

Arsenic trioxide therapy for relapsed acute promyelocytic leukemia: a bridge to transplantation

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Background and Objectives. Arsenic trioxide (ATO) has been reported to be a safe and effective treatment for relapsed acute promyelocytic leukemia (APL). The aim of this study was to evaluate the efficacy and toxicity as well as the eligibility to stem cell transplantation (SCT) in a series of 7 patients with relapsing APL, managed with ATO.

Design and Methods. Seven patients with relapsing APL while on maintenance treatment with all-trans-retinoic acid (ATRA) or who were ATRA refractory-received ATO at a dose of 10 mg daily by 2-hour intravenous infusion until complete remission (CR). After consolidation chemotherapy, patients were programmed to receive autologous or allogeneic stem cell transplantation (SCT) according to donor availability. The median age of the patients was 55 (21-71) years: 2 patients presented with concomitant extramedullary relapse.

Results. Six patients (86%) achieved CR after a median of 35 ATO doses (20-49) with negligible toxicity; one patient died from pneumonia. After consolidation with a four-day course of cytarabine at 1 g/m² and mitoxantrone 6 mg/m², two patients underwent allogeneic SCT, two received PML/RAR α negative autologous peripheral blood stem cells collected after consolidation plus granulocyte colony-stimulating factor, one failed mobilization and received a second consolidation course. One elderly patient refused further treatment and relapsed 6 months later. After a median follow-up of 15 months from CR2 achievement, 5 patients are alive in continuous CR.

Interpretation and Conclusions. The high CR rate and the mild toxicity confirm that ATO represents a valid alternative to salvage chemotherapy for patients relapsing while on ATRA treatment or who are ATRA-refractory. Allogeneic or autologous SCT after ATO-induced CR is feasible in the majority of patients.

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Key words: arsenic trioxide, promyelocytic leukemia, relapse, stem cell transplantation.

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The combination of all-trans retinoic acid (ATRA) with chemotherapy has marked a major advance in the treatment of acute promyelocytic leukemia (APL), resulting in a significant increase in complete remission (CR) rate as well as in a nearly two-fold increase in survival.¹ Contemporary strategies for newly diagnosed patients include ATRA plus anthracycline-based chemotherapy for induction and consolidation, and repeated courses of ATRA as maintenance.²⁻⁵ However, relapse still occurs in 20-30% of cases, mainly in patients with adverse prognostic characteristics at diagnosis.⁶⁻⁸ A substantial proportion of relapsing patients can be induced into CR2 with aggressive salvage chemotherapy, however treatment is often toxic and rarely curative.⁴ Stem cell transplantation represents the treatment of choice, once CR2 has been achieved by virtue of high dose chemoradiotherapy conditioning regimens and graft-versus-leukemia effect. However, transplantation results may be hampered by toxicities of the previous intensive salvage chemotherapy, therefore transplant-related morbidity and mortality still remain a major problem.⁹

Arsenic trioxide (ATO) has been reported as a safe and effective agent for the treatment of APL, with mild to moderate side effects in the majority of cases.¹⁰⁻¹² The mechanisms behind the therapeutic efficacy of ATO for APL are not definitely elucidated. The drug induces partial differentiation of APL cells after prolonged exposure, through degradation of both wild type PML and PML/RAR α chimeric proteins.¹³ In addition, ATO also induces apoptosis, possibly by indirectly impairing H₂O₂ catabolism with induction of a decrease in mitochondrial membrane potential, release of cytochrome C, and activation and upregulation of caspases 1, 2, 3, and 8.¹³

In this study we describe the clinical characteristics and treatment results in a series of 7 patients with relapsed APL managed with ATO, on the assumption that such treatment, by inducing fewer complications than conventional salvage chemotherapy, would result in a reduction of SCT-related morbidity and mortality, once further CR had been achieved.

Table 1. Patient's characteristics and clinical outcome.

