

The Role of Arsenic Treatment after Induction in Alternative and Long-Term Cases for the Prevention of Acute Promyelocytic Leukemia Recurrence

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Abstract

Introduction: Arsenic has been used as an effective medicine in the treatment of severe promyelocytic leukemia in recurrence and resistance cases toward ATRA. In this study, it has been used as induction and maintenance therapy after remission.

Method & Material: We studied 31 patients diagnosed by APL. Arsenic was started at a dose of 0.15 mg/kg (daily) until patient's bone marrow remission. (1) We started Arsenic as a consolidation therapy after 28 days rest and then we continued the treatment with Arsenic each 3-4 months during 2 years for 14 days.

Results: 4 patients died (12.9%) during the first 15 days of treatment. 27 patients (87%) went into remission. 2 patients refused the continuation of treatment regardless the remission. 25 patients received a long term treatment. The disease of 3 out of 25 patients recurred during follow -up period.

1 patient died during the treatment after recurrence and 3 others given ATRA & Arsenic went into remission. Now, It has been past 2 months since the end of their remission.

The recurrence appeared in the form of full involvement of thoraco-lumbar which was observed as an extensive tumor on MRI and was found to cover the mentioned area.

1 patient faced CNS fungal infection during neutropenia period and then recovered after operation and proper treatment; however his vision was severely damaged.

As 4 patients faced leukocytosis over 1000/000ml, we were obliged to discontinue arsenic for 3-4 days and chemotherapy by Danurobicine was prescribed for 2 days.

The patient's follow-up and the median survival time were 54 and 48 months, respectively. The overall survival was 80.6%.

Discussion: Arsenic as the first line therapy for APL is an effective treatment. Consistent long- term therapy with intervals will reduce the risk of disease recurrence.

Key word: APL, Arsenic Trioxide,

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Introduction

Acute Promyelocytic Leukemia (APL) is one of the most dangerous AML subordinates that contain a hazardous clinical symptom named DIC, which caused a lot of mortality in the past times. Another specification of APL is the presence of 3 genetic translocation in the chromosomal examination of this disease; but microscopic morphological

appearance of bone marrow and peripheral blood samples shows differences in these 3 chromosomal disorders.

For instance, Faggot cells mostly describe classic AML M3 15; 17 translocation. Two other chromosomal abnormalities include T (17; 11) and T (17; 5) and the treatment response rate to these 2 types is much less.

Table- 1. Patients' clinical symptoms and hematology criteria

Male	Female	Laboratorial DIC	Clinical DIC
19	12	95% Patients	60% Patients

Nowadays, all-trans retinoic acid is an accepted protocol in APL treatment mostly followed by Anthracycline. 2 years of DALY & 4 years of QALY were 70-80 and 55%-80%, respectively. (2-10) Maintenance therapy with ATRA and low-dose chemotherapy improves the outcomes and reduces the recurrence rate. Previously, Arsenic was used as a second-line of treatment in recurred patients with ATRA. (13-16) The maintenance therapy for AML-M3 patient treated with ATRA as an induction treatment was the use of Methotrexate and Mercaptopril after consolidation period.

The use of Arsenic as a maintenance has been studied in a limited way. There have been 2 studies in this regard, including 2 Arsenic courses and "Powell BL" that has been published in "J clinical oncol 2007 Asco meeting abstract" which contained acceptable outcomes. (17)

We have studied the use of Arsenic as maintenance during 2 years in order to evaluate its drug toxicity and compliance as well as the decrease of recurrence rate. Arsenic affects the development of promyelocytic cells toward mature cells and also causes the decrease of micro vascular density in bone marrow.

Material & Method

Investigation on translocation (15, 17) based on Fish method accomplished in Shariati hospital and private laboratories for the patients with CBC & PLT abnormalities or DIC, after bone marrow aspiration and probable diagnosis of APL.

Since sept- Oct. 2005 till May 2009, 31 patients who were admitted to Imam Reza, Taleghani hospitals and Kermanshah Medical Science University hospital, recruited in this study

All patients were new cases and the only exclusion criterion was cerebral hemorrhage at the beginning of diagnosis.

