Original Article

Treatment of Relapsed Acute Promyelocytic Leukemia by Arsenic Trioxide in Iran

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Abstract

Background: Although standard first line treatment of acute promyelocytic leukemia is All trans retinoic acid (ATRA) and chemotherapy, some patients relapse and need a second line of treatment. Relapsed cases of promyelocytic leukemia can be salvaged with arsenic trioxide.

Methods: Between May 1999 and Jan. 2010, we treated 31 relapsed cases of promyelocytic leukemia with arsenic trioxide. These cases relapsed after previous treatment with ATRA and chemotherapy. We applied arsenic trioxide as 0.15 mg/kg iv infusion until complete remission. After achieving complete remission patients received 2-4 consolidation therapy in the same schedule as remission induction.

Results: The median age of patients was 27 years. Complete remission rate was 77.4%. We observed four mortalities during remission induction. With a median follow up of 32 months, ten more relapses occurred. Two year disease-free survival and overall survival for the entire cohort was 54.6% and 81.1%, respectively.

Conclusion: Our result is the same as other studies. Thus, we suggest that arsenic trioxide can be used as salvage therapy in patients who relapsed. Despite a good complete remission rate, the relapse rate during the first two years of treatment is high and hematopoietic stem cell transplantation should be considered after achieving complete remission.

Keywords: acute promyelocytic leukemia, arsenic trioxide, relapse

Introduction

The treatment of acute promyelocytic leukemia (APL) changed by finding drugs that target its specific molecular changes. Combining these newly discovered drugs with chemotherapy dramatically changed the fate of this disease.[1–3] Arsenic trioxide is a Chinese drug, which emerged as salvage therapy for APL by the discovery of its effect on relapsed cases.[4–7] The toxicity profile of arsenic trioxide is different in some aspects from ATRA and chemotherapy.

Although arsenic trioxide is effective in relapsed APL, the optimal treatment schedule is not well defined.

We previously reported the results of single-agent arsenic trioxide in patients with newly diagnosed APL.[8] Here, we report our results in relapsed cases of APL and compared them with the results of relapsed cases in other centers in order to standardize our results in new cases.[8]

Materials and Methods

We treated 31 cases of relapsed APL from May 1999 until Jan 2010. Diagnosis of these relapsed cases was suggested by their clinical presentation, histomorphology of their peripheral blood and bone marrow aspiration/biopsy, and proven by detection of PML-RARa by RT-PCR, as previously reported.[8]

The Institutional Review Board approved the protocol and all patients enrolled in this trial signed an approved consent form.

Primary physicians usually referred patients to us and patients suspected of APL relapse started treatment in our hospital before confirmation of relapse and its histomorphology. Then, if morphology and RT-PCR confirmed the relapse, treatment continued and those patients were entered into our database.

Arsenic trioxide was manufactured by the pharmacy faculty at Tehran University of Medical Sciences and prepared in 10 mg vials. We administered arsenic trioxide as a 0.15-mg/kg/day two hour iv infusion until complete remission (CR) or a maximum of 60 days.

After achievement of CR, patients received a second course of arsenic trioxide for 28 days on a daily basis, six days each week, as consolidation therapy. Since 2006, the number of consolidation courses increased from one to four. Patients received two courses of 28 day consolidation therapy with one-month intervals between induction and the first and second courses of consolidation. Then, they were given two additional 28 day courses of consolidation, one and two years after remission induction (Figure 1).

Supportive care and treatment of complications

Patients were evaluated for disseminated intravascular coagulation (DIC) and given platelet and fresh frozen plasma or cryoprecipitate as needed, according to institutional standards and accepted guidelines. Patients were evaluated every other day for electrolyte imbalances, fasting blood glucose, liver, and renal function tests and ECG abnormalities. These abnormalities were corrected as indicated. Peripheral blood smears of patients were studied for maturation levels every other day. If patients had symptoms of APL differentiation syndrome,[9] dexamethasone was given as a 10 mg iv infusion twice daily until symptoms improved. If WBC increased >$10x10^9$/L and/or symptoms of APL differentiation syndrome appeared, arsenic trioxide was reduced to 5 mg/day, as a 24 hour slow infusion. In severe cases the drug was temporarily

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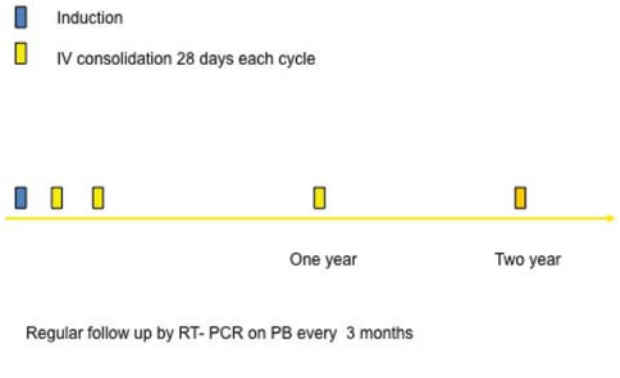

Figure 1. Treatment of APL by arsenic trioxide.

