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ORIGINAL ARTICLE

Long-term retrospective study of retinoic acid combined with arsenic and chemotherapy for acute promyelocytic leukemia

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Abstract

Chemotherapy, all-trans retinoic acid (ATRA), and arsenic are effective options for acute promyelocytic leukemia (APL). We conducted a 20-year retrospective analysis of newly diagnosed (ND) APL patients treated with arsenic, ATRA and mitoxantrone. After achieving complete remission (CR), patients received 3–5 cycles of chemotherapy followed by AS4S4 maintenance for 3 years. Eighty-eight ND APL patients were treated with either oral AS4S4 ($n=42$) or arsenic trioxide (ATO) ($n=46$). The 8-year overall survival (OS) rate was 100% in the AS4S4 group and 90% in the ATO group. The disease-free survival (DFS) rates were 100% and 87.1% ($p=0.027$), respectively. Patients in the ATO group had more side effects. A subsequent cohort of 33 ND APL patients received triple therapy with oral AS4S4, ATRA, and chemotherapy. The 13-year OS and DFS rates were 100% and 90.9%. Our long-term analyses show that APL patients with oral AS4S4 had better outcomes compared to ATO, with no need for hospitalization.

Keywords Acute promyelocytic leukemia · All-trans retinoic acid · AS4S4 · Arsenic trioxide · Chemotherapy

Introduction

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) characterized by a balanced reciprocal translocation, t(15;17) (q22;q12-21), resulting in the fusion of promyelocytic leukemia (*PML*) gene with the retinoic acid receptor alpha (*RARa*) gene. Since the 1960s and 1970s, APL remains among the most aggressive and lethal AML subtypes with a high mortality rate [1, 2]. Currently, APL has become a curable form of AML with a complete remission (CR) rate of about 100%, best overall survival (OS) of more than 90%, and relapse-free survival (RFS) of more than 80% [3–6]. The approach to the treatment of APL has gone through several stages of progress. Anthracycline chemotherapy was first found to improve APL outcomes in the 1980s and 1990s [7, 8]. In the 1990s, a China-based study found that front-line all-trans retinoic acid (ATRA) therapy significantly improved the CR rate up to 90% and reduced mortality and incidence of disseminated intravascular coagulation (DIC) during the induction period, a significant milestone for APL therapy [9–13]. Subsequently, researchers in China found that adding arsenic (intravenous arsenic trioxide (ATO) or oral As_4S_4) to induction and maintenance therapy could significantly improve the CR rate and prolong RFS, resulting in another significant achievement in APL therapy. [14–21] Currently, the National Comprehensive Cancer Network (NCCN) and other guidelines suggest ATRA combined with ATO or chemotherapy as APL therapy and divide APL patients into low-risk and high-risk subgroups. Standard therapies vary depending on the patient's risk characterization [22, 23] to overcome the inferior results of high-risk classified s patients.

In this study, we retrospectively analyzed 20 years of long-term follow-up data of newly diagnosed (ND) APL patients who received the triple therapy of arsenic (As_4S_4/ATO) combined with ATRA and anthracycline-based chemotherapy. All APL patients in the study achieved CR and long-term OS and RFS.

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Patients and methods

We conducted a retrospective study of ND APL patients from 2001 to 2018 treated at the Beijing Daopei Hospital (2001–2008) and Hebei Yanda Lu Daopei Hospital (2008–2018). As defined by the 2021 NCCN guideline [22], patients who had abnormal promyelocytes in bone marrow with the abnormal karyotype t(15;17) or *PML::RARA* rearrangement were enrolled.

Ethics

The study protocol was approved by the Ethics Committee of Beijing Daopei Hospital and Hebei Yanda Lu Daopei Hospital according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients or their guardians.

Assessments

Cytogenetic analyses were performed on all patients with ND APL, and reverse transcription polymerase chain reaction (RT-PCR) for *PML::RARA* was performed on bone marrow (BM) aspirate samples. CR was defined, according to the 2021 NCCN guideline, by white blood cell (WBC), platelet counts and BM blasts [22]. The minimal residual disease (MRD) was assessed by quantitative monitoring of the *PML::RARA* fusion gene at a sensitivity threshold of 1×10^{-5}.

