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Original Article

Early application of arsenic trioxide improved the clinical outcomes of acute promyelocytic leukemia

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Abstract: Nowadays, acute promyelocytic leukemia (APL) is the most potentially curable leukemia. Recent studies indicate all-trans retinoic acid (ATRA) plus arsenic trioxide (ATO) would be an alternative to ATRA plus chemotherapy (CT) for low-to-intermediate-risk APL. This study investigated whether early application of ATO was beneficial for the long-term outcomes of APL. We applied two induction therapies, consisted of ATRA combined with low-dose CT and ATRA plus ATO followed by the same consolidation and maintenance treatments. A total of 132 newly diagnosed low-to-intermediate-risk APL patients were included and retrospectively investigated. The ATO group achieved an earlier and durable molecular complete remission with the median time of 90 days compared with the low-dose CT group (112 days, *P*=0.02), while the liver toxicity was higher in the ATO group (20% vs. 4.2%, *P*=0.01). The 3-year relapse rate was significant lower in ATO group (1.8% vs. 12.1%, *P*=0.02). The 3-year event-free survival in ATO and low-dose CT group were 93.1% and 80.3%, respectively (*P*=0.03). In conclusion, early application of ATO in induction therapy of APL attained quick and sustained molecular remission, which reduced the relapse rate and may benefit the long-term outcomes.

Keywords: Acute promyelocytic leukemia, all-trans retinoic acid, arsenic trioxide, low-dose chemotherapy, clinical outcomes

Introduction

Acute promyelocytic leukemia (APL), an unique leukemia subtype of acute myeloid leukemia (AML), is cytogenetically characterized by the PML/RARα chimeric protein generated by the t (15; 17) (q22; q21) chromosomal translocation [1]. APL was once regarded as the most fetal leukemia as it was correlated with a striking risk of early hemorrhagic death due to its frequent occurrence of hyperfibrinolysis, life-threatening coagulation and thrombocytopenia [2, 3].

Due to the standard treatment combining all-trans retinoic acid (ATRA) and anthracycline-based chemotherapy (CT) greatly improved the prognostic, APL is considered potentially curable leukemia [4]. As reported in several large multicenter trails, this current strategy yields the overall complete remission rate of 90%-95% and long-term disease-free survival exceeding 80% [5-7]. However, the main adverse reactions of anthracycline-based chemotherapy are associated with highly severe infection and second carcinoma. In recent years, arsenic trioxide (ATO) has emerged to be the most effective single agent in the treatment of APL. It induces sustained molecular remission in a high rate of relapsed and newly diagnosed patients [8-11]. Clinical and experimental studies demonstrated that ATO and ATRA acted synergistically leading to an enhancement of anti-leukemic effects without chemotherapy-related toxicity. It has been proved ATRA in combination with ATO is not inferior and maybe superior to the standard regimen [12, 13]. With the widely and efficiently use of ATO, it has been adopted combining with ATRA by the 2014 NCCN guidelines as the first-line treatment for APL.

In this study, we applied two induction therapies, consisted of ATRA combined with low-

dose chemotherapy and ATRA plus arsenic trioxide followed with the same consolidation and maintenance treatments for newly diagnosed low-to-intermediate-risk APL. On the one hand, we studied the advantages of a low-dose chemotherapy, and on the other hand we aimed to study whether early application of arsenic trioxide would improve the long-term outcomes of APL patients.

Methods

Inclusion and exclusion criteria

Eligible patients were older than 14 years with newly diagnosed APL classified as low-to-intermediate-risk (WBC at diagnosis, $\leq 10\times10^9$/L). The diagnose of APL is based on French-American-British (FAB) morphological classification criteria and clinical symptoms and (+) for t (15; 17) by either cytogenetic or molecular testing. Patients with variant non-PML gene rearrangements were excluded. From October, 2009 to January, 2017, a total of 132 patients were included from the Second Affiliated Hospital of Xi'an Jiaotong University and Xi'an Central Hospital. 72 patients were treated with ATRA plus low-dose chemotherapy while 60 patients received ATRA and ATO combination protocol.

