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ORIGINAL RESEARCH

Maintenance therapy with all-trans retinoic acid and arsenic trioxide improves relapse-free survival in adults with low- to intermediate-risk acute promyelocytic leukemia who have achieved complete remission after consolidation therapy

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Bin Liang[1,*]
Zhouyi Zheng[1,2,*]
Yifen Shi[1]
Jingjing Chen[1]
Xudong Hu[1]
Honglan Qian[1]
Zhijian Shen[1]
Songfu Jiang[1]
Kang Yu[1]
Jianhua Feng[1,3]

[1]Division of Hematology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, [2]Division of Hematology-Oncology, Traditional Chinese Medical Hospital of Zhuji, Shaoxing, [3]Division of Pediatric Hematology-Oncology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jianhua Feng; Kang Yu
Division of Hematology, The First Affiliated Hospital of Wenzhou Medical University, Ouhai Zone, Wenzhou 325000, Zhejiang, People's Republic of China
Tel +86 577 5557 8999 (ext 669889)
Fax +86 577 5557 8999
Email wzfjh@126.com; yukang62@126.com

Background: Currently, the optimal maintenance therapy for patients with acute promyelocytic leukemia (APL) who have achieved complete remission (CR) after completing consolidation chemotherapy remains controversial. The comparative effectiveness of the all-trans retinoic acid (ATRA) plus arsenic trioxide (As_2O_3) maintenance strategy with classic ATRA plus chemotherapy has not been evaluated. In this study, we compared the efficacy and toxicity of maintenance therapy with ATRA plus As_2O_3 and classic ATRA plus chemotherapy in low- to intermediate-risk APL patients reaching the first CR after induction and consolidation therapy.

Methods: A retrospective review of 58 adult patients diagnosed with APL was conducted. After receiving consolidation therapy and achieving CR, 30 patients were administered maintenance therapy with an ATRA plus As_2O_3 regimen (ATRA+As_2O_3 group), whereas 28 patients were administered 3-monthly cycles of an ATRA plus chemotherapy regimen (ATRA+chemotherapy group).

Results: Grade 3–4 neutropenia was significantly more frequent in the ATRA+chemotherapy group (N=9, 32.1%) than in the ATRA+As_2O_3 group (N=0) (P=0.001). At a median follow-up of 49.1 months (range: 9.7–97.4 months) from the completion of consolidation, no relapses were observed in the ATRA+As_2O_3 group, whereas seven relapses occurred in the ATRA+chemotherapy group. The risk of relapse in the patients administered ATRA+As_2O_3 maintenance was significantly lower than that in those administered ATRA+chemotherapy maintenance (P=0.004). Based on log-rank analysis, only maintenance therapy with ATRA and As_2O_3 was associated with a significantly higher relapse-free survival (P=0.0159).

Conclusion: Maintenance therapy with ATRA and As_2O_3 was beneficial in low- to intermediate-risk APL patients who were effectively treated to achieve CR. Further clinical trials with reliable designs are needed to confirm these observations.

Keywords: acute promyelocytic leukemia, all-trans retinoic acid, arsenic trioxide, maintenance therapy, survival

Introduction

Acute promyelocytic leukemia (APL) is a distinct clinical and pathologic entity associated with fusion of the promyelocytic leukemia (*PML*) gene with the retinoic acid receptor α (*RARA*) gene (*PML–RARA*), formed by the t(15;17)(q22;q21) chromosomal translocation.[1] The use of differentiation induction therapy with all-trans retinoic acid

(ATRA) has significantly improved the prognosis of APL. The combination of ATRA and anthracycline-based chemotherapy that is currently considered the standard of care for newly diagnosed APL[2] yields complete remission (CR) rates of approximately 80%–95% and long-term disease-free survival (DFS) rates exceeding 80%.[3,4] Therefore, much focus has been placed on the prevention of relapse for APL patients in CR.