UPN	Age/gender	Months from CR1	WBC	ATO total dose	WBC peak	Concomitant CHT	Response	Days to CR	RT-PCR after consolidation	Transplant
1	60/M	9	1.4	350	81.3	no	CR	28	neg	n.d.
2	71/F	8	1.1	490	1.5	no	CR	33	pos	n.d.
3	55/M	16	2.0	200	3.5	no	CR	40	neg	ABMT
4	69/M	15	1.7	280	18.1	no	CR	38	neg	ABMT
5	53/F	23	16.6	150	82.0	yes	ID	–	–	–
6	41/F	24	0.8	340	88.6	yes	CR	34	neg	ALLO
7	21/F	13	4.2	430	70.0	no	CR	32	neg	MUD

Design and Methods

Seven APL patients with overt clinical relapse were entered into this study. They all fulfilled morphologic criteria for APL (M3 n=4, or M3v n=3) at the time of relapse. Diagnosis was confirmed by the presence of the t(15;17) translocation and PML/RAR α gene rearrangement in all cases. The patients' characteristics and clinical outcome are summarized in Table 1. Their ages ranged from 21 to 71 years (median: 55 years). There were 3 males and 4 females. White blood cell (WBC) count before the start of therapy ranged from 0.8 to 16.6 $\times 10^9/L$ with a median of 1.7 $\times 10^9/L$. Platelet count ranged from 12 to 44 $\times 10^9/L$, with a median of 32 $\times 10^9/L$. Three patients had signs of disseminated intravascular coagulation: 1 severe, 2 mild. Five patients were in first relapse from CR achieved with the AIDA protocol² and all were on maintenance therapy with intermittent pulses of ATRA. Two patients were in second relapse, refractory to salvage attempts with chemotherapy plus ATRA. The median time of first CR duration was 15 months. Two patients presented with concomitant extramedullary relapse (central nervous system + middle ear + lymphnodes; skin + lymphnodes).

ATO (As₂O₃) vials were supplied by Dr. Varini from the Pharmacy of Careggi Hospital, Florence. Briefly, arsenic trioxide 99.8% (Carlo Erba, Milan, Italy) was dissolved under vertical laminar flow in water for injection at boiling point, until the final concentration of 0.1%. The solution, sterilized and stored in vials (10 mg in 10 mL), proved stable for more than 2 years. After obtaining written informed consent, patients received a daily dose of 10 mg (0.13–0.17 mg/kg) of ATO diluted in 500 mL of normal saline over 2 hours by i.v. infusion until all visible leukemic cells were eliminated from the bone marrow. Complete blood counts, electrolytes and measurement of coagulation parameters were performed at least 3 times a week. The ECG was monitored weekly. Coagulopathy was treated using tranexamic acid, fresh plasma and platelet transfusion. Aggressive

fluid and electrolyte replacement was performed when required. Meningeal involvement was treated with intrathecal methotrexate until clearance of blasts from cerebrospinal fluid.

Response was evaluated by standard criteria: CR was defined as less than 5% of blasts and promyelocytes in bone marrow aspirate with evidence of maturation of all cell lines and restoration of peripheral blood counts. Severity of treatment-related toxicity was graded according to the WHO criteria.¹⁴ Disease-free survival (DFS) was calculated from the time of CR2 achievement to the time of relapse, death from any cause, or last follow-up. Overall survival (OS) was calculated from start of ATO to death or last follow-up, according to the Kaplan and Meier life tables.¹⁵

Patients who fulfill criteria for CR were programmed to receive a consolidation course consisting of cytosine arabinoside 1 g/m² on days 1 through 4 (intravenous infusion over 6 hours) followed 3 hours later by mitoxantrone 6 mg/m² i.v. bolus days 1 through 4. Subsequently, after reverse transcriptase-polymerase chain reaction (RT-PCR) analysis for PML/RAR α transcript, autologous or allogeneic SCT was planned, according to donor availability and RT-PCR results.

Results

Six patients (86%) achieved CR 28–40 days after the start of treatment. The median number of ATO doses required for induction was 35 (range 20–49). One patient in second relapse (UPN5), who showed a rapid increase of WBC count from 16.2 to 82 $\times 10^9/L$ with exacerbation of hemorrhagic syndrome, received two doses of mitoxantrone 10 mg/m²; nonetheless, the patient continued to deteriorate and died on day 25 from the start of ATO from *Pseudomonas aeruginosa* sepsis and pneumonia. His bone marrow was severely hypoplastic. Overall toxicity for patients achieving remission was acceptable: transient elevation (grade 2) of transaminases was observed in one patient, grade

1 skin rash in two. ATO rapidly improved coagulopathy without inducing aplasia, and morphologic differentiation of leukemic promyelocytes was observed in peripheral blood as well as in bone marrow in all cases. Hyperleukocytosis $>20 \times 10^9/L$ peaking after 13-19 days was recorded in 4 patients (Figure 1) and, although no case of typical ATRA syndrome occurred, concomitant chemotherapy with two pulses of mitoxantrone (10 mg/m^2) was given to two patients. No relevant cardiac toxicity was recorded; only one patient showed transient Q-T prolongation. No patient experienced significant neuropathy or musculoskeletal pain.

