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Interferon- α and zidovudine for relapsed/refractory adult T cell leukemia/lymphoma: case reports of Japanese patients

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Abstract Combination therapy with interferon- α and zidovudine (IFN/AZT) has been regarded as standard care for acute and indolent (i.e., chronic and smouldering) ATL based on reports involving a limited number of patients. This treatment approach has not been evaluated in Japan, a major endemic area of this disease in the world. This is the first Japanese report of IFN/AZT for ATL. It is impossible to draw any definitive conclusion from this small study; however, IFN/AZT showed clear anti-ATL effects for refractory/relapsed ATL patients. This report would contribute for developing future ATL treatment in Japan.

Keywords ATL · Interferon · Zidovudine

1 Case reports

The prognosis of adult T cell leukemia/lymphoma (ATL) remains poor [1]. Combination therapy with interferon- α and zidovudine (IFN/AZT) has been regarded as standard care for acute and indolent (i.e., chronic and smouldering) ATL based on reports involving a limited number of

patients [1–5]. This treatment approach has not been evaluated in Japan, a major endemic area of this disease in the world, because of the lack of approval of both agents for the treatment of ATL under national health insurance. This is the first Japanese report of IFN/AZT for ATL.

We performed a pilot study of IFN/AZT for patients with ATL, aiming to elucidate its feasibility and efficacy. This study was reviewed and approved by the Fukuoka University Ethics Committee and Institutional Review Board of Fukuoka University Hospital. All patients provided written informed consent. Three patients with acute ATL who relapsed or were refractory to conventional chemotherapy were included in this study. We used a similar treatment schedule to that detailed in previous reports [2–4]: daily subcutaneous administration of IFN (SumiferonTM, Dainippon Sumitomo Pharma, Osaka, Japan) at 6×10^6 units/day for 11 weeks after induction with 3×10^6 units/day for the first week, and daily oral administration of AZT (GlaxoSmithKline, Tokyo, Japan) at 600 mg/day. The treatment response was determined according to the response criteria for ATL [5] and toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 3.0).

Patient 1 (Fig. 1a) A 63-year-old man with acute ATL achieved complete remission with modified EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisolone). Patchy skin lesions with histologically proven infiltration of ATL cells, lymphadenopathy, and marked elevation of soluble interleukin-2 receptor (sIL-2R) level and white blood cell (WBC) counts developed 15 months after the last treatment, and hence IFN/AZT was initiated. The increase in WBCs before the treatment with IFN/AZT was due to granulocytosis, and it was considered to be induced by

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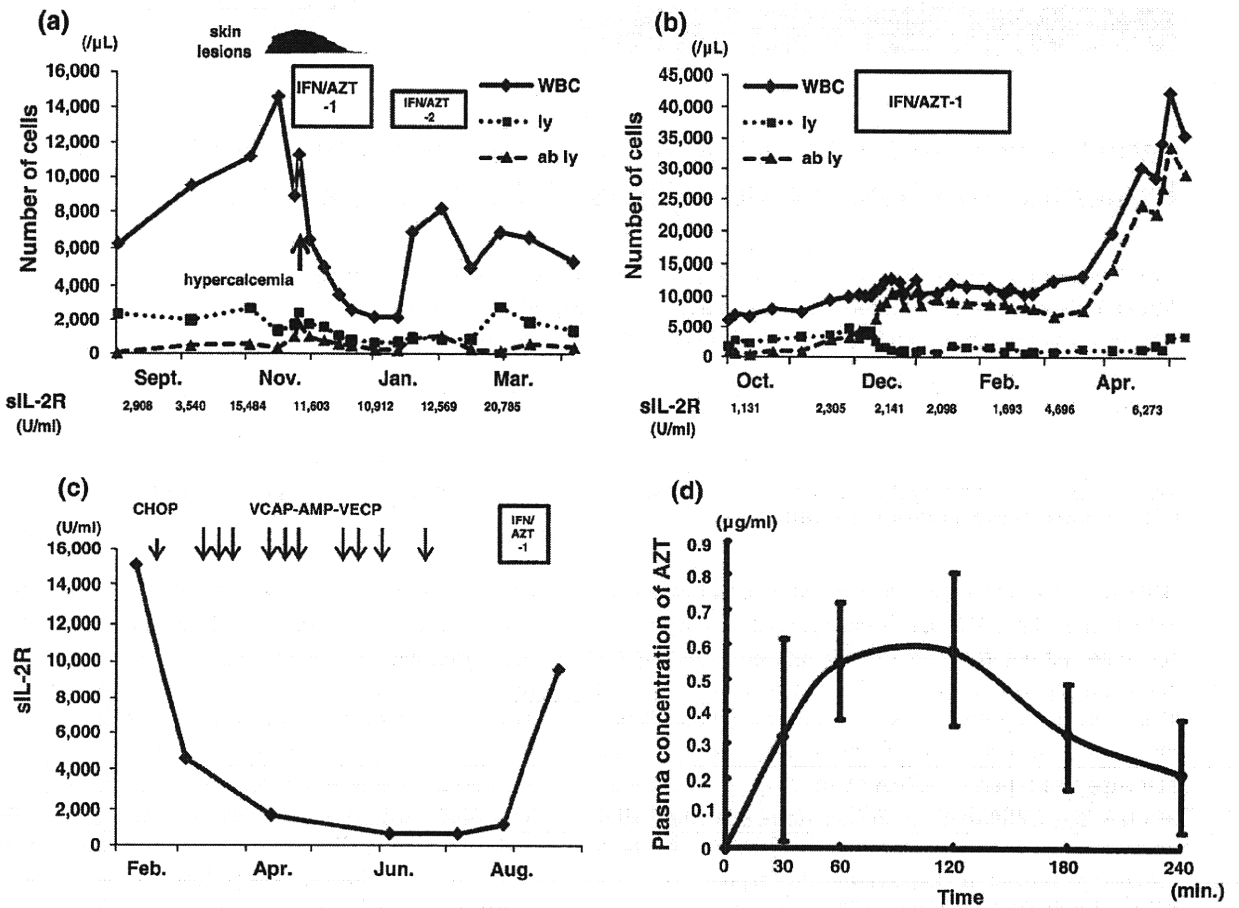


