Histologic subtypes and OS according to PT/NKCL subtypes

There were 53 patients with PTCL-U, 46 with angioimmunoblastic T-cell lymphoma (AITL), 18 with ALCL, 17 with NKTCL, one with subcutaneous panniculitis-like T-cell lymphoma (SCPTCL), and one with enteropathy-type T-cell lymphoma (ETCL).

A Kaplan–Meier analysis showed that patients diagnosed with PTCL-U and NKTCL had significantly inferior survival curves than patients with ALCL and AITL (Figure 2). The 5-year OS of patients with ALCL, AITL, NKTCL, and PTCL-U was 61% (95% CI, 35–79%), 55% (95% CI, 39–68%), 41% (95% CI, 19–63%), and 38% (95% CI, 25–51%), respectively.

Prognostic parameters for OS in patients with PT/NKCLs

The clinical characteristics of the 136 patients with PT/NKCLs examined using a univariate analysis and their cut-off values are listed in Table II. The following clinical parameters were significantly associated with reduced survival in a univariate analysis: pretreatment serum TP levels, gastrointestinal (GI) tract involvement, histologic subtype, and pretreatment serum Alb levels (Table III). None of the parameters used in the IPI were prognostically significant.

Eight variables reached the cut-off value of $p < 0.3$ in a univariate analysis (Table III) and were subsequently evaluated in a multivariate analysis. Consequently, only pretreatment TP levels (hazard ratio [HR], 2.21; 95% CI, 1.28–3.83; $p = 0.004$) and the histologic subtype (HR, 1.73; 95% CI, 1.08–2.77; $p = 0.024$) remained significant. Pretreatment serum TP levels, with a cut-off value of 6.3 g/dL, which was determined by the lower limit value of the normal range, clearly separated patients with PT/NKCLs into two groups with different outcomes (Figure 3).

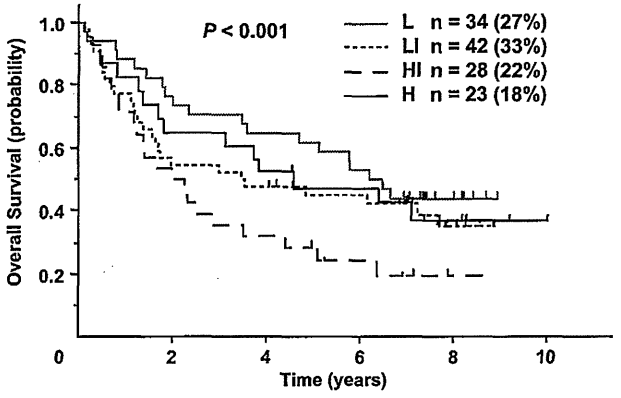

Figure 1. OS according to the IPI. Patients with T- and NK-cell lymphomas ($n = 127$) with complete data sets available for the IPI. L, low risk; LI, low-intermediate risk; HI, high-intermediate risk; H, high risk.

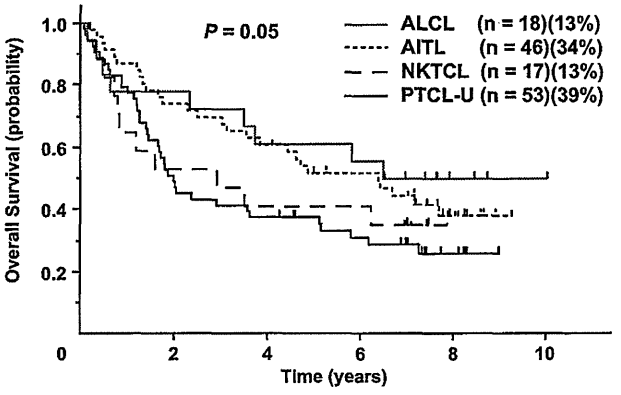

Figure 2. OS according to WHO histologic subtype ($n = 134$). ALCL, anaplastic large cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; NKTCL, extranodal NK/T-cell lymphoma, nasal type; PTCL-U, peripheral T-cell lymphoma, unspecified.

