RESEARCH ARTICLE

Blood Science

OPEN

Long-term outcome of using Ara-C or not in children's APL

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Abstract

The use of cytarabine (Ara-C) in treating acute promyelocytic leukemia (APL) is controversial. This study was conducted to demonstrate the effect of treatment with or without Ara-C on long-term event-free survival (EFS) or overall survival (OS). All patients received all-trans retinoic acid (ATRA) + arsenic trioxide (ATO) induction therapy, followed by the course of idarubicin (IDA) and ATO, then were randomly allocated to 2 groups for consolidation therapy, with patients in the daunorubicin (DNR) group received DNR, in the DNR + Ara-C (DA) group received DNR + Ara-C. Maintenance therapy consisted of oral ATRA, 6-mercaptopurine, and methotrexate for 1.5 years. Thirty patients in DA group and 35 patients in DNR group, all achieved complete remission. At follow-up, there was 1 death and 3 relapses in DNR group, compared to none in DA group. There was no statistically significant difference in EFS (P = 0.140) and OS (P = 0.398) between 2 groups, with EFS being 100% in DA group and 91.4% ± 0.047 in DNR group, and OS being 100% in DA group and 97.1% ± 0.028 in DNR group. Our study found no prognostic significance of Ara-C, this may be related to the small sample size. We still recommend the addition of Ara-C during treatment, which has a more positive impact on early remission and late prognosis of patients.

Key Words: Acute promyelocytic leukemia; All-trans retinoic acid; Arsenic trioxide; Cytarabine; Pediatric

1. INTRODUCTION

All-trans retinoic acid (ATRA) and arsenic trioxide (ATO) chemotherapy is highly effective in the treatment of acute promyelocytic leukemia (APL), making APL a curable disease with high complete remission (CR) and overall survival (OS) rates.[1,2] Anthracycline-based chemotherapy and ATRA combination therapy are curative for at least 80% of newly diagnosed APL patients.

Pediatric APL is relatively rare among patients with APL but accounts for 25% to 30% of childhood acute myeloid leukemia (AML).[3,4] Effective integration of ATRA and ATO in the treatment of APL significantly improves the prognosis and we can see a significant increase in CR and OS rates. Many global clinical trials are now reporting impressive results, with 90% to 100% of patients achieving CR in several large multicenter trials, while OS rates can reach 86% to 97%.

ATO has been the most effective single agent for the treatment of APL, and ATRA in combination with chemotherapeutic agents such as anthracycline was widely used before the addition of ATO treatment to combination therapy until the combination of ATO and ATRA became the optimal treatment regimen according to current guidelines.[5,6]

Although the use of cytarabine (Ara-C) is controversial, the role of Ara-C in the treatment of children with APL is less clear.[6,7] Ara-C is a cell cycle-specific drug that is metabolized to the active complex cytidine triphosphate, which potently inhibits DNA polymerase synthesis, thereby inhibiting cellular DNA polymerization and synthesis. Previously, we conducted a prospective study to determine whether Ara-C could be omitted from consolidation chemotherapy which demonstrated the feasibility of omitting Ara-C from the regimen. However, there are fewer reports on the effect of Ara-C use on long-term survival in children.[8] Here we present the results of our center's study of newly diagnosed APL patients between March 2010 and February 2016, focusing on the impact of Ara-C treatment on long-term survival outcomes to better understand the diagnosis and treatment of APL in children over a 12-year period.

2. METHODS

2.1. Objectives of the study and eligibility criteria

The study was a prospective, randomized, single-center trial. Inclusion criteria were children under 14 years of age, no pre-existing or concurrent malignancies, no cardiac contraindications

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

The project was supported in part by the National Key Research and Development Program of China (2021YFE0106900), the CAMS Innovation Fund for Medical Sciences (CIFMS 2022-I2M-1-022; 2021-I2M-1-041), the National Natural Science Foundation of China (82270144), and the Haihe Laboratory of Cell Ecosystem Innovation Fund (22HHXBSS00039).

Blood Science (2025) 7, 1–6:e00225.