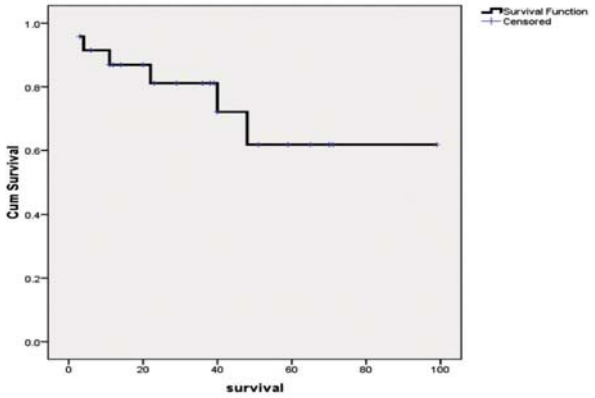

Figure 2. Survival of relapsed cases of APL after treatment with arsenic trioxide.

discontinued and resumed after patient stabilization.

In cases of severe liver function abnormalities (bilirubin >5 mg/dL) or major renal function impairment (creatinine >3 mg/dL) arsenic trioxide was held until resolution of these abnormalities, then restarted at half dose and gradually increased to full dose. Patients were hospitalized during remission induction but for consolidation, arsenic trioxide was given in the outpatient chemotherapy facility.

Follow up

After achieving to CR, patients were followed monthly, we performed physical examination, hemogram monthly. Also we did RT-PCR for the detection of PML/RAR in blood samples as previously reported,[8] every three months.

Statistical analyses

A CR was defined as less than 5% blasts in bone marrow, absence of immature cells in peripheral blood, and normalization of white blood cells and platelet counts in the peripheral blood. APL differentiation syndrome was defined as previously reported.[9] Overall survival (OS) and disease-free survival (DFS) curves were done with the Kaplan-Meier method. OS was measured from diagnosis of relapse until last follow-up or death. DFS was measured from time of CR until relapse, last follow up or death.

Results

Median age of patients was 27 (10 – 79) years. Median white blood cell and platelet count at relapse were 5.8×10^9/L (0.5×10^9 – 44×10^9) and 34×10^9/L (2×10^9 – 261×10^9).

Response to remission induction and toxicities

During remission induction four patients died (12.9%) and 77.4% achieved complete morphologic remission. Median day to CR was 30 days. Seven (22.6%) patients did not achieve CR (including the four early deaths).

The cause of mortality during remission induction was due to APL differentiation syndrome in one case and intracranial hemorrhage in two cases. The fourth patient died due to disease progression despite treatment.

During treatment, APL differentiation syndrome was noted in 9 (29%) cases, of which eight cases were managed with dexamethasone and by reducing the dose of arsenic trioxide and ninth patients died due to APL differentiation syndrome.

Liver dysfunction defined as an increase of transaminase to more than three times the upper limit of normal happened in three cases and renal function abnormality, as an increase of creatinine levels to more than normal, occurred in one case. One patient showed evidence of mild pericardial and pleural effusion, managed with dexamethasone.

Patient survival and follow up

Median follow up of patients was 32 months from diagnosis of relapse. Relapse happened in 10 out of 24 CR cases (41.6%).

Median DFS was 29 months; one and two year disease-free survival was 85% and 54.6%, respectively.

Overall survival was 86.9% and 81.1% for one and two year follow-up, respectively (Figure 2).

Conclusion

Although treatment of new and relapsed cases of APL is successful with current therapies, the results differ from country to country, and between patients treated in clinical trials compared with those treated in general practice.[10] Therefore, comparing the results between centers is difficult. The major causes of differences between centers are the patient population referred to centers, facilities for rapid diagnosis and treatment initiation, facilities for supportive care, and staff expertise in centers that manage these complicated and very critical patients. Despite these difficulties for comparing patient treatment in different countries, comparing patients with similar characteristics and treatment may be helpful when studying the results of novel trials in these centers.

Arsenic trioxide can induce CR in 80 – 90% of relapsed APL and one to three-year survival is 50 – 70%.[6,7,11] CR rate in our cases was in the lower range of reported remission rate, of which there are many possible reasons for this lower rate. We started a protocol for treatment of new cases of APL by arsenic trioxide in 1999,[8] therefore we treated all new cases after 1999 without ATRA and chemotherapy. Thus, all relapsed cases in this study were referred from elsewhere in the country and some of these cases had delay for starting treatment. Despite the higher failure

of treatment at the onset of arsenic trioxide, the one – two year survival was the same as other reports.

Despite good results with remission induction and maintenance therapy with arsenic trioxide, many patients relapse again after sole treatment with arsenic trioxide. The five-year survival rate of APL patients managed with stem cell transplantation is 70 – 80%.[12–14] These rates are much higher than continuous single agent arsenic trioxide treatment. In these cases, it would be a good option for cases who achieve CR.

In summary, our results show the same rate of CR and survival as previous reports. We suggest choosing hematopoietic stem cell transplantation for patients who achieve CR to increase their chances of long term survival.

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