Comparison of clinical and biologic characteristics among histologic subtypes

The distribution of Ann Arbor stage, PS, LDH, and IPI was unbalanced among histologic subtypes (Table IV). However, the ratio of low serum TP level, which remained significant by the multivariate analysis, was not statistically different among the histologic subtypes, in addition to two or more extranodal sites, BM, and GI tract involvement (Table IV). Patients with NKTCL more frequently had a localized disease and an ambulatory PS (ECOG PS of 0 or 1 was 100%), and less frequently had B symptoms compared with other histologic subtypes. Patients with ALCL, AITL, and PTCL-U had a more advanced disease and lower PS (26–39%), and more than half of them had B symptoms. Seventy percent or more of the ALCL and NKTCL patients were classified as the low/low-intermediate-risk group according to the IPI scoring, while 58% of the AITL patients were in the high-intermediate (HI)/high (H)-risk group, and the proportion of the HI/H-risk group of the patients with PTCL-U was intermediate between that of the HI/H-risk group of patients with ALCL/NKTCL and AITL (Table IV).

Discussion

Both serum TP and Alb levels were prognostic factors in a univariate analysis, but only TP remained significant in a multivariate analysis. Among the prognostic studies to date, only one report found that TP was significant in a multivariate analysis in PT/NKCLs [20]. TP and Alb levels may reflect patient exhaustion resulting from severe constitutional symptoms, or the patient's inability to tolerate

Table II. Clinical and biologic characteristics of 136 patients with peripheral T- and NK-cell lymphomas.

Characteristic and cut-off value	No. of patients with available data	No. of patients	%
Sex	136		
Male		91	67
Female		45	33
Age (years)	136		
≤60		95	70
≥60		41	30
Ann Arbor CS	135		
I, II		26	19
III, IV		109	81
Dimensions of largest tumor	131		
<5 cm		88	67
≥5 cm, <10 cm		29	22
≥10 cm		14	11
Extranodal sites	132		
0, 1		93	70
≥2		39	30
BM involvement	135		
No		106	79
Yes		29	21
GI tract involvement	135		
No		118	87
Yes		17	13
Liver involvement	135		
No		115	85
Yes		20	15
Spleen involvement	135		
No		107	79
Yes		28	21
Other involvement	135		
No		77	57
Yes		58	43
ECOG PS	135		
0, 1		95	70
≥2		40	30
B symptoms	133		
Absent		62	47
Present		71	53
LDH	129		
Normal range		53	41
Higher than normal		76	59
TP (g/dL)	131		
≥6.3		101	77
<6.3*		30	23
Alb (g/dL)	130		
≥3.7		62	48
<3.7*		68	52
AST (IU/L)	132		
≤40		112	85
>40		20	15
Hb (g/dL)	132		
≥10.0		114	86
<10.0		18	14
Histologic subtype	136		
AITL		46	34
ALCL		18	13
SCPTCL		1	1
NKTCL		17	13
PTCL-U		53	39
ETCL		1	1

*The lower limit value of the normal range.
CS, clinical stage; BM, bone marrow; GI, gastrointestinal; ECOG, Eastern Cooperative Oncology Group; PS, performance status; LDH, lactate dehydrogenase; TP, total protein; Alb, albumin; AST, aspartate transaminase; Hb, hemoglobin; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; SCPTCL, subcutaneous panniculitis-like T-cell lymphoma; NKTCL, extranodal NK/T-cell lymphoma, nasal type; PTCL-U, peripheral T-cell lymphoma, unspecified; ETCL, enteropathy-type T-cell lymphoma.

Table III. Clinicopathological parameters influencing survival of patients with peripheral T- and NK-cell lymphomas in a univariate analysis.

Parameter	Cut-off value	Hazard ratio	*p*-Value
TP* (g/dL)	<6.3†	2.39	0.0003
GI tract involvement*	Yes	1.81	0.049
Histologic subtype*	NKTCL+PTCL-U+ETCL	1.71	0.015
Alb* (g/dL)	<3.7†	1.68	0.021
Extranodal sites*	>1 site	1.46	0.11
Hemoglobin* (g/dL)	<10.0	1.39	0.28
B symptoms*	Present	1.35	0.17
ECOG PS*	>1	1.31	0.24
Ann Arbor stage	>2	1.26	0.42
Age	>60	1.22	0.38
LDH	>1×normal	1.22	0.37
BM involvement	Yes	1.01	0.98