In addition to ATRA, arsenic trioxide (As_2O_3) has been shown to induce sustained molecular remission in APL patients who relapse after treatment with ATRA-containing regimens.[5–7] Of greater relevance, several studies have shown that the early addition of As_2O_3 to induction and/or consolidation regimens might provide another approach to improve the outcome of APL.[8–12] However, for APL patients who have achieved CR after completing consolidation therapy, the role of maintenance therapy remains a matter of discussion, especially for the low- to intermediate-risk category. Maintenance with different combinations of ATRA, chemotherapy, and As_2O_3 has been used over different time periods. Two previous randomized studies reported the benefit of maintenance therapy with ATRA and/or low-dose chemotherapy (6-mercaptopurine [6-MP] and methotrexate [MTX]),[13,14] and this was later confirmed by the analysis of long-term outcomes.[15,16] However, the Italian GIMEMA group demonstrated no significant benefits in 12-year DFS in patients administered maintenance therapy with any of those three options (6-MP plus MTX, ATRA, and both), compared with observation in APL patients achieving molecular CR by the AIDA 0493 protocol (ATRA plus idarubicin [IDA]).[17] Thus, for patients achieving molecular CR after intensive induction and consolidation therapy, the benefit of maintenance therapy has been questioned. Until recently, a meta-analysis conducted by Muchtar et al that included nine randomized controlled trials suggested that maintenance therapy improves DFS. As for the type of maintenance regimen, ATRA and chemotherapy compared with ATRA alone improves DFS.[18] However, incorporation of As_2O_3 into an effective therapeutic arsenal against APL further confounds the effects of maintenance therapy. The results of several of the latest trials have demonstrated the efficacy and safety of ATRA plus As_2O_3-based maintenance therapy in newly diagnosed APL patients.[19,20] Furthermore, to our knowledge, the comparative efficacy of the ATRA plus As_2O_3 maintenance strategy with classic ATRA plus chemotherapy has not been evaluated.

In this study, a retrospective analysis was conducted to compare the efficacy and toxicity of maintenance therapy with ATRA plus As_2O_3 and classic ATRA plus chemotherapy in low- to intermediate-risk APL patients reaching the first CR (CR1) after induction and consolidation therapy.

Patients and methods

Population and study design

APL was initially diagnosed based on morphology and immunophenotyping, and confirmed genetically by the presence of the *PML–RARA* fusion gene and/or the t(15;17) chromosomal translocation. Eligible patients included adults (≥15 years) with newly diagnosed APL, classified as low- to intermediate-risk category (white blood cell [WBC] count at diagnosis $\leq 10\times10^9$/L). The treatment strategies employed are shown in Figure 1. Remission induction therapy consisted of oral ATRA (25 mg/m^2/day [day 1 until CR]) plus IDA (10–12 mg/m^2/day [days 2, 4, and 6]) with or without intravenous As_2O_3 (0.16 mg/kg/day [days 1–28]). This was followed by four cycles of consolidation. Each cycle included the ATRA plus IDA or mitoxantrone (Mitox) regimen (ATRA: 25 mg/m^2/day [days 1–14] and IDA: 10–12 mg/m^2/day [days 1–3], or Mitox: 6 mg/m^2/day [days 1–3]). During induction and consolidation therapy, IDA dosage was decided based upon the patient's age: 12 mg/m^2/day for patients aged 15–60 years; 10 mg/m^2/day for those aged 61–70 years. To avoid central nervous system (CNS) relapse, all patients received at least three intrathecal injections of three drugs containing MTX (10 mg), dexamethasone (5 mg), and cytarabine (50 mg) during consolidation therapy.