Received July 27, 2024; Accepted February 16, 2025.

http://dx.doi.org/10.1097/BS9.0000000000000225

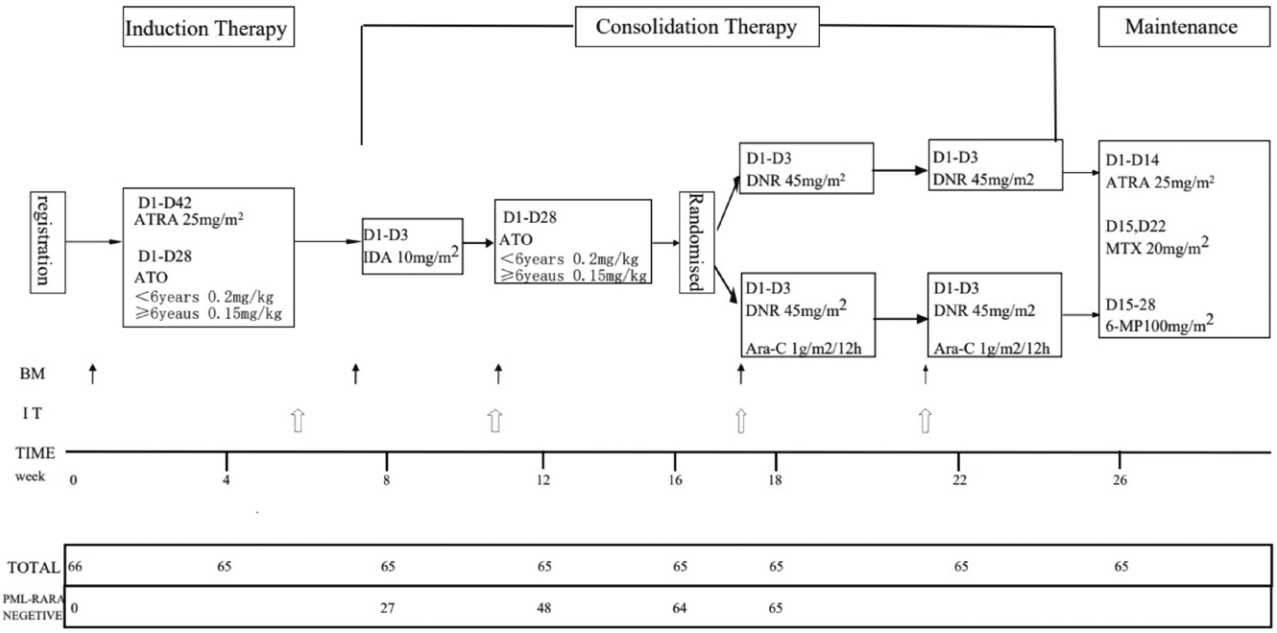

Figure 1. The China children with APL study 2010 (CCAPL 2010) regimen and measurable residual disease (MRD) test results. 6-MP = 6-mercaptopurine, Ara-C = cytosine arabinoside, ATO = arsenic trioxide, ATRA = all-trans-retinoic acid, BM = bone marrow aspiration, DNR = daunorubicin, IT = intrathecal injection, MTX = methotrexate.

to anthracyclines, and newly diagnosed APL without prior chemotherapy. No molecular diagnosis was required for enrollment. However, subsequent molecular and cytogenetic confirmation is mandatory for eligibility and inclusion in the analyses by either confirmation of the t(15;17) translocation by conventional cytogenetics or fluorescence in situ hybridization (FISH) or molecular positivity for the PML/RARA fusion gene by polymerase chain reaction (PCR). In this open-label trial, patients were randomly assigned to the Ara-C (DA) or no Ara-C group (DNR). The primary endpoint was 12-year event-free survival (EFS) and CR.