After CR achievement, the 71-year old patient (UPN 2) refused chemotherapy, received two further 7-day courses of ATO as consolidation but relapsed six months later and died of progressive disease. In this patient, at the time of morphologic CR, the RT-PCR for PML/RAR α was still positive (RT-PCR sensitivity of 10^{-4}). The remaining five patients received the planned four-day consolidation course with mitoxantrone and ARA-C. No relevant side effects apart from myelosuppression were recorded during this treatment and, after completing chemotherapy, all patients were found to be PCR negative for PML/RAR α hybrid and were scheduled to receive SCT. Two underwent HLA-matched allogeneic bone marrow transplantation (one from a sibling and one from an unrelated donor); two received PML/RAR α -negative autologous peripheral blood stem cells ($5-5.2 \times 10^6/\text{kg CD34}^+$) successfully collected after consolidation chemotherapy plus G-CSF; one failed mobilization and received a second identical course of chemotherapy, after refusing bone marrow harvest. The toxicity of SCT was negligible in 3 cases, while the patient transplanted from a related donor suffered from grade 2 acute cutaneous graft-versus-host disease (GVHD). At the closing of this study on September 30, 2001, five patients were in hematologic and molecular remission after a median follow-up of 15 months (range, 10 to 17) from the achievement of CR2. The survival of the whole group is shown in Figure 2.

Discussion

The introduction of ATRA has significantly improved the disease-free and overall survival in APL; nonetheless, relapse still occurs in 20-30% of patients.³⁻⁸ A further CR can be attained by salvage chemotherapy, but the achievement of long-term survival seems strictly related to the possibility of undergoing SCT. However, therapeutic results in terms of eligibility to SCT as well as of transplant-related morbidity and mortality can be influenced

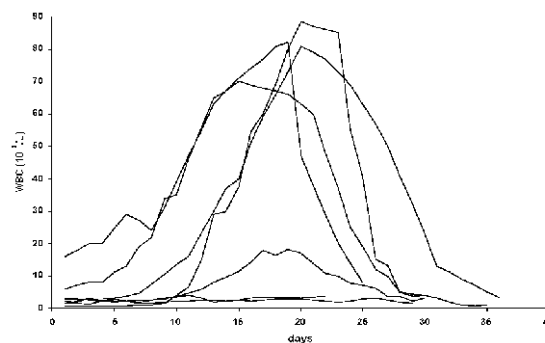


Figure 1. Daily total leukocyte count of 7 patients during ATO treatment.

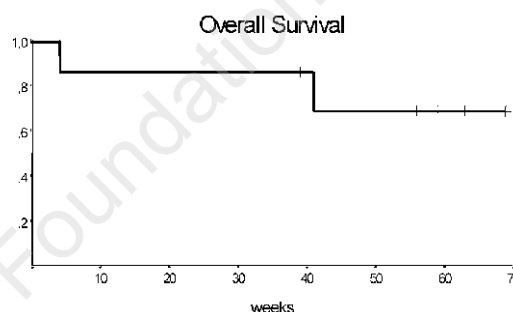


Figure 2. Overall survival.

by the toxicities of previous treatments.⁹ Therefore, attempts to induce CR with relatively low toxicity are advisable. ATRA alone can induce occasional and short-term remissions in patients previously treated with ATRA,¹⁶ but patients relapsing while on ATRA treatment or recently treated with this drug have been found to be highly resistant.¹⁷⁻²⁰ The new synthetic retinoid Am80^{21,22} and the liposomal ATRA²³ can in turn induce a second CR with mild adverse effects in about 50% of relapsed APL; however, an adequate ATRA-free period is required also for these agents.

Aggressive salvage chemotherapy induces CR in absence of severe toxicity in most patients with molecular relapse,⁵ while results in overt hematologic relapse are less encouraging. Indeed, these patients often present with a clinical picture of disseminated intravascular coagulation and a proportion of them can die during the reinduction attempt. Furthermore, once CR is achieved, any transplantation procedure can be hampered or precluded by the toxicity of previous treatment.

