Treatment of acute promyelocytic leukemia with arsenic trioxide without ATRA and/or chemotherapy

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Introduction: Arsenic trioxide is effective and approved for treatment of relapsed or refractory acute promyelocytic leukemia (APL) cases resistant to all-trans retinoic acid (ATRA), but its effect on new cases of APL is not clear.

Materials and methods: We studied 111 patients with APL. Arsenic trioxide was infused at 0.15 mg/kg daily dose, until complete remission was achieved. Then, after 28 days of rest, arsenic trioxide was infused daily for 28 days as consolidation therapy. We studied minimal residual disease (MRD) by semi-sensitive reverse transcription polymerase chain reaction (RT–PCR) on peripheral blood samples.

Results: Complete remission was observed in 95 patients (85.6%). With the median (range) follow-up period of 16.5 (1–57) months, 1- and 2-year disease-free survival was 88.3% and 63.7%, respectively; 24 patients relapsed, 19 of whom achieved a second complete remission, again by arsenic trioxide. Third and fourth remissions were seen in some relapsed patients, again by arsenic trioxide. For patients in complete remission, 1- and 3-year survival was 95.5% and 87.6%, respectively. MRD was positive in four (8.3%) out of 48 cases during 1 year after remission induction; three of them relapsed clinically.

Conclusions: Arsenic trioxide is effective as first-line treatment for APL. Results of arsenic trioxide combination therapy with chemotherapy/ATRA requires further study.

Key words: APL, arsenic trioxide, minimal residual disease

Introduction

Acute promyelocytic leukemia (APL) is a well-defined subtype of leukemia with specific and peculiar characteristics. The most important characteristic of this disease is translocation between chromosomes 15 and 17 in leukemic cells and the presence of PML/RARA fusion gene product in affected cells [1].

Today, accepted protocols for treatment of APL contain all-trans retinoic acid (ATRA), which is usually combined with an antitumor agent. Overall survival and 2–4 year event-free survival are 70–80% and 55–85%, respectively [2–10]. Maintenance therapy by ATRA with or without low-dose chemotherapy improves the results and reduces the relapse rate [6, 8, 11].

Recently, some groups observed that an ancient drug, arsenic trioxide, is useful for treatment of resistant or relapsed cases of APL after treatment with ATRA [12–15]. Arsenic trioxide is the most active single agent against APL cells, which induces maturation and apoptosis in APL cells [1] and reduces microvascular density of bone marrow.

Soignet et al. [16] showed that arsenic trioxide could induce a high molecular remission rate in relapsed APL cases. Today arsenic trioxide is accepted for treatment of such cases and has improved the results of treatment of APL, which is comparable to stem cell transplantation [17]. The role of this drug in the induction of remission or consolidation phase of new cases of APL is less clear.

The purpose of our study is to define the efficiency and the safety of arsenic trioxide in the treatment of new cases of APL and their follow-up.

Materials and methods

Acute promyelocytic leukemia diagnosed by clinical manifestations, morphologic FAB criteria, cytogenetics or fluorescence in situ hybridization study for detection of t(15;17) and/or RT–PCR for PML-RARA transcript.

Between May 2000 and January 2005, 111 APL patients were enrolled in our study. Pregnant women and patients with severe renal, hepatic or
cardiac dysfunction (creatinine >2 mg/dl, bilirubin >5 mg/dl and ejection fraction <50%), and patients with intracranial hemorrhage at presentation, were excluded from this study.

Seventeen patients were relapsed and 94 were new cases. Three patients had relapsed after previous stem cell transplantation (one after allogeneic and two after autologous stem cell transplantation) and 14 patients had relapsed after previous treatment by ATRA and chemotherapy. None of the relapsed cases had used ATRA or chemotherapy for maintenance therapy.

Hematological values and clinical characteristics of patients are shown in Table 1. Arsenic trioxide was prepared as 10 mg/10 ml vials, manufactured by the pharmaceutical faculty of Tehran University of Medical Sciences and was approved by the Deputy of Food and Drugs of the Ministry of Health and Medical Education for this clinical trial.

This clinical trial was approved by a local ethics review board and consent forms were obtained before treatment.

**Induction of remission**

After diagnosis of APL according to above criteria, arsenic trioxide was started immediately as a 2-h intravenous infusion of 0.15 mg/kg in 500 ml dextrose water. Treatment continued until achievement of complete remission by morphologic criteria or to a maximum of 60 days. Also, we did not use any chemotherapeutic agents or leukopheresis during treatment.

**Supportive care during treatment**

Prothrombine time, activated partial thromboplastin time, fibrin degradation products, and fibrinogen were measured at the time of diagnosis and regularly during the treatment. In the presence of disseminated intravascular coagulopathy, fresh frozen plasma and platelets were transfused.

