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ORIGINAL RESEARCH

Highly Curative Treatment of High-Risk Acute Promyelocytic Leukemia: Induction and Consolidation with ATRA+ATO+anthracyclines and Maintenance with ATRA+RIF

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Background: The aim of the study was to evaluate the efficacy and safety of induction and consolidation with all-trans retinoic acid (ATRA) +arsenic trioxide (ATO) +anthracyclines and maintenance with ATRA +Realgar-*Indigo naturalis* formula (RIF) for high-risk APL.

Methods: Twenty-one patients with high-risk APL treated with ATRA+ATO+ anthracyclines for induction and consolidation and ATRA+RIF for maintenance from 2012 to 2021 were analyzed. Endpoints include morphological complete remission (CR) and complete molecular remission (CMR), early death (ED) and relapse, survival and adverse events (AEs).

Results: After induction treatment, all 21 patients (100%) achieved morphological CR and 14 people (66.7%) achieved CMR. Five of the 21 patients did not undergo immunological minimal residual disease (MRD) examination after induction; however, 14 of the remaining 16 patients were MRD negative (87.5%). The median time to achieve CR and CMR was 26 days (range: 16–44) and 40 days (range: 22–75), respectively. The cumulative probability of achieving CR and CMR in 45 days was 100% and 76.2% (95% CI: 56.9–91.3%), respectively. All patients achieved CMR and MRD negativity after the three courses of consolidation treatment. The median follow-up was 66 months (25–142), with no central nervous system relapse and bone marrow morphological or molecular relapse until now, and all patients survived with 100% overall survival and 100% event-free survival. Grade 4 adverse events (AEs) were observed in 3 patients (14.3%) during the induction period including arrhythmia (n = 1), pulmonary infection (n = 1) and respiratory failure (n = 1); and the most frequent grade 3 AEs were pulmonary infection, accounting for 62.0% and 28.6%, respectively, during induction and consolidation treatment, followed by neutropenia, accounting for 42.9% and 38.1%, respectively.

Conclusion: For newly diagnosed high-risk APL patients, induction and consolidation with ATRA+ATO+anthracyclines and maintenance with ATRA+RIF is a highly curative treatment approach.

Keywords: high-risk acute promyelocytic leukemia, all-trans retinoic acid, arsenic trioxide, realgar–*Indigo naturalis* formula, anthracyclines, event-free survival

Introduction

In the era dominated by all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) treatments, acute promyelocytic leukemia (APL) has become one of the most curable forms of acute leukemia. For low- or intermediate-risk APL patients, the standard treatment regimen is now ATRA combined with ATO without chemotherapy (chemotherapy-free), boasting a cure rate close to 95%.[1] However, some unresolved issues existed for the treatment of high-risk APL patients. First, the long-term outcome of high-risk APL patients remains a challenge, especially in real-world clinical settings,

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where the early death rate is between 38% and 50% and the relapse rate is between 21.0% and 34.2%.[2,3] Second, while ATRA+ATO+ anthracyclines as the standard induction treatment have achieved high morphological and molecular complete remission (CR) rates,[4–7] however, the role of this regimen in the consolidation phase has not been fully demonstrated. Third, the effectiveness of maintenance treatment of ATRA+ Realgar-*Indigo naturalis* formula (RIF) in low- or intermediate-risk patients has been reported as extremely curative,[8,9] however, it is not verified in high-risk patients. In order to solve the above issues, we hypothesized that ATRA+ATO+anthracyclines consolidation and ATRA+ RIF maintenance could reverse the poor prognosis of patients with high- risk APL. In this real-world clinical study, we observed the long-term follow-up of 21 patients of high-risk APL received induction and consolidation with ATRA+ATO + anthracyclines and maintenance with ATRA+ RIF, mainly observing morphological and molecular CR, early death (ED) and relapse, survival and adverse events (AEs).