Treatment protocols

Once diagnosed as APL, patients will be adopted into clinical pathways as soon as possible, especially given prompt ATRA treatment and massive transfusion supports. In the low-dose CT group, daunorubicin was intravenously offered at 10 mg/d on days 2, 4, 6, 8 and ATRA was given pro at 25 mg/m^2 in two divided doses daily until complete commission (CR). In the ATO group, ATO was given intravenously at 10 mg/d until CR and ATRA was given the same dose as in the low-dose CT group. All participants achieved CR after received 3 courses of consolidation chemotherapy: homoharringtonine (2 mg/m^2, days 1-7) and cytarabine (100 mg/m^2, days 1-5); daunorubicin (40 mg/m^2 days 1-3) and cytarabine (100 mg/m^2, days 1-5); mitoxantrone (6 mg/m^2, days 1-3) and cytarabine (100 mg/m^2, days 1-5). During the intermittent of chemotherapy, ATRA was given pro at 25 mg/m^2. After completion of consolidation, patients whose PML/RARα fusion gene testing were negative would begin with the maintenance treatment with sequential use of ATRA (25 mg/m^2/d×14 days), arsenic trioxide (10 mg/d×28 days) and oral methotrexate (15 mg/m^2/wk×4 wks) every 3 months for a cycle. The above regimens for maintenance treatments should be applied for five cycles.

During induction therapy, platelet transfusions were administered if the count is less than 30×10^9/L, and cryoprecipitate and/or fresh frozen plasma were given to maintain fibrinogen above 1.5 g/L. Patients with evidence of retinoic acid syndrome were treated with dexamethasone and reduced-dose or even discontinued temporarily use of ATRA. Central nervous system (CNS) prophylaxis was given 4-6 times altogether for all patients after complete remission (CR).

Evaluation of response

The criteria of CR and relapse of APL were assessed according to the NCCN guidelines. Quantitative reverse transcriptase polymerase chain reaction (RT-PCR) or fluorescence in situ hybridization (FISH) was applied for molecular monitoring. It was monitored after induction therapy, consolidation treatment, every 3 months during maintenance therapy, and then every 6 to 12 months afterward for 2 years.

The overall survival (OS) counted from the start of therapy until death, event-free survival (EFS) from the start of therapy to disease relapse, development of secondary malignancy, or death from any cause. Early death (ED) was defined as death within 30 days of admission, irrespective of its causes.

Statistical analysis

Comparisons of the characteristics between groups were performed by the independent samples t-test or Wilcoxon rank sum test for continuous variables. Categorical variables were compared by Pearson's chi-squared test, continuous-corrected chi-squared test or Fisher exact test. The survival possibility data including OS, EFS and cumulative incidence of relapse (CIR) were assessed using the Kaplan-Meier method. Statistical analysis was performed using SPSS18.0 for windows software. $P<0.05$ was considered statistically significant (two-sided).

Results

Patients characteristics at diagnosis

132 eligible patients were enrolled in this study and the main demographic, clinical, and bio-

Table 1. Baseline of patients in low-dose chemotherapy and arsenic trioxide groups

Characteristic		Low-dose Chemotherapy	Arsenic Trioxide	*P*
Age, y (range)		41.5 (14-75)	37.5 (16-77)	0.49
Sex (N)	Male	33	24	0.50
	Female	39	36	
Hb (g/L) median (range)		85 (48-115)	74 (57-135)	0.72
PLT (10^9/L) median (range)		18.5 (5-89)	39.5 (3-77)	0.31
WBC (10^9/L) median (range)		1.89 (0.51-9.02)	2.63 (1.22-9.93)	0.22
Blasts of BM median (range)		76.5 (57-91)	88.5 (49-95)	0.03*
Symptoms (N)	Fever (+)	24	27	0.17
	Fever (-)	48	33	
	Bleeding (+)	42	36	0.85
	Bleeding (-)	30	24	

N, number; y, years; BM, bone marrow; *, $P<0.05$.

Table 2. Outcomes of induction therapy and long-term follow-up

Items	Low-dose Chemotherapy	Arsenic Trioxide	*P*
Morphologic CR, N (%)	66 (91.7)	57 (95.0)	0.68
Days to hematologic CR, median (range)	37 (20-57)	28 (20-71)	0.41
Days to molecular CR, median (range)	112 (39-266)	90 (48-140)	0.02*
ED, N (%)	5 (6.9)	2 (3.3)	0.59
Relapse, N (%)	9 (13.6)	1 (1.8)	0.04*
3-years OS (%)	88.8	95.0	0.22
3-year EFS (%)	80.3	93.1	0.03*
3-years CIR (%)	12.1	1.8	0.02*

CR, complete remission; ED, early death; N, number; OS, overall survival rate; EFS, event-free survival rate; CIR, cumulative incidence of relapse; *, $P<0.05$.

logic characteristics of patients in each group were showed in **Table 1**. 39 females and 33 males were adopted in the low-dose CT group with a median age of 41.5 years while 36 females and 24 males with a median age of 37.5 years in the ATO group. According to NCCN risk stratification of APL, all patients were classified as low-to-intermediate-risk (WBC at diagnosis, $\leq 10\times10^9$/L). The ATO group had higher percentage of bone marrow blast cells than the low-dose CT group (88.5 vs. 76.5, $P=0.03$). The other baseline characteristic, such as WBC, Hb, PLT levels and symptoms indicated no difference between two groups ($P>0.05$).