During the chemotherapy period, BM examination (including morphology and quantitative *PML::RARA*) and lumbar puncture to obtain cerebrospinal fluid (CSF, including morphology, protein, glucose, and flow cytometry) was conducted every month. After demonstrating that the *PML::RARA* gene was no longer detected, BM punctures were performed every three to six months for three years. If the CSF test was normal, lumbar puncture intrathecal injection could be conducted up to 6 times. Chromosomal testing methods, fusion genes, and mutation genes were described in the Supplementary Methods. Gene mutation tests were carried out since 2008.

Preparation of As_4S_4

As_4S_4 was prepared from mined, natural realgar. Chia-Si Lu has interpreted the molecular structure of As_4S_4 for more than 50 years. Highly purified As_4S_4 was also mixed with an equal amount of ground Seman platycladi and put into capsules containing 250 mg of As_4S_4 [19, 20]. In the remission induction period, the oral dose and administration of As_4S_4 for newly diagnosed APL was 50–60 mg/kg of body weight per day divided into three daily doses.

Treatment process

Patients with genetical and chromosomal confirmed APL were treated with oral As_4S_4 at 50-60 mg/kg for 28 days or intravenous ATO 0.15 mg/kg for 28 days, combined with ATRA 25-45 mg/m^2 for 28 days, and Mitoxantrone (NVT) 1.5-3 mg/m^2 for 5–7 days in the first month. When the peripheral blood WBC was higher than 10×10^9/L during the first induction therapy, the ATRA was ceased until the WBC decreased to less than 10×10^9/L. After achieving CR, patients underwent 3–5 cycles of consolidation and intensive chemotherapy. The low-risk patients received three chemotherapy cycles, while high-risk (WBC > 10×10^9/L) patients underwent 4–5 chemotherapy cycles. The main chemotherapy regimen included (1) Idarubicin (IDA) 12 mg/m$^2\times3$ days, or Daunorubicin (DNR) 45-60 mg/m$^2\times3$ days, (2) Cytarabine (Ara-C) 75 mg/m$^2\times7$ days + Aclamycin (ACLA) 14 mg/m$^2\times4$ days, (3) NVT 6 mg/m$^2\times3$ days. For the patients with WBC > 10×10^9/L, and especially for patients with WBC > 50×10^9/L or extramedullary disease (EMD) in the first induction chemotherapy, add (4) Ara-C 1-2 g/m$^2\times3$ days, and/or (5) Thiotepa 100 mg/ m$^2\times1$ day.

During the chemotherapy period, 50–60 mg/kg of As_4S_4 or intravenous ATO 0.15 mg/kg × 15 days/30 days + ATRA 25-45 mg/m$^2\times15$ days/30 days (administered for 15 days followed by a 15-day off period every month) were continued for 6 months. If the neutropenia developed after chemotherapy, As_4S_4 or intravenous ATO would be stopped temporarily until the neutrophils recovered.

The APL patients then proceeded to a maintenance treatment: ATRA 25-45 mg/m$^2\times15$/30 days and suspended when the total course of therapy reached one year. Arsenic was given continuously (50–60 mg/kg of oral $As_4S_4\times15$/30 days or intravenous ATO 0.15 mg/kg × 15/30 days), and the withdrawal time was delayed for 15 days every six months, until maintenance therapy every 15 days per 90 days. The total course of treatment continued for 3 years. (Fig. 1). Adverse events were assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [24]

Statistic methods

Patients' CR rate was analyzed by Chi-square test. The OS and RFS probabilities were estimated using the Kaplan–Meier method and were compared using the log-rank test. Calculations were performed with Prism software (version 5.0). *P*-values were determined by Chi-square Test.