2.2. Treatment protocol

The patients received ATRA + ATO induction therapy, followed sequentially by a 3-day consolidation course of idarubicin (IDA) and a 28-day consolidation course of ATO. They were randomly allocated to 2 groups for consolidation therapy, with patients in the DNR group received only 2 courses of DNR, while patients in the DA group were treated with DNR + Ara-C for 2 courses. The maintenance regimen consisted of oral ATRA, 6-mercaptopurine, and methotrexate for a period of 1.5 years. All patients received a first prophylactic intrathecal injection of Ara-C, methotrexate, and dexamethasone upon achievement of CR. Patients with an initial white blood cell (WBC) count greater than 10×10^9/L received a single intrathecal injection per course. Intrathecal injections were given every other day until their counts normalized in patients with an indication of central nervous system (CNS) leukemia. This trial was registered on ClinicalTrials.gov and was conducted in accordance with the Declaration of Helsinki (identifier: NCT01191541). The regimen is shown in Figure 1.

2.3. Patient characteristics

Between March 2010 and February 2016, 66 pediatric patients (≤14 years) with genetically confirmed APL were admitted to our hospital. The last follow-up was performed in January 2024, with a median follow-up of 104 months (ranging from 15 to 164 months). One patient was randomized despite not starting treatment due to financial reasons. The main clinical and biological characteristics of these patients are shown in Table 1.

2.4. Criteria for response and end points

Molecular remission was defined as the absence of detectable PML/RARA fusion transcripts. Molecular relapse was defined as detecting the fusion oncogene PML/RARA across various samples within a period of 2 weeks. EFS was defined as the time from diagnosis to the time at last follow-up or an event (ie, relapse or death). The OS was calculated from the date of diagnosis to the date of death from any cause or the last follow-up visit in survivors.

2.5. Supportive measures and management of complications

Treat coagulopathies with fresh frozen plasma or fibrinogen until all signs of significant coagulopathy have resolved, and give platelet transfusions to maintain platelet counts above 50×10^9/L in such patients. If the patient's peripheral blood WBC count is above 25×10^9/L, administer hydroxyurea (1–1.5 g/d) or homoharringtonine (HHT, 1–2 mg/d for 5–10 days), and Ara-C if necessary. If the patient develops edema, unexplained fever, and dyspnea, consider that the patient may have differentiation syndrome, discontinue ATRA and ATO or both and administer dexamethasone at a dose of 5 to 10 mg/m² intravenously until the above signs and symptoms resolve. Administer febrile antibiotics and antifungals as needed.

2.6. Statistical analysis

In designing the experiment in 2016, our main objectives were to demonstrate the noninferiority of DNR alone compared to DNR + Ara-C in terms of the EFS rate at 2 years. Based on the assumption that the EFS rate in the 2 groups is 95%, with a margin of –14%, 5% type 1 error, and 80% power, a total of 31 evaluable patients per group are required to draw a noninferiority conclusion.

Table 1

Clinical and biological characteristics of the eligible patient.

Parameter	Total	DNR group	DA group	*P*
N	66	36	30	
Age				0.213
Median	8	7	8	
Range	2–14	2–14	2–13	
Sex				0.814
Male	43	23	20	
Female	23	13	10	
WBC count, 10^9/L				0.203
≤10	44	22	22	
>10	22	14	8	
				0.296
Median	4.71	5.745	4.25	
Range	0.82–202.4	0.82–202.4	0.99–130	
Bone marrow blast, %				0.741
Median	45.25	45.25	45.25	
Range	0–100	0–98	0–100	
Hemoglobin, g/L				0.179
Median	79	81	78	
Range	44–127	49–127	44–124	
PML-RARA				0.766
Long transcript	26	14	12	
Short transcript	13	8	5	
Variable	17	8	9	
Not done	10	6	4	

DA = DNR + Ara-C, DNR = daunorubicin, PML-RARA = promyelocytic leukemia-retinoic acid receptor alpha, WBC = white blood cell.

The patients' characteristics were summarized using cross-tabulations for categorical variables and quantiles (such as the median) for continuous variables. Nonparametric tests, including χ^2 and Fisher exact tests, were used to analyze comparisons between groups. The Kaplan–Meier method was used to estimate EFS and OS, and log-rank tests were used for comparisons. All *P* values were 2-sided. Statistical significance was determined for values of 0.05 or less. SPSS 25.0 software was used for all statistical analyses.

