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ORIGINAL RESEARCH

Consolidation therapy of arsenic trioxide alternated with chemotherapy achieves remarkable efficacy in newly diagnosed acute promyelocytic leukemia

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Background: Currently, all-trans retinoic acid (ATRA) combined with daunorubicin and ATRA combined with arsenic trioxide (ATO) therapies are considered the standard induction therapy regimens for adult patients newly diagnosed with acute promyelocytic leukemia (APL). However, there is no consensus concerning the optimal consolidation and maintenance therapies after induction therapy. In this study, we explored a new therapeutic strategy for APL that may be simple, effective, and safe.

Methods: The patients in our study were divided into high white blood cell (WBC) group and low WBC group according to the numeration of leukocytes at the first visit. The low WBC group received ATRA and ATO until complete remission (CR), and the high WBC group received anthracycline, ATRA, and ATO until CR. After achieving hematologic CR, ATO was alternated with chemotherapy for consolidation therapy. Three cycles were completed in the 1st year with no maintenance therapy. The patients were followed for a median of 5 years after their initial treatment.

Results: After induction therapy, the rate of CR for the 18 patients was 100%. The rate of negativity for the *PML/RARα* fusion gene following induction therapy was 100%. There was no mortality during the treatment. Both the 5-year event-free survival rate and 5-year overall survival rate were 100%. No relapses occurred during the follow-up period.

Conclusion: This study proposes a novel treatment for APL that is efficient, well-tolerated, and very simple to perform.

Keywords: acute promyelocytic leukemia, all-trans retinoic acid, arsenic trioxide, consolidation therapy, new therapeutic strategy, survival

Introduction

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML) that is characterized by its morphology, t(15;17) translocation leading to the formation of the PML/RARα fusion gene, and life-threatening coagulopathy.[1] The prognosis of APL has changed from the worst among AMLs to currently the best among AMLs due to the application of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO).[2–5] A consensus has been reached that ATRA alone or in combination with ATO, with the proper addition of anthracyclines according to white blood cell (WBC) count, is able to achieve complete remission (CR) and results in negativity for the PML/RARα fusion gene.[6,7] Currently, there is no consensus regarding the optimal consolidation and maintenance therapies after induction therapy. Additionally, whether the early involvement of maintenance therapy benefits low-risk patients who

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have already achieved molecular CR is still being debated. Because the regimen administered after remission determines the long-term survival rate of APL, in this article, we explored an effective, safe, and simple therapeutic strategy for APL that would potentially provide a remedy to this issue.

Patients and methods

Ethics statement

This study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center, and written informed consent was obtained from every volunteer and patient prior to treatment. Additionally, this study was conducted in accordance with the Declaration of Helsinki.

Patients

The patients included in this study met the following criteria: 1) newly diagnosed APL in accordance with the morphological criteria (M0–M7) of the French–American–British classification system for myelocytic leukemias;[8] 2) confirmation of APL diagnosis by both a cytogenetic assay for t(15;17) (q24;q21) and a reverse transcription polymerase chain reaction assay for PML/RARα; 3) the patients had completed the whole induction therapy and consolidation therapy. In our country, due to the economic and other reasons, some patients could not complete the treatment, or before the completion of the treatment, serious cerebral hemorrhage and serious infections occurred that led to the early death of the patients. The patients with APL who were transferred to our hospital on relapse were not included in our study. The patients included in our study were the ones who achieved the complete treatment.

Eighteen patients initially diagnosed with adult APL were enrolled from January 2002 to December 2012 at the Sun Yat-sen University Cancer Center. The patients received regular treatment. To evaluate the efficacy and safety of the treatment, complete data of 18 cases (including ten males and eight females, median age: 34 years; range: 19–64 years; refer Table 1 for the patients' clinical details) were analyzed and summarized in this long-term and systematic follow-up study. The patients were followed for a median of 5 years after their initial treatment. The deadline for follow-up was December 2014.

Treatment strategies

According to the classification system of Sanz et al,[9] patients can be divided into three groups based on their WBC count: low risk of relapse (WBC count $<10\times10^9$/L, platelet count $>40\times10^9$/L), intermediate risk of relapse (WBC count $<10\times10^9$/L, platelet count 40×10^9/L), and high risk of relapse (WBC count $\geq10\times10^9$/L, platelet count $\leq40\times10^9$/ L) (Table 1).