*These variables were used in a multivariate analysis.
†The lower limit value of the normal range.
TP, total protein; GI, gastrointestinal; NKTCL+PTCL-U+ETCL, extranodal NK/T-cell lymphoma, nasal type, peripheral T-cell lymphoma, unspecified, and enteropathy-type T-cell lymphoma versus angioimmunoblastic T-cell lymphoma, anaplastic large cell lymphoma, and subcutaneous panniculitis-like T-cell lymphoma; Alb, albumin; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; BM, bone marrow.

intensive chemotherapy. One of the potential reasons why TP is superior to Alb as a prognostic factor is that hypergammaglobulinemia might be a relevant and favorable prognostic factor. Unfortunately, in older trials, such as JCOG9002 and JCOG9203, where half of patients with AITL were registered, immunoglobulin levels were not monitored. Patients with TP < 6.3 g/dL were found in 33, 17, 12, and

25% of ALCL, AITL, NKTCL, and PTCL-U, respectively (Table IV). The meaning of TP should be confirmed for each histologic subtype in future studies.

One reason for the conflicting results concerning the histologic subtypes of PT/NKCLs between the studies may be because disease prognosis differs depending on the geographic distribution of the various subtypes [22]. Another considerable reason for the discrepant outcome between the histologic subtypes is that one-third of patients with AITL progress so rapidly that those with a poor performance status (PS) are excluded from prospective multicenter clinical trials. Patients with a PS of 3 were excluded in two of the clinical trials, JCOG9203 and JCOG9809, in the present study.

A recent report from GELA showed that neither the IPI nor the PIT model predicted the survival of patients with AITL [14]. The 5-year OS of patients with AITL in our study population was superior to that described in the GELA study (55% [95% CI, 39–68%) vs. 33% [95% CI, 26–41%] [14]). One possible explanation for this difference is that these studies used different treatments. Another explanation is that the agreement level of the expert hematopathologists with the consensus diagnosis for some of the T-cell lymphoma subtypes was generally poor [21,22], and different AITL diagnostic criteria might have been used for the different study groups.

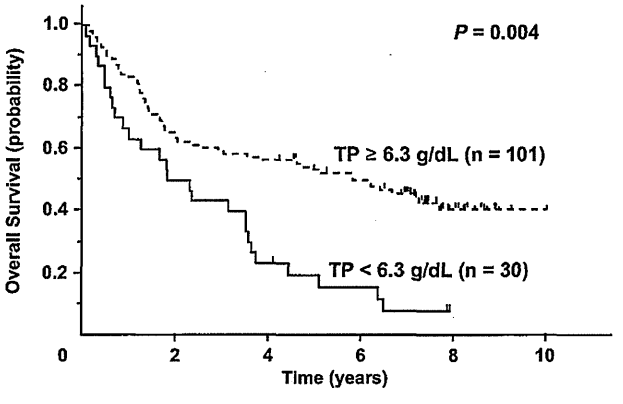

Figure 3. OS according to pretreatment total serum protein levels ($n=131$).

The majority of ALCL cases are positive for the anaplastic large cell lymphoma kinase (ALK) protein, but cases without ALK expression were also included in this category. Unfortunately, the proportion of ALK-negative cases, which usually have a poor prognosis [23], could not be determined in this study. The immunoreactivity to ALK was not systematically assessed, because this distinction was not included in the eligibility criteria in any of the original clinical trials in this study.

The important prognostic factors, as well as prognostic models, may differ according to the treatment regimen. PT/NKCLs are relatively rare, and are treated with various therapies according to the disease state. A Taiwanese group revealed that patients with PTCL who received only CPA, VCR, and PSL as induction chemotherapy had a markedly unfavorable outcome [24]. Therefore, a homogeneous population of patients who have received at least anthracycline-containing regimens should be analyzed when the prognostic factors of PTCL are investigated. Our study was a combined analysis of multicenter prospective clinical trials, as GELA was previously [14]. The IPI was originally described for patients with aggressive lymphomas treated with DXR-containing combination chemotherapies, and has been known to predict the survival of patients with aggressive B-cell lymphomas, as shown in this study and other studies, but not always for patients with PT/NKCLs [21,25]. Moreover, previous reports have shown that the IPI poorly predicts the survival of patients with AITL [14], ALCL [26], PTCL-U [26], or NKTCL [27].

