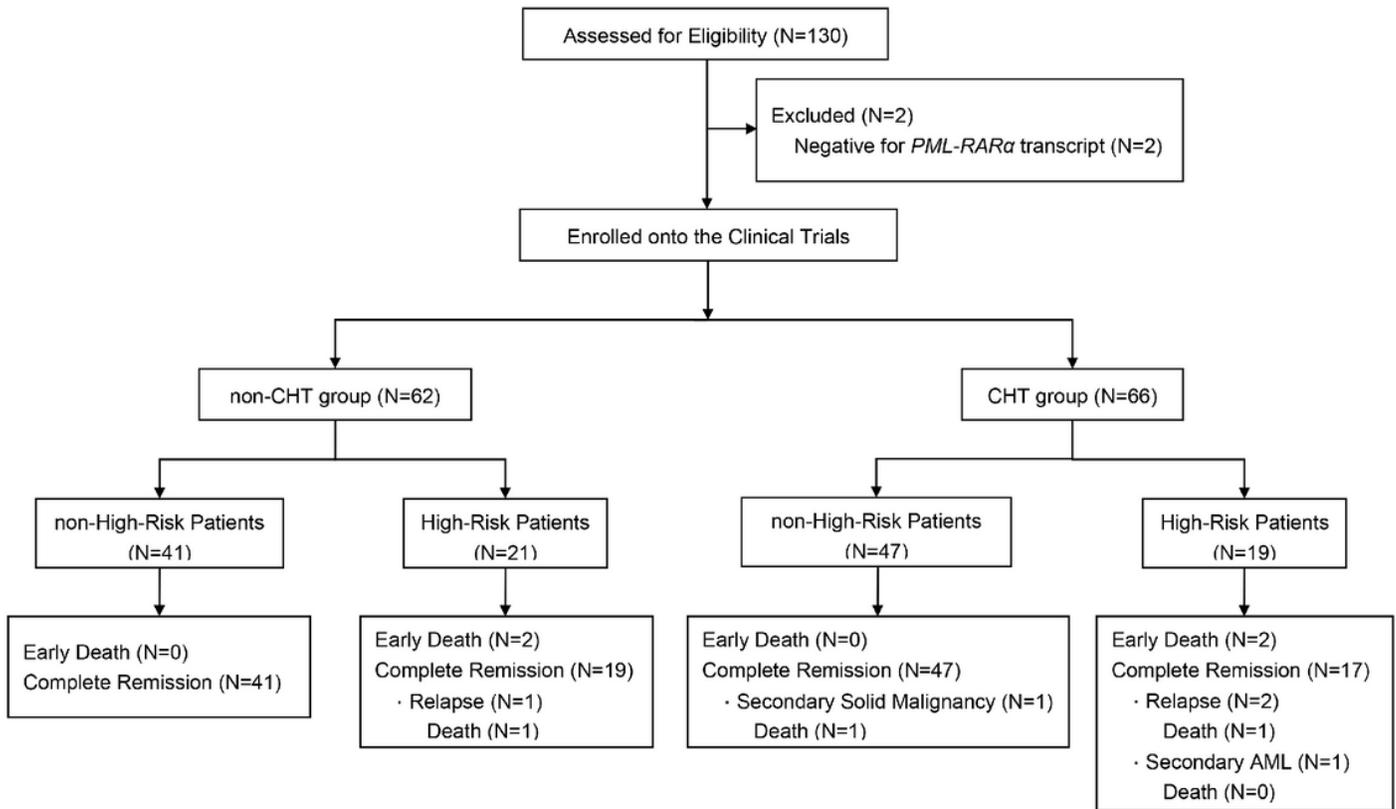
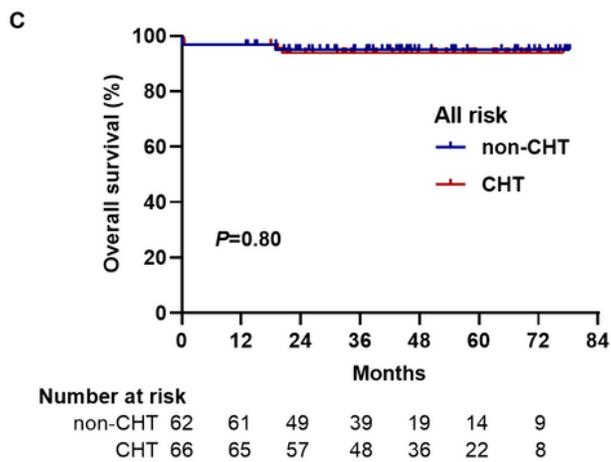
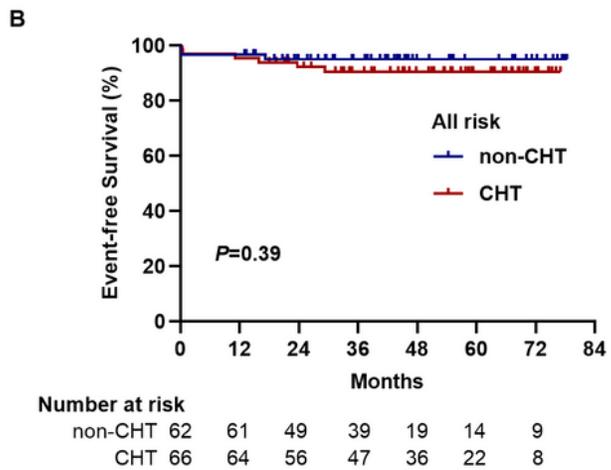
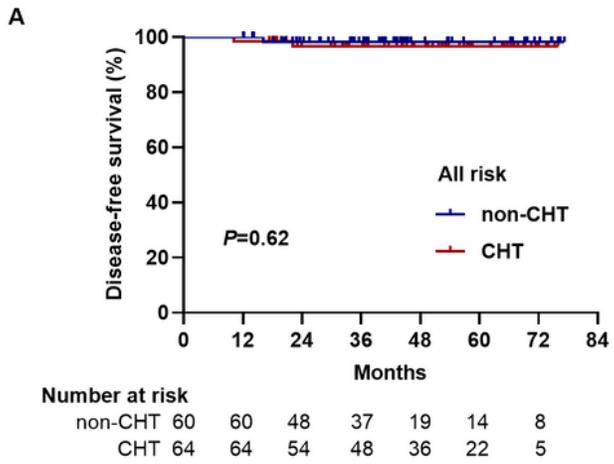