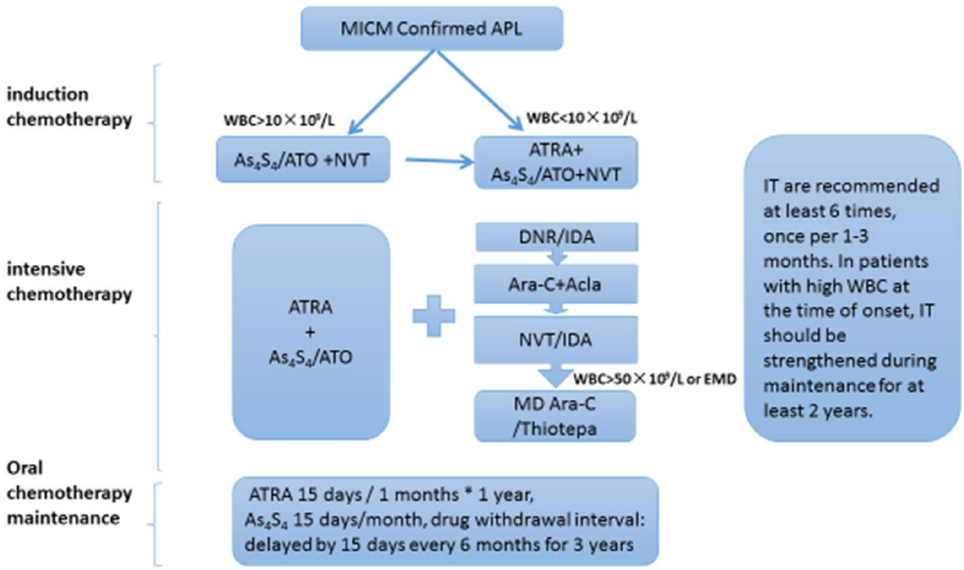

Fig. 1 The Treatment Scheme of the ATO/ As_4S_4-Based Triple Agent Protocol. *MICM* Morphology, immunotherapy, cytogenetics, molecules, *ATRA* All trans retinoic acid, *ATO* arsenic trioxide, *NVT* Mitoxantrone; IDA Idarubicine, *DNR* daunorbicine, *Ara-C* Cytarabine, *Acla* Aclacinomycin, *MD* middle dose, *IT* Intrathecal chemotherapy

Table 1 Comparison of baseline characteristics of the 88 APL patients treated with As_4S_4 and the ATO from 2001 to 2008

Characteristic	As_4S_4 Group $n=42$	ATO Group $n=46$	p value
Gender: M/F	20/22	23/23	0.823
Median age, years (range)	32 (10–62)	30 (7–72)	1.000
Fever, *n* (%)	31 (73.8)	20 (43.5)	0.004
Anemia, *n* (%)	39 (92.9)	33 (71.7)	0.010
Bleeding, *n* (%)	32 (76.2)	35 (76.1)	0.991
Infection, *n* (%)	15 (35.7)	10 (21.7)	0.147
Relapse risk (Sanz)			
Low, *n* (%)	11 (26.2)	12 (26.1)	0.991
High, *n* (%)	31 (73.8)	34 (73.9)	0.955
Coagulopathy*, n (%)	26 (61.9)	22 (47.8)	0.185
Suspected CNSL**,n (%)	5 (11.9)	3 (6.5)	0.471

*Including prothrombin time, activated partial thromboplastin time and fibrinogen;

**_CNSL_ central nervous system leukemia. *M* male, *F* female

Results

The long-term survival of newly diagnosed APL patients, enrolled between 2001 and 2008

Eighty-eight patients with ND APL were enrolled from June 2001 to December 2008 and followed until December 2012. The first treatment was oral As_4S_4 ($n=42$) or intravenous ATO ($n=46$). Detailed patient characteristics are provided in Table 1. All patients received combined chemotherapy regimens of ATRA and NVT. Both groups achieved hematological CR within one month, and no treatment-related deaths occurred. All patients achieved *PML::RARA* molecular complete remission (MCR) confirmed by RT-PCR at a median time of 2 months (range: 1–7 months). In the As_4S_4 group, both the 8-year OS and RFS rate was 100%, with a median follow-up time of 66 months (range: 15–106 months). In the ATO group, the 8-year OS was 90.0%, and the RFS was 87.1%, with a median follow-up time of 42 months (range: 14–104 months). There was a significant difference in the RFS between the two groups ($p=0.027$) (Fig. 2). However, no significant difference in OS was observed between the groups ($p=0.177$). Five patients (10.7%) in the ATO group experienced relapse, including four patients with central nervous system leukemia (CNSL) and one patient with myeloid sarcoma in the external auditory meatus. They subsequently received oral As_4S_4 alone with local radiotherapy and have been alive for more than 62 months with sustained HCR and MCR without relapse. All four patients with CNSL received additional chemotherapy with IDA or MD Ara-C and intrathecal chemotherapy. Two of the CNSL patients received oral As_4S_4 concurrently and have been alive for more than 59 and 94 months, respectively, with consistent MCR and HCR without CNS relapse. The remaining two patients subsequently had hematological relapse. In the As_4S_4 group, 23 patients were followed up for 18 years until November 2021. Except for one patient who died of cervical cancer at the 7th year of follow-up, and another patient with myasthenia gravis at the 10th year of follow-up, the remaining 21 patients are alive and healthy, with an 18-year OS and RFS of 95.6%.

