Leukemia (2004) 18, 1587–1590

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Treatment of children with newly diagnosed acute promyelocytic leukemia with arsenic trioxide: a single center experience

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A total of 11 children (five males and six females) with hypergranular type of acute promyelocytic leukemia (APML) were treated with intravenous arsenic trioxide (As_2O_3) between December 1998 and October 2003. Eight cycles of As_2O_3 (0.15 mg/kg/day) were administered (induction, consolidation and six cycles of maintenance) over a period of 12 months. The median WBC count at diagnosis was 3400/mm^3 (range: 800–9800). In all, 10 patients (91%) achieved hematological remission at a mean duration of 48 days (range: 41–60) with all 10 patients achieving molecular remission at a median duration of 81 days (range: 64–109). Toxicity was minimal with leukocytosis in six patients, ichthyosis and hyperpigmentation of skin in five and mild peripheral neuropathy in one patient. One patient who relapsed 6 months after completing therapy achieved a second hematological and molecular remission with As_2O_3. With a median follow-up of 30 months (range: 4–62), the overall (OS) survival is 91% with a relapse-free survival (RFS) of 81%. As_2O_3 achieves hematological and molecular remission in majority of newly diagnosed children with APML with minimal toxicity, but long-term follow-up is required to evaluate late effects of As_2O_3 and study the minimum dose and duration required for a sustained remission.

Leukemia (2004) **18,** 1587–1590. doi:10.1038/sj.leu.2403480
Published online 9 September 2004
Keywords: APML; children; arsenic trioxide

Introduction

The incidence of acute promyelocytic leukemia (APML) in children varies between 8 and 30% of all cases of AML depending upon the geographic location.[1] The frontline therapy for APML using a combination of ATRA and chemotherapy has shown initial remission rates of 69–97% with event-free survival (EFS) ranging between 64 and 77% in studies from various countries including India.[2–6] Treatment with ATRA, however, is not financially possible for all patients in economically poor countries and hence alternative therapeutic strategies have been explored. Arsenic trioxide (As_2O_3) was initially used in the treatment of relapsed APML with remission rates of 80–90% and long-term DFS of 60–80%.[7,8] Subsequent reports from various centers including ours showed that As_2O_3 as primary therapy can achieve remission rates in 70–80% of patients.[9–11] There is, however, very limited data on its use in children and we share our experience with its use in newly diagnosed children with APML.

Patients and methods

Patients

A total of 11 children with newly diagnosed APML, who could not afford treatment with ATRA and hence were treated with As_2O_3 between December 1998 and October 2003, were included in this study. All patients met the morphological criteria for diagnosis according to the French–American–British (FAB) classification. The diagnosis was confirmed using conventional cytogenetics and either fluorescent *in situ* hybridization (FISH) for 15;17 or reverse transcriptase polymerase chain reaction (RT-PCR) for detecting PML-RARα transcripts. The initial three patients were treated as a part of an institutional study protocol after approval by the Institutional Review Board but subsequently since 2001, As_2O_3 has become part of the standard treatment protocol at our institution for patients with APML who cannot afford treatment with ATRA.

Treatment with As_2O_3

Intravenous As_2O_3 was prepared by dissolving specified quantities of As_2O_3 (AR grade (99.8% purity) from SD Fine Chemicals Ltd, Boisar, India) in sterile pyrogen-free distilled water at 60°C for 20 min. No other additives were used in its preparation. The final product had a concentration of 1 mg/ml and was supplied as 10-ml vials. As_2O_3 was administered at a dose of 0.15 mg/kg/day as an intravenous infusion in 500 ml of 5% dextrose saline over 4 h. Induction therapy was given till achievement of hematological remission (or a maximum of 60 days) followed by consolidation therapy for 28 days after a gap of 4 weeks. Maintenance therapy consisted of 10 days of As_2O_3 every month for 6 months (Figure 1).

Toxicity

Patients were monitored for toxicity particularly with regard to cardiac and hepatic function. Leukocytosis (WBC counts $>5000/mm^3$) during induction therapy was treated with hydroxyurea. If WBC counts were not under control with hydroxyurea, single or multiple doses of anthracyclines were used. Cutaneous examination was performed regularly during treatment and on subsequent follow-up. If patients had symptoms of peripheral neuropathy, nerve conduction studies were carried out to document the presence of a neuropathy.