Patients' clinical symptoms and hematology criteria are demonstrated in table-1. 48.4% of patients aged 14-24 and 48.5% aged between 25-55 years old. The follow-up period was approximately 54 months. Patients were provided with 10mg/10 ml Arsenic vials by Shariati hospital & Hematology - Oncology Research Center. It was continued until early 2008. Having introduced Arsenic in Kermanshah, the patients brought it themselves. Arsenic and the clinical trial have already acquired the ethics committee approval in Tehran.

Remission Induction: After APL diagnosis, arsenic vial dissolved in 500 cc serum was administered at a dose of 15mg/kg. Then, the treatment was continued until the full remission was achieved in terms of morphology to a maximum of 45 days.

Conservative Processes during Treatment: CBC, PLT, PT, PTT and Fibrinogen exams were requested daily for patients. Also EKG and weight measurement were checked.

PLT count was kept over 50,000 so it was necessary for the patients to receive PLT daily, especially after bleeding.

Products such as FFP and Cryoprecipitate were prescribed.

In AML-M3 patients with Laboratory evidence of DIC, when the bleeding is absent FFP and Cryoprecipitate are not recommended, because they would increase the risk of DIC in such group of patients. So, a combination of FFP and Cryoprecipitate is indicated for patients with bleeding.

Hepatic, renal and blood glucose tests have been performed twice weekly. In order to consider QTC, daily EKG was also performed.

K and Mg were prescribed as a part of treatment algorithm in case of prolonged QTC.

When the hepatic exams increased to more than twice the normal or the Bilirubin increased to more than 5mg/dl or the creatinin concentration increased to more than 2 mg/dl, Arsenic was discontinued for a while. Then the treatment started after several days when the test results came back to normal again.

APL differentiation syndrome is the most dangerous Arsenic complication that may lead to mortality. Its clinical symptoms are weight increase, fever, dyspnea and polycyrosis. Moreover, its Paraclinical symptom is the considerable increase in cell count. In this case, Arsenic was discontinued and Dexametazone 8 mg/TDS was started.

In case of pulmonary bleeding, patients were transferred to ICU and Novoseven was started in case of availability.

Consolidation therapy: Arsenic in outpatient's consolidation Therapy was started after 28 days and EKG and other related tests were requested on a weekly basis.

Maintenance Therapy: Arsenic therapy was used to treat the patient for 2 years, every 3-6 months, for a period of 14 days.

Definition of Outcome: Patients were considered to be in remission when the neutrophil count was greater than 1,000 or PLT count was greater than 80,000. The achievement of remission was also associated with the decrease of promyelocytes to 10-15 % with normal morphology and decrease of Myeloblast to less than 5% in bone marrow aspiration.

Disease free survival (DFS) was considered from full remission to recurrence and survival was considered from the start of treatment to the current time or till the time of death.

Statistical Analysis: DFS and overall survival (OS) by Kaplan-meier Method

Results

4 patients (12%) died within the first 15 days of treatment. 27 patients (87%) went into remission.

The average period of remission was 30 days. (Between 25-45 days)

The average hospitalization period was 30 days and 27 patients went into remission. 3 patients died because of the lack of response to the treatment, disease development and consequently pulmonary and cerebral hemorrhage.

APL differentiation led to the death of 1 patient. The average period of death was about 15 days, since the start of induction treatment.

Hyper Leukocytosis: The average WBC count was over 6000/mm³ at the time of diagnosis. Cell count was over 45,000/mm³ in 7 patients. Count over 1000/000 was observed in 4 patients during the treatment and after the start of Arsenic.

The average follow-up period was 48 months. Recurrence observed in 4 patients.

1 patient died because of the lack of response to Arsenic during the treatment.

3 patients achieved remission by combination therapy of arsenic and ATRA. They are currently in remission period.

The recurrence happened very strangely in one patient in the form of paraplegia. In MRI, a large tumor observed on thoracolumbar. No bone marrow involvement was observed. The patient went into remission by combination therapy of Arsenic and ATRA, simultaneously.

One patient got headache and loss of vision during the treatment period. After MRI, the probability of fungal infection propounded and patient survived by Amphotericin-B therapy, however, his vision was severely damaged.