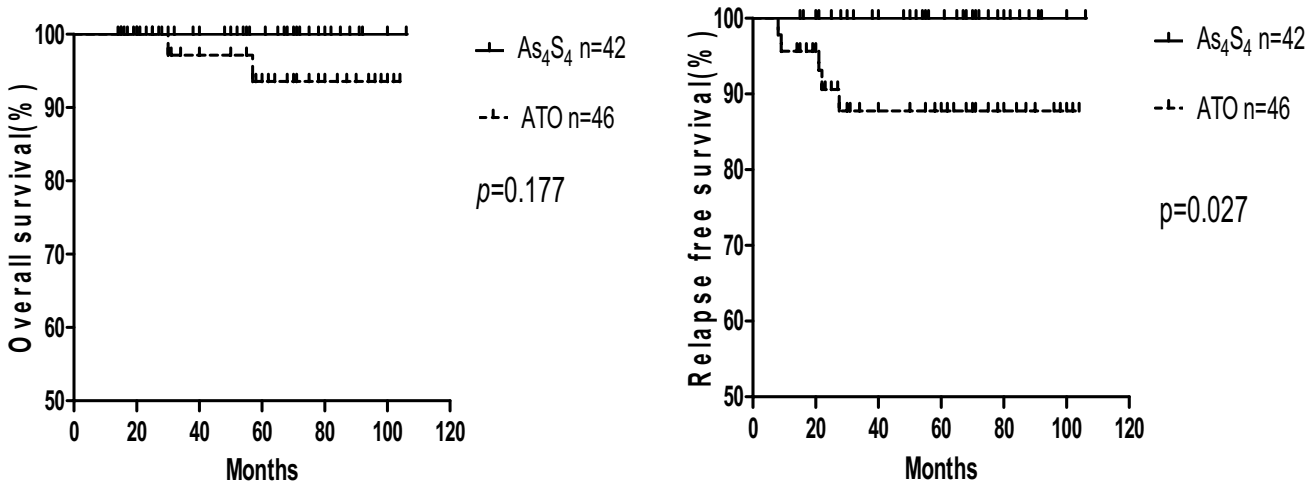

Fig. 2 OS and RFS of 88 newly diagnosed APL patients in the oral As_4S_4 and ATO groups from 2001 to 2008. The 8-year OS and RFS rates were 100% in the $\mathbf{A_{S4}S_4}$ group, and in the ATO group, the 8-year OS rate was 90.0%, and the RFS rate was 87.1%. There was a significant difference of RFS between the two groups ($p=0.027$), while the OS were not significantly different ($p=0.177$)

Table 2 Adverse effects of the patients treated with As_4S_4 and the ATO from 2001 to 2008

Adverse events	$\mathbf{A_{S4}S_4}$ Group $n=42$	ATO Group $n=46$	p value
Moderate APL-DS, n	2	4	0.678
Infections, n	2	6	0.270
Hepatic dysfunction, n	5	12	0.092
Cardiac toxicity, n	2*	5**	0.437
Respiratory failure, n	0	2	0.495
Electrolyte abnormalities, n	0	2	0.495
Edema, n	1	1	1.000
Total, n	12	32	<0.05

ATO arsenic trioxide, *APL-DS* APL differentiation syndrome;

*Asymptomatic QTc prolongation; **Including heart failure (2), tachycardia (2), premature ventricular beat (1)

Adverse effects of ATO and the As_4S_4 triple therapy among newly diagnosed APL patients enrolled between 2001 and 2008