Table IV. Comparison of clinical and biologic characteristics of patients with peripheral T- and NK-cell lymphomas according to histologic subtype.

Parameter	ALCL ($n=18$) (%)	AITL ($n=46$) (%)	NKTCL ($n=17$) (%)	PTCL-U ($n=53$) (%)	p-Value
Sex (male/female)	72/28	65/35	82/18	62/38	0.45
Age (≤60/>60)	72/28	65/35	65/35	74/26	0.79
Ann Arbor stage (I+II/III+IV)	33/67	2/96	47/53	21/79	<0.001
Extranodal sites (≤1/≥2)	83/17	67/26	65/35	66/32	0.57
ECOG PS (0+1/≥2)	61/39	59/39	100/0	74/26	0.01
LDH (≤N/>N)	67/28	15/83	71/18	38/57	<0.001
B symptoms (no/yes)	44/56	35/63	71/29	45/51	0.10
IPI (L/LI/HI/H)	50/22/11/11	7/33/30/28	41/29/18/0	28/34/17/15	0.003
BM involvement (no/yes)	100/0	67/30	88/12	75/25	0.12
GI tract involvement (no/yes)	83/17	96/2	100/0	77/23	0.54
TP <6.3 (no/yes)	61/33	80/17	82/12	72/25	0.62

ALCL, anaplastic large cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; NKTCL, extranodal NK/T-cell lymphoma, nasal type; PTCL-U, peripheral T-cell lymphoma, unspecified.

There are several potential reasons why the IPI model did not retain its prognostic significance for patients with PT/NKCLs in our study. The extent of disease and presence of extranodal sites were no longer significant prognostic factors, probably because PT/NKCLs *per se* are characterized by both the presentation of disease in an advanced stage, III or IV [10,12,13], and in two or more extranodal sites (Table I) [12,13]. Moreover, DLBCL has different characteristics from PT/NKCLs, which are more frequently associated with a poor PS and B symptoms [10,12] (Table I). The IPI incorporates age, LDH, and the abovementioned factors, except for B symptoms. Consequently, PT/NKCLs should have different prognostic factors than those for DLBCL.

An early GELA study noted that the freedom-from-relapse survival of patients with PTCL, unlike patients with B-cell lymphoma, was not impacted by either LDH or bone marrow (BM) involvement [10]. BM involvement, which is one of the risk factors adopted in the PIT, was not a significant adverse factor in our study including other histologic subtypes besides PTCL-U. Although patients with NKTCL had the property of a localized disease, 53% of them had advanced diseases, and 12% of them had BM involvement in this study (Table IV). Instead of BM involvement, we found that GI involvement was significantly associated with survival in a univariate analysis. However, when we tried additional univariate analysis excluding NKTCL and ETCL, this was not significant, although the GI tract was not involved in any patients with NKTCL, as shown in Table IV, and there was a sole patient with ETCL.

New prognostic models have been proposed for certain categories of PT/NKCLs, such as the PIT model [13] and clinical–pathologic prognostic score [28] for PTCL-U and a prognostic model for NKTCL [29]. In addition, new molecular prognostic markers such as CD15 [28], EBER-ISH [25,30], cytotoxic T-cell phenotype [31,32], various chemokine receptors [33,34], Ki-67 [28], and the proliferation-core signature [35] have been investigated for PTCL-U. As for NKTCL, P19 [27], Ki-67 [36], and FOXP3-positive regulatory T-cells [37] have been proposed as predictors for clinical outcome. Although biochemical data, β_2-microglobulin combined with the adjusted IPI, has been reported to predict the outcome after autologous hematopoietic stem cell transplant in relapsed/refractory PTCL [38], we had no available data to analyze in four out of the six clinical trials included in this study. Allowing for or to validate these prognostic factors with homogeneous treatment, histology-specific therapy is warranted. As PT/NKCLs have variable characteristics dependent on histologic subtype (Table IV), patients with PT/NKCLs should not be studied as a whole, and studies in future should be performed for each histologic subtype. However, pretreatment serum low TP levels might be an adverse prognostic factor independent of histologic subtype, because its frequency was not different among the histologic subtypes (Table IV). Therefore, this prognostic factor should be noteworthy even with regard to each histologic subtype.

