Therapeutic potential of arsenic trioxide with or without interferon-α for relapsed/refractory adult T-cell leukemia/lymphoma

Arsenic trioxide (As_2O_3) with or without interferon-α (IFN) was given to 4 patients with relapsed/refractory adult T-cell leukemia/lymphoma (ATLL). Treatment with As_2O_3 and IFN showed an encouraging response in two moderately-aggressive ATLL patients, while As_2O_3 alone was ineffective in two patients with very aggressive and rapidly progressing ATLL. Further studies are needed to clarify the role of As_2O_3 and its usefulness when combined with IFN for the treatment of ATLL.

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Induction of apoptosis and growth inhibition on ATLL cell lines by As_2O_3 with or without interferon-α (IFN) have been reported previously.[1-3] Notably a French phase II trial of As_2O_3 and IFN therapy in seven patients with relapsed/refractory ATLL showed complete remission (CR) in 1 patient and partial remission (PR) in 3 patients.[4] We report here the results of a pilot study of As_2O_3 with or without IFN for patients with relapsed/refractory ATLL carried out in a highly HTLV-I endemic area in Japan.

Patients with relapsed/refractory acute, lymphoma or unfavorable chronic type of ATLL[5,6] were included. According to the original protocol, patients received a daily administration of As_2O_3 (0.15 mg/kg/day) alone. This protocol was later modified to add intramuscular administration of 3×10^6 unit of IFN (Sumiferon™, Sumitomo pharmaceuticals, Osaka, Japan) three times a week during As_2O_3 treatment. In consideration of safety issues and on the basis of *in vitro* experimental results,[1,2] the dose of As_2O_3 and IFN was set as the approved dose for the treatment of acute promyelocytic leukemia and chronic myelocytic leukemia respectively. This study was reviewed and approved by the Fukuoka University Ethics Committee and Institutional Review Board of Fukuoka University Hospital. The As_2O_3 solution was prepared as previously described.[7] All patients provided their written informed consent. Treatment response was determined by the criteria described by Yamada *et al.*,[8] and toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC version 2.0).

Patients' characteristics and results of As_2O_3 therapy are summarized in Table 1. Adverse events observed during the treatment were managed with standard approaches. Patients 1 and 2 were heavily treated with multiple conventional chemotherapeutic agents prior to As_2O_3 treatment and their performance status was poor. Furthermore, disease progression was extremely rapid as suggested by the evidence that, in these patients, doubling time of serum LDH levels which correlated with tumor burden was 1 to 3 days (*data not shown*). On the other hand, As_2O_3 and IFN therapy produced promising effects in patients 3 and 4, who achieved PR and improvement of thrombocytepenia caused by massive bone marrow infiltration of ATLL cells, respectively (Figure 1). Most importantly, PR was maintained for as long as 8 months in patient 3 who had previously required uninterrupted conventional chemotherapy to avoid progression of ATLL.

Table 1. Patients' characteristics and results of As_2O_3 therapy.

Patient	*1*	*2*	*3*	*4*
Age	35	66	75	78
Gender	Male	Male	Female	Male
ATLL subtype	Acute	Lymphoma	Chronic*	Chronic→ Acute
Interval from diagnosis to As_2O_3 therapy (months)	65	27	52	12
Previous chemotherapy				
Number of regimens	6	5	2	2
Best response	CR	PR	SD	SD
At As_2O_3 therapy				
Interval from previous therapy (days)	26	14	33	42
Involved organ	PB,LN,L,Sp,S	LN,L,BM	PB,S	BM
PS	3	3	1	1
As_2O_3 therapy				
Combination with IFN	No	No	Yes	Yes
Treatment duration (days)	4	2	33, 20, 28, 13	18, 17
Response	PD	PD	PR	SD**
Overall survival (months)	3	5	26	7
Toxicity (graded by NCI-CTC version 2)		1		
Anemia				
Neutropenia				4
Thrombocytopenia			2	
Nausea		2		
Skin rash		1		1
Peripheral neuropathy			1	
Weight gain	1	1		
Fever		1		2
Hypokalemia			1	
QTc prolongation	1		1	3

*CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; R/R: relapsed and refractory; PB: peripheral blood; LN: lymph node; L: liver; Sp: spleen; S: skin; BM: bone marrow; *; unfavorable chronic type ATLL **; improvement of thrombocytopenia due to massive infiltration of ATLL cells to bone marrow.*