There were no arsenic-related deaths in the cohort. Among the 88 patients, patients in the ATO group experienced more adverse effects than those in the As_4S_4 group (32/46 vs. 12/42, $p<0.05$) during induction period, but without significant differences in the individual impact factors (Table 2). There were five patients with cardiac toxicity in the ATO group, including 2 with Grade 1–2 heart failure, 2 with mild tachycardia, and 1 with mild premature ventricular beat. Two patients had incidents of mild asymptomatic QTc prolongation in the As_4S_4 group. The incidence of Grade 1–2 abnormal liver function was also higher in the ATO group than in the As_4S_4 group but the difference was not statistically significant (Table 2). During the treatment, no patient discontinued therapy due to abnormal organ function. At the end of the chemotherapy cycles and during the maintenance therapy with ATO or As_4S_4 group, the main side effect was a slight decrease of WBC and neutrophils (neutrophils $>1\times10^9$/L), with no incidence of severe neutropenia. In the As_4S_4 group, 23 patients were followed up for 18 years until November 2021. Four of the patients have given birth to healthy children following their recovery.

The long-term survival of 33 ND APL patients, enrolled between 2008 and 2018

Because the RFS and safety was better in the As_4S_4 group than in the ATO group from the data enrolled from 2001 to 2008, since 2008, we mainly utilized the triple therapy of oral arsenic As_4S_4 combined with ATRA and chemotherapy for APL patients. From September 2008 to May 2018, 33 ND APL patients (15 children and 18 adults) were enrolled and followed until November 2021. Among them, 11 (33%) patients had additional chromosomal abnormalities other than t(15;17). During the first course of treatment, 20 patients (61%) had a highest WBC count of greater than 10×10^9/L. There were four patients (12%) with CNSL. Among patients with the *PML::RARA* fusion gene type, there were 23 cases with the long type, 4 cases with the short (S) type, and 2 cases with the variant (V) type. Among the 20 patients with gene mutation data, 3 were *FLT3-ITD* positive, and other gene mutations occasionally detected included *NRAS, RUNX1, WT1, CSF3R*, and *ASXL1*.

All 33 patients achieved MCR. The 10-year OS rate was 100%, and the 10-year RFS rate was 90.9% (Fig. 3). The median follow-up time was 98 months (range:

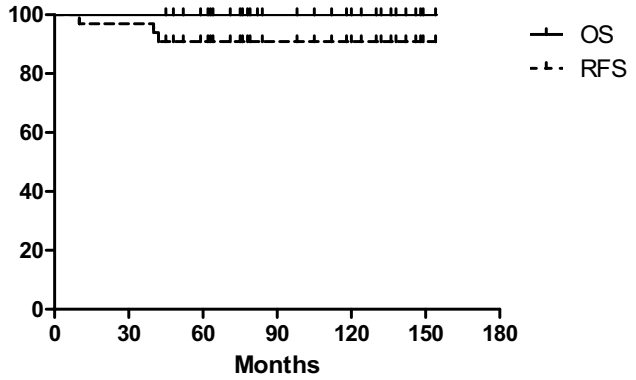

Fig. 3 OS and RFS of 33 newly diagnosed APL patients treated with oral $A_{S4}S_4$ -based triple therapy from 2008 to 2018. The 10-year OS of 33 APL patients with oral $A_{S4}S_4$ based triple therapy was 100%, and the relapse-free survival rate was 90.9%

45–154 months). Of the 33 patients, three patients relapsed (1 hematological relapse, 1 MRD relapse, and 1 CNSL relapse), all of the three patients were in the high-risk group with the WBC > 10×10^9/L, and had long type *PML::RARA* fusion gene, without *FLT3-ITD*. There were no significant differences in relapse rate revealed in an analysis of patient characteristics, including age, gender, presence of CNSL, WBC count, and others (Table 3). Two of them discontinued the As_4S_4 or had a dose reduction during the As_4S_4 oral maintenance period. The triple therapy and lumbar puncture injection of chemotherapy drugs proceeded again after relapse. All 3 patients achieved CR again, and the long-term BM and CSF obtained were MRD negative till now, and their updated OS was 138 months, 82 months, and 79 months, respectively.