Methods

Patients

We analyzed 21 consecutive high-risk APL patients treated from 2012 to 2021 at the First Affiliated Hospital of University of Science and Technology of China, using an ATRA+ATO+anthracyclines regimen for induction and consolidation, followed by ATRA+RIF for maintenance. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of University of Science and Technology of China (approval number: 2022-RE-457) and was conducted in accordance with the Declaration of Helsinki; the written informed consent was waived due to the retrospective nature of the review.

Treatment

Induction therapy commenced immediately upon strong suspicion of APL with ATRA (35–45 mg/m²/day in divided doses) and, upon confirmation, idarubicin (IDA) (8–12 mg/m²/day) or daunorubicin (DNR) (45–60 mg/m²/day) for 3–4 days, and ATO (0.16 mg/kg/day) until CR was achieved.

If the patient achieved morphological CR, then followed by three courses of consolidation treatment with ATRA (35~45 mg/m^2/day in divided doses) combined with ATO (0.16 mg/kg/day) for 14 days and IDA (8~12 mg/m^2/day) or DNR (45~60 mg/m^2/day) for 3 days. The dose of ATRA and anthracycline can be appropriately reduced in patients who are older or in poorer physical conditions to avoid severe adverse events. Maintenance treatment consisted of ATRA (25~35mg/m^2/day in divided doses) 15 days on and 15 days off in the first month, RIF (60 mg/kg/day) 15 days on and 15 days off in the second month, and then RIF (60 mg/kg/day) 15 days on and 15 days off in the third month, for a total of 8 cycles with a maintenance period of 24 months. The treatment schema is shown in Figure 1A.

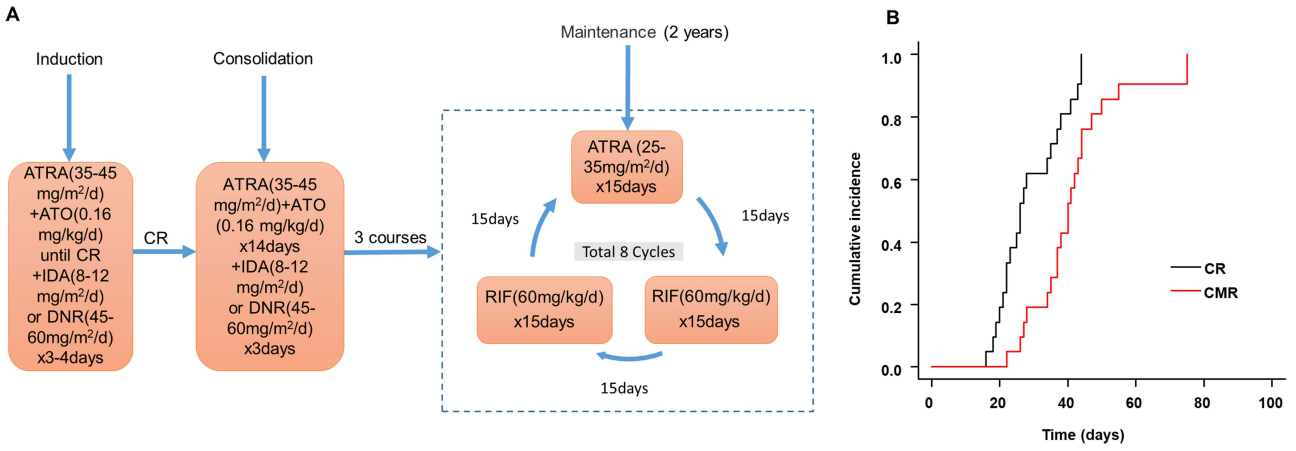

Figure 1 Treatment schema and complete remission. Treatment schema for High-risk acute promyelocytic leukemia (**A**), and the cumulative incidence rate of morphological complete remission and complete molecular remission (**B**).

