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Treatment for adult T-cell leukemia

Abstract The purpose of this study was to clarify the clinical efficacy of multidrug chemotherapy for aggressive adult T-cell leukemia (ATL). We report the therapeutic results of treatment of patients with aggressive ATL undertaken between 1986 and 1995. A total of 120 newly diagnosed patients with a performance status of 0–3 and aged <70 years at diagnosis were entered into the study. Clinical features, including clinical subtypes, serum levels of lactate dehydrogenase and blood urea nitrogen, the response to chemotherapy, and doses of individual chemotherapeutic agents, were evaluated. Of the 120 patients enrolled, 97 had acute-type and 23 lymphoma-type ATL. The complete response rate and median survival of these patients were 25.3% and 9 months, respectively. The 2- and 5-year survival rates were 18.4% and 8%, respectively, and five patients have been alive for >5 years and are disease-free. These long-term survivors had good prognostic factors at diagnosis. There was no correlation between the doses of the various chemotherapeutic agents and the survival duration. These results indicate that ordinary combined chemotherapy has limited ability to improve the prognosis of aggressive ATL. Our previous study indicated that expression of P-glycoprotein in ATL cells might be involved in resistance to chemotherapeutic agents, particularly doxorubicin, vincristine, and etoposide. Therefore, new therapeutic strategies will be necessary to improve the prognosis of ATL patients.

Key words Aggressive ATL · Intensive chemotherapy · Drug resistance

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Introduction

Adult T-cell leukemia (ATL) has been proven to be caused by human T-cell leukemia virus type I (HTLV-I) [9] and is characterized by proliferation of mature T cells expressing CD3, CD4, and CD25 [3]. According to the classification of the Lymphoma Study Group, a subgroup of the Japan Clinical Oncology Group (LSG-JCOG), ATL is divided into four clinical subtypes: smoldering, chronic, lymphoma, and acute [11]. Smoldering and chronic ATL usually have a mild clinical course with or without chemotherapy; in contrast, lymphoma- and acute-type ATL have an aggressive clinical course.

Despite the progress made in combination chemotherapy for malignant lymphoma and acute leukemia, the prognosis of acute- and lymphoma-type ATL patients remains poor. In this study, we report the results of therapy for these aggressive ATLs with the aim of clarifying the clinical efficacy of multidrug chemotherapy for ATL.

Patients and methods

Patients

Between January 1986 and December 1995 a total of 120 aggressive-type ATL patients who fulfilled the following criteria were entered in this study: (1) histologically and/or cytologically proven lymphoid malignancy with mature T-lymphocytes expressing mainly CD3, CD4, and CD25 on the cell surface; (2) serum anti-HTLV-I antibody positivity; (3) acute- or lymphoma-type ATL according to the LSG-JCOG criteria [11]; (4) a performance status (PS) at diagnosis of between 0 and 3 according to World Health Organization criteria, including a PS of 4 if caused by hypercalcemia; and (5) an age at diagnosis of <70 years.

Clinical features and chemotherapy

The clinical subtype, age, PS, serum levels of lactate dehydrogenase (LDH) and blood urea nitrogen (BUN), which are prognostic factors for ATL [5], and frequency of hypercalcemia at diagnosis were determined. During the 10-year course of the study we treated ATL

Table 1 Chemotherapeutic regimens (*VCR* Vincristine, *CPM* cyclophosphamide, *PDN* prednisolone, *ADM* doxorubicin, *MTX* methotrexate, *VDS* vindesine, *BLM* bleomycin, *PCZ* procarbazine, *MCNU* ranimustine, *THP* pirarubicin, *VP-16* etoposide, *PEP* peplomycin, *MMC* mitomycin C, *CBDCA* carboplatin, *i.t.* intrathecal administration)