White blood cell counts and peripheral blood smears were observed daily. Liver and renal functions were assessed regularly and fasting blood sugar, sodium, potassium, calcium, magnesium and urine analysis were tested twice weekly. Electrocardiograms were studied every other day and QTc intervals measured. In case of prolonged QTc, magnesium and potassium were infused for correction of QTc. Patients’ weight was measured daily and diuretics prescribed for severe edema or weight gain. If the liver enzymes increased to >10 times the upper limit of normal, or bilirubin to >5 mg/dl or creatinin to >2 mg/dl, arsenic trioxide was discontinued for several days. After correction of any abnormalities, drug administration was restarted with half of original dose and rapidly increased to full dose. In cases with hepatic or renal complications or APL differentiation syndrome during induction of remission phase, a full dose of arsenic trioxide was used as the consolidation phase, without any significant complications. APL differentiation syndrome (defined as weight gain, fever, polyserositis and dyspnea with or without radiographic markers of pulmonary infiltration) was treated by dexamethasone 10 mg twice daily, until patients’ symptoms improved. For patients whose APL differentiation syndrome progressed to adult respiratory distress syndrome or pulmonary hemorrhage, we immediately used assisted ventilation with oxygen supplementation and activated factor seven (Novo seven®) for some patients.

Peripheral blood smears were observed daily and bone marrow studied every 10 days for remission and maturation evaluation.

After complete remission was achieved, treatment was discontinued and patients discharged.

**Consolidation therapy**

After 28 days rest, consolidation therapy was started. It consisted of outpatient infusion of arsenic trioxide at daily dose of 0.15 mg/kg, 6 days a week, for a total of 28 infusions. During this period, patients visited every week and complete blood count (CBC), liver enzymes, renal function and electrocardiogram were evaluated.

**Follow-up**

After consolidation therapy, patients visited every month and then every 3 months. At each visit, their CBC, liver and renal function were studied.

**Definition of outcome**

Complete remission was defined using the classic definition: neutrophil count >1500/mm³, platelet count >100 000/mm³ and immature cells (promyelocytes and myeloblasts) <5% of nucleated bone marrow cells. Disease-free survival was measured from the time of complete remission until relapse or censorship of patients’ data. Overall survival was measured from the time of diagnosis and beginning of treatment by arsenic trioxide until the time of death or censorship of patients’ data.

**Minimal residual disease**

After complete remission, 48 patients evaluated for minimal residual disease (MRD). RT–PCR studies were performed on peripheral blood samples, searching for mRNA of PML–_RARA isoforms. MRD was studied after the consolidation phase and 12 months after complete remission. Sensitivity of RT–PCR was 10–3 for MRD detection. Sequences of forward and reverse primers are shown in Table 2.

**Statistical analysis**

Median values were measured for complete remission and hospitalization time. Disease-free and overall survival were calculated using the Kaplan–Meier method. Importance of risk factors for relapse and survival (including age, sex, white blood cell count at presentation, APL differentiation syndrome, hyperleukocytosis, treatment as new case versus relapsed cases, and MRD status) calculated by Fisher’s exact test, log-rank test and logistic regression.

**Results**

**Complete remission**

Complete remission was observed in 95 patients (85.6%). The median time for complete remission was 30 days (range 20–43).

**Minimal residual disease**

Sequence of primers used for diagnosis and follow up of minimal residual disease by nested RT–PCR

<table>
<thead>
<tr>
<th>Primer</th>
<th>Sequence (5′–3′)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M2</td>
<td>AGTGTACGCTTCCTTCATCA</td>
</tr>
<tr>
<td>M4</td>
<td>AGCTGTAGGGCCAGTGTGAGCCGGTACC</td>
</tr>
<tr>
<td>R5</td>
<td>CACTAGTGAGGCGGAGGAGT</td>
</tr>
<tr>
<td>R8</td>
<td>CAGAATGTGCTCGTCTGGTCTCAAT</td>
</tr>
</tbody>
</table>

WBC, white blood cell.

**Table 1. Patients’ characteristics**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Type of disease</th>
<th>Median age, years (range)</th>
<th>Median WBC count at presentation</th>
<th>Median hospitalization time, days</th>
<th>Median highest WBC count for patients with hyperleukocytosis, /mm³ (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Relapsed</td>
<td>27 (6–79)</td>
<td>2050</td>
<td>32</td>
<td>49 500 (10 200–167 700)</td>
</tr>
<tr>
<td>Male</td>
<td>New cases</td>
<td></td>
<td></td>
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Median length of hospitalization was 32 days for the remission induction phase. Remission was observed in 82 new cases (86.3%) and 13 (76.5%) relapsed cases. This difference was not statistically significant. Sixteen patients died in the induction phase owing to complications of disease or treatment. Causes of death were cardiac arrest in two patients, APL differentiation syndrome in eight patients (with pulmonary hemorrhage and/or acute respiratory distress syndrome), cerebral hemorrhage in three patients and disseminated aspergillosis in one patient. Two patients did not respond and died due to disease progression after chemotherapy. The median time of death was day 20 (range 2–55) during the induction phase.