From February 2008 to November 2014, all adult patients with newly diagnosed APL reaching CR1 after induction and consolidation received 2 years of maintenance therapy with either the ATRA plus As_2O_3 regimen (ATRA [25 mg/m^2/day] for 14 days, As_2O_3 [0.16 mg/kg/day] for 14 days, and sequential use of the two agents with an interval of 14 days), or eight 3-monthly cycles of the ATRA plus chemotherapy regimen (ATRA [25 mg/m^2/day] for 14 days of each cycle, alternating with 6-MP [50 mg/m^2/day] and MTX [10–15 mg/m^2/week] for the remainder of each cycle). This retrospective study was reviewed and approved by the Institutional Review Board (IRB) at the First Affiliated Hospital of Wenzhou Medical University. The requirement for informed consent was waived by the IRB due to the retrospective nature of this study, but patient confidentiality was protected.

Molecular monitoring

Regular real-time quantitative polymerase chain reaction assays for the *PML–RARA* fusion transcript were performed on the bone marrow sample obtained at diagnosis, after induction and each consolidation cycle, and subsequently,

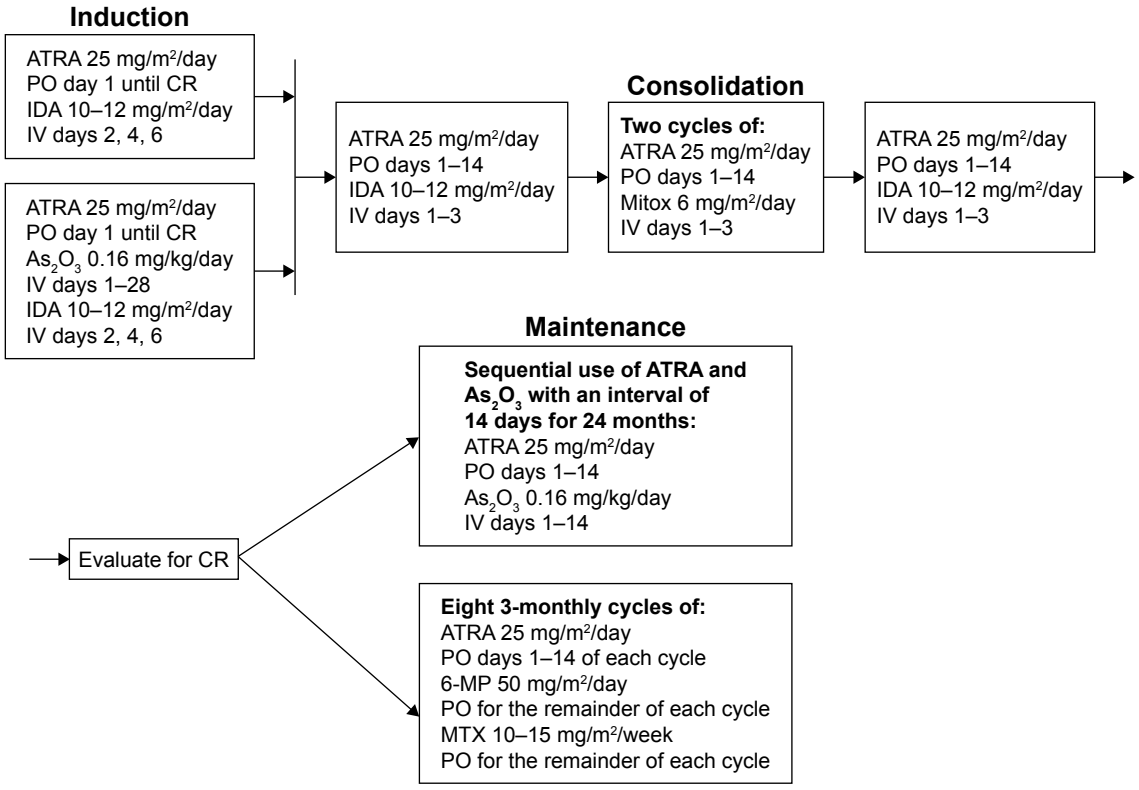

Figure 1 Treatment schedule of APL patients classified as low- to intermediate-risk category.
Abbreviations: 6-MP, 6-mercaptopurine; APL, acute promyelocytic leukemia; As_2O_3, arsenic trioxide; ATRA, all-trans retinoic acid; CR, complete remission; IDA, idarubicin; IV, intravenous; Mitox, mitoxantrone; MTX, methotrexate; PO, per oral.