Fig. 1 Clinical course (a–c) and the serum concentration of AZT determined by high-performance liquid chromatography (HPLC) (c). **a** Patient 1, **b** Patient 2, and **c** Patient 3. **d** Serum concentrations of AZT in the 3 patients (Mean \pm standard deviation of the 3 patients). IFN/AZT-1: interferon- α (IFN) at 3×10^6 units/day for 7 days

followed by 6×10^6 units/day. Zidovudine (AZT) at 600 mg/day. IFN/AZT-2: IFN at 3×10^6 units/day with AZT at 600 mg/day. WBC white blood cells, *ly* lymphocytes, *ab.ly.* abnormal lymphocytes, *sIL-2R* soluble interleukin-2 receptor

ATL [6]. IFN/AZT was effective, leading to a rapid disappearance of skin lesions and decrease in the WBC count within a month. Of note, hypercalcemia observed soon after the initiation of IFN/AZT was controlled by zoledronate, and it did not recur. IFN/AZT was withheld for a week in the 7th treatment week due to malaise, with forced resumption at a half dose of IFN. The emergence of new lymph node lesions and elevation of *sIL-2R* were observed 2 months after the termination of IFN/AZT.

Patient 2 (Fig. 1b) A 62-year-old woman developed acute ATL after 4 years' observation with no treatment for smouldering ATL. She was treated with THP-COP (pirarubicin, cyclophosphamide, doxorubicin, vincristine, and prednisolone) and achieved partial remission. Disease progression occurred after 2 months and IFN/AZT was started. Although she responded modestly, disease progression was suppressed during treatment since there was a

rapid increase in both the number of ATL cells in the peripheral blood (PB) and *sIL-2R* level after the termination of IFN/AZT.

Patient 3 (Fig. 1c) A 48-year-old man was diagnosed with acute ATL. He showed a partial response to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) followed by VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisolone), AMP (doxorubicin, rami-mustine, and prednisolone), and VECP (vindesine, etoposide, carboplatin, and prednisolone), but this was not durable. Moreover, this regimen was not tolerable due to severe myelosuppression: IFN/AZT was therefore initiated. However, IFN/AZT was given for only 22 days, during which time no therapeutic effects on ATL were observed. The ATL lesions could not be eradicated even by a subsequent myeloablative conditioning regimen in preparation for allogeneic stem cell transplantation.

Table 1 Best response by lesions and adverse toxicities observed in this study

	Case 1	Case 2	Case 3
(a) Best response by lesions			
Lymph nodes	n/a	n/a	PD
Extranodal	SD	n/a	n/a
Spleen/liver	n/a	n/a	n/a
Skin	CR	n/a	n/a
Peripheral blood	SD	PD	n/a
Bone marrow	n/a	n/a	n/a
(b) Toxicities graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 3.0)			
Leukopenia	G1 (day 33)	G0	G2 (day 22)
Neutropenia	G4 (day 33) ^a	G4 (day 20) ^a	G2 (day 22)
Thrombocytopenia	G2 (day 27)	G0	G3 (day 22)
Elevation of AST	G0	G2 (day 20)	G1 (day 22)
Elevation of ALT	G2 (day 20)	G3 (day 20)	G1 (day 22)
Febrile neutropenia	G0	G3 (day 19)	G0
Appetite loss	G1 (day 9)	G2 (day 20)	G2 (day 10)
Malaise	G2 (day 44)	G2 (day 20)	G0
Flu-like-symptom	G1 (day 2)	G2 (day 2)	G2 (day 2)

CR complete remission, SD stable disease, PD progressive disease, n/a not applicable

^a IFN and AZT were interrupted until the number of neutrophils recovered equal or more than 1000/ μ L according to the protocol

Although none of the patients showed a marked response to IFN/AZT, as shown in Table 1a, one patient demonstrated clear anti-ATL effects, which resulted in the complete disappearance of skin lesions. Most importantly, the elevation of sIL-2R, a marker of tumor burden, was controlled during IFN/AZT in patients 1 and 2. No grade 3/4 non-hematological toxicity was encountered other than the transient elevation of alanine aminotransferase (ALT) and febrile neutropenia (Table 1b). The plasma concentration of AZT determined by high-performance liquid chromatography (HPLC) is shown in Fig. 1d, and the mean value of the area under the concentration–time curve (AUC) was 1.59 ± 0.51 mg h/L, which is comparable to previous reports on patients with human immunodeficiency virus infection not receiving IFN [7].

It is impossible to draw any definitive conclusion from this small study; however, IFN/AZT could stabilize the disease rather than induce durable remission. On the other hand, patients with aggressive ATL have achieved durable remission even in a salvage setting in previous overseas studies [2–4]. Therefore, predictive factors to determine the responsiveness to IFN/AZT should be determined if they exist. In addition, surprising results showing that IFN/AZT prevented the progression from indolent to aggressive (i.e., acute or lymphoma) ATL were recently reported in a retrospective study [8]. The effectiveness of this novel approach for patients with indolent ATL should be elucidated in a large prospective study.

Conflict of interest The authors declare no competing financial interests.

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