**hyperleukocytosis**
Median white blood cell count was 2050/mm³ at the time of diagnosis. In 18 patients (16.2%) white blood cell count was >10 000/mm³, Hyperleukocytosis (white blood cell count >10 000/mm³) occurred in 65 patients (58.6%) during treatment. The median day for the beginning of hyperleukocytosis was 10 days (range 2–22) after starting treatment and the median highest leukocyte count in this group was 49 500/mm³ (range 10 200–167 700). There was no significant difference in white blood cell count at disease onset between patients with and without hyperleukocytosis, and it did not increase early mortality of treatment. We did not observe any association between hyperleukocytosis and APL differentiation syndrome, remission rate and relapse rate. Overall and disease-free survival were not significantly different for patients with and without hyperleukocytosis.

**APL differentiation syndrome**
APL differentiation syndrome usually manifested as weight gain, fever and respiratory distress, and in fatal cases rapidly terminated in pulmonary hemorrhage and respiratory failure. This complication was observed in 23 patients (20.7%); 10 of them succumbed during this complication (eight died due to APL differentiation syndrome and respiratory failure, one due to brain and pulmonary aspergillosis after resolution of APL differentiation syndrome and one due to intracranial hemorrhage).

There was no difference between new cases and relapsed subgroups. The death rate was significantly higher in patients with APL differentiation syndrome (P < 0.006).

**disease-free and overall survival analysis**
Median time of follow-up was 16.5 months (range 1–57). Relapse was observed in 24 patients (25.3%) in complete remission and median time of relapse after first complete remission was 17 months. One- and 2-year disease-free survival for patients in complete remission was 88.3% and 63.7%, respectively.

Disease-free survival was the same in new cases and patients who were treated after relapse following previous ATRA and chemotherapy.

For patients who relapsed after the first course of arsenic trioxide treatment, treatment was restarted with arsenic trioxide with the same schedule as the first treatment. Nineteen complete remissions observed in this group (79.2%) and median time of relapse for this group was 18 months.

One- and 3-year survival for patients in complete remission were 94.5% and 87.6%, respectively (Figure 1). Survival was the same in new cases of acute promyelocytic leukaemia and patients who treated after relapse following previous ATRA and chemotherapy.

We could not find any independent risk factor for relapse and survival in complete remission patients, except positive MRD following consolidation or during follow-up (P = 0.01 and <0.0001 respectively).

**molecular follow-up of patients**
Forty-eight patients were followed up by semi-sensitive RT–PCR for detection of PML–RARA fusion gene mRNA during the first year after complete remission.

All patients were in complete hematological remission at the time of MRD assessment. RT–PCR was positive in four patients (8.3%), three of whom relapsed clinically.

**retreatment of relapse**
Twenty-four patients who relapsed were retreated with the same treatment (arsenic trioxide) as before. Again, we observed 19 complete remissions (79.2%), and five patients died during second remission induction by arsenic trioxide.

**discussion**
We suggest that the complete remission rate of new cases of APL treated by arsenic trioxide is comparable to an ATRA–chemotherapy regimen. In European APL study group experience, event-free survival was 84% for patients who were treated by concomitant chemotherapy and ATRA and 77% for patients on a sequential regimen [18].

With arsenic trioxide alone, overall survival and complete remission rates were comparable to those of the European group study, although we suggest that adding maintenance therapy by intermittent infusion of arsenic trioxide with or without oral chemotherapy, or adding chemotherapy to induction or consolidation phase, may improve results. Recently, we increased the consolidation phase of arsenic trioxide to four...
cycles (two cycles after complete remission, and one 1 year and 2 years after complete remission, to reduce relapse rate).

ATRA without chemotherapy could not induce a durable remission [19–22], so we suggest that arsenic trioxide is superior to ATRA for new cases and can induce a durable remission and good disease-free survival. Also, long-term treatment with ATRA can induce drug metabolism in the liver, which reduces its efficiency. So possibly, arsenic trioxide would be part of frontline regimen in future.

In APL patients treated with arsenic trioxide, the most important limitation was APL differentiation syndrome, which is sometimes fatal. Although it is possible to control this complication by corticosteroids, better supportive care and use of activated factor seven in patients with pulmonary hemorrhage, it is sometimes fatal. This should be a subject for future studies to control this complication by early chemotherapy, use of ATRA in combination with arsenic trioxide and improved supportive care.

Detection of MRD is another possible subject for study to improve the results of treatment and to start arsenic trioxide early for these patients. It has been shown that if MRD is negative twice after complete remission, risk of relapse is minimal [5, 23, 24]. By a more sensitive RT–PCR (10⁻⁴ versus 10⁻³ in our study) after induction phase, Soignet et al. [16] observed that 85% of patients were negative for MRD. In our study, MRD was negative in 91.7% of patients for 1 year after complete remission.

Also, we suggest that early treatment after detection of MRD may improve the results of arsenic trioxide therapy and may prevent high mortality of relapse [25–27].

Recently, we completed a study on patients’ samples by a sensitive quantitative real-time PCR every 3 months, and we could define a threshold for relapse (unpublished data), which will be useful for early detection and treatment to improve results. We suggest that quantitative PCR is more accurate and predictive than regular PCR, and should be repeated for each patients at regular intervals (at least every 3 months, during first 2–3 years after remission) to predict relapse and early treatment.

references