In conclusion, TP is a significant prognostic factor to predict the outcome of PT/NKCLs. A validation study is required in order to establish the importance and meaning of TP in patients with each histologic subtype of PT/NKCLs. Further, the new therapeutic strategies, including new agents and/or first-line high-dose chemotherapy followed by autologous or allogeneic hematopoietic stem cell transplant, should be explored for patients with lower TP levels and/or higher-risk histologic subtypes in the future.

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Appendix. Supporting information

Antibodies used for immunophenotyping.

Antigen	Antibody	Poly/Mono	Source	
CD20	L26	M	DAKO	Glostrup, Denmark
CD3	PS1	M	Novocastra	Newcastle, UK
CD4	1F6	M	Novocastra	Newcastle, UK
CD5	4C7	M	Novocastra	Newcastle, UK
CD8	4B11	M	Novocastra	Newcastle, UK
CD10	56C6	M	Novocastra	Newcastle, UK
CD15	MMA	M	Becton Dickinson	San Jose, CA, USA
CD21	1F8	M	DAKO	Glostrup, Denmark
CD23	1B12	M	Novocastra	Newcastle, UK
CD30	BerH2	M	DAKO	Glostrup, Denmark
CD45	LCA	M	DAKO	Glostrup, Denmark
CD45RO	UCHL1	M	DAKO	Glostrup, Denmark
CD56	NCC-LU-243	M	Nihon Kayaku	Tokyo, Japan
CD79a	CD79a	M	DAKO	Glostrup, Denmark
CD246	ALK1	M	DAKO	Glostrup, Denmark
bcl-2	124	M	DAKO	Glostrup, Denmark
cyclin D1	SP4	M	Nichirei	Tokyo, Japan
MUM1	MUM1P	M	DAKO	Glostrup, Denmark
Ki-67	MIB1	M	DAKO	Glostrup, Denmark
TdT	anti-TdT	P	DAKO	Glostrup, Denmark

TdT, terminal deoxyribonucleotide transferase; M, monoclonal; P, polyclonal.

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ORIGINAL REPORT

Phase I Study of KW-0761, a Defucosylated Humanized Anti-CCR4 Antibody, in Relapsed Patients With Adult T-Cell Leukemia-Lymphoma and Peripheral T-Cell Lymphoma

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ABSTRACT

Purpose
KW-0761, a defucosylated humanized anti-CC chemokine receptor 4 (CCR4) antibody, exerts a strong antibody-dependent cellular cytotoxic effect. This phase I study assessed the safety, pharmacokinetics, recommended phase II dose and efficacy of KW-0761 in patients with relapsed CCR4-positive adult T-cell leukemia-lymphoma (ATL) or peripheral T-cell lymphoma (PTCL).

Patients and Methods
Sixteen patients received KW-0761 once a week for 4 weeks by intravenous infusion. Doses were escalated, starting at 0.01, 0.1, 0.5, and finally 1.0 mg/kg by a 3 + 3 design.

Results
Fifteen patients completed the protocol treatment. Only one patient, at the 1.0 mg/kg dose, developed grade 3 dose-limiting toxicities, skin rash, and febrile neutropenia, and grade 4 neutropenia. Other treatment-related grade 3 to 4 toxicities were lymphopenia (n = 10), neutropenia (n = 3), leukopenia (n = 2), herpes zoster (n = 1), and acute infusion reaction/cytokine release syndrome (n = 1). Neither the frequency nor severity of toxicities increased with dose escalation. The maximum tolerated dose was not reached. Therefore, the recommended phase II dose was determined to be 1.0 mg/kg. No patients had detectable levels of anti-KW-0761 antibody. The plasma maximum and trough, and the area under the curve of 0 to 7 days of KW-0761, tended to increase dose and frequency dependently. Five patients (31%; 95% CI, 11% to 59%) achieved objective responses: two complete (0.1; 1.0 mg/kg) and three partial (0.01; 2 at 1.0 mg/kg) responses.

Conclusion
KW-0761 was tolerated at all the dose levels tested, demonstrating potential efficacy against relapsed CCR4-positive ATL or PTCL. Subsequent phase II studies at the 1.0 mg/kg dose are thus warranted.

