Acute Myeloid Leukemia

Superiority of an arsenic trioxide-based regimen over a historic control combining all-trans retinoic acid plus intensive chemotherapy in the treatment of relapsed acute promyelocytic leukemia

There is still no consensus on the best approach for the treatment of relapsing acute promyelocytic leukemia. All-*trans* retinoic acid plus chemotherapy is hampered by potential mechanisms of resistance, and the safety profile of chemotherapy may be considered as not acceptable before stem cell transplantation. Arsenic trioxide provides an option for these patients.

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We retrospectively collected data on 25 consecutive patients with relapsed acute promyelocytic leukemia (APL) re-induced with arsenic trioxid (AS_2O_3) (Trisenox®) alone (0.15 mg/kg/day i.v until complete remission or a maximum of 60 days) in different French Institutions. Twenty-one patients (84%) achieved complete remission after initial AS_2O_3 treatment. Early death was observed in two cases and resistance in two. Molecular remission, as measured by reverse transcriptase-polymerase chain reaction (RT-PCR) of bone marrow specimens for *PML-RARα* transcripts, was documented in eight (38%) of the 21 patients achieving hematologic complete remission. Amplification of such a leukemia-specific marker by RT-PCR can identifiy one leukemic cell among 10^5 normal cells. Of the 21 patients who achieved hematologic complete remission, nine received at least a second cycle of AS_2O_3 at the same daily dose given for a cumulative total of 25 days, followed in two cases by consolidation chemotherapy (idarubicin + cytarabine ± all-trans retinoic acid [ATRA]) and in all patients by maintenance therapy (including methotrexate plus 6-mercaptopurine ± AS_2O_3 ± ATRA) for 2 years. The 12 other remitters underwent hematopoietic stem cell transplantation (SCT) with a median time to transplant of 4.7 months: nine received unpurged autologous SCT and three genoidentical allogeneic SCT, after at least a second cycle of AS_2O_3 followed in five patients by one course of consolidation chemotherapy (anthracycline + ATRA + cytarabine). At a median follow-up of 2.5 years, only three relapses (14%) have been observed (median time to relapse, 7.1 months). Seventy-five percent of the patients in continuous complete remission were *PML-RARα* negative according to sensitive nested RT-PCR analysis. AS_2O_3-based therapy resulted in a 2-year leukemia-free survival and a 2-year overall survival of 90% and 77%, respectively. Favorable prognostic factors for survival were transplantation as post-remission therapy (p=0.01) and less than three therapeutic lines (p=0.0005).

Our data confirm that patients in first or subsequent relapse following ATRA-anthracycline-based therapy will benefit when they are treated with AS_2O_3 either before maintenance therapy or before transplantation. Molecular remission is a mandatory therapeutic objective in APL, as was recently established by an international expert panel.[1] Early therapeutic intervention at the time of molecular relapse provides a survival advantage over treating hematologic disease recurrence.[2,3] In our series, two patients were retreated at time of molecular relapse and showed a favorable outcome. Molecular remission was also recommended before harvesting stem cells in the setting of a planned autologous SCT. All our autografted patients were in molecular remission before transplantation. The administration of at least two cycles of AS_2O_3 prior to SCT seems sufficient for an optimal outcome, as in the US multicenter trial, in which conversion to RT-PCR negativity occurred in 86% of patients after two cycles of this treatment.[4]

As previously reported,[5] the significant adverse effects were few and manageable. The results appear more favorable than those of our previous strategy based on ATRA and intensive timed-sequential chemotherapy

Table 1. Main characteristics and outcome of patients in both cohorts.