Hematological monitoring and support

Complete blood counts, prothrombin time (PT), activated partial thromboplastin time (APTT), liver and renal functions were closely monitored. Platelet transfusions were given to maintain platelet counts more than 20 000/mm^3. Fresh frozen plasma (15 ml/kg) was infused if there was significant coagulopathy even in the absence of clinical bleeding. Bone marrow examination was carried out to assess remission once abnormal promyelocytes had cleared from peripheral blood along with normal platelet counts. Hematological remission (CR) was defined as absence of abnormal promyelocytes from peripheral

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Received 18 March 2004; accepted 9 June 2004; Published online 9 September 2004

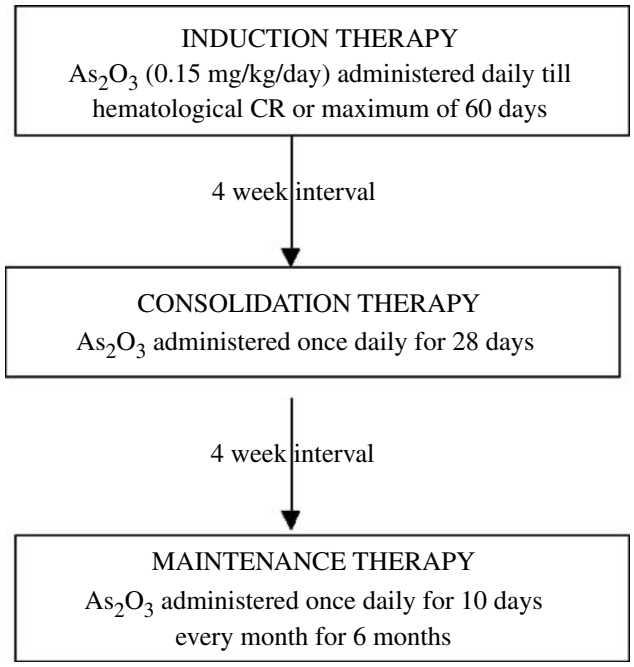

Figure 1 Protocol for treatment of patients with APML with As_2O_3.

blood with ANC $>1000/mm^3$, normal platelet counts and absence of abnormal promyelocytes in the bone marrow.

Molecular monitoring

RT-PCR for detecting PML-RARá transcripts was performed, as previously described by van Dongen *et al*,[12] at diagnosis, at the time of attaining hematological CR, prior to consolidation therapy, twice during maintenance therapy (3 months apart) and subsequently every 6 months. With a nested amplification, the RT-PCR had a sensitivity of 10^{-4} for bcr-3 transcripts and 10^{-3} for bcr-1 transcripts from cells of APML patients.

Results

Patients

There were five male and six female subjects with a median age of 12 years (range: 6–14). All had the hypergranular type of APML. The median WBC and platelet counts at diagnosis were 3.4×10^9/l (range: 0.8–9.8) and 18×10^9/l (range: 6–242) respectively. None of the 11 patients had any significant coagulopathy at diagnosis. All patients were RT-PCR positive for PML-RARα transcripts, while only nine showed the presence of t(15;17) on routine karyotyping. Two patients showed additional chromosomal abnormalities on routine karyotyping.

Hematological remission

A total of 10 patients (91%) achieved hematological remission, while one patient expired on day 5 of therapy due to an intracranial hemorrhage. The mean duration to achieving hematological remission was 48 days (range: 41–60). Eight patients (80%) have completed treatment, while two (20%) are still on treatment.

Table 1 Patient characteristics, survival and complications

Patient no.	*Age/ sex*	*Counts at diagnosis ($\times 10^9$/l)*	*Remission status*	*Complications*	*Follow-up (months)*
1	14/F	1.6	CR	NIL	62
2	14/F	1.4	CR	I	47
3	7/F	9.8	CR	L, C, I	43
4	12/M	1.5	CR	NIL	32
5	13/M	0.8	CR	L, C, PN	30
6	6/M	1.6	CR then relapse	I	22
7	11/F	5.7	EXPIRED DAY 5	L	0.5 E
8	14/M	3.3	CR	L, C	21
9	14/F	6.1	CR	I	13
10	15/M	2.0	CR	L, C	8
11	13/F	3.6	CR	L, C	3

L, leukocytosis; C, coagulopathy; I, ichthyosis/hyperpigmentation of skin; PN, peripheral neuropathy.

Toxicity

Leukocytosis during induction therapy was seen in six (60%) patients and occurred at a mean interval of 9 days (range: 2–15) after initiation of therapy. The median peak WBC count in these six patients was 29×10^9/l (range: 16.9–45.8). Hydroxyurea was used in all six patients for a mean duration of 12 days (range: 4–18) with a median cumulative dose of 415 mg/kg (range: 54–815). One patient received a single dose of anthracycline (Mitoxantrone) to achieve rapid reduction in blood counts. In three patients, As_2O_3 had to be temporarily discontinued for a mean of 3 days (range: 2–5), but it was successfully restarted in all patients. Dexamethasone was not used in any of the patients with leukocytosis. The median number of red cell and platelet units transfused during induction therapy were 3 (range: 0–16) and 11 (range: 0–27), respectively. Five patients (45%) developed coagulopathy during treatment requiring the use of fresh frozen plasma (FFP) over a mean duration of 4 days (range: 2–6). No patients required transfusions during consolidation and maintenance therapy. No cardiac or hepatic toxicity was seen. Minor toxicities seen included ichthyosis and hyperpigmentation of skin (seen in five patients) that resolved following cessation of therapy and mild reversible peripheral neuropathy in one patient (Table 1).