3. RESULTS

3.1. Safety

During induction therapy, retinoic acid syndrome (RAS) was diagnosed in 9 patients (13.8%) but did not result in any deaths. Four (6.2%) of the 65 patients suffered Common Terminology Criteria for Adverse Events (CTCAE V.4.0) grade 1–2 hepatotoxicity; Other ATO-related adverse reactions included generalized edema (eg, chest, abdomen, head, and eyelids) in 11 cases (17.0%), nausea in 2 cases (3.1%), skin pigmentation in 2 cases (3.1%), bone pain in 3 cases (4.6%), cardiac arrhythmia in 1 case, and ECG alteration in 2 cases (3.1%); and other ATRA-related adverse reactions included headache in 24 cases (36.9%), rash in 3 cases (4.6%), nausea in 7 cases (10.8%), chest tightness, chest pain in 3 cases (4.6%), abdominal pain in 2 cases (3.1%), bone pain in 8 cases (12.3%), skin peeling in 4 cases (6.2%), and DIC in 3 cases (4.6%). ATRA or ATO treatment was promptly discontinued upon the appearance of symptoms, resulting in the reversal of most toxic events.

During the consolidation of treatment, side effects included sepsis in 6 cases (9.2%), hepatotoxicity in 4 cases (6.2%), cardiac mass in 1 case (1.5%), electrocardiogram changes in 2 cases (3.1%), and cardiac enzyme elevation in 1 case (1.5%), among which 6 cases of sepsis in 5 cases in the DA group, and 1 case in the DNR group. Ultimately, 30 patients were incorporated into the DA group receiving a total of 57 courses of treatment. In contrast, the DNR group consisted of 35 patients who received 73 courses of treatment. A comparison of the hematology toxicity between the 2 groups was conducted based on the actual application of the treatment. The proportion of courses in the DA group that involved platelet and red blood cell (RBC) transfusions was 91.2% (52/57) and 24.6% (14/57), respectively. During the consolidation phase, no blood products were required in the DNR group. A total of 84.2% (48/57) and 5.5% (4/73) of patients in the DA and DNR groups, respectively, exhibited WBC counts below 1.0×10^9/L ($P = 0.000$). The median lowest WBC count was 0.62×10^9/L in the DA group (range 0.02–1.82×10^9/L). The median duration of neutropenia was 0 days (range 0–9 days) in the DNR group and 6 days (range 0–13 days) in the DA group ($P = 0.000$). No deaths occurred during consolidation therapy. Additionally, 2 of the 65 patients exhibited Common Terminology Criteria for Adverse Events (CTCAE V.4.0) grade 1–2 hepatotoxicity, both of whom were classified as DA group.

During the follow-up period, particular attention was paid to the potential for long-term complications, including neurotoxicity and interstitial lung damage, in patients who had received Ara-C. However, no such complications were identified in the 31 patients included in the study.

According to the symptoms, we correspondingly gave antibiotics and hepatoprotective medications to the treatment, and the majority of the patients' adverse events were reversed. The adverse events were reversed in most of the patients. As of the date of follow-up, no cases of malignancy have been reported.

3.2. High white blood cells and their management

During induction, 59 of 65 patients (90.8%) experienced leukocytosis, with peak leukocyte counts ranging from 12.8 to 267.8×10^9/L (median 38.0×10^9/L). Additionally, 24 of 65 patients (36.9%) had peak leukocyte counts that exceeded 50×10^9/L.

Twenty-eight patients received HHT at doses of 1 to 2 mg/d for 2 to 15 consecutive days (median 7 days). After achieving