every 3 months for 3 years. Molecular relapse was defined as the reappearance of *PML–RARA* positivity after achievement of molecular remission at the end of consolidation that could be verified in a subsequent consecutive sample taken 2 weeks later. Frank relapses were confirmed by morphological and molecular analyses.

Statistical analysis

All data were censored on November 1, 2016. Relapse-free survival (RFS) was measured from the completion of consolidation until relapse of any kind. The probability of RFS was calculated using the Kaplan–Meier method. Differences in RFS were tested using log-rank analysis. Categorical variables were compared using the Fisher's exact test or chi-square test. Numerical variables were compared using the Wilcoxon rank-sum test. A two-tailed *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using the Stata version 12 software (StataCorp LP, College Station, TX, USA).

Results

Patient characteristics

In total, 58 eligible patients reaching CR1 after induction and consolidation therapy received maintenance therapy with either ATRA plus As_2O_3 (ATRA+As_2O_3 group, N=30) or ATRA plus chemotherapy containing 6-MP and MTX (ATRA+chemotherapy group, N=28). The median age of the participants was 41 years (range: 15–70 years), and six were older than 60 years. Characteristics of the 58 patients according to the type of maintenance regimen are presented in Table 1. Significant differences were noted between the two maintenance groups in terms of sex and WBC count at diagnosis. The percentage of male patients in the ATRA+chemotherapy group (67.9%) was significantly higher than that in the ATRA+As_2O_3 group (40.0%) (*P*=0.034), while the percentage of patients with a WBC count at diagnosis $<5\times10^9$/L was significantly lower in the ATRA+chemotherapy group (71.4%) than in the ATRA+As_2O_3 group (93.3%) (*P*=0.027).

Adverse events observed during maintenance

All 58 patients receiving maintenance therapy were reviewed, to evaluate the incidence of toxicity during maintenance (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03).[21] A total of 24 adverse events (seven in the ATRA+As_2O_3 group vs 17 in the ATRA+chemotherapy group) were reported in

Table 1 Clinicopathologic characteristics of 58 patients with APL receiving different maintenance regimens

Characteristic	ATRA+As_2O_3 maintenance (N=30)	ATRA+chemotherapy maintenance (N=28)	*P*-value
Age (years), median (range)	41 (15–64)	43.5 (17–70)	0.4933
15–39, n (%)	12 (40.0)	12 (42.9)	0.557
40–60, n (%)	16 (53.3)	12 (42.9)	
>60, n (%)	2 (6.7)	4 (14.2)	
Sex			
Male, n (%)	12 (40.0)	19 (67.9)	0.034
Female, n (%)	18 (60.0)	9 (32.1)	
WBC count ($\times10^9$/L), median (range)	1.49 (0.52–6.83)	2.14 (0.85–8.7)	0.0165
<5, n (%)	28 (93.3)	20 (71.4)	0.027
5–10, n (%)	2 (6.7)	8 (28.6)	
Platelet count, $\times10^9$/L, median (range)	20.5 (2–176)	28.5 (3–135)	0.4884
≤40, n (%)	24 (80.0)	17 (60.7)	0.107
>40, n (%)	6 (20.0)	11 (39.3)	
Hemoglobin (g/L), median (range)	81 (39–144)	90.5 (44–149)	0.1435
Induction regimens			
ATRA+As_2O_3+IDA, n (%)	8 (26.7)	3 (10.7)	0.121
ATRA+IDA, n (%)	22 (73.3)	25 (89.3)	

Abbreviations: APL, acute promyelocytic leukemia; As_2O_3, arsenic trioxide; ATRA, all-trans retinoic acid; IDA, idarubicin; WBC, white blood cell.