Treatment with As_2O_3

A total of eight cycles of As_2O_3 was administered to patients who have completed treatment. The mean duration of hospital stay during induction therapy was 14 days (range: 0–26). One patient, who had normal platelet counts at diagnosis, had the entire induction therapy administered on an outpatient basis. None of the patients required admission during their consolidation or maintenance cycles. The mean dose of As_2O_3 used during induction was 359 mg (range: 180–600) amounting to a mean dose of 9.1 mg/kg (range: 7.1–12.2). The cumulative dose of As_2O_3 used in patients who have completed treatment was 962 mg (range: 655–1480) amounting to a mean dose of 26 mg/kg (range: 21–30).

Molecular remission

Nine patients (81.8%) had the bcr-1 isoform, while one patient each had the bcr-2 and bcr-3 isoform. All 10 patients (100%) who achieved hematological remission also achieved molecular remission. The median time to achieving molecular remission was 81 days (range: 64–109). A total of nine patients (90%) were RT-PCR transcript negative for PML-RARα at the end of consolidation therapy, while one patient (10%) became RT-PCR transcript negative during maintenance therapy.

Follow-up

One patient had a hematological relapse 6 months after completion of therapy. He had complex cytogenetic abnormalities along with a t(15;17) on routine karyotyping at diagnosis. He achieved a second hematological and molecular remission following repeat induction therapy with As_2O_3 and is presently on consolidation therapy. With a median follow-up duration of 30 months (range: 3–60), the leukemia-free survival (EFS) is 81% with an overall survival (OS) of 91% (Figures 2 and 3).

Discussion

Children with APML have a good chance of cure following treatment with ATRA and chemotherapy. However, financial constraints preclude the use of ATRA in the majority of patients in economically poor countries and hence effective alternative therapies are necessary.

Treatment with As_2O_3 achieves remission rates of more than 90%, which is similar to data from children treated with ATRA and chemotherapy.[2,3] There is however no data regarding the use of As_2O_3 as primary therapy in children. Ma Jun *et al* in their study of 62 children with relapsed APML showed remission rates of 81% with a 7-year DFS of 65% (Blood 2001; abstract 3119). The high remission rates coupled with ease of administration and the minimal toxicity seen during treatment makes As_2O_3 an attractive option in children. The intravenous formulations of As_2O_3 may have an advantage even in infants and toddlers with APML, where ATRA may be difficult to administer because of the difficulty in solubilization of ATRA capsules. The short duration of hospital stay during induction therapy and the absence of need for hospital admission during consolidation and maintenance therapy also adds to the therapeutic value of arsenic. This therapeutic efficacy of As_2O_3 is even more meaningful for developing countries since the cost of treatment with As_2O_3 (US $2000) is a fraction of the cost of treatment with ATRA (US $15 000) since no local formulations of ATRA exist. This data is, however, preliminary since the median duration of follow-up in our study is only 30 months and hence we are unable to comment on the long-term survival with As_2O_3 and late toxicity if any. This report is the first to look at the use of intravenous As_2O_3 in children with newly diagnosed APML.

In conclusion, As_2O_3 achieves hematological and molecular remission in a majority of children with newly diagnosed APML. The ease of administration coupled with minimal toxicity makes it an attractive option in children. Long-term follow-up however is required to assess long-term remission and late side effects in children.

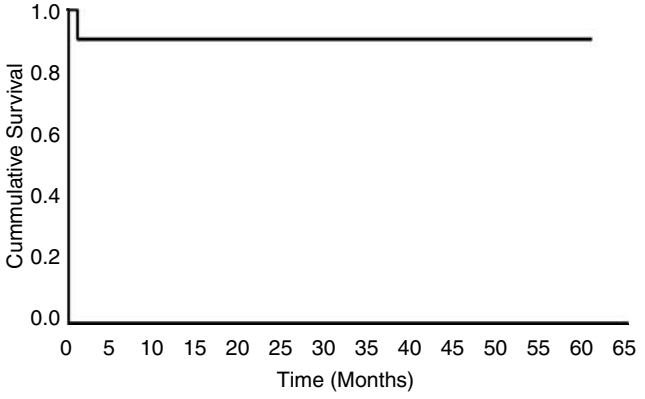

Figure 2 Overall survival in 11 children with APML treated with As_2O_3.

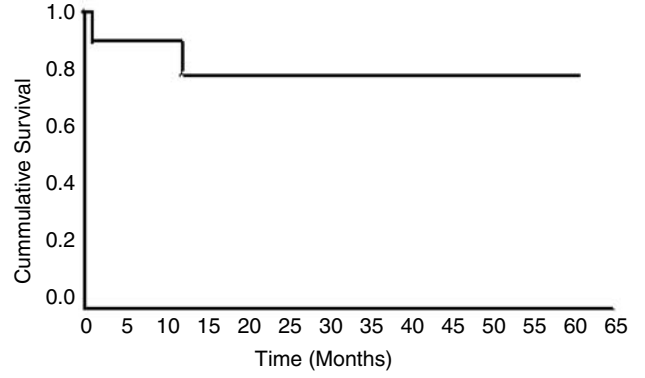

Figure 3 Event-free survival in 11 children with APML treated with As_2O_3.

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