Regimen	Composition
LSG1/LSG2	VCR+CPM+PDN+ADM
	VCR+CPM+PDN+ADM+MTX
CV′P	CPM+VDS+PDN
LSG4	VCR+CPM+PDN+ADM+BLM (VEPA-B)
	MTX+VDS+CPM+PDN+ADM (M-FEPA)
	MTX+CPM+PCZ+PDN+ADM (VEPP-B)
RCM	CPM+PDN+VDS+MCNU
	CPM+PDN+MTX+THP
	CPM+PDN+VP-16+PEP
	CPM+PDN+MMC+ADM
CHOP+VP-16+	VCR+CPM+PDN+ADM
MCNU+mitoxantrone	VP-16+MCNU+mitoxantron+G-CSF
LSG15	VCR+CPM+ADM+PDN (VCAP)
	ADM+MCNU+PDN (AMP)
	VDS+VP-16+CBDCA+PDN (VECP)
	with MTX+PDN i.t.

patients using multidrug combined chemotherapy regimens such as CV'P [6], LSG1/LSG2 [10], LSG4 [12], LSG15, a response-oriented multidrug (RCM) protocol [17], and the CHOP protocol followed by etoposide, vindesine, ranimustine, and mitoxantrone administration with granulocyte colony-stimulating factor [13] (Table 1). Response was evaluated according to criteria previously reported elsewhere [17]. In brief, a complete response (CR) was defined as the disappearance of all clinical evidence of disease, normalization of laboratory data, and improvement in PS. Treatment protocol LSG15 is now being assessed; therefore, we evaluated the doses of chemotherapeutic agents given during the initial 3 months of treatment instead of analyzing responses to individual protocols.

Statistical methods

The survival interval was calculated as the period between the start of chemotherapy and the last follow-up date (August 1996) or death, and the survival duration was calculated using the Kaplan-Meier method. The generalized Wilcoxon test and the Cox-Mantel test were used to examine the effect on survival duration of various prognostic factors. Dividing patients into four subgroups according to survival duration (≤5 months, 6–12 months, 13–23 months, and ≥24 months), we also examined the difference between chemotherapeutic agent dose during the initial 3 months of therapy, the chemotherapeutic response, the clinical features at diagnosis, and the survival duration using one-way analysis of variance, Fisher's PLSD test, and the χ^2 statistical method using a commercially available statistical-analysis kit.

Results

The clinical features at diagnosis of the 120 patients enrolled are shown in Table 2; 97 patients had acute-type and 23 lymphoma-type ATL. Poor prognostic factors in terms of an age of ≤40 years, a PS of 2–4, high LDH levels (>450 Wroblewski units), and high BUN levels (>18 mg/dl) were seen in 98.3%, 48.3%, 83.3%, and 23.3% of the patients, respectively. The median survival time (MST) of these 120 patients was 9 months; 2-year and 5-year survival rates were 18.4% and 8%, respectively (Fig. 1). The survival curves generated for lymphoma-type and acute-type ATL were similar. Patients with acute-type ATL, a PS of 0 or 1, and normal LDH levels had significantly better MSTs and survival rates (PS $P<0.01$ as determined by the Cox-Mantel test, LDH $P<0.05$ as determined by the generalized Wilcoxon test; Table 3).

Using multidrug combination chemotherapy, 23 of 97 patients (23.7%) with acute-type ATL and 8 of 23 patients (34.8%) with lymphoma-type ATL attained CRs, for an overall CR rate of 25.3% (Table 4). No patient who survived for ≤5 months showed a CR; however, with longer survival duration the CR rate increased in patients with both acute- and lymphoma-type ATL, and most of those who survived for >2 years achieved CRs.

Table 2 Clinical characteristic of patients with aggressive ATL at diagnosis

Characteristic	Acute-type ATL	Lymphoma-type ATL
Gender (M/F)	40/57	11/12
Age (<40:≤40 years)	2:95	0:23
Mean ± SD (years)	58.1 ± 8.2	61.4 ± 5.1
PS (0:1:2:3:4[a])	8:42:25:18:4	2:10:4:3:4
LDH:		
Normal	17	3
<2×N	30	10
2×N–3×N	18	4
>3×N	32	6
BUN normal	75/97	17/23
Hypercalcemia	35/97	7/23

[a] Due to hypercalcemia

Table 3 Survival rates obtained in patients with acute-type ATL

	PS		LDH		
Parameter	0/1 (n = 50)	2/3/4[a] (n = 47)	Normal (n = 17)	High (n = 80)	Totals (n = 97)
Median survival (months)	11*	5*	12**	6**	8.0
2-year survival (%)	25.3	8.5	32.7	13.8	17.1
5-year survival (%)	6.1	6.4	6.5	6.6	6.1