Outcomes of the treatment

A total of 123 patients achieved morphological CR (93.2%) in our study. Hematologic CR was achieved in 66 of 72 patients in the low-dose CT group (91.7%) and in 57 of the 60 patients in the ATO group (95.0%) ($P=0.68$). The median days to hematological CR were similar in groups ($P=0.41$). However, the regimen of ATRA plus ATO obtained quicker median days to molecular CR than the low-dose CT group with 90 days (range, 48-140 days) vs. 112 days (range, 39-266 days), respectively ($P=0.02$).

Six patients in the low-dose chemotherapy group died during the induction therapy: 5 from the cerebral hemorrhage within 30 days and 1 from respiratory failure on day 36. In the arsenic trioxide group, 3 patients terminated induction treatment on days 10, 21, 48 because of cerebral hemorrhage. There was no statistical difference between groups regarding the early death ($P=0.59$) (**Table 2**).

Main side-effects during induction therapy

Hematologic toxicity: In the induction therapy of APL, the sustained days with grade 3 to 4 neutropenia and thrombocytopenia were calculated. The duration of PLT lower than 50×10^9/L and neutrophil counts lower than 1×10^9/L in the low-dose chemotherapy group were both similar to those in the ATO group (*P>0.05*) (**Table 3**).

Nonhematologic toxicity: The ATO group showed higher liver impairment than the low-dose CT

Table 3. Toxicities and side effects during induction

Toxicity profile	Low-dose Chemotherapy	Arsenic Trioxide	*P*
Thrombocytopenia (III-IV), N (%)	68 (95.8)	57 (95.0)	0.84
Duration, median (range)	21 (0-39)	22 (0-44)	0.50
Neutropenia (III-IV), N (%)	59 (83.1)	51 (85.0)	0.77
Duration, median (range)	27 (0-70)	29 (5-45)	0.49
Hepatotoxicity, N (%)	3 (4.2)	12 (20.0)	0.01*
Cardiac arrhythmia, N (%)	9 (12.7)	6 (10.0)	0.63
Lung infection, N (%)	33 (46.8)	30 (50)	0.69
Renal toxicity, N (%)	6 (8.5)	3 (5.0)	0.67
Differentiation syndrome, N (%)	32 (45.1)	21 (35.0)	0.24
DIC, N (%)	30 (42.3)	20 (33.3)	0.30
Gastrointestinal reaction, N (%)	12 (16.9)	8 (13.3)	0.57

NA, Not Available; DIC, disseminated intravascular coagulation; N, number; *, *P*<0.05.

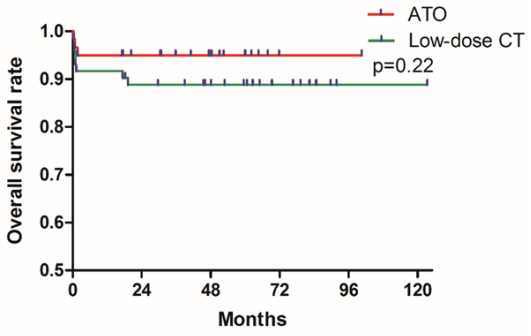

Figure 1. Overall survival rate of low-dose CT group and ATO group.

group (20.0% vs. 4.2%, *P*=0.01). Patients who suffered liver function lesion during induction therapy mostly exerted slight and moderate elevated levels of aminotransferases and hepatic function returned to normal in all of them within 1-2 weeks after supportive therapy without termination of ATO. In addition, the other nonhematologic toxicities such as retinoic acid syndrome, disseminated intravascular coagulation, cardiac, renal comorbidities and gastrointestinal reaction showed no significant difference between low-dose chemotherapy and arsenic trioxide (**Table 3**).

Post-induction therapy and follow-up analysis

Patients in two groups were followed up until January 30, 2017, and the median follow-up was 39 months (range, 12-74 months). A total of 9 patients occurred relapse in the low-dose chemotherapy group (6 overt morphologic and 3 molecular relapses) and only 1 was molecular relapse in the arsenic trioxide group (13.6% vs. 1.8%, *P*=0.04) (**Table 2**). In low-dose chemotherapy group, 7 (77.8%) of the 9 patients who relapsed received arsenic trioxide salvage therapy and achieved molecular remission and remained alive at final follow-up. The other two died of cerebral hemorrhage during salvage treatment. The molecular relapsed patient in arsenic trioxide group achieve CR after re-induction therapy.