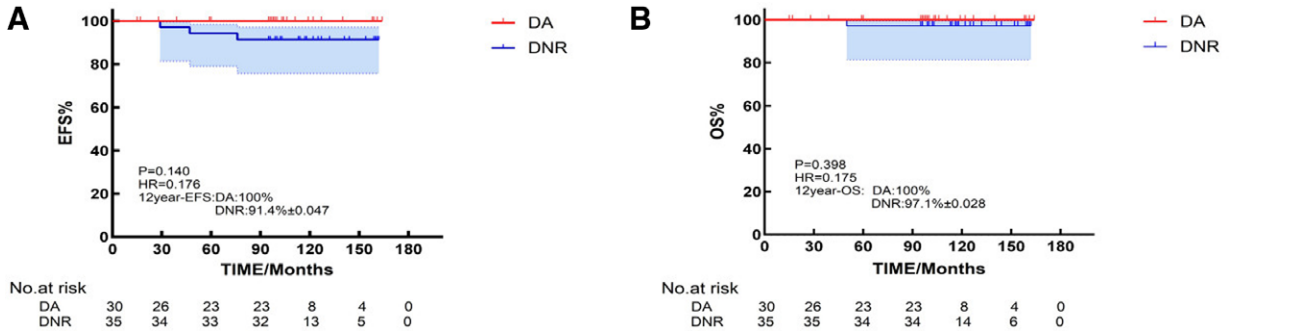

Figure 2. EFS or OS of DA/DNR subgroups. Kaplan–Meier analysis of (A) EFS, DNR group vs DA group; (B) OS, DNR group vs DA group. DA = DNR + Ara-C, DNR = daunorubicin, EFS = event-free survival, OS = overall survival.

a CR, 11 (11/28, 39.3%) of the patients who received HHT tested negative for promyelocytic leukemia-retinoic acid receptor alpha (PML-RARA) fusion transcripts, while 16 (16/37, 43.2%) of the patients who did not receive HHT tested negative for PML-RARA fusion transcripts. The proportion of patients negative for PML-RARA fusion transcripts was not significantly different between those treated with and without HHT (P = 0.749).

Eleven patients received induction therapy with Ara-C at a dose of 50 mg/m^2 every 12 hours, with sequential doses ranging from 50 to 1000 mg (median 300 mg), 4 of whom were in the low- and intermediate-risk groups, and 7 of whom were in the high-risk group. After achieving CR, 5 (5/11, 45.5%) patients treated with Ara-C tested negative for PML-RARA fusion transcripts, whereas 22 (22/54, 40.7%) patients not treated with Ara-C tested negative for PML-RARA fusion transcripts. There was no statistically significant difference in the proportion of patients with negative PML-RARA fusion transcripts between patients treated with or without Ara-C (P = 1), and there were no significant differences in baseline white blood cell (WBC) (P = 0.093), haemoglobin (Hb) (P = 0.165), and PLT counts (P = 0.514) and outcomes between the 2 groups.

3.3. CR and measurable residual disease test

At the end of the induction period, all patients achieved hematological complete remission (HCR), which lasted from 22 to 44 days, with a median of 31 days. Of the 65 patients who underwent measurable residual disease (MRD) testing, all patients achieved complete (molecular) remission (**Fig. 1**) after the third consolidation cycle (ie, the first DNR/DA cycle), with 27 (41.5%) of the patients tested after induction were negative for PML-RARA fusion transcripts, 58 of 65 patients (89.2%) had a negative PML-RARA sample at the end of the first consolidation treatment, and 64 of 65 patients (98.5%) had a negative sample at the end of the second ATO treatment. Baseline characteristics did not differ significantly between the induction and IDA chemotherapy positive and negative cohorts.

3.4. Efficacy and relapse

As of January 2024, there was no statistically significant difference in EFS (P = 0.140) and OS (P = 0.398) between 2 groups, with EFS being 100% in DA group and 91.4% ± 0.047 in DNR group, and OS being 100% in DA group and 97.1% ± 0.028 in DNR group (**Fig. 2**).

There were 43 patients in the low- and intermediate-risk group, 22 of whom were in the DA group and 21 in the DNR group, 2 of whom relapsed in the DNR group, and there was no statistically significant relationship between the addition of Ara-C during the consolidation phase and EFS (P = 0.192). There were 22 patients in the high-risk group, of which 8 were in the DA group and 14 were in the DNR group, of which 1 person in the DNR group relapsed, and there was also no statistically significant relationship between the addition of Ara-C during the consolidation phase and EFS (P = 0.48), and there was no difference in the effect of the use of Ara-C during the consolidation phase on the EFS of the patients in the different SANZ subgroups.

A total of 3 patients had relapses, 1 of whom died, all 3 of whom were from the DNR group (1 had a hematological relapse 29 months after MCR, another had a molecular relapse 47 months after MCR, and another had a hematological relapse 62 months after MCR). For the first case, we re-ran the entire chemotherapy course, after going through the entire course of chemotherapy, the patient again achieved molecular and hematologic remission but then relapsed again 17 months after the second CR and died.

