

Retrospective analysis of 119 cases of pediatric acute promyelocytic leukemia: Comparisons of four treatment regimes

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Abstract. Clinical trials have demonstrated that pediatric acute promyelocytic leukemia (APL) is highly curable. Small-scale studies have reported on the treatment of APL using one or two treatment regimes. Here, we report a multiple center-based study of 119 cases of pediatric APL treated with four regimes based on all-*trans*-retinoic acid (ATRA). We retrospectively analyzed the clinical characteristics, laboratorial test results and treatment outcome of the pediatric APL patients. Regime 1 used an in-house developed protocol, regime 2 was modified from the PETHEMA LPA99 protocol, regime 3 was modified from the European-APL93 protocol, and regime 4 used a protocol suggested by the British Committee for Standards in Haematology. The overall complete remission rates for the four regimes were 88.9, 87.5, 97.1 and 87.5%, respectively, which exhibited no statistical difference. However, more favorable results were observed for regimes 2 and 3 than regimes 1 and 4, in terms of the estimated 3.5-year disease-free survivals, relapse rates, drug toxicity (including hepatotoxicity, cardiac

arrhythmia, and differentiation syndrome) and sepsis. In conclusion, the overall outcomes were more favorable after treatment with regimes 2 and 3 than with regimes 1 and 4, and this may have been due to the specific compositions of regimes 2 and 3.

Introduction

Acute myeloid leukemia (AML) accounts for approximately 20% of acute leukemia cases in children (1). Acute promyelocytic leukemia (APL) is morphologically identified as AML-M3 according to the French-American-British (FAB) classification. APL represents 5-8% of AML cases in children (2). It is characterized by accumulation of immature granulocytes called promyelocytes, which feature bilobulated nuclei and Auer rods (3). Cytogenetically, APL promyelocytes carry a balanced reciprocal translocation between chromosomes 15 and 17, t(15;17), which results in a fusion protein PML/RAR α encoded by the promyelocytic leukemia (*PML*) gene fused with the gene for retinoic acid receptor α (RAR α) (4). Immunophenotypically, APL promyelocytes express CD33, CD13 and CD117 antigens, and less frequently CD34 and human leukocyte antigen DR (5). Five decades ago APL was considered the most fatal type of acute leukemia and the treatment of APL was a nightmare for physicians; event-free survival (EFS) of APL patients including children was only 35% (6).

Due to the development of various combinations of chemotherapy based on all-*trans*-retinoic acid (ATRA) and anthracycline, the 5-year disease-free survival (DFS) or EFS rate of pediatric APL patients has reached 75-80% based on recent studies (7-17). Thus, APL is now curable in most cases. Recently a study on childhood AML in Japan reported a 93.1% overall survival (OS) rate and 94% EFS rate for patients

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treated with ATRA, anthracyclines and cytarabine (at both the induction and consolidation stages) (16). Despite of the reported high survival rate, the outcome of APL treatment in many developing countries including China appears to vary dramatically, largely depending on how the therapeutic regimes are designed and delivered (14,18). A study based in Taiwan reported that the overall survival and EFS of 6 APL children treated with ATRA during induction were 83 and 67%, respectively (19). Zhang *et al* (20) reported that 65 Chinese APL children had better outcome with EFS, DFS, and overall survival achieved 77.5, 85.4 and 88.9%, respectively. However, another study found that the EFS of 16 APL children treated with an in-house protocol and 14 with a modified PETHEMA LPA99 protocol were 38 and 79.6%, respectively (12). Such large variations prompted us to identify which components included in the widely used regimes play a pivotal role in prognosis of the disease. Here, we conducted a retrospective, multiple center-based study on 119 cases of pediatric APL following treatment with four different chemotherapy regimes based on ATRA. We found that the overall outcomes were more favorable after treatment with regimes 2 and 3 than with regimes 1 and 4, and this added benefit may have been due to the presence of a Chinese herbal medicine formula, Realgar-Indigo naturalis formula (RIF), and the absence of high-dose cytarabine (Ara-C) in regimes 2 and 3.