* $P<0.01$; ** $P<0.05$
[a] Due to hypercalcemia

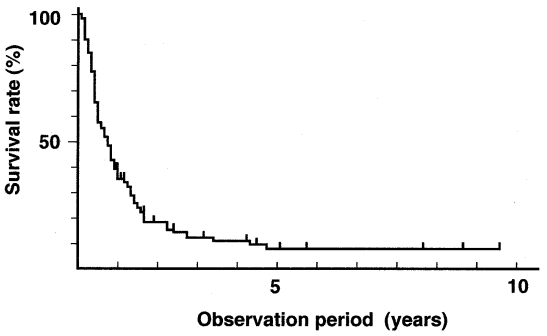

Fig. 1 Duration of survival of patients with aggressive ATL

Table 4 Relationship between the CR rate and survival duration

Survival duration (months)	Patients showing CR/total surviving for time indicated (%)		
	Acute-type ATL	Lymphoma-type	Totals
≤5	0/37 (0)	0/6 (0)	0/43 (0)
6–12	4/31 (12.9)	1/6 (16.6)	5/37 (13.5)
13–23	5/14 (35.7)	4/8 (50.0)	9/22 (40.9)
≥24	14/15 (93.3)	3/3 (100)	17/18 (94.4)
Totals	23/97 (23.7)	8/23 (34.8)	39/120 (25.3)

To compare long-term survivors and patients who survived for <2 years, we analyzed the doses of chemotherapeutic agents given during the initial 3 months of treatment and the clinical features at diagnosis. The doses of chemotherapeutic agents received by patients surviving for <2 years were similar to those given to long-term survivors, and there was no correlation between the dose of chemotherapeutic agents and the survival duration. In contrast, LDH and BUN levels measured at diagnosis in patients surviving for <2 years were significantly higher than those determined in long-term survivors (LDH $P<0.01$, BUN $P<0.05$; Table 5). Long-term survivors also had a significantly better PS and a lower frequency of hypercalcemia (≥5.6 mEq/l corrected Ca) at diagnosis ($P<0.01$).

Discussion

The results of chemotherapy for ATL as described previously are summarized in Table 6. Our previous data included ATL patients of PS 4 and aged >70 years. CR rates reported for the VCR, CPM, 6-mercaptopurine, and PDN (VEMP) [7]; VCR, CPM, ADM, and PDN (VEPA) [7]; CV'P [6]; and RCM protocols [17] ranged from 12% to 21%; similar results were reported by the Nagasaki group [16]. In contrast, CR rates obtained in ATL patients treated using the LSG1/LSG2 [10] and LSG4 protocols [12], which were conducted by the LSG-JCOG as a cooperative study on the treatment of malignant lymphoma, including ATL, were 28% and 42%, respectively. These CR results were significantly better than those obtained previously, but there was no apparent improvement in survival duration.

In our initial studies, almost all patients died within 2 years [6,7]; however, in the present study, 18 of 120 patients with aggressive ATL survived for >2 years. Of these, 7 died of ATL within 5 years, and only 5 patients have survived disease-free for >5 years. The doses of chemotherapeutic agents used during the initial 3 months of treatment were similar among the four groups differentiated by survival duration. There was also no correlation between the survival duration and the dose of individual chemotherapeutic agents given. These data suggest that the existence of long-term survivors in the present study is due to their having had good prognostic factors at diagnosis.