Currently, the patients who have responded to the treatment after recurrence are in remission for about 2 months.

Figures-1 A & B demonstrates the recurrence percentage that leads to death (based on age and sex).

Patients' overall survival was 80%. In Figures- 2 A, B and C, patients' survival and survival based on sex differentiation are demonstrated.

Discussion

Considering overall survival rate and full remission, APL cases treated by Arsenic are comparable with regimens including ATRA. In case of the use of ATRA as an induction therapy after remission, if consolidation chemotherapy is not included by ATRA, long term remission will not be achieved and the use of Anthracycline may be followed by cardiovascular complications. APL syndrome differentiation as a complication of ATRA may cause mortality. Consideration of supportive measures beside the use of Arsenic may have a better control on the disease.

In previous studies, Arsenic was considered as a unique medication in induction, consolidation and maintenance therapy. Moreover, the use of Arsenic was found to lead to less use of Anthracycline in cardiovascular disorders apart from any outcome effects.

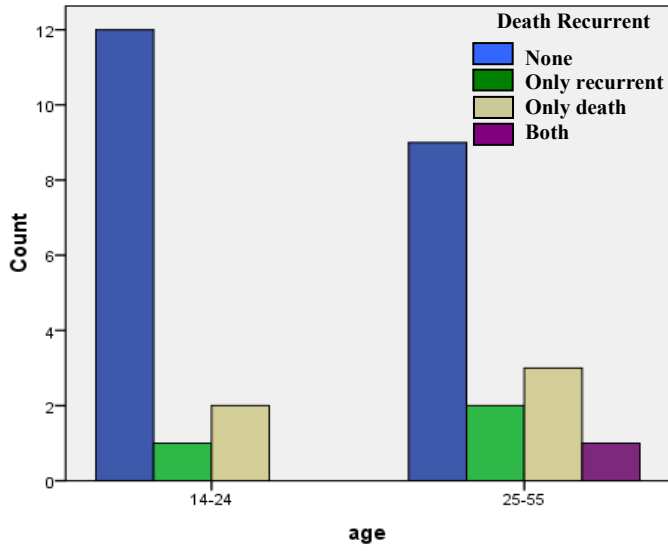
Some patients received less consolidation therapy because of drug adverse events (especially Anthracycline and/or age). So, maintenance therapy with Arsenic is recommended for such patients in order to decrease the recurrence rate.

According to the study by Powel Bel & Colleagues, there have been 2 arms including 2 courses of ATO as maintenance and 1 course without Arsenic. EFS rates in arms 1 and 2 were 77% and 59%, respectively. (Pvalue= 0.001). The overall survival was about 80%. So, the use of Arsenic as maintenance therapy improved EFS and provided a considerable improvement in OS.

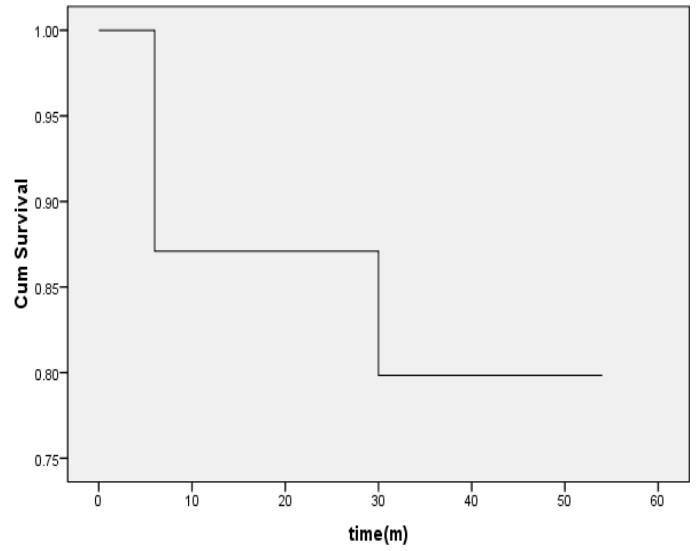
The toxicity of Arsenic is in acceptable minimum level; however the benefit of Arsenic as maintenance therapy induces 85% molecular response that consequently leads to the increase of survival.