Table 1 Clinical characteristics at baseline

Characteristic	n	%
Age, years		
Median (range)	34 (19–65)	
<40	11	61.1
≥40	7	38.9
Sex		
Male	10	55.6
Female	8	44.4
WBC count ($\times10^9$)		
Median (range)	2.02 (0.3–77.8)	
<10	13	72.2
≥10	5	27.8
PLT count ($\times10^9$)		
Median (range)	33 (11–133)	
≤40	12	66.7
>40	6	33.3
LDH (U/L)		
Median (range)	196 (96.8–816)	
Normal	13	72.2
> normal	5	27.8
Risk stratification		
Low risk	6	33.3
Intermediate risk	7	38.9
High risk	5	27.8
Hemoglobin (g/L), median (range)	74 (47–115)	
RBC ($\times10^9$), median (range)	2.5 (1.2–3.8)	
Peripheral promyelocytes (%), median (range)	67 (25–92)	
Marrow promyelocytes (%), median (range)	77.5 (28.8–91.5)	
Fibrinogen (g/L), median (range)	1.6 (0.4–5.8)	

Abbreviations: LDH, lactic dehydrogenase; PLT, platelet; RBC, red blood cell; WBC, white blood cell.

Our induction therapy was administered as follows: 30 mg/m^2 ATRA orally per day and 0.16 mg/kg ATO intravenously per day until CR. When the patient's WBC count exceeded 10×10^9/L, the patient was given hydroxyurea (daily doses of 20–40 mg/kg) or daunorubicin and cytarabine (Ara-c)/idarubicin and cytarabine regimen (daunorubicin: 60 mg/m^2 per day for 3 days and Ara-C: 100 mg/m^2 per day for 3–5 days, or idarubicin: 10 mg/m^2 per day for 3 days and Ara-C: 100 mg/m^2 per day for 3–5 days) until the patient's WBC count $<10\times10^9$/L (Figure 1).

Our consolidation therapy was administered as follows: ATO alternated with chemotherapy during consolidation therapy after hematologic CR. Three cycles were completed in the 1st year. Each cycle included the daunorubicin plus ATRA regimen (daunorubicin, 60 mg/m^2 per day [days 1–3] and ATRA 30 mg/m^2 per day [days 1–28]) or the idarubicin plus ATRA regimen (idarubicin 10 mg/m^2 per day [days 1–3] and ATRA 30 mg/m^2 per day [days 1–28]), plus the ATO regimen (0.16 mg/kg per day for 14 days). In addition, high-risk patients received one more course of high-dose Ara-C (3 g/m^2) at the end of consolidation therapy (Figure 1).

To avoid central nervous system relapse, all patients received at least once intrathecal injection of three drugs

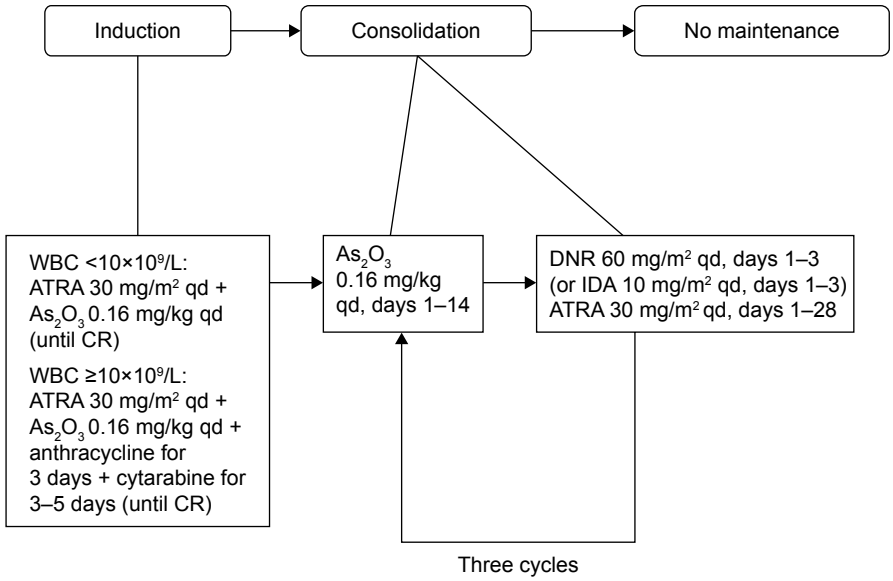

Figure 1 Flowchart depicting the detailed information of this regimen.
Abbreviations: ATRA, all-trans retinoic acid; CR, complete remission; DNR, daunorubicin; IDA, idarubicin; qd, every day; WBC, white blood cell.