Abbreviations: ATRA, all-trans retinoic acid; ATO, arsenic trioxide; IDA, idarubicin; DNR, daunorubicin; RIF, Realgar–*Indigo naturalis* formula; CR, complete response; CMR, complete molecular remission.

During induction treatment, patient's blood routine, coagulation, liver and kidney functions, electrolytes and electrocardiogram were closely monitored, and blood products such as platelets, fibrinogen, cryoprecipitate, frozen plasma, and red blood cells were actively transfused. When a patient is highly suspected or diagnosed with differentiation syndrome (DS), dexamethasone (10 mg twice a day) is given promptly, and ATRA is administered in reduced doses or stopped until signs and symptoms disappear. ATO is discontinued if QTc interval >470 ms until the QTc interval returned to normal. Cytarabine 50 mg and dexamethasone 5 mg with or without methotrexate (MTX) 10 mg were intrathecally administrated during each consolidation course to prevent central nervous system (CNS) recurrence. Bone marrow examination was performed after induction and before the second and third consolidation courses, and every 3 months in maintenance phase, and every 6 months after maintenance.

Definitions and Statistical Analysis

Early death was defined as death from any cause occurring within 30 days after the diagnosis of APL. Diagnosis of DS follows Montesinos standards.[10] CR, overall survival (OS) and event-free survival (EFS) have been defined as before.[11] Complete molecular remission (CMR) was defined as being negative for PML-RARa by quantitative reverse-transcription PCR (qRT-PCR). Minimal residual disease (MRD) was detected by leukemia-related immunophenotypic methods, and MRD negativity was defined as less than 0.01% blasts in bone marrow using eight-color flow cytometry. The probability of OS and EFS is estimated according to Kaplan–Meier curve. The cumulative incidence function was used to estimate the probability of reaching CR and CMR. The statistical analysis is carried out using R statistical software.

Results

Clinical Characteristics

Clinical characteristics and laboratory tests are shown in Table 1. Our study analyzed twenty-one patients diagnosed with high-risk APL, including 14 males (66.7%). The median age was 36 years (range: 17–64). The Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score was based on the physical fitness status at the time of admission, with 16 patients (76.2%) scoring 0–1 and 5 patients (23.8%) scoring 2. Bleeding was the primary presentation on admission in 11 patients (52.4%), and gingival bleeding and skin petechiae were common. The median initial white blood cell count was 28.17×10^9/L (range: 10.62–135.87). The median initial platelets and fibrinogen were 24×10^9/L (range: 4–67) and 1.50 g/L (range: 0.50–2.71), respectively, and the median platelet and fibrinogen transfusion were 7U (range: 2–18) and 3 g (range: 0–32), respectively. By bone marrow aspiration, the patient's median initial bone marrow blasts and PML-RARA/ABL percentage were 88.5% (range: 62.5–97.5) and 22.73% (range: 2.90–47.54), respectively. Among the 21 patients, the t(15;17) was found in 11 cases (52.4%), t(15;17) plus other cytogenetic abnormalities in 2 cases (9.5%), cytogenetic normal in 4 cases (19.0%), and the remaining 2 cases (9.5%) were undetermined and 2 cases (9.5%) had unknown results. After induction treatment, 21 patients (100%) achieved morphological CR; qRT-PCR was conducted in

Table 1 Clinical Characteristics

Characteristic	Value
Median age, years (range)	36 (17–64)
Age ≥ 60 years, No. (%)	2 (9.5)
Sex, No. (%)	
Male	14 (66.7)
Female	7 (33.3)
Median BSA, m2 (range)	1.81 (1.53–2.13)
ECOG-PS, No. (%)	
0–1	16 (76.2)
2	5 (23.8)

(*Continued*)

Table 1 (Continued).