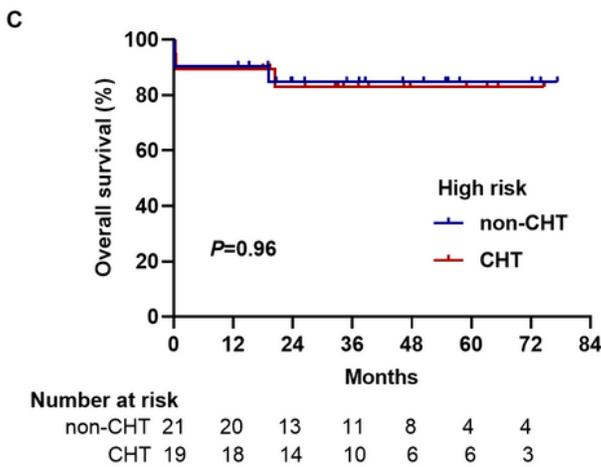
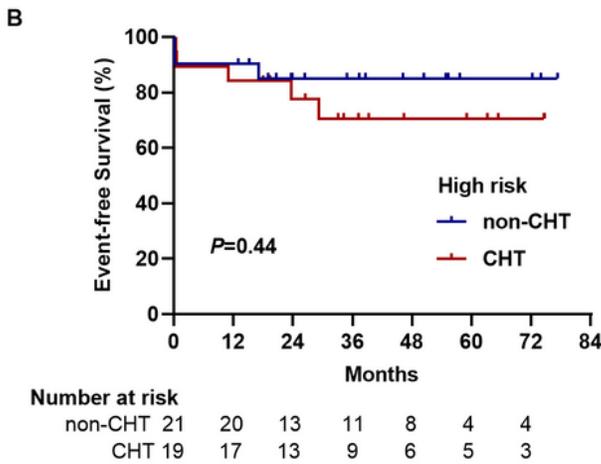
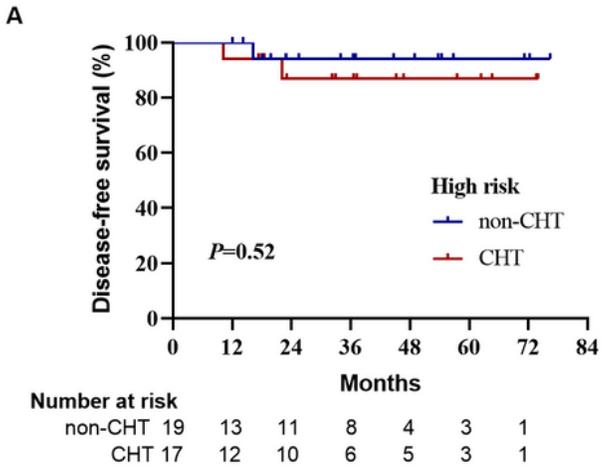
Figure 1

Trial profile



**Figure 2**

Survival outcomes for the all APL patients. (A) Disease-free survival. (B) Event-free survival. (C) Overall survival.



**Figure 3**

Survival outcomes for high-risk APL patients. (A) Disease-free survival. (B) Event-free survival. (C) Overall survival.