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Research paper

Comparison of induction therapy in non-high risk acute promyelocytic leukemia with arsenic trioxide or in combination with ATRA

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ABSTRACT

Background: Acute promyelocytic leukemia (APL) is a curable form of acute myeloid leukemia; in recent years, the use of new treatment strategies, such as combination therapy, have led to improved APL outcomes. Here, outcomes of patients treated with a combination of arsenic trioxide (ATO) and all-trans-retinoic acid (ATRA) are compared against patients treated with single ATO therapy.

Patients and methods: In total, 67 patients with non-high-risk APL were evaluated. A group of 30 patients received ATO, and another group of 37 patients received ATO plus ATRA. ATO infusion at a dose of 0.15 mg/kg/day was continued till complete remission was achieved or till 60 days of consumption, and after 28 days of rest, second ATO course was initiated for 28 days as consolidation. Four courses separated by 28-day rest were planned. In the second group, 45 mg/m^2/day ATRA was added to ATO protocol.

Results: All patients except one in the ATO group and all patients in the ATO plus ATRA group were alive after a median follow-up of 18 and 17 months, respectively; 2.5-year overall survival in the ATO group was 86% (p-value = .32). Five patients in the ATO group experienced relapse, and 2.5-year leukemia-free survival in this group was 60%. No relapse occurred in the ATO plus ATRA group (p-value = .01). Differences in the mean of white blood cell (p-value = .67), platelet (p-value = .15), liver (p-value = .37), and renal (p-value = .95) dysfunctions were not significant.

Conclusion: Although ATO has been considered a first-line therapy in patients with APL, several studies have reported improved outcomes with a combination of ATO plus ATRA. This study demonstrated a significant decrease in relapse with this combination compared with single ATO therapy and supported the importance of ATRA in APL treatment.

1. Introduction

Acute promyelocytic leukemia (APL) is a lethal but potentially curable form of Acute myeloid leukemia (AML), and it responds better to chemotherapy than other forms of AML [1]. APL has a distinct genetic morphology compared with other acute leukemia. Specific chromosomal marker for APL is t(15; 17), with promyelocytic leukemia-retinoic acid receptor alpha (PML-RARA) oncogene activation. All-trans-retinoic acid (ATRA) in conjunction with an attenuated dose of chemotherapy (anthracyclines alone or in combination with other drugs) is the conventional and standard therapy for APL during remission induction and maintenance phase. This approach is associated with a high rate of hematologic toxicity, including potentially lethal disseminated intravascular coagulation (DIC) and other complications, such as secondary neoplasms [2]. Arsenic trioxide (ATO) has desirable therapeutic effects and lower hematologic complications in APL. ATRA degrades PML-RARA oncoprotein, and ATO specifically binds with the PML moiety of the PML-RARA oncoprotein, inducing APL cell maturation.

In recent years, several large independent clinical trials have reported the effectiveness of ATO as an alternative of chemotherapy [3–8]. At present, ATO is the treatment of choice in relapsed and refractory APL [9]; however, based on results of previous trials, expert panels of the United States and Canada have recommended ATO plus ATRA in the induction therapy for non-high-risk APL and as an alternative treatment in high-risk APL [10]. Moreover, there are some other

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options for the first-line treatment of newly diagnosed APL, including oral realgar-indigo naturalis formula, which contains tetra-arsenic tetra-sulfide (As_4S_4) plus ATRA [11], ATRA plus ATO combined with gemtuzumab ozogamicin in high-risk patients [12], ATRA alone, and ATO alone [13,14].

It is not evident whether the addition of ATRA is mandatory for ATO-based regimens. ATRA plus ATO treatment in low- and intermediate-risk APL (according to the Sanz criteria) produced the outcomes same as those produced with ATRA plus chemotherapy. Results of our previous study and studies of Indian and Chinese populations (mostly phase 2 trials) have reported good outcomes with ATO alone [14,15]. Thus, in this study, we aimed to improve the previous treatment schedule and to study the role of ATRA in ATO-based treatments. We retrospectively compared the outcomes of patients newly diagnosed with non-high-risk APL, who were treated with single ATO therapy or a combination of ATO plus ATRA as the first-line treatment.

2. Methods and materials

2.1. Patients

This was a retrospective cohort study that included patients with APL who were treated in our center between 2012 and 2016. The diagnosis was confirmed on the basis of cytogenetic or molecular confirmation of t(15; 17) or PML-RARA presence in all patients. The inclusion criteria were age above 15 years, good performance status, and normal vital organs function. Only low- and intermediate-risk group patients with white blood cell (WBC) counts of < 10,000 at presentation according to the Sanz definition were enrolled in the study. Written informed consent was obtained from all patients enrolled in this study for chart review.