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INTRODUCTION

The successful use of monoclonal antibodies (mAb) has evolved into a promising approach to treating cancer over the last decade. In the field of hematologic malignancies, development of the therapeutic mAb rituximab has changed the standard of therapy for patients with B-cell lymphomas and has markedly improved prognosis.[1-3] In contrast, the prognosis of patients with T-cell neoplasms remains very poor.[4] The 5-year overall survival (OS) for common subtype of peripheral T-cell lymphoma (PTCL), such as PTCL not otherwise specified (NOS) and angioimmunoblastic T-cell lymphoma, is 32% compared with only 14% for adult T-cell leukemia lymphoma (ATL).[4] A recent phase III trial for newly diagnosed aggressive ATL demonstrated that a dose-intensified multidrug chemotherapy with vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP), doxorubicin, ranimustine, and prednisone (AMP), and vindesine, etoposide, carboplatin, and prednisone (VECP) was more effective than biweekly cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).[5] However, the median survival time and OS at 3 years were still unsatisfactory, at approximately 13 months and 24%, respectively.[5,6]

CC chemokine receptor 4 (CCR4) is a chemokine receptor expressed on T-helper type 2[7] and regulatory T cells (Treg).[8-10] Because numerous studies, including our own, have demonstrated CCR4 to be expressed on certain types of T-cell neoplasms,[11-17] we hypothesized that this molecule might represent a novel molecular target for immunotherapy against relapsed or refractory T-cell lymphomas.[16-21] Accordingly, we developed KW-0761, a next generation humanized anti-CCR4 mAb, with a defucosylated Fc region, which markedly enhanced antibody-dependent cellular cytotoxicity (ADCC) due to increased binding affinity to the Fcγ receptor on effector cells.[21,22]

Herein, we report the results of a phase I study designed to assess the safety, pharmacokinetics, recommended phase II dose, and efficacy of KW-0761 in patients with relapsed CCR4-positive ATL and other peripheral T-cell lymphomas (PTCL).

PATIENTS AND METHODS

Investigational Drug and Eligibility

KW-0761 is a defucosylated humanized immunoglobulin G1 (IgG1) 1 mAb generated from a mouse anti-CCR4 mAb[7] by Kyowa Hakko Kirin Co Ltd.[23,24]

Patients between 20 and 69 years of age with CCR4-positive aggressive ATL (acute type, lymphoma type, or unfavorable chronic type)[25,26] or PTCL with CCR4 expression were eligible. CCR4 expression was confirmed by immunohistochemistry or flow cytometry using an anti-CCR4 mAb (KM2160, Kyowa Hakko Kirin Co Ltd),[12,14,15] and confirmed by the review committee with a central evaluation. Patients with relapse after at least one prior course of chemotherapy were eligible. All patients were required to have an Eastern Cooperative Oncology Group performance status of 0 or 1. Eligibility criteria also included the following laboratory values: an absolute neutrophil count 1,500/uL, platelet count 75,000/uL, hemoglobin 8.0 g/dL, AST 2.5 the upper limit of the normal range (UNL), ALT 2.5 UNL, total bilirubin 1.5 UNL, serum creatinine 1.5 UNL, corrected serum calcium 11.0 mg/dL, negative for hepatitis B surface antigen and for hepatitis B virus DNA, and arterial partial oxygen pressure 65 mmHg or arterial blood oxygen saturation 90%. All subjects underwent electrocardiography to confirm the absence of abnormalities requiring treatment and that the left ventricular ejection fraction was at least 50%.

Patients were excluded if they had any severe complication, an infectious complication or active tuberculosis, a history of organ transplantation, active concurrent cancers, CNS involvement, a bulky mass requiring emergent radiotherapy, or tested positive for hepatitis C virus antibody and/or HIV antibody.

The institutional review boards of the participating institutions approved this study, and all patients gave written informed consent according to the Declaration of Helsinki.

Study Design

This was a multicenter dose-escalation study with three to six patients at each dose level to determine the maximum-tolerated dose (MTD) and estimate the recommended phase II dose. Cohorts of patients received KW-0761 at 0.01, 0.1, 0.5, and 1.0 mg/kg, weekly for 4 weeks by intravenous infusion. Premedications (antihistamine and antipyretic) were administered before each KW-0761 treatment.

If no dose-limiting toxicity (DLT) was observed in a cohort of three patients at a given dose level, the next cohort of three new patients would be treated with the next higher dose. If DLT was experienced by one or two of the three patients at any dose, three additional patients would be treated at the same dose level. If three or