23 patients (seven in the ATRA+As_2O_3 group vs 16 in the ATRA+chemotherapy group) (Table 2).

Hematologic toxicity

Grade 3–4 neutropenia was significantly more frequent in the ATRA+chemotherapy group (N=9, 32.1%) than in the ATRA+As_2O_3 group (N=0) (*P*=0.001). Grade 3–4 thrombocytopenia was not observed in either group during maintenance.

Nonhematologic toxicity

Three out of 30 patients (10.0%) in the ATRA+As_2O_3 group and four out of 28 patients (14.3%) in the ATRA+chemotherapy group had reversible liver function derangements during maintenance (*P*=0.701). Prolongation of the QT interval, defined as a corrected QT interval ≥450 ms in men and ≥460 ms in women calculated using the Framingham formula,[22] was observed in two patients (6.7%) in the ATRA+As_2O_3 group, and was not observed in the ATRA+chemotherapy group (*P*=0.492). There were no reports of life-threatening cardiac arrhythmias. Dyspepsia was reported in one patient (3.3%) in the ATRA+As_2O_3 group and in three patients (10.7%) in the ATRA+chemotherapy group (*P*=0.344). Two out of 58 patients experienced other adverse events, including herpes zoster reactivation (one in the ATRA+chemotherapy group) and hemolysis (one in the ATRA+As_2O_3 group). All clinical signs improved after symptomatic treatment only or observation, with the exception of hemolysis that was resolved with temporary discontinuation of As_2O_3 and symptomatic treatment.

Relapse and survival

At a median follow-up of 49.1 months (range: 9.7–97.4 months) from the completion of consolidation, no relapses were observed in the ATRA+As_2O_3 group, whereas seven relapses were observed in the ATRA+chemotherapy group. Of the seven relapsed patients, five presented with

Table 2 Adverse events during maintenance therapy

Adverse events	ATRA+As_2O_3 maintenance (N=30)	ATRA+chemotherapy maintenance (N=28)	*P*-value
Neutropenia (grade 3–4)	0	9	0.001
Liver function derangement	3	4	0.701
QT prolongation	2	0	0.492
Dyspepsia	1	3	0.344
Herpes zoster reactivation	0	1	0.483
Hemolysis	1	0	1.000

Abbreviations: ATRA, all-trans retinoic acid; As_2O_3, arsenic trioxide.

frank relapse (bone marrow, N=4; CNS, N=1), and two presented with molecular relapse. Death occurred in one patient, 8.8 months after relapse. The other six patients who relapsed received salvage therapy with As_2O_3, and all achieved molecular CR and remained alive at the final follow-up.

To define the risk of relapse in patients during maintenance, the impacts of sex, age (≤40 years vs >40 years), WBC count at diagnosis ($\leq 5\times10^9$/L vs $>5\times10^9$/L), platelet count at diagnosis ($\leq 40\times10^9$/L vs $>40\times10^9$/L), hemoglobin level at diagnosis (<100 g/L vs ≥100 g/L), and types of induction regimen (ATRA+As_2O_3+IDA vs ATRA+IDA) and maintenance regimen (ATRA+As_2O_3 vs ATRA+chemotherapy) on relapse were all analyzed. The risk of relapse in patients administered ATRA+As_2O_3 maintenance was significantly lower than that in those administered ATRA+chemotherapy maintenance (P=0.004). Other parameters analyzed showed no significant effects on the rate of relapse (Table 3).

Furthermore, the impacts of sex, age, WBC count at diagnosis, platelet count at diagnosis, hemoglobin level at diagnosis, and types of induction and maintenance regimens on RFS were analyzed. Maintenance with ATRA and As_2O_3 was associated with a significantly higher RFS (P=0.0159, log-rank; Table 4). The RFS according to the type of maintenance regimen administered is shown in Figure 2. However, no relapse was observed in the ATRA+As_2O_3 group, hampering the multivariate analysis to test whether maintenance with ATRA and As_2O_3 was an independent factor for RFS.