Materials and methods

Eligibility of patients. Informed consents were obtained from the parents or guardians of the children (under the age of 18) diagnosed with APL who were enrolled at the Departments of Pediatrics, in the leukemia wards of six collaborative hospitals in China from September 1997 to December 2008. The diagnosis was based on the FAB classification, detection of the PML/RAR α fusion gene by RT-PCT or fluorescent *in situ* hybridization (FISH), and detection of t(15;17) in bone marrow cells aspirated from the patients, as well as the morphology of the cells. Following the eligibility screening, 119 cases were retrospectively enrolled in this study. The patients were divided into four groups based on the therapeutic regimes received, with 36, 16, 35 and 32 patients in regimes 1-4, respectively as described below.

Treatment. The therapeutic regimes consisted of multi-stage treatments including induction and consolidation (for all 4 regimes), maintenance (for regimes 2, 3 and 4), and reinforcement (for regime 3 only) (Fig. 1). Regime 1 used a protocol developed in-house including ATRA, daunomycin (DNR), Novantrone (NVT), and high-dose Ara-C (2 g/m², IV). Regime 2 used a modified PETHEMA LPA99 protocol including ATRA, methotrexate (MTX), NVT, DNR, and RIF. Regime 3 used a modified European-APL93 protocol including ATRA, RIF, DNR, NVT, DA [DNR plus low-dose Ara-C (150 mg/m², IV)], NA [NVT plus low-dose Ara-C (150 mg/m², IV)] and 6-mercaptopurine (6MP). Regime 4 used a protocol suggested by the British Committee for Standards in Haematology, including ATRA, DNR, and Ara-C [at a low-dose (200 mg/m², IV) and high dose (2 g/m², IV) alternatively at various stages]. The details of the regimes are shown in Fig. 1.

Supportive therapy. Supportive therapy was provided to almost all of the patients, which was crucial to prevent the development of serious or even fatal complications such as coagulopathy and retinoic acid syndrome. Counter-coagulopathy therapy included transfusions of platelets, plasma, and cryoprecipitate to maintain the fibrinogen level above 1.5 g/l and the platelet count above 3x10¹⁰/l until clinical resolution of coagulopathy (21). Retinoic acid syndrome is another complication characterized by dyspnea, unexplained fever, weight gain, peripheral edema, pulmonary nodular infiltrates and pleuropericardial effusion. It develops rapidly and is potentially fatal. Upon observation of the earliest signs of retinoic acid syndrome, treatment with high-dose steroids was initiated immediately by administering dexamethasone at 0.3 mg/kg/dose twice daily intravenously for at least 4 days to the children (22). In addition, hydroxyurea was administered to control leukocytosis when required.

Definitions. Complete remission (CR) was defined according to the US National Cancer Institute criteria as the presence of less than 5% of blast cells in bone marrow aspirates (23). DFS refers to the duration from the date of diagnosis until the date of the last follow-up for any event, e.g., failure to achieve remission, relapse, secondary malignancy, or death from any cause. The DFS was calculated based on time from the date of hematologic CR until death or hematologic relapse.

Statistical methods. The relationship of a patient's clinical characteristics to his/her treatment outcome was analyzed using the Cox Regression Proportional Hazard Model. Multivariate analysis was used. Clinical, demographic, biologic characteristics, treatment outcomes, and toxicity of the patients were compared using χ^2 tests, Fisher exact tests, and one-way ANOVA. DFS of the four regimes was further analyzed using the Kaplan-Meier method, and the log-rank test was used for comparison between different treatment groups. Survival rates were represented as the mean percentage \pm standard error (SE). Statistical differences were considered significant at a P-value (2-sided) <0.05 or highly significant at a P-value (2-sided) <0.01.

Results

Clinical characteristics and laboratory test results of the patients. The 119 patients included 80 males and 39 females. Data were retrieved for a median follow-up time of 43 months (ranging from 1 to 147 months). Approximately half of the patients were from rural areas. The median age of the patients was 8.9 years, and 3.4% of the patients were under the age of 2. Paleness, hemorrhage, and organomegalies were present in 90.8, 74.6 and 35.5% of the patients, respectively. Fever was found in 63.8% of the patients, and bone pain was experienced by 22.7% of the patients.