containing methotrexate (10–15 mg), dexamethasone (5 mg) or prednisolone (40 mg), and Ara-C (40–50 mg) during their consolidation therapy. Coagulation and fibrinolysis parameters, such as fibrinogen, fibrin degradation product, D-dimer level, prothrombin time, and activated partial thromboplastin time, were monitored to direct the use of low-dose heparin, platelet transfusion, and fresh plasma when necessary. Hepatic toxicity was given particular caution as follows: ATO should be decreased to half the original dose (0.08 mg/kg per day) in the case of grade 0–1 liver dysfunction and ought to be withdrawn immediately in the case of grade 2–4 liver dysfunction. The patients with a suspected APL differentiation syndrome received dexamethasone treatment.

There was no maintenance therapy. After induction and consolidation therapy, bone marrow samples were obtained every 3 months for the first 2 years and every 6 months from 2 to 5 years after CR. The PML/RARα fusion gene was regularly monitored every 6 months for 3 years after the consolidation therapy was completed.

Definitions

The main end points analyzed were CR, event-free survival (EFS), and overall survival (OS). Hematologic CR, molecular CR, hematologic relapse, and molecular relapse were defined according to the criteria recommended by the US National Cancer Institute. EFS for CR patients was the time to the observation of an event, for example, failure to achieve CR, relapse after achieving CR, such as hematologic relapse, molecular relapse, extramedullary relapse, and death. The OS was defined as the time interval from the date of the initial diagnosis to death from any cause or to the last follow-up in censored patients.

Results

Patient characteristics

In total, 18 patients (ten males and eight females) with a median age of 34 years were included in this study. The median follow-up time was 52 months (range: 24–122 months). The laboratory test results of the 18 patients revealed that the median WBC count was 2.02×10^9/L (range: 0.3×10^9/L to 77.8×10^9/L), the median hemoglobin level was 74 g/L (range: 47–115g/L), and the median platelet count was 33×10^9/L (range: 11×10^9/L to 133×10^9/L). Six patients were at low risk, seven were at intermediate risk, and five were at high risk. Elevated lactic dehydrogenase level (>245 U/L) was observed in 27.8% of the patients. The median peripheral promyelocyte count was 67% (range: 25%–92%), and the median marrow promyelocyte count was 77.5% (range: 28.8%–91.5%) (Table 1).

Treatment outcome

All 18 patients finished the induction regimen and were evaluated for response. None of the patients died as a result of the treatment. After induction therapy, the CR rate of the 18 patients was 100%. The rate of PML/RARα fusion gene negativity was 100%. The estimated median duration of EFS and OS could not be determined, as the 5-year EFS rate and the 5-year OS rate were both 100%. No relapse occurred during the follow-up period (Table 2, Figures 2 and 3).

Table 2 Induction response

Clinical parameter	All patients (N=18)
Hematologic CR, number (%)	18 (100.0)
Molecular CR, number (%)	18 (100.0)
Time from treatment to hematologic CR (days), median (range)	28 (17–48)
Time from treatment to molecular CR (days), median (range)	48 (38–70)
Differentiation syndrome, number (%)	1 (5.6)
Duration of hyperleukocytosis (days), median (range)	5 (2–10)

Abbreviation: CR, complete remission.

Toxicity

There was no mortality during treatment. Gastrointestinal adverse reactions occurred in eight patients. No serious cardiotoxicity was observed. Differentiation syndrome occurred in one patient. Liver function tests showed increased levels of alanine transaminase and aspartate transaminase in five cases, but these levels reduced to the normal range after the treatment for 1–2 weeks with liver-protecting drugs. No treatment interruption or dose reduction occurred due to liver toxicity. Fever occurred in 55.6% of the patients, and bone pain was experienced by 16.7% of the patients. Skin reaction was observed in 5.6% of the patients. None of the patients developed a secondary neoplasm during the follow-up period (Table 3).