Patients' characteristics	*ATRA-EMA therapy (50 patients)*	*AS_2O_3-based therapy (25 patients)*
Clinical characteristics at relapse		
Age (years)	47 (20 - 65)*	53 (21 - 80)
FAB subtype (M3/M3v)	46 / 4**	24 / 1
N. of relapses (R1/R2/R3)	50/0/0	21 / 3 / 1
Molecular biology (bcr1/bcr2/bcr3)	ND	40%/10%/50%
Front-line therapy		
DNR + AraC	1	–
ATRA + DNR + AraC	41	25
Ida + AraC	2	–
ATRA + Ida + AraC	1	–
DNR + AraC + CCNU	5	–
Last CR duration (months)	17 (6 - 286)	18 (0.9 - 112)
Hematologic characteristics at relapse		
WBC count ($\times10^9$/L)	1.95 (0.8 - 65.2)	2.85 (0.5 - 42.9)
Platelet count ($\times10^9$/L)	65 (5 - 260)	64 (4 - 281)
BM blast cells (%)	68 (6 - 95)	47 (0 - 95)***
Induction therapy		
CR/failure	45 (90%) / 5 (10%)	21 (84%) / 4 (16%)
Median time to CR	47 days	49 days
Granulocyte recovery >0.5$\times10^9$/L	34 days (22 - 43)	18 days (0 - 52)
Platelet recovery >50$\times10^9$/L	40 days (22 - 89)	0 day (0 - 52)
Side effects		
APL differentiation syndrome	14%	18%
Severe infection (WHO ≥2)	54%	27%
Prolongation of the QT/QTc interval	–	11%
Post-remission therapy		
Post-remission chemotherapy	9	9
Autologous SCT	22	9
Allogeneic SCT	11	3
No post-remission therapy	3	0
Treatment outcome		
All patients		
2-year leukemia-free survival	47%	90%
2-year overall survival	51%	77%
Patients in second line therapy who received ATRA + DNR + AraC as first line treatment¶		
2-year leukemia-free survival	46%	89%
2-year overall survival	47%	88%

**median (range); **number of patients; ***two patients were only in molecular relapse; ¶This comparison involved 41 patients who received ATRA-EMA therapy and 21 patients who received AS_2O_3-based therapy. AraC: cytarabine; BM: bone marrow; CCNU, lomustine; CR: complete remission; DNR: daunorubin; Ida: idarubicin; ND: not determined; N.: number; SCT: stem cell transplantation; WBC: white blood cell.*

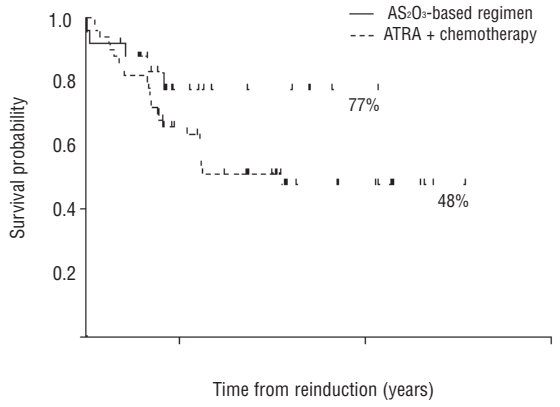

Figure 1. Comparison of outcomes in patients treated with the AS_2O_3-based regimen and in historic controls (all patients).

(etoposide plus mitoxantrone plus cytarabine).[6] The main characteristics of patients in both cohorts are presented in Table 1. While the proportions of patients in complete remission were comparable, 2-year leukemia-free survival and 2-year overall survival rates were higher in patients receiving AS_2O_3-based therapy than in the historic controls (Figure 1). When considering only patients receiving SCT, results showed a benefit with AS_2O_3-based regimen in terms of 2-year leukemia-free survival (100% vs 54%) and 2-year overall survival (100% vs 61%), the historic control showing a high mortality associated with the allogeneic SCT procedure.[6] There were several disadvantages of using ATRA combined with chemotherapy. This combination may result in severe myelosuppression. Only 63% of patients who underwent cytapheresis proceded to autologous SCT. This was mainly related to serious infection during induction chemotherapy and a poor condition at the time of harvesting. Although intensive chemotherapy prior to cell harvesting may play an important role in reducing the tumor burden before stem cell collection (almost all patients were PCR negative for *PML-RARα* after timed-sequential chemotherapy), the use of chemotherapy before transplantation could be responsible for the higher mortality rate observed after allogeneic SCT.[6] This observation was confirmed by the European APL group which reported a 40% death rate from transplant-related complications in 20 patients receiving allogeneic SCT. A relapse rate of 16% and a transplantation-related mortality of 4% were observed among 45 patients after autologous SCT.[7]

Despite the limitations of a retrospective study, our results confirm the recommendations of the European APL Group of Experts.[8] AS_2O_3 could be considered as the first-choice therapy in relapsed APL patients. Due to its ability to induce molecular remission and in lights of its limited myelosuppression and other toxicities, AS_2O_3 represents the treatment of choice before SCT.[9,10]

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