Poor prognostic factors are believed to be infectious complications due to T-cell immunodeficiency, a poor PS, liver dysfunction, kidney dysfunction, gastrointestinal lesions, hypercalcemia, and resistance to chemotherapeutic agents. We have previously examined expression of P-glycoprotein (Pgp), a product of the *mdr1* gene, in ATL cells [4]. Our data revealed that 8 of 20 patients were Pgp-positive at initial presentation; 6 patients who were initially Pgp-negative and responded to chemotherapy were Pgp-positive and refractory to chemotherapy at relapse. Moreover, *mdr1* mRNA expression in Pgp-positive ATL cells was increased during relapse. These data might explain the lack of correlation between the survival duration and the dose of individual chemotherapeutic agents given, such as

Table 6 Comparison of response and median survival according to the chemotherapy regimen used

Regimen	Number of patients	CR (%)	Median survival (months)	Reference
VEMP	25	12.0	5.5	[7]
VEPA	16	18.8	4.0	[7]
CV'P	10	0	6.3	[6]
RCM	43	20.9	6.0	[17]
VEPA (e.g.)	110	–	5.5[a] 8.7[b]	[16]
LSG1/LSG2	54	27.8	7.5	[10]
LSG-4	43	41.9	8.0	[12]
CHOP+VP-16+ MCNU+mitoxantrone	81	35.8	8.5	[13]

[a] Acute type
[b] Lymphoma type

Table 5 Clinical characteristics of ATL at diagnosis and survival duration

	Survival duration			
	≤5 months	6–12 months	13–23 months	≥24 months
Number of patients	43	37	22	18
Age (years)	59.2±8.0	56.7±8.4	61.5±6.6	58.3±6.4
PS* (0, 1/2, 3)	13/30	24/13	12/10	13/5
LDH (WU)	1908±1788*	1317±1244	941.3±966.4	793.6±555.8
BUN (mg/dl)	22.7±15.0**	18.1±10.1	15.6±6.4	16.0±4.2
Hypercalcemia	26/43	12/37	3/22	1/18

* $P<0.01$ vs values at 13–23 and ≥24 months; ** $P<0.05$ vs values at 13–23 and ≥24 months

ADM, VCR, and VP-16, because these drugs are known to be affected by Pgp-associated multidrug resistance. If so, ADM, VCR, and VP-16 dose intensification may not produce apparent improvements in ATL prognosis.

The effects of treatment using several new drugs such as deoxycoformycin [14], irinotecan [15], and sobuzoxane [8]; monoclonal antibodies to interleukin 2 receptors [18]; and a combination of interferon-alpha and zidovudine [2] have been reported. These therapies had activity in advanced ATL resistant to prior chemotherapy; however, the survival duration was unsatisfactory. More recently, induction of ATL cell apoptosis by anti-APO-1 (or anti-Fas) antibodies has been described [1]. Not only new combination chemotherapy protocols but also strategies including biotherapy targeted to cell-surface components or substances involved in ATL cell apoptosis might be necessary to improve the prognosis of aggressive ATL.