Laboratorial test results of the 119 patients indicated that the median white blood cell (WBC) count was 8.79x10⁹/l (range, 0.9x10⁹/l to 191x10⁹/l), the median hemoglobin level was 71 g/dl (range, 25-117 g/dl), and the median platelet number was 28x10⁹/l (range, 4x10⁹/l to 344x10⁹/l). Elevated lactic dehydrogenase (LDH) (>450 U/l) was present in 34 of 106 tested patients, of whom 5.7% (6/106) had LDH levels over 1,000 U/l. The immunophenotyping for CD13, CD33 and

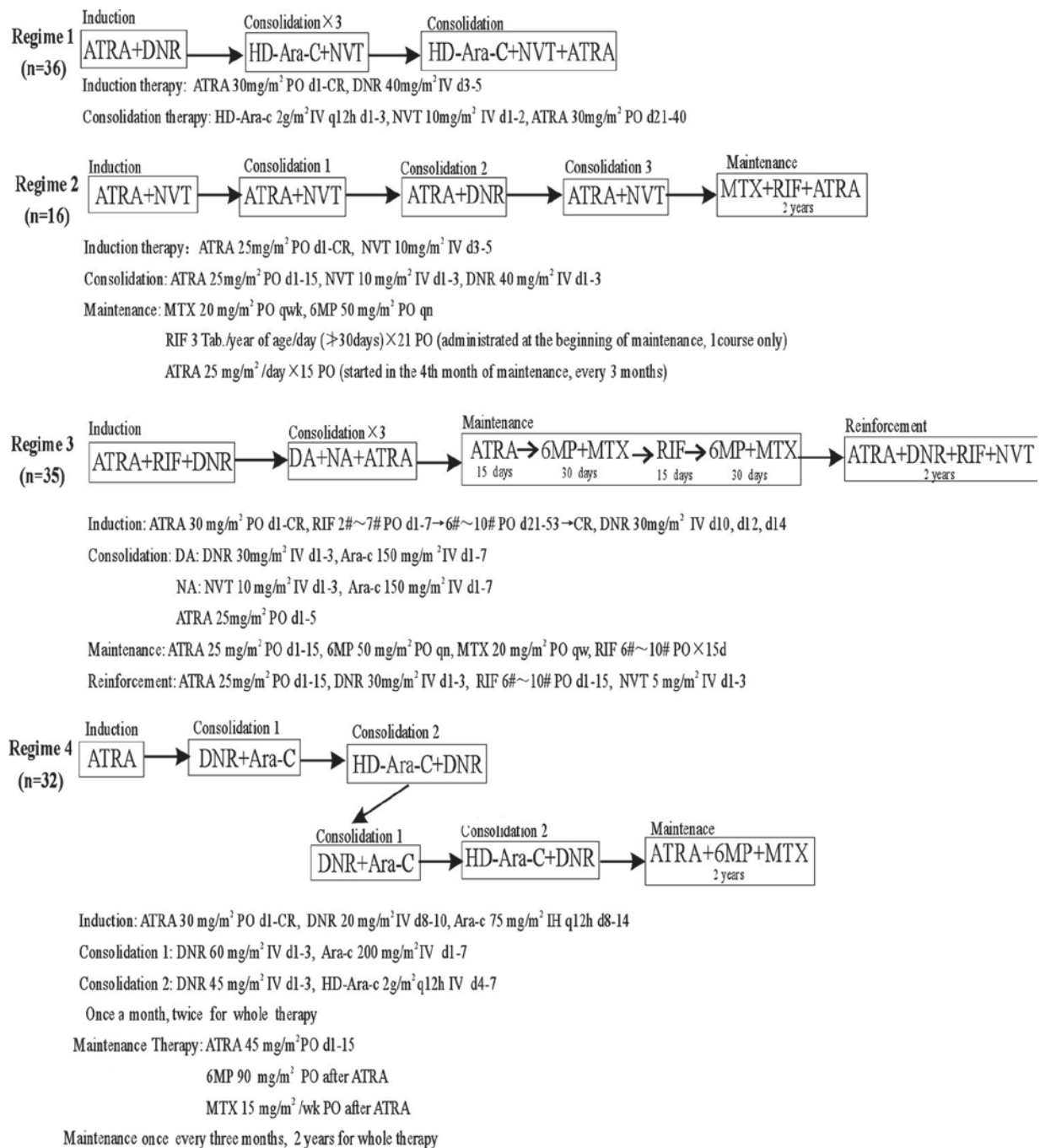


Figure 1. Therapeutic regimens and patient groups included in the study. Ara-C, cytarabine; ATRA, all-*trans*-retinoic acid; DNR, daunomycin; HD, high-dose; DA (DNR and Ara-C); MTX, methotrexate; NVT, Novantrone; 6MP, 6-mercaptopurine; NA (NVT and Ara-C); RIF, Realgar-Indigo naturalis formula; PO, *per os*; IV, intravenously; d, day; wk, week; q12h, every 12 hours; qwk, every week; qn, every night; Tab./#, tablets; IH, hypodermic injection.