For the second case, after we detected a molecular relapse, we performed 2 rounds of 4 weeks of oral Realgar-Indigo naturalis formula (RIF) from 50 mg/kg/d D1 to 7, 80 mg/kg/d D8–14 as the first course of treatment and 80 mg/kg/d D8–14 as the second course of treatment. In the absence of a molecular remission, we repeated consolidation therapy with Ara-C as did the treatment regimen in the third case. Re-entry of consolidation therapy with the addition of Ara-C as salvage therapy resulted in a second CR in all cases.

4. DISCUSSION

Following previous findings that ATO is the most effective drug alone in the treatment of APL and that its combination with ATRA is currently the most commonly used treatment regimen in adults, minimizing the intensity of chemotherapy. We conducted a clinical trial in 2010 to determine whether ATO in combination with ATRA was safe and effective in children and whether after 2 courses of added ATO, Ara-C could be omitted in consolidation therapy to minimize the intensity of chemotherapy.

As of 2010, the role of Ara-C in the use of the combination of ATRA and ATO for the treatment of pediatric APL had not been investigated. In 2018, our study found that there was no statistically significant difference in 5-year EFS and OS with or without the use of Ara-C,[8] it can be omitted in pediatric APL when we extended the follow-up period from 5 to 12 years, we found no statistically significant association between Ara-C and EFS in the consolidation phase.

However, 3 of the relapsed patients belonged to the DNR group, while there were no relapses in the DA group. Furthermore, the survival curves indicated a trend towards improved survival in the DA group compared to the DNR group. These findings suggest that Ara-C may reduce the

relapse rate and have a considerable impact on long-term prognosis. It is possible that the lack of significance in the consolidation phase is due to the relatively small sample size. As the sample size is increased, it may be that a beneficial effect of Ara-C on long-term prognosis will be identified. This suggests that Ara-C may have considerable implications for long-term prognosis.

In our study, no CNS or other extramedullary relapse occurred so far indicating a protective effect of Ara-C which has a high penetration property into the CNS and can pass the blood/brain barrier.[9]

In some of the studies, large doses of Ara-C were added during the consolidation and induction periods. We found a significant relationship between Ara-C and the reduction of relapse rate, the relapse rate of 11.4% after 10 years is less than half compared with the data of the literature for high-risk APL treated without HD Ara-C.[10] For some studies based on the prognosis of high-risk patients with APL such as Adès et al,[9] Sanz et al[10] reported that the risk-adapted treatment with ATRA, IDA, and Ara-C for high-risk patients significantly improved the CR.[11] These results allow us to speculate on a possible supra-additive effect of the combination of ATRA plus Ara-C that might support the improvement observed in high-risk patients.[10]

Interestingly, in vitro studies with human NB4 promyelocytic leukemia cells have showed an increased sensitivity to Ara-C after treatment with ATRA.[12] In these experiments, the combination effect was supra-additive, with the greatest cytotoxicity and potency of Ara-C administration when it was closely followed by ATRA administration.

This may suggest that when the sample size is sufficient, the application of Ara-C in the consolidation phase has a better efficacy on the long-term prognosis of patients, and Ara-C may have a strong association with the long-term survival of patients. We believe that especially for children in the high-risk group, Ara-C can be added in the induction period for tumor reduction therapy, in view of the cardiotoxicity of anthracyclines and the increased coagulation abnormalities induced by the rapid killing of leukemic cells after their application, we chose to use Ara-C for slow leukocyte depletion.

Therefore, we suggest that in the treatment of APL in children, when leukocytosis occurs during the induction phase and is difficult to control with the combination of hydroxyurea and allopurinol, Ara-C infusion can be used to reduce leukocytosis, which also has a greater statistically significant; and in the consolidation phase of the treatment, we suggest that the same chemotherapeutic regimen as the current regimen can be used, as well as the use of the combination of DNR and Ara-C and that the dosage of Ara-C can be the same as the current regimen or increased accordingly.