Table 3 Impacts of clinicopathologic features on relapse in 58 APL patients during maintenance therapy

Clinicopathologic parameters	Outcome		*P*-value
	Remission	Relapse	
Sex			0.432
Male	26	5	
Female	25	2	
Age (years)			1.000
≤40	25	3	
>40	26	4	
WBC count ($\times10^9$/L)			0.592
≤5	43	5	
>5	8	2	
Platelet count ($\times10^9$/L)			0.661
≤40	35	6	
>40	16	1	
Hemoglobin (g/L)			0.083
<100	39	3	
≥100	12	4	
Induction regimens			0.327
ATRA+As_2O_3+IDA	11	0	
ATRA+IDA	40	7	
Maintenance regimens			0.004
ATRA+As_2O_3	30	0	
ATRA+chemotherapy	21	7	

Abbreviations: APL, acute promyelocytic leukemia; As_2O_3, arsenic trioxide; ATRA, all-trans retinoic acid; IDA, idarubicin; WBC, white blood cell.

Table 4 Impacts of clinicopathologic parameters on RFS in 58 APL patients during maintenance therapy

Clinicopathologic parameters	3-year RFS	*P*-value (log-rank)
Sex		0.4376
Male	0.8640	
Female	0.9630	
Age (years)		0.8146
≤40	0.8889	
>40	0.9305	
WBC count ($\times10^9$/L)		0.6536
≤5	0.9128	
>5	0.9000	
Platelet count ($\times10^9$/L)		0.3020
≤40	0.8733	
>40	1.0000	
Hemoglobin (g/L)		0.0895
<100	0.9491	
≥100	0.8125	
Induction regimens		0.2724
ATRA+As_2O_3+IDA	1.0000	
ATRA+IDA	0.8908	
Maintenance regimens		0.0159
ATRA+As_2O_3	1.0000	
ATRA+chemotherapy	0.8182	

Abbreviations: APL, acute promyelocytic leukemia; As_2O_3, arsenic trioxide; ATRA, all-trans retinoic acid; IDA, idarubicin; RFS, relapse-free survival; WBC, white blood cell.

Due to the relatively high number of patients in our cohort receiving the ATRA+IDA protocol during the induction phase, we further analyzed the impacts of clinicopathologic features on relapse and RFS during maintenance therapy in 47 APL patients receiving ATRA+IDA as the induction regimen. The risk of relapse in the patients who received

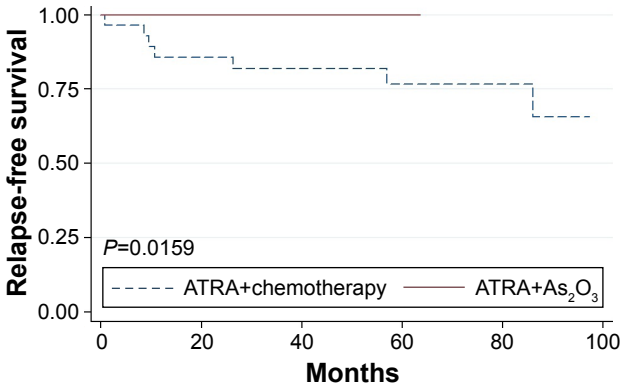

Figure 2 Relapse-free survival according to the type of maintenance regimen. Relapse-free survival is estimated from the completion of consolidation.
Abbreviations: As_2O_3, arsenic trioxide; ATRA, all-trans retinoic acid.