Thomas *et al.* reported a 90% CR rate in 50 cases of relapsed APL, but among 11 patients who subsequently underwent allogeneic SCT, 8 died while in CR either from severe infection or from graft-versus-host disease; toxicity deriving from intensive chemotherapy before transplantation was advocated as being responsible for the high mortality rate observed in this study.²⁴ An interesting alternative to conventional chemotherapy could be Mylotarg, as suggested by a recent report.²⁵

Preliminary studies from China suggested that ATO represents a useful salvage treatment for APL patients relapsed after or refractory to ATRA and chemotherapy.¹⁰ More recently, the efficacy and safety of this compound has been confirmed.¹²

In our series of 7 patients relapsing while on ATRA treatment ($n = 5$) or in second relapse and refractory to salvage therapy with ATRA plus chemotherapy ($n = 2$), CR was achieved in 6 cases (86%). One patient died after receiving chemotherapy to control extreme leukocytosis which developed during the ATO treatment. Although clinical practice does not advocate cessation of ATO in the setting of hyperleukocytosis, which resolves spontaneously in the majority of cases,²⁶ some fatal complications have been reported.²⁷ We cannot exclude that severe myelosuppression contributed to the development of pneumonia in our patient. Overall, toxicity observed in our series, including patients with a median age of 55 years, was mild. Of note, no severe cardiac toxicity was recorded, apart from transient prolongation of the Q-T interval in one patient.

Adverse events reported with ATO include fluid retention, peripheral neuropathy, QT prolongation, hyperglycemia, hypokalemia and skin reactions.²⁸ Most of these side effects are not life-threatening, but ATO may result significantly or even fatally toxic at doses currently used: cardiac arrhythmias²⁹ as well as sudden and unexplained deaths during or after treatment have been reported;³⁰ thus, aggressive electrolyte replacement and ECG monitoring are mandatory. Even though cardiac toxicity could be reduced without loss of efficacy using lower dosages,³¹ it is advisable to deliver ATO with caution in patients with pre-existing cardiac abnormalities.

After ATO reinduction, we used the four-day course of chemotherapy with the aim of CR consolidation and peripheral blood stem cell harvesting. The treatment was well tolerated and only one patient failed mobilization. Molecular evaluation immediately after ATO treatment was not routinely performed but after consolidation chemotherapy all patients resulted to be in molecular remission. Thus, we cannot elucidate the role of ATO in the

achievement of molecular response. However, in a recent multicenter trial, 86% of evaluable patients converted to being negative for the presence of PML/RAR α transcript after ATO alone.¹²

In our series, 4 patients out of 5 achieving molecular CR, including one aged 69 years, underwent SCT. The only patient not transplanted was a poor mobilizer, who had refused bone marrow harvest. However, this patient too, consolidated with an additional course of cytarabine plus mitoxantrone, is still in molecular CR. Overall, the toxicity of transplantation was mild, consisting of cutaneous grade 2 GVHD in one case. It is conceivable that the low toxicity of the previous salvage therapeutic strategy, including ATO and one short consolidation course of chemotherapy accounted for the favorable outcome of SCT in our series.

In conclusion, in a small number of cases our results confirm that ATO may represent a recommendable option for relapsed APL. The high CR rate, achievable with a minimal degree of myelosuppression and manageable toxicity, resulted in a high percentage of eligibility to allogeneic and autologous SCT, substantially lowering transplant-related morbidity and mortality.

Contributions and Acknowledgments

FL was responsible for the study design and writing the paper. GG, RF and MA collaborated in patient care, follow-up and data management. SC and CN performed the cytogenetic studies. FF oversaw the work and revised the manuscript.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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PEER REVIEW OUTCOMES

Manuscript processing

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What is already known on this topic

Arsenic trioxide has been established as a highly effective agent in *de novo* and relapsed APL and its activity is non-cross resistant with respect to ATRA.

What this study adds

Feasibility of auto and allograft after ATRA-induced second CR.

Potential implications for clinical practice

Although the exact place of arsenic trioxide in APL is still a matter of investigation, use of this agent at relapse appears a valid option particularly in patients relapsing shortly after ATRA discontinuation.

Francesco Lo Coco, Deputy Editor