3-year OS indicated no difference between low-dose CT group and arsenic trioxide group (*P*=0.22) (**Figure 1**). However, 3-year CIR was higher in the low-dose chemotherapy group than the arsenic trioxide group (*P*=0.02) (**Figure 2**). Moreover, 3-years EFS was 93.1% in the ATO group and 80.3% in the low-dose CT group (*P*=0.03) (**Figure 3**).

Discussion

ATRA (targeting RARα proteins) and ATO (targeting PML proteins) are two key molecular-target drugs for APL. Studies indicated that combined ATRA and ATO degraded PML-RARα synergistically resulting in the eradication of APL-initiating cells with acceptable tolerability [14-18]. Recent years, with the advent of ATO into curing relapsed, refractory or newly diagnose APL, the regimen of ATRA plus ATO is regarded as an alternative to chemotherapy in induction of low-risk de novo APL. Therefore, the chemotherapy dose and drugs would be gradually reduced or even replaced by ATO in order to lower the incidence of ED and toxicity profiles [19].

In this study, we compared the efficiency, toxicity and long-term outcomes of two induction therapy, consisted of ATRA plus low-dose chemotherapy and ATRA combined with arsenic trioxide, which were followed by the same consolidation and maintenance treatments. As a result, arsenic trioxide group achieved a quicker and sustained molecular CR and less relapse rate than the other group. In addition, the outcome of ED rate, myelosuppression, infection rate and non-hematological toxicities were similar between groups besides the liver impair-

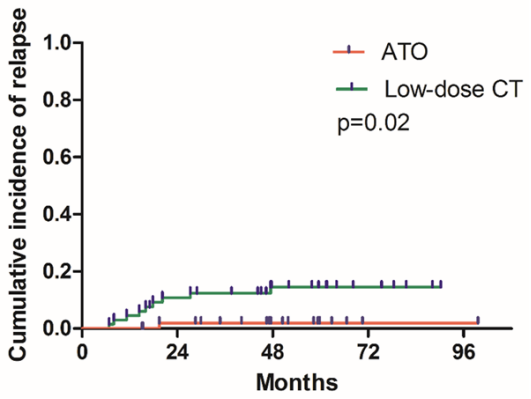

Figure 2. Cumulative incidence of relapse rate of low-dose CT group and ATO group.

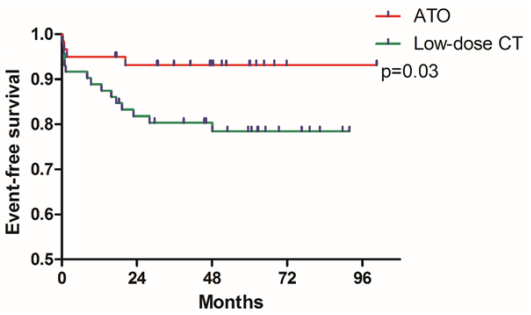

Figure 3. Event-free survival rate of low-dose CT group and ATO group.

ment. The arsenic trioxide group showed high liver impairment which was mild and reversible after supportive therapy (P=0.01). As we used low-dose chemotherapy plus ATRA treated newly diagnosed low-intermediate risk stratification APL patients, the ED, III-IV grades thrombocytopenia and neutropenia and infection rate were lower compared with previous reported standard regimen [3, 20].

Pilots studies suggested ATRA combined with arsenic trioxide dramatically improve the long-term outcomes. In a randomized, prospective multicenter study, 2-year EFS rates were 97% in the ATRA-ATO group and 86% in the ATRA-chemotherapy approach (P<0.05). OS was also longer with ATRA-ATO (P=0.02) [21]. Another randomized study in 2015 also achieved high 4-year EFS rates and decreased 4-year CTR (P<0.05) [13]. Our study had a similar result with the present outcomes. In our study, the arsenic trioxide group showed higher 3-year EFS and lower 3-years CIR than the low-dose CT setting. Besides, 3-years OS in low-dose CT and arsenic trioxide group were 80.3% and 93.1%, respectively (P=0.22).

The observed advantage in the 3-year EFS with arsenic trioxide probably due to the lower relapse rate in this group. Patients in the low-dose chemotherapy group had delayed mCR, and the PML/RARα fusion gene of 2 patients were still positive after the 3 cycles consolidation therapy. Therefore, early application of arsenic trioxide in induction therapy may improve the long-term outcomes for low-to-intermediate-risk APL.

In conclusion, early application of ATO in induction therapy of APL attained quick and sustained molecular remission, which reduced the relapse rate and may benefited for the long-term outcomes.

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Disclosure of conflict of interest

None.

Authors' contribution

HC and AH contribute to conception and design and manuscript writing. XW, TH and JL performed data analysis and data acquisition. WZ, YC, XC, YY, XM and YS offered clinical data and performed quality control. All authors reviewed the manuscript and approved the final authorship.

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