MPO was carried out on 91 of the 119 patients, and the rates of positive specimens were 98.3, 97.2 and 87% for the three antigens, respectively. Our data demonstrated no significant difference between the four regimens in terms of age, gender, WBC count, hemoglobin level, platelet count, and LDH level of the patients tested before the treatment (Table I).

Treatment outcome. After the remission induction, the CR rate for the four regimens was 88.9 (32/36), 87.5 (14/16), 97.1 (34/35) and 87.5% (28/32), respectively, without statistical difference between the regimens. The 3.5-year DFS for the

four treatment regimens was 72.2±8.6, 87.5±8.3, 93.6±4.4 and 64.6±13%, respectively, with the DFS for regime 2 statistically higher than that for regime 1 ($P<0.05$), and DFS for regime 3 statistically higher than those for regimes 1 ($P<0.01$) and 4 ($P<0.01$) (Table II and Fig. 2). The relapse rate for the 4 regimens was 25, 6.3, 5.7 and 28.1%, respectively, with a statistically significant difference detected between regimes 1 and 2 ($P<0.05$), and between regimes 3 and 4 ($P<0.05$) (Table II and Fig. 2). Although all four regimens resulted in high CR rates, regimes 1 and 4 were associated with lower DFS and higher relapse rates than regimes 2 and 3. Thus, it appears that

Table I. Clinical characteristics and laboratory results at diagnosis of the APL patients classified into the four treatment groups.

Characteristics	Regime 1	Regime 2	Regime 3	Regime 4	P-value
Age, years, median (range)	7.7 (1.6-12.4)	8.2 (2.2-17.5)	8.7 (0.5-14.6)	10 (2.2-14.9)	0.196
Male/female (n)	26/10	9/7	22/13	20/12	0.065
WBC, 10 ⁹ /l, range (median)	1.2-127.5 (3)	1.1-143.4 (7.7)	0.2-145.7 (11.1)	1.9-191 (32.3)	0.055
Hb, g/l, range (median)	25-116 (70)	38-98 (76)	32-117 (72)	34-128 (71)	0.500
Platelet, 10 ⁹ /l, range (median)	4-344 (29)	7-190 (30)	8-164 (26)	9-146 (40)	0.984
LDH, U/l, range (median)	153-1,314 (245)	120-1,561 (357)	28-1,470 (283)	15-1,995 (314)	0.607

WBC, white blood cells; Hb, hemoglobin; LDH, lactate dehydrogenase.

Table II. Outcome of the patients following treatment with the four different regimes.

Treatment outcome	Regimes				P-value	
	1	2	3	4	<0.05	<0.01
Number of cases	36	16	35	32		
Complete response, n (%)	32 (88.9)	14 (87.5)	34 (97.1)	28 (87.5)		
Relapse, n (%)	9 (25.0)	1 (6.3)	2 (5.7)	9 (28.1)	1/3, 3/4	
3.5-year DFS, %	72.2±8.6	87.5±8.3	93.6±4.4	64.6±13	1/2	1/3, 3/4
Toxicity, n (%)						
Hepatotoxicity	22 (61.1)	3 (18.8)	7 (20.0)	15 (46.9)	2/4, 3/4	1/2, 1/3
Headache	4 (11.1)	2 (12.5)	4 (11.4)	5 (15.6)		
Skin reaction	7 (19.4)	3 (18.8)	8 (22.9)	7 (21.9)		
Dryness of lips	13 (36.1)	4 (25.0)	13 (37.1)	11 (34.4)		
Fluid retention	3 (8.3)	2 (12.5)	10 (28.6)	3 (9.4)	1/3, 3/4	
Cardiac arrhythmia	2 (5.6)	0	0	6 (18.8)	1/4, 2/4	3/4
Differentiation syndrome	0	0	0	4 (12.5)	1/2, 2/4	3/4
Sepsis	25 (69.4)	3 (18.8)	6 (17.1)	20 (62.5)		1/2, 1/3, 2/4, 3/4

Values are expressed as the number of cases (percentage of total case number treated with the regime). DFS, disease-free survival.