Discussion

Currently, APL is a subtype of AML that does not require stem cell transplantation for treatment, as conventional chemotherapy alone is sufficient to cure APL. The advent of ATRA and ATO for the treatment of APL allowed the rate of CR to reach 90%, but it is also associated with a relapse rate of 15%–25%.[10–13] The physiopathology of APL is a maturation arrest in the promyelocytic stage caused by the PML-RARα

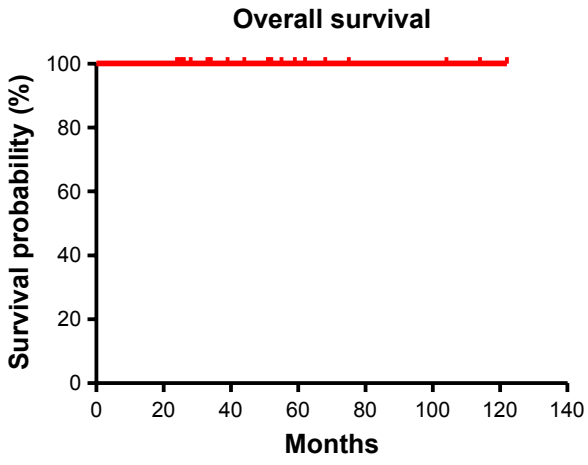

Figure 2 Kaplan–Meier curve of overall survival.

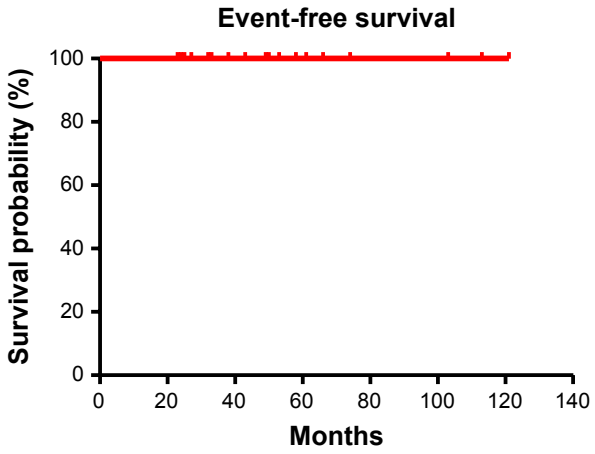

Figure 3 Kaplan–Meier curve of event-free survival.

chimeric protein.[14,15] First discovered in 1980, ATRA induces differentiation of leukemic promyelocytes into mature granulocytes by ligation of the PML-RARα receptor.[16] Moreover, ATO binds to the PML-RARα protein and causes the dose-dependent degradation or apoptosis of APL cells. During induction therapy with these two drugs (ATRA+ATO), the patients can achieve CR, but the inability of these two drugs to remove minimal residual leukemia can lead to relapse.[17–19] Studies[20,21] have shown that mice achieved CR after treatment with ATRA and ATO appeared to reproduce the PML-RARα fusion gene after receiving bortezomib (a proteasome inhibitor) treatment, which suggests that leukemic stem cells are not cleared by ATRA and ATO in mice. Further study showed that ATO should be combined with standard chemotherapy to clear minimal residual leukemia.[22]

A meta-analysis of adults with APL demonstrated that the use of ATRA and ATO compared to ATO alone increased the rate of CR, shortened the time to remission, and generated a better remission rate during 1 year of follow-up.[23] In a study published in 2013, Lo-Coco et al[13] observed that ATRA and ATO were not inferior to ATRA with chemotherapy in cases of newly diagnosed adults with APL. The combination of ATRA and ATO is currently approved in North America and Europe for the treatment of newly diagnosed and relapsed adults with APL. The consensus has been reached that ATRA

Table 3 Toxicity profile

Toxicity	n	%
Liver dysfunction	5	27.8
Cardiac arrhythmia	2	11.1
Gastrointestinal adverse reaction	8	44.4
Bone pain	3	16.7
Skin reaction	1	5.6
Fever	10	55.6

combined with daunorubicin and ATRA combined with ATO are standard induction therapy regimens for adult patients newly diagnosed with APL. Therefore, in our study, the low WBC group received ATRA and ATO, and the high WBC group received anthracycline, ATRA, and ATO. It turned out that we achieved a high rate of CR.