Discussion

With the discovery and wide application of ATRA and ATO, APL has changed from the leukemia with the highest mortality to one with the best therapeutic outcomes [1–18]. Since the 1990s, Dr. Daopei Lu from Beijing discovered that another oral arsenic agent, realgar (whose main component is As_4S_4), also produces a high CR rate of 87.5% among APL patients, as well as RFS rates at 1 and 3 years of approximately 86.1% and 76.6%, respectively, and published by 2002 [19–21]. Later results of other Chinese cohort studies based on the oral arsenic agent resulted in excellent outcomes including a one-year OS rate of 100% [25]. Based on substantial medical evidence, including from the Southwest Oncology Group, and the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) pilot study, the NCCN acute leukemia guideline and Chinese guidelines for diagnosis and treatment of APL state that the long-term survival rate of APL has been significantly improved following the utilization of ATRA combined with arsenic or chemotherapy [22, 26]. Still, the 3-year and 5-year OS rate of APL patients remained about 90–100%, and the RFS rate is about 80–90%, which is not enough to enable all APL patients to survive long-term without leukemia [3, 22, 27, 28]. Moreover, there was still no clear conclusion on how to use the three types of drugs, including the best sequence and combinations to maximize patient outcomes.

Table 3 Relapse rate among 33 newly diagnosed APL patients treated with $A_{S4}S_4$ from 2008 to 2018

Subgroups (*n*)	Relapse rate	P value
Gender		
Male vs. Female	3/22 vs. 0/11	0.199
Age		
≤ 14 yrs vs. > 14 yrs	1/7 vs. 2/26	0.905
PML::RARa type		
Long vs. short vs. variant vs. no data	3/23 vs. 0/4 vs. 0/2 vs. 0/4	0.697
Cytogenetics		
t(15;17) only vs. t(15;17) plus vs. no data	0/14 vs. 1/10 vs. 2/9	0.193
Gene mutation		
With mut vs. without mut vs. no data	2/10 vs. 1/10 vs. 0/13	0.185
CNSL		
With vs. without	1/4 vs. 2/29	0.238
WBC		
$< 10 \times 10^9$/L vs. $\geq 10 \times 10^9$/L vs. no data	0/5 vs. 3/22 vs. 0/6	0.693
Time of *PML::RARa* transformed into negative		
≤ 3 months vs. > 3 months vs. no data	1/17 vs. 2/11 vs. 0/5	0.404

WBC white blood cell, *CNSL* central nervous system leukemia

With many years of experience in researching APL therapies, Dr. Daopei Lu demonstrated that a three-drug combination regimen consisting of arsenic, ATRA and chemotherapies (mainly with anthracyclines) starting from induction chemotherapy and followed by maintenance treatment with arsenic for up to 3 years could make 100% of APL patients achieve MCR, with long-term OS and RFS rates of 100% and 94%, respectively [20, 29, 30]. Our retrospective follow-up analysis of approximately 20 years demonstrated that the triple therapy was safe and highly effective for APL patients.

The current APL risk stratification is based on the GIMEMA and PETHEMA clinical trials completed in 2000 [23]. Patients segregated into low-risk (WBC counts $\leq 10 \times 10^9$/L) and high-risk (WBC counts $> 10 \times 10^9$/L) subgroups have distinctive RFS curves ($p < 0.0001$) [22, 23]. Generally, during the induction therapy with ATRA, WBC can increase significantly, up to as high as 100×10^9/L. In such high WBC scenarios, serious side effects of DIC probably occur. Chemotherapies such as NVT and arsenic are recommended to be used simultaneously to effectively clear the APL cells and reduce the severity of DIC. Another benefit of such triple therapy is that it reduces the migration of excess APL cells to EMD, thereby preventing long-term relapse, such as the CNSL. After passing this potentially dangerous period of the induction phase, chemotherapy should be performed for 3 cycles with mainly anthracycline chemotherapy. Especially for those patients with a high WBC count, the chemotherapy should be increased from 3 to 4–5 cycles. Our data showed that the 10-year OS was 100%. Notably, increasing the number of chemotherapy cycles are beneficial for those high-risk patients such as the patients with extremely high WBC, and S or V type *PML::RARA* gene [31, 32].