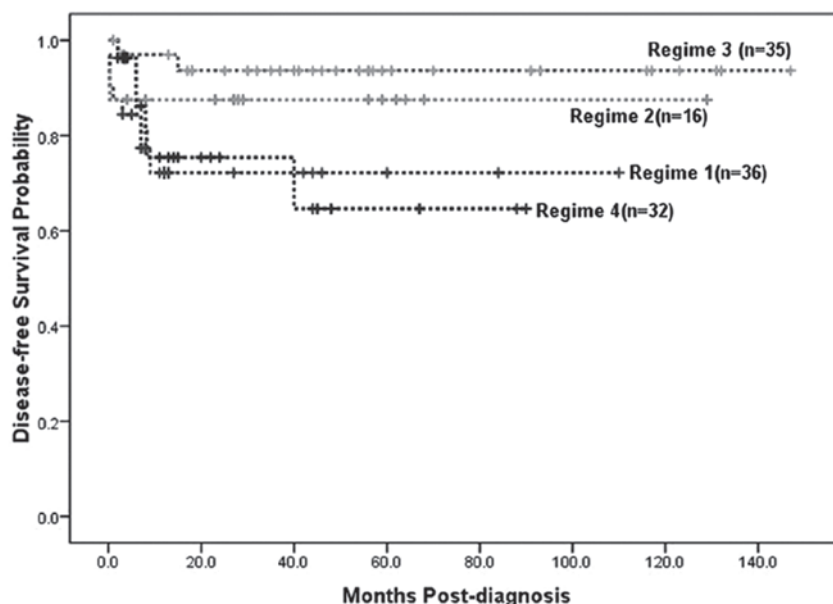


Figure 2. Disease-free survival of the APL patients treated with the four different regimes. Data were analyzed using the Kaplan-Meier survival calculation method. Vertical crossing lines indicate censors taken during the follow-up times.

the overall outcome for regimes 2 and 3 was more favorable than that for regimes 1 and 4.

Toxicity. The occurrence of hepatotoxicity, headache, skin reaction, dryness of lips, fluid retention, cardiac arrhythmia, differentiation syndrome, and sepsis was recorded for all the patients during all the therapeutic stages (Table II). Of note, hepatotoxicity and sepsis occurred statistically more frequently in regimes 1 and 4 than in regimes 2 and 3. Fluid retention was observed more with regime 3 than with regimes 1 and 4. Cardiac arrhythmia occurred more with regimes 1 and 4 than regimes 2 and 3. Differentiation syndrome occurred only in regime 4. Based on the above findings, the incidence of general toxicity and sepsis was lower for treatment regimes 2 and 3 than with regimes 1 and 4.

Discussion

In the present study, data was collected and analyzed regarding the clinical characteristics, laboratory test results and treatment outcome of 119 cases of pediatric APL treated with four different chemotherapy regimes. Similar to previous reports (7-9), the WBC counts of 47% of the patients were higher than $10 \times 10^9/L$. High WBC counts combined with or without low platelet counts have been considered as indices of relapse risk (9,17,24). However, we found that the WBC and platelet counts and hemoglobin and LDH levels, tested before treatment, had no significant influence on prognosis of the pediatric APL patients (data not shown). Instead, the various therapeutic regimes imposed significantly different impacts on the outcomes of the patients.

Regimes 1-4 resulted in a CR rate of 88.9, 87.5, 97.1 and 87.5%, respectively, a 3.5-year DFS rate of 72.2, 87.5, 93.6 and 64.6%, respectively, and a relapse rate of 25, 6.3, 5.7 and 28.1%, respectively. Although all four regimes led to high CR rates, regimes 1 and 4 resulted in lower DFS and higher relapse than regimes 2 and 3. Therefore, the overall outcome for regimes 2 and 3 was more favorable than regimes 1 and 4.

It does not appear that the comparably short treatment without maintenance for regime-1 patients was accountable for their poor survival, as the regime-4 patients had maintenance treatment, yet both their CR and 3.5-year DFS rates were the lowest. Therefore, these different outcomes might have mainly resulted from the different components in the regimes. Although all four regimes included ATRA and DNR, plus other various chemotherapeutic agents, regimes 2 and 3 had two obvious features. They included the Chinese herbal medicine formula RIF, and no Ara-C (regime 2) or only low-dose (150 mg/m^2) Ara-C (regime 3). In contrast, Ara-C was used at a high dose (2 g/m^2) during all the consolidation treatments in regime 1, and at low doses (30 or 45 mg/m^2) in two of the consolidation treatments and intermediate (300 mg/m^2) and high (2 g/m^2) doses, respectively, in the other two consolidation treatments in regime 4. It appears that the use of the Chinese herbal medicine formula RIF and avoidance of the high-dose Ara-C may have reduced the treatment-related toxicity, relapse rate, and the frequency of sepsis, hence contributing to the optimal outcome of the patients treated with regimes 2 and 3.