Cytotoxicity of As_2O_3 and augmentation of its effects by combining with IFN in fresh ATLL cells obtained from patient 3 revealed *in vitro* by trypan blue exclusion dye. Peripheral blood mononuclear cells (PBMNC) were separated by Ficoll-Hipaque density sedimentation from heparinized peripheral blood obtained from patient 3 before starting the treatment. More than 90% of separated PBMNCs were ATLL cells as determined by the expression of CD4 and CD25 by flow cytometry. These cells were cultured with As_2O_3 (1.0 and 2.0 μM) and/or IFN (10 U/mL) for 120 hours. The concentrations of As_2O_3 were set according to pharmacokinetics in humans.[9,10] Treatment with As_2O_3 decreased the number of viable ATLL cells as compared with control in a dose and time dependently, and IFN which had been ineffective alone, significantly enhanced the effects of As_2O_3 (*data not shown*).

Patients included in our study had been much more heavily treated before As_2O_3 treatment than those in the French study.[4] It is difficult to determine the efficacy in patients 1 and 2 since disease progression was rapid and treatment was terminated early. Their clinical course suggests that As_2O_3 has a modest therapeutic potential, if any, on patients with heavily-treated and rapidly progressing ATLL. In contrast, the significant therapeutic response in patients 3 and 4 suggests that moderately-aggressive ATLL could benefit from As_2O_3 therapy.

In conclusion, although this study involved only a

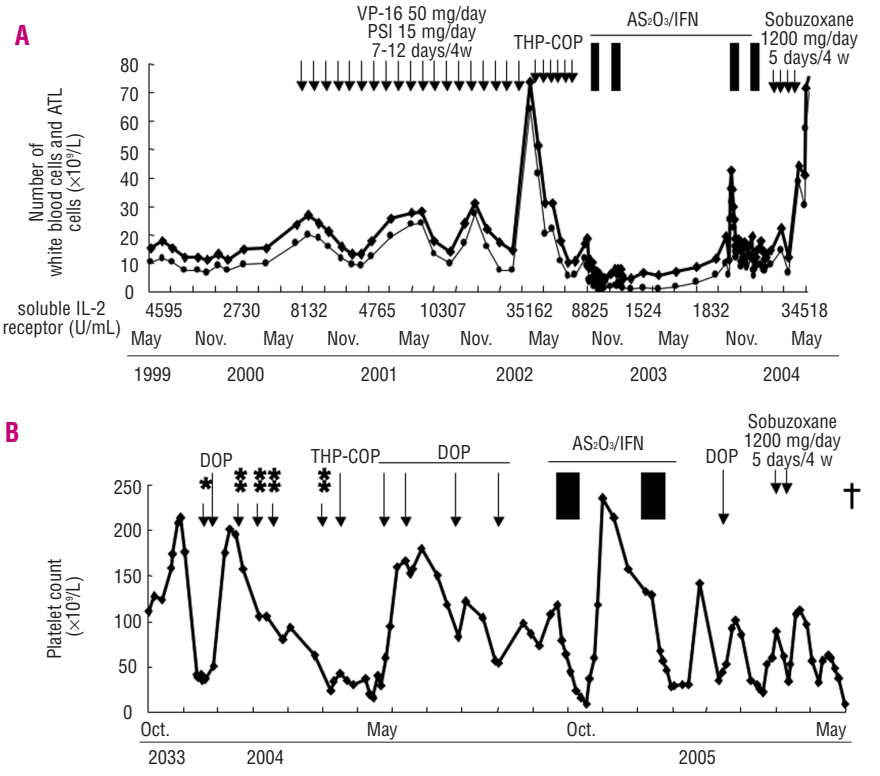

Figure 1. Clinical course in patient 3 (A) and patient 4 (B). A. Treatment, the number of white blood cells (bold line) and ATLL cells (thin line) are shown. The patient died in November 2004. B. Treatment and platelet count are shown. VP-16; etoposide, PSL; prednisolone, THP-COP; pirarubicin. cyclophosphamide, vincristine and prednisolone, DOP; dexamethason, vincristine, peplomysin, *; etoposide 100 mg (3 days) and PSL 60 mg (5 days), **; etoposide 50 mg (5 days).

limited number of patients, it does provide important information about who could benefit from As_2O_3 therapy. Moderately-aggressive relapsed/refractory ATLL patients are promising candidates, while those who are heavily-treated or presenting very aggressive ATLL do not appear to benefit. Further studies are needed to determine the efficacy of As_2O_3 treatment and its usefulness when combined with IFN for the treatment of ATLL.

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