At present, the main focus of APL treatment is on the consolidation and maintenance therapy. The primary goal of medical staff is to reduce the costs of treatment and the pain associated with it, while maintaining a high long-term EFS rate and improving patient prognosis. Xin et al[6] suggested that the regimen administered after remission determines the long-term survival rate. The long-term survival rate was lower in patients treated with chemotherapy alone. Chemotherapy combined with ATRA or ATO showed a significantly improved OS rate and recurrence-free survival rate compared with chemotherapy alone. The highest OS rate was achieved when ATRA, ATO, and chemotherapy are combined and used alternatively. Due to the limitations of ATRA and ATO, the use of chemotherapeutic drugs in the consolidation therapy regimen cannot be ignored.[24,25]

Our study is unique in that it incorporates consolidation therapy instead of maintenance therapy: ATO and chemotherapy are used in turn during consolidation therapy after hematologic CR. As we know, the main limitation of anthracycline is the risk of cardiotoxicity with cumulative doses. For children and elderly patients who are physically weak, bone marrow suppression and secondary severe infections are likely to occur after stronger standard chemotherapy, and the treatment-related mortality with this therapy is high. In our study, we used ATO alternated with conventional chemotherapy. With this strategy, the bone marrow of patients has a relatively long time to recover, which can help patients, particularly those who are weak, to better tolerate their next course of treatment. ATO has been proven to be quite safe. When compared with anthracyclines, bone marrow myelosuppression by ATO appears to be minor. The common adverse effects of ATO are grade 1–2 hepatotoxicity, gastrointestinal adverse reactions, neurotoxicity, and very rarely, grade 3–4 hepatotoxicity, and these adverse effects are usually reversible.[15,26,27] In our study, the treatment was not discontinued in any patients due to ATO toxicity. ATO was alternated with chemotherapy, which allowed the interval between ATO treatments to be extended, and avoided the deposition of ATO. In our study, ATO was found to be quite safe.

This treatment program takes a total of 7 months, including 1 month of induction therapy and 6 months of ATO combined with sequential chemotherapy. The patients were regularly monitored for the presence or absence of PML-RARα fusion gene every 6 months for 2 years after consolidation therapy was completed with no further maintenance therapy. The molecular biology of APL cells changes 3 months before hematologic relapse or extramedullary relapse. Therefore, after consolidation therapy, the patients should be regularly monitored for the presence or absence of PML-RARα fusion gene. Once the PML-RARα fusion gene is observed, which suggests the risk of early recurrence, intervention must be implemented as soon as possible. For patients and doctors, this treatment program is simple, well planned, and achieved good patient compliance. Moreover, in our study, the rate of CR for the 18 patients was 100%, and the rate of PML/RARα fusion gene negativity was 100%. Both the 5-year EFS rate and the 5-year OS rate were 100%. There was no mortality and no relapse during the follow-up period. Although chemo-free induction and consolidation therapy using ATRA/ATO in Lo Cocco's *NEJM* paper acquire surprising results, the follow-up time is not very long.[13] This regimen was indeed proven to be a very effective and convenient therapy regimen with lower toxicity compared with most therapy regimens reported previously.[12,28]

In summary, the regimen in our study had many advantages. First, this regimen prolonged the interval between standard chemotherapy cycles, effectively reducing the incidence of severe bone marrow suppression after chemotherapy and lowering the incidence of serious infections. Second, this regimen extended the interval between ATO treatments, avoiding the deposition of ATO. Third, this regimen significantly reduced the patient's total medical expenses due to the shortened treatment duration.

Our aim is to deliver the most timely and best quality treatment to each newly diagnosed patients with APL. However, for low-risk patients, ATO+ATRA combined with less chemotherapy may be a more appropriate choice. For high-risk patients, we are still searching for a better treatment regimen: in a follow-up series of clinical trials, we will examine whether median-dose or high-dose chemotherapy combined with ATO is better for the treatment of high-risk patients.

Our results confirmed that this chemotherapy regimen achieved ideal outcomes in patients with APL. However, the time and cost of three consecutive ATO treatments and three courses of standard chemotherapy are still unbearable for some patients. It would be even more appealing if the treatment regimen could achieve the same efficacy with fewer ATO treatments and standard chemotherapy cycles, or the use of oral medications. Finding an approach to achieve this would be our goal in the further study.

Conclusion

This study presented a simple treatment regimen for patients with APL with impressive efficacy and high tolerability. Compared with other treatments discussed in other reports in the literature, this regimen has obvious advantages (such as being simple, effective, and safe). The most notable advantages are the high EFS and OS rates and no relapse during the follow-up period. The efficacy was so great that this regimen may be considered a breakthrough in the treatment of APL. The disadvantage of our study is that the number of cases is small, so more studies are necessary to confirm our findings. The next steps are to expand the samples of cases, simplify the treatment plan, and design a more cost-effective treatment.

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Disclosure

The authors report no conflicts of interest in this work.

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