Acknowledgement

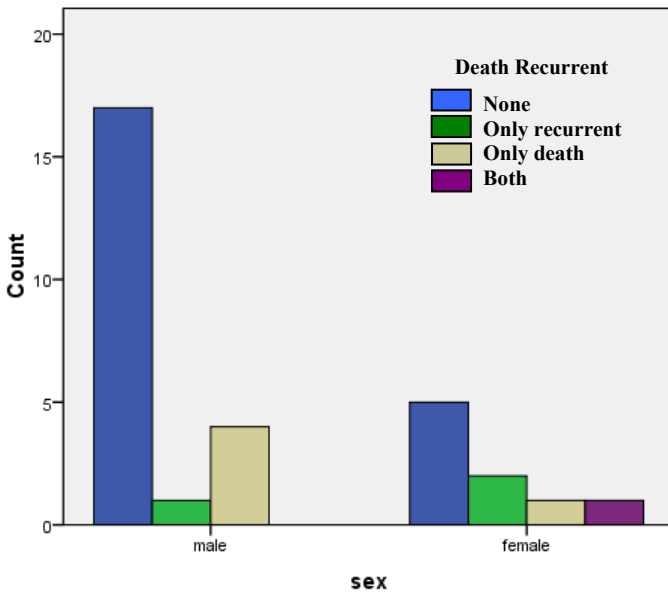
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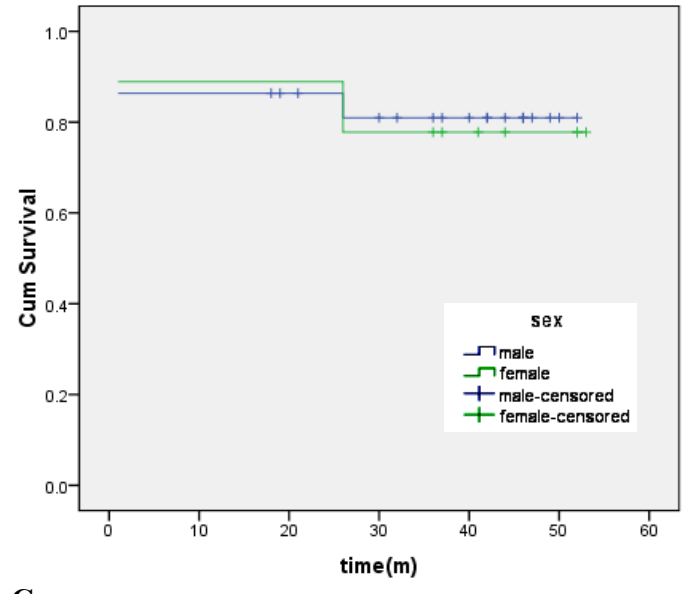
A



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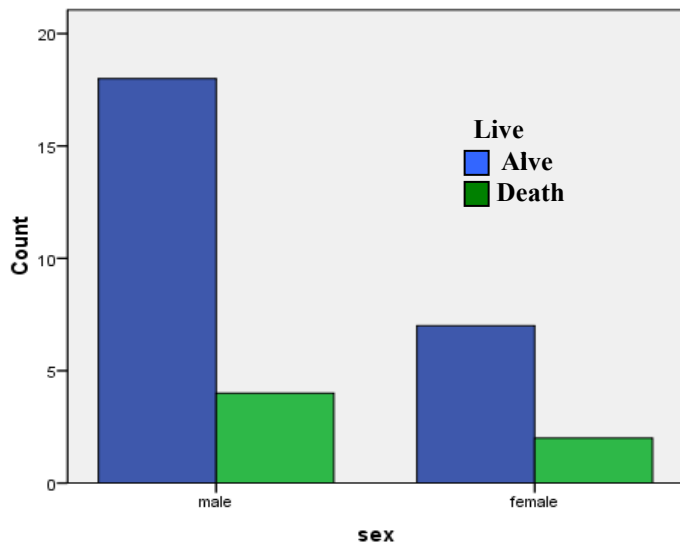
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C

Figures-1 A & B. These figures demonstrates the recurrence percentage that leads to death (based on age and sex).

Figures- 2 A, B and C. These figures are demonstrated patients' survival and survival based on sex differentiation.



A

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