Table 5 Impacts of clinicopathologic features on relapse during maintenance therapy in 47 APL patients receiving ATRA+IDA as an induction regimen

Clinicopathologic parameters	Outcome		*P*-value
	Remission	Relapse	
Sex			0.295
Male	20	5	
Female	20	2	
Age (years)			0.727
≤40	20	3	
>40	20	4	
WBC count (×10⁹/L)			0.492
≤5	33	5	
>5	7	2	
Platelet count (×10⁹/L)			0.331
≤40	27	6	
>40	13	1	
Hemoglobin (g/L)			0.086
<100	30	3	
≥100	10	4	
Maintenance regimens			0.007
ATRA+As_2O_3	22	0	
ATRA+chemotherapy	18	7	

Abbreviations: APL, acute promyelocytic leukemia; As_2O_3, arsenic trioxide; ATRA, all-trans retinoic acid; IDA, idarubicin; WBC, white blood cell.

Table 6 Impacts of clinicopathologic parameters on RFS during maintenance therapy in 47 APL patients receiving ATRA+IDA as an induction regimen

Clinicopathologic parameters	3-year RFS	*P*-value (log-rank)
Sex		0.4381
Male	0.8337	
Female	0.9545	
Age (years)		0.7301
≤40	0.8696	
>40	0.9079	
WBC count (×10⁹/L)		0.7274
≤5	0.8904	
>5	0.8889	
Platelet count (×10⁹/L)		0.2928
≤40	0.8436	
>40	1.0000	
Hemoglobin (g/L)		0.1158
<100	0.9351	
≥100	0.7857	
Maintenance regimens		0.0264
ATRA+As_2O_3	1.0000	
ATRA+chemotherapy	0.7958	

Abbreviations: APL, acute promyelocytic leukemia; As_2O_3, arsenic trioxide; ATRA, all-trans retinoic acid; IDA, idarubicin; RFS, relapse-free survival; WBC, white blood cell.

ATRA+As_2O_3 maintenance therapy was significantly lower than that in those who received the ATRA+chemotherapy maintenance (*P*=0.007; Table 5). In addition, Kaplan–Meier analysis showed that maintenance with ATRA and As_2O_3 was associated with a significantly higher RFS (*P*=0.0264, log-rank; Table 6). Similarly, a multivariate analysis to test whether maintenance with ATRA and As_2O_3 was an independent factor for RFS was hampered by the absence of relapse in the ATRA+As_2O_3 group. Futhermore, there were too few APL patients (N=11) receiving ATRA+As_2O_3+IDA as the induction regimen to make a similar analysis.

Discussion

In the present study, we retrospectively compared the efficacy and toxicity of ATRA plus As_2O_3 and classic ATRA plus chemotherapy as maintenance therapy in low- to intermediate-risk APL patients who achieved CR following consolidation therapy. The number of APL patients who received standard induction and consolidation with ATRA and anthracycline-based chemotherapy was 47 (81.0%) and 58 (100%), respectively. The 3-year RFS for patients receiving maintenance therapy with ATRA plus As_2O_3 and ATRA plus chemotherapy was 100% and 81.82%, respectively, with a statistically significant difference (*P*=0.0159). These clinical data suggest that maintenance with ATRA and As_2O_3 confers a survival benefit in low- to intermediate-risk APL patients achieving CR after effective induction and consolidation with ATRA and anthracycline-based chemotherapy. Our results are consistent with observations from previous studies that report favorable survival attributed to the use of As_2O_3 during maintenance.[19,20,23] Altogether, these findings show that As_2O_3-based maintenance therapy might be another approach to improve the outcome in APL patients achieving CR.

In contrast to ATRA that targets the *RARA* moiety of *PML–RARA*, As_2O_3 exerts its therapeutic effects by targeting the *PML* moiety, thereby inducing differentiation and apoptosis of leukemic promyelocytes, as well as the inhibition of leukemic progenitor self-replication and antiangiogenic effects.[24–27] The synergistic effects between ATRA and As_2O_3 have been demonstrated at both the biological[28,29] and clinical levels. For example, recent studies report that the combination of ATRA with As_2O_3 administered for initial induction and consolidation therapy improves outcomes compared with standard ATRA plus chemotherapy, particularly in low- to intermediate-risk APL patients.[30,31] Therefore, based on our observations regarding the benefit of maintenance therapy with ATRA and As_2O_3, the best timing for the use of As_2O_3 in APL, whether during initial remission induction, consolidation, or maintenance, should be further investigated.