Characteristic	Value
Pre-treatment	
Initial bleeding symptoms, No. (%)	11 (52.4)
Median white blood cell, $\times 10^9$ /L (range)	28.17 (10.62–135.87)
Median platelet, $\times 10^9$ /L (range)	24 (4–67)
Fibrinogen level, g/L (range)	1.50 (0.50–2.71)
Hemoglobin level, g/dl (range)	70 (43–150)
Median AST, IU/L (range)	26 (10–328)
Median ALT, IU/L (range)	26 (5–182)
Baseline QTc interval, ms (range)	350 (304–394)
Peripheral blood blasts, % (range)	91 (1–96)
Bone marrow blasts, % (range)	88.5 (62.5–97.5)
PML-RARA/ABL, % (range)	22.73 (2.90–47.54)
Cytogenetics, No. (%)	
t (15;17)	11 (52.4)
t (15;17) plus other cytogenetic abnormalities	2 (9.5)
Normal	4 (19.0)
Undetermined	2 (9.5)
Unknown	2 (9.5)
Induction treatment	
Platelet transfusion (U)	7 (2–18)
Fibrinogen transfusion (G)	3 (0–32)
Red blood transfusion (U)	5.5 (0–12.5)
Peak QTc interval, ms (range)	400 (358–476)
Morphological CR, No. (%)	21 (100.0)
Median Time from diagnosis to CR, days (range)	26 (16–44)
PML-RARA/ABL negative, No. (%)	14 (66.7)
Median Time from diagnosis to CMR, days (range)	40 (22–75)
Immunological MRD negative, No. (%)	14/16 (87.5)
Post-remission follow-up	
Molecular relapse, No. (%)	0 (0)
CNS relapse, No. (%)	0 (0)
Overall survival (OS), No. (%)	21 (100.0)
Event-free survival (EFS), No. (%)	21 (100.0)
Follow-up among survivors in months, median (range)	66 (25–142)

Abbreviations: BSA, body surface area; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; AST, aspartate aminotransferase; ALT, alanine aminotransferase; QTc, corrected QT interval; CR, complete remission; CMR: complete molecular remission; MRD, minimum residual disease; CNS; central nervous system.

all 21 patients and 14 people (66.7%) achieved CMR. Five of the 21 patients did not undergo immunological MRD examination after induction; however, 14 of the remaining 16 patients were MRD negative (87.5%). The median time to achieve CR and CMR was 26 days (range: 16–44) and 40 days (range: 22–75), respectively. The cumulative probability of achieving CR and CMR in 45 days was 100% and 76.2% (95% CI: 56.9–91.3%), respectively (Figure 1B). All patients achieved CMR and MRD negativity after the three courses of consolidation treatment. The median follow-up was 66 months (25–142), and there are no CNS relapse and bone marrow morphological or molecular relapse until now, and all patients survived with 100% OS and 100% EFS.

Adverse Events

Toxic reactions were graded according to the National Cancer Institute's universal toxicity criteria, and treatment-related AEs during induction and consolidation therapy are shown in Supplementary Table 1. Grade 4 AEs were observed in 3

patients (14.3%) during the induction period including arrhythmia (n = 1), pulmonary infection (n = 1) and respiratory failure (n = 1). The most frequent grade 3 AEs were pulmonary infection, accounting for 62.0% and 28.6%, respectively, during induction and consolidation treatment, followed by neutropenia, accounting for 42.9% and 38.1%, respectively. Two cases (9.5%) had grade 3 bleeding events, manifested as hematemesis, occurred during induction treatment. DS occurred in 5 cases (23.8%), and the details are shown in Supplementary Table 2. Treatment-related liver damage was only grade 1–2 and observed in 10 patients (7 patients in induction and 3 patients in consolidation period). Throughout the maintenance phase, patients received outpatient care, with no AEs above Grade 2 reported.