In the pre-ATO era, higher cumulative doses of anthracyclines have been shown to be associated with better APL outcomes.[13] However, higher cumulative doses may also lead to cardiotoxicity, especially in children.[14] In our study, the cumulative dose of anthracyclines was 420 mg/m^2. To date, no serious anthracycline-related cardiotoxicity has occurred. It should also be noted that for children with malignancies, exposure to moderate or high cumulative doses of anthracycline may increase the risk of therapy-related myelodysplastic syndromes (t-MDS) AML, the anthracycline works by inhibiting DNA topoisomerase II.[15] Thus, the cumulative dose of Anthracycline may be strongly associated with long-term outcomes and adverse events in children with APL.

Over the past few years, ATRA-ATO combination regimens have recently been shown to be more effective than ATRA-chemotherapy (ATRA-CHT) in large randomized trials in adults.[16–18] For pediatric APL patients, in 2 large randomized trials of BCH-APL2005,[19] we found that the cytotoxic effects of treatment regimens using ATO and ATRA-based regimens were lower than those of ATRA-CHT, and that ATO in combination with ATRA was no less effective than that of ATRA-CHT, and even superior to that of ATRA-CHT in long-term follow-up. Standard-risk pediatric APL patients tolerate ATRA and ATO therapy well.[20,21] As for high-risk groups, although there are fewer reports on the effect of Ara-C use on long-term survival in children, a recent study has shown the role of Ara-C in pediatric APL. This study indicated that Ara-C significantly improved the long-term EFS of pediatric HR-APL. The 8-year EFS was >96% and was comparable to that of NHR-APL treated without Ara-C. The study strongly suggests that Ara-C may have beneficial effects only in pediatric HR-APL,[22] which is consistent with our finding.

It is noteworthy that there were no early deaths in our study. Four (6.1%) patients with intracranial hemorrhage were admitted to our hospital and none died. Early recognition of APL, timely administration of ATRA/ATO, aggressive supportive therapy, proactive intervention in the management of high leukocytes and complications and the limitation of anthracyclines were employed may explain this result.[23]

In conclusion, our findings suggest that ATRA-ATO combination therapy is beneficial, and we also recommend the addition of Ara-C during the consolidation period, which may has a more positive impact on the late prognosis of patients. In addition, whether increased use of ATO helps to further improve prognosis also requires further study.

4.1. Restriction

In our China children with APL study 2010 (CCAPL2010) trial, it is still not known whether it is feasible to omit chemotherapy during treatment, so there is a risk of overtreatment with this regimen in low-risk APL patients. In addition, appropriate treatments for children with high-risk APL require further research.

The incidence of pediatric APL as a proportion of APL overall is inherently small and the incidence of pediatric APL in AML is low. We included all patients admitted for treatment between 2010 and 2016 in the protocol and only collected 65 cases due to the low prevalence of APL in children and the design of a single-center study at the outset of the experimental design. A multicenter prospective study will be considered for future investigation of the role of Ara-C in long-term prognosis. The method of increasing the equal proportion of cases to 2-fold does not guarantee positive statistical significance and direct correlation of the results.

ACKNOWLEDGMENTS

The project was supported in part by the National Key Research and Development Program of China (2021YFE0106900), the CAMS Innovation Fund for Medical Sciences (CIFMS 2022-I2M-1-022; 2021-I2M-1-041), the National Natural Science Foundation of China (82270144), and the Haihe Laboratory of Cell Ecosystem Innovation Fund (22HHXBSS00039).

We thank all of the patients who participated in this study and all of the participants and research staff in our hospital. We thank the AIYOU and SHENHUA foundations for their financial support for our study of leukemia in children. We thank Lynne Hyman (AJE Research Communication Partner) for her professional writing services.

AUTHOR CONTRIBUTIONS

L.Z. and X.Z. designed the clinical trial. W.Y., Y.Z., Y.G., Y.C., and X.C. executed the research and collected the data. Y.Z., C.X., and C.W. analyzed the data, drafted the original manuscript, and contributed to the statistical analysis. All authors reviewed and approved the final version of this manuscript. Y.Z. and C.X. contributed equally to this article.

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