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References

1. Debatin KM, Goldmann CK, Bamford R, Waldmann TA, Krammer PH (1990) Monoclonal-antibody-mediated apoptosis in adult T-cell leukemia. Lancet 335:497
2. Gill PS, Harrington W Jr, Kaplan MH, Ribeiro RC, Bennet JM, Liebman HA, Bernstein-Singer M, Espina BM, Cabrall L, Allen S, Kornblau S, Pike MC, Levine A (1995) Treatment of adult T-cell leukemia-lymphoma with combination of interferon alpha and zidovudine. N Engl J Med 332:1744
3. Hattori T, Uchiyama T, Tobinai T, Takatsuki K, Uchino H (1981) Surface phenotype of Japanese adult T-cell leukemia cells characterized by monoclonal antibodies. Blood 76:645
4. Kuwazuru Y, Hanada S, Furukawa T, Yoshimura T, Sumizawa A, Utsunomiya A, Ishibashi K, Saito T, Uozumi K, Maruyama M, Ishizawa M, Arima T, Akiyama S (1990) Expression of P-glycoprotein in adult T-cell leukemia cells. Blood 76:2065
5. Lymphoma Study Group [1984–1987] (1991) Major prognostic factors of patients with adult T-cell leukemia-lymphoma: a cooperative study. Leuk Res 15:81
6. Makino T, Uozumi K, Shimazaki T, Otsuka M, Kuwazuru Y, Saito T, Utsunomiya A, Hanada S, Hashimoto S (1988) Combination chemotherapy for adult T-cell leukemia (ATL) using cyclophosphamide, vindesine and prednisolone (CV'P). J Jpn Soc Cancer Ther 23:2657
7. Nomura K, Matsumoto M (1981) Clinical features of adult T-cell leukemia in Kagoshima, the southernmost district in Japan – comparison with T-cell lymphoma. Acta Haematol Jpn 44:200
8. Ohno R, Masaoka T, Shirakawa S, Sakamoto S, Hirano M, Hanada S, Yasunaga K, Yokomaku S, Mitomo Y, Nagai K, Yamada K, Furue H, for the MST-16 Study Group (1993) Treatment of adult T-cell leukemia/lymphoma with MST-16, a new oral antitumor drug and a derivative of bis(2,6-dioxopiperazine). Cancer 71:2217
9. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC (1980) Detection and isolation of type-C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci USA 77:7415
10. Shimoyama M, Ota K, Kikuchi M, Yunoki K, Konda S, Takatsuki K, Ichimaru M, Ogawa M, Kimura I, Tominaga S, Tsugane S, Taguchi H, Minato K, Takenaka T, Tobinai K, Kurita S, Oyama A, Hisano S, Kozuru M, Matsumoto M, Nomura K, Takiguchi T, Sugai S, Yamaguchi K, Hattori T, Kinoshita K, Tajima K, Suemasu K, for the Lymphoma Study group [1981–1983] (1988) Chemotherapeutic results and prognostic factors of patients with advanced non-Hodgkin's lymphoma treated with VEPA and VEPA-M. J Clin Oncol 6:128
11. Shimoyama M, Members of the Lymphoma Study Group [1984–1987] (1991) Diagnostic criteria and classification of clinical subtypes of adult T-cell leukemia/lymphoma. A report of the Lymphoma Study Group (1984–1987). Br J Haematol 79:428
12. Shimoyama M, Shiakawa S, members of the JCOG-LSG (1993) Treatment outcome and prognostic factors of patients with advanced aggressive T and B lymphoma treated with 2nd generation LSG4 protocol. Jpn J Clin Hematol 32:1247
13. Taguchi T, Kinoshita K, Takatsuki K, Tomonaga M, Araki K, Arima N, Ikeda S, Uozumi K, Kohno H, Chiyoda S, Tsuda H, Nishimura H, Hosokawa T, Matsuzaki H, Momita S, Yamada O, Miyoshi I (1996) An intensive chemotherapy of adult T-cell leukemia/lymphoma: CHOP followed by etoposide, vindesine, ranimustine and mitoxantron with granulocyte colony-stimulating factor support. J AIDS Hum Retrovirol 12:182
14. Tobinai K, Shimoyama M, Inoue S, Takayasu S, Mikuni C, Kozuru M, Oda S, Nakajima H, Members of the DCF Study Group (1992) Phase I study of YK-176 (2'-deoxycoformycin) in patients with adult T-cell leukemia-lymphoma. Jpn J Clin Oncol 22:164
15. Tsuda H, Takatsuki K, Ohno R, Masaoka T, Okada K, Shirakawa S, Ohashi Y, Ota K, CPT-11 Study Group on Hematological Malignancy (1994) Treatment of adult T-cell leukemia-lymphoma with irinotecan hydrochloride (CPT-11). Br J Cancer 70:771
16. Tsukasaki K, Ikeda S, Murata K, Maeda T, Atogami S, Sohda H, Momita S, Jubashi T, Yamada Y, Mine M, Kamihiri S, Tomonaga M (1993) Characteristics of chemotherapy-induced clinical remission in long survivors with aggressive adult T-cell leukemia/lymphoma. Leuk Res 17:157
17. Uozumi K, Hanada S, Ohno N, Ishitsuka K, Shimotakahara S, Otsuka M, Chuman Y, Nakahara K, Takeshita T, Kuwazuru Y, Saito T, Makino T, Iwahashi M, Utsunomiya A, Arima T (1995) Combination chemotherapy (RCM protocol: response-oriented cyclic multidrug protocol) for the acute or lymphoma type adult T-cell leukemia. Leuk Lymphoma 18:317
18. Waldmann TA (1994) New approaches to the treatment of ATL. In: Takatsuki K (ed) Adult T-cell leukemia. Oxford Medical, Oxford New York Tokyo, p 238