Discussion

The induction treatment with ATRA combined with anthracyclines and ATO, a combination of all three drugs, was the basis for patients to obtain morphological CR. Initially, the application of ATRA 35~45 mg/m^2 can improve the coagulation function of APL patients as soon as possible and reduce the early death caused by fatal bleeding. Additionally, an adequate dosage of ATRA can obtain higher concentration and enable patients to attain CR in a shorter time. Our previous clinical studies have shown the superiority of ATRA 45 mg/m^2 over ATRA 25mg/m^2,[12] despite the latter being recommended in the Chinese guidelines. Furthermore, the combination of ATRA with ATO has been shown in clinical studies to provide further morphological and molecular remission, allowing more patients to achieve long-term survival. Several studies indicated that severe DS occurred earlier during the treatment course (median of 6 days) and moderate DS appeared relatively later (median of 15 days); however, for high-risk APL with significantly elevated white blood cells, use of ATRA and arsenic will accelerate the excessive and rapid growth of white blood cells in the patient's peripheral blood, which lead to the early occurrence of DS and rapid deterioration of the clinical condition. Early combination of anthracyclines such as IDA in patients with high-risk APL can control the rapid growth of leukocytes during induction treatment of ATRA and can effectively prevent the occurrence of DS. At the same time, early use of anthracyclines can also reduce the possibility of leukemia extramedullary infiltration and then prevent disease relapse after remission.

Consolidation treatment, utilizing the triple regimen of ATRA+ATO+anthracyclines, further eradicates residual leukemia cells, deepens molecular remission, and lays the groundwork for subsequent maintenance treatment. In the recent large randomized clinical trial APL2012,[13] patients undergoing consolidation treatment with three courses of ATRA+ATO+IDA/DNR had better long-term outcomes than patients consolidated with ATRA+ chemotherapy (2 courses of ATRA plus anthracycline and cytarabine and 1 course of ATRA plus mid-dose cytarabine) (7 year-CIR 5.1% vs 9.9%, 7 year-DFS 93.2% vs 87.4%). At present, there is still controversy about the optimal maintenance treatment approaches. Previous reports indicated that ATRA, ATO, anthracyclines, 6-mercaptopurine (6-MP), methotrexate (MTX), RIF alone or in combination are used for maintenance. In this study, ATRA combined with RIF maintenance treatment was used for 24 months. RIF is an oral herbal compound in which As4S4 is the main active ingredient and the combination of *Indigo naturalis* and *Salvia miltiorrhiza* enhances the expression of Aquaglyceroporin 9 (AQP9) to promote arsenic transport into APL cells, thereby accelerating PML-RARα degradation.[14] Compared with intravenous ATO, oral RIF offers greater convenience and tolerability, making it an ideal choice for maintenance treatment. A recent clinical study evaluated ATRA and RIF, without chemotherapy as an outpatient consolidation therapy and no maintenance for 54 patients of high risk APL, however, two patients relapsed after consolidation in a short time with a cumulative incidence of relapse of 6.2% (a median follow-up of 13.8 months), which indicated that consolidation with anthracyclines might be necessary or the duration of maintenance treatment should be long enough.[15]

Conclusions

In conclusion, this study demonstrated that induction and consolidation with ATRA+ATO+anthracyclines and maintenance with ATRA+RIF is a highly curative treatment approach for high-risk APL with manageable AEs. However, this is a retrospective study in a single-center without a control cohort for statistical comparison, and the patient number is small. A multi-center prospective and comparative study should be conducted to further confirm the clinical efficacy of this protocol. In addition, long-term safety of this protocol should be monitored; for example, the cumulative dosage of anthracycline drugs is relatively high, and the chemotherapy related cardiac toxicity should be closely followed, including B-type natriuretic peptide (BNP), electrocardiogram, echocardiography, etc.

Ethics Approval and Informed Consent

This study was approved, and the written informed consent was waived by the ethics committee of the first affiliated hospital of University of Science and Technology of China (2022-RE-457) due to the retrospective nature of the review, and confirmed that the data was anonymized and maintained with confidentiality. The study was conducted in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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