In addition, based on the conclusion of the GIMEMA and PETHEMA clinical trials, patients in many studies were treated with identical induction (AIDA schedule) regimens. After completion of consolidation therapy, patients with *PML::RARA* negative disease were given oral mercaptopurine (6-MP), intramuscular methotrexate (MTX), and oral ATRA [23]. A large amount of published clinical data show that efficacy outcomes with ATRA plus arsenic as maintenance therapy are significantly better compared to outcomes using ATRA, 6-MP and MTX. The long-term RFS increased from 70 to 80% to 80–90% with the ATRA plus arsenic as maintenance therapy [11, 18, 27, 28]. According to the NCCN guideline and Chinese guidelines for diagnosis and treatment of APL, for the low-risk APL subgroup, the guideline-recommended regimen is retinoic acid ± arsenic or retinoic acid ± chemotherapy as induction therapy, followed by retinoic acid and arsenic for 0.5–2 years as maintenance chemotherapy. For the high-risk APL subgroup, the recommended regimen is a combination of two or three drugs and subsequent maintenance therapy also for 0.5–2 years [22, 26]. Currently, the 3-year or 5-year long-term RFS is about 80–100%, but longer term follow-up is still pending [22, 25, 33]. Our clinical data shows that extending the maintenance therapy with ATO/ As_4S_4 up to about 3 years can result in long-term RFS without increasing adverse effects. In our study, all 33 ND APL patients achieved a nearly 100% OS for more than 10 years. Although three of the patients have relapsed midway, two of them admitted that they stopped receiving maintenance oral As_4S_4 therapy for a period of time. These patients also achieved MRD (−) CR again after restarting the As_4S_4 and have remained relapse-free till now.

Because APL cells have pseudopodia and are highly migratory, they are prone to produce extramedullary lesions, especially CNSL [34, 35]. Our study confirmed that intensive chemotherapy, especially drugs that can cross the blood brain barrier (BBB), including arsenic [36], as well as IDA, NVT, Thiotepa and enhanced lumbar puncture chemotherapy, are helpful for APL patients to achieve CR and longer term remission [8, 37]. Extending the maintenance oral As_4S_4 therapy to 3 years can also increase the probability of achieving long-term RFS for the high-risk APL patients.

Since 2008, we have added gene mutation screening in the first BM tests. There is ample evidence that some gene mutations, such as *FLT3-ITD*, are poor prognostic factors for patients with AML [22, 38]. Meanwhile, some studies reported that gene mutations such as *FLT3-ITD* do not affect the prognosis and treatment of APL [39]. In our analysis, we found that gene mutations, particularly *FLT3-ITD*, did not affect the overall prognosis of APL patients.

The most commonly used arsenic therapy type is intravenous ATO. The side effects of ATO and the risk of sudden death have been reported in the early literature on the use of ATO [40–42]. In recent years, with the control of the dosage and purity of ATO, no serious toxicity has been reported. Our analysis from 2001 to 2008 also showed that ATO was associated with side effects, but no deaths occurred. Meanwhile, oral As_4S_4 is more convenient for patients and has fewer side effects than intravenous ATO (although there is no statistically significant difference). Most patients did not develop cardiac or hepatic toxicities or neutropenia [29, 30], [43]. Following induction and consolidation chemotherapy, patients could return to normal life without hospitalization. The more than 20-year long-term follow-up data showed the As_4S_4 treatment was safe without increasing the risk of secondary tumors [20, 29, 30, 33]. Notably, several female patients have given birth to healthy children following the treatment.

In conclusion, our 20-year retrospective study demonstrated that the triple therapy including ATRA combined with arsenic and anthracycline-based chemotherapy had excellent efficacy and safety for newly diagnosed APL patients. If the arsenic regimen was maintained for about 3 years, the long-term RFS of more than 10 years was

nearly 100%. Moreover, oral As_4S_4 was safe and convenient for patients, and did not require hospitalization. However, because this was a relatively small study, it is necessary to accumulate more cases to provide convincing data on the efficacy outcomes of the triple therapy in APL patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12185-022-03507-5.

Data Availability All authors declare no competing financial interests.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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