In addition to efficacy, safety is another major concern regarding the treatment of low- to intermediate-risk APL patients. In our study, we alternated As_2O_3 with conventional

chemotherapy. Myelosuppression was observed significantly less frequently in patients administered maintenance therapy with ATRA and As_2O_3 than in those administered chemotherapy. The commonly observed adverse effects during maintenance with ATRA and As_2O_3 included hepatotoxicity, gastrointestinal reactions, and prolongation of the QT interval, all of which were manageable. Of note, one patient developed hemolysis during maintenance with ATRA plus As_2O_3, and the exact reason for this is unknown. Although the drug-induced immune hemolysis was anticipated, a negative direct antiglobulin test result was observed. Another major concern after long-term exposure to inorganic arsenic compounds is the increased risk of secondary tumors.[32,33] No instances of secondary tumors were observed in the present study. In fact, the average total dosage of As_2O_3 for maintenance was 26.9 mg/kg in the present study, which is similar to that in the Shanghai trial (28.3 mg/kg).[34] Thus, APL patients could benefit from As_2O_3-based maintenance without overtreatment.

One of the limitations of our study is the retrospective nature; thus, heterogeneity of the data was difficult to be ruled out. Therefore, caution should be taken when interpreting the results of the present study, as they might not be applicable to other populations. Another limitation of the present study is the fact that a greater number of patients received the ATRA plus IDA protocol during the induction phase. Two pilot studies have proven the high efficacy of chemotherapy-free regimens based on As_2O_3 in newly diagnosed APL.[35,36] Subsequently, several recent reports provide evidence of the efficacy and safety of ATRA plus As_2O_3, with or without a chemotherapy protocol, for first-line therapy in patients with newly diagnosed APL.[37–39] Furthermore, a recent meta-analysis by Ma et al showed significant benefits of the ATRA plus As_2O_3 protocol, compared with the standard ATRA plus chemotherapy protocol, particularly in low- to intermediate-risk APL patients.[30] In line with results of these pilot studies, the final results of the randomized Italian-German APL0406 trial demonstrated the advantages of ATRA plus As_2O_3 over ATRA plus chemotherapy for induction and consolidation therapy in low- to intermediate-risk APL.[31] These data suggest that the standard first-line treatment for newly diagnosed APL is now shifting towards induction and consolidation regimens that include ATRA and arsenic. Thus, the variables associated with frontline induction and consolidation therapies in the present study might work against future outcomes. For example, a recent randomized non-inferiority study demonstrated that DFS was not significantly different among low- to intermediate-risk APL patients who were reaching molecular CR after consolidation therapy including As_2O_3 and received ATRA+chemotherapy maintenance therapy vs those who received no maintenance therapy, and suggested that maintenance therapy may not be needed if patients are treated with an intensive post-remission regimen including As_2O_3.[40] The question of whether maintenance with ATRA and As_2O_3 benefits low- to intermediate-risk APL patients in whom As_2O_3 has been incorporated in induction and consolidation will need to be addressed in future studies.

In conclusion, the present study, conducted in a well-defined cohort, albeit a retrospective single-center analysis of a relatively small number of subjects, showed that maintenance therapy with ATRA and As_2O_3 was beneficial for low- to intermediate-risk APL patients who were effectively treated to achieve CR. In addition, the use of As_2O_3 in maintenance precluded the need for myelosuppressive chemotherapy. However, further clinical trials with reliable designs are needed to confirm the results of the present study.

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Disclosure

The authors report no conflicts of interest in this work.

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