2.2. Initial treatment

Following stabilization of patients immediately after the suspicion of diagnosis and before the confirmation via reverse transcription polymerase chain reaction (RT-PCR) or cytogenetic characterization, ATO at a dose of 0.15 mg/kg/day in 500 ml N/S was intravenously (i.v.) infused over 2 h. Vital signs were carefully monitored during drug infusion. ATO administration was continued till a morphological complete remission (CR) was achieved or after 60 days of ATO consumption. In the group of patients who were treated by ATO plus ATRA protocol, 45 mg/m^2/day ATRA was added to the ATO protocol till CR was achieved. ATO infusion was discontinued in cases of severe liver or renal toxicity or drug intolerance status. Platelet count (PLT) was maintained at > 50,000 during DIC period or 20,000 after DIC control, and Hb was maintained at > 10 g/dl. If fibrinogen level fell below 150 g/dl, fresh frozen plasma was infused daily. If WBC count increased to > 10,000/μl any time during the treatment or if the patient presented with APL differentiation symptoms, ATO infusion was put on hold for 24 h and restarted with at a dose half of the initial ATO dose.

2.3. Consolidation treatment

After achieving CR, patient received 4 courses of consolidation, each with ATO administered for 28 days (as 2-h infusion of ATO at 0.15 mg/kg/day in week days except Fridays), with 28-day rest between consecutive courses (i.e., first consolidation was initiated after 28 days of rest after CR, the second consolidation was initiated after 28 days of rest following the first consolidation, and so on). In the group of patients who were treated with ATO plus ATRA protocol, 45 mg/m^2/day ATRA was administered for 14 days of every 28-day course during consolidation (i.e., patients received ATRA for 14 days during each course of consolidation concomitant with ATO and for 14 days during each course of rest. Consequently, patients received 7 courses of ATRA, with each course lasting 14 days).

2.4. Manage complications and follow-up

In the case of severe APL differentiation syndrome (dyspnea-functional class 2 or more, hemoptysis, severe pericardial/pleural effusion, or increase in creatinine levels), ATO dose was reduced to 0.07 mg/kg/day till symptoms were controlled, and 10 mg of dexamethasone was administered twice daily till APL differentiation symptoms disappeared. In the case of hypokalemia or QT interval prolongation, magnesium was infused but treatment was continued as per the protocol.

All patients were carefully followed up during treatment, and their clinical and biochemical indices were monitored. Quantitative polymerase chain reaction (qPCR) or RT-PCR was performed at every 14 days during remission induction, at every month till results of PCR became negative, at every 3 months till 3 years of follow-up, and finally, at every 6 months.

2.5. Disease-free survival (DFS)

DFS is defined as the time between the start of treatment and relapse, death, or the last contact with patients without relapse or death event.

2.6. Overall survival (OS)

OS is measured from the time of the start of treatment to the time of death, or last contact with surviving patients.

2.7. Statistical analysis

Continuous variables were compared between two groups using Student's t or Mann–Whitney *U* test. Categorical variables were compared between groups using Chi-squared or Fisher's exact test. Survival curves for DFS and OS were estimated using Kaplan–Meier estimator, and their 95% confidence intervals (CIs) were calculated through log-transformation. Differences between the groups were evaluated using log-rank test. A *p*-value of 0.05 was considered statistically significant. All analyses were performed in IBM SPSS Statistics software version 20.

3. Results

3.1. Patient characteristics

The study included 67 patients who were newly diagnosed with APL, and who were treated in our center between 2012 and 2017. Among the enrolled patients, 30 patients with a median age of 29 years (range, 15–70) received ATO alone and 37 patients with a median age of 37 years (range, 15–60) received ATO plus ATRA. There were no significant differences between the two group in terms of patients age (*p*-value = .23) and other baseline characteristics. All patients were low or intermediate risk as per the Sanz risk group definition, and all patients with WBC count of > 10,000/μl were excluded from the study. Median WBC counts at diagnosis were 1840/μl in the ATO group and 1800/μl in the ATO plus ATRA group (*p*-value = .67). The median platelet counts at diagnosis were 25,000/μl in the ATO group and 27,000/μl in the ATO plus ATRA group (*p*-value = .15). Patients' demographic data are summarized in Table 1.

3.2. Survival and relapse

All patients except one patient in the ATO group were alive and all patients in the ATO plus ATRA were alive after a median follow-up of 18 and 17 months, respectively. In the ATO group, 2.5-year OS was 86% (*p*-value = .32), with 5 patients undergoing relapse (16.7%) (Fig. 1). In the ATO plus ATRA group, 2.5- year leukemia-free survival was 60%, with no relapse (*p*-value = .01) (Fig. 2).