Traditional Chinese medicine (TCM) is a unique medical system used for thousands of years by the Chinese and other

ethnic populations in China as well as many other countries. TCM doctors usually prescribe a combination of plant species or minerals to treat diseases (25,26). Increasing evidence has demonstrated that TCM can be used as alternative medicine to treat diseases that have no cure using conventional medicine, or as supportive medicine to enhance therapeutic efficacy and reduce adverse effects of conventional medicine such as chemotherapy. RIF contains realgar, indigo naturalis, tetra-arsenic tetrasulfide, indirubin and tanshinone IIA as its major active ingredients.

Wang *et al* (27) reported that RIF, when used in a murine APL model, promoted ubiquitination and degradation of the PML/RAR α oncoprotein by inducing expression and transportation of aquaglyceroporin-9 which degraded PML/RAR α . It also enhanced G1/G0 arrest of APL cells by regulating multiple targets of the cell cycle. Notably, recent multi-center clinical trials showed that a CR rate of 98% and a 5-year overall survival rate of 87% were achieved in adult APL patients receiving RIF, with only moderate adverse effects such as gastrointestinal discomfort and rash (25,26,28). Furthermore, Luo *et al* (12) reported that a modified PETHEMA LPA99 protocol by including RIF had an improved overall outcome for 13 Chinese children with APL. These lines of evidence are consistent with the added beneficial effect of including RIF in regimes 2 and 3 in the present study (Table I and Fig. 2). In addition, compared to arsenic trioxide, a widely used anti-leukemia drug analogous to tetra-arsenic tetrasulfide, RIF is relatively inexpensive, can be taken orally and shortens the hospital stay of patients (29).

Ara-C is an anti-metabolite chemotherapeutic drug, which acts by impeding cancer cells from making and repairing DNA required for cell proliferation. Ara-C has been used to treat acute leukemia, several types of head and neck cancers, and non-Hodgkin's lymphoma. In induction or consolidation treatment for AML, high doses of either DNR or Ara-C often result in improved remission and survival rates (30-33). However, among these studies, only Weick *et al* (33) compared two doses of Ara-C, 1,400 and 24,000 mg/m^2 , for induction chemotherapy, and found no difference in overall survival rate of the patients.

The dose of Ara-C used during consolidation has also been extensively explored in single-arm trials. Mayer *et al* (34) reported a large, randomized study of 596 patients with AML in first remission, which suggested a dose-response relationship with Ara-C. Patients who received the dose of 3,000 mg/m^2 had an improved disease-free and overall survival, especially for those who were under 60 years of age. However, an important finding of this study is that high-dose Ara-C was effective only in patients who had 'favorable', 'intermediate' or normal karyotypes upon treatment (34). As our patients all had abnormal karyotypes by the nature of the disease, high (2 g/m^2) doses of Ara-C used in the regimes may not have helped, but instead counteracted, the outcome of the young patients. One of the serious side effects of Ara-C, like many other chemotherapeutics, is increased risk of fatal infection due to reduced WBC count, which might have contributed to the short 3.5-year EFS and CR rate of the patients on regimes 1 and 4.

Overall, our present study, the largest scale study to date concerning pediatric APL in China to our knowledge, has

revealed important information for the treatment of pediatric APL. We found that the modified PETHEMA LPA99 protocol (for the regime 2) and the modified European ALP93 protocol (regime 3), both including RIF and the absence of high-dose Ara-C, achieved a more favorable overall outcome, less chemotherapy treatment-related toxicity, and lower frequency of sepsis and relapse for APL children, than the in-house protocol (regime 1) and the protocol suggested by the British Committee for Standards in Haematology (regime 4). The inclusion of RIF and exclusion of high-dose Ara-C may have contributed to the beneficial effects of regimes 2 and 3 on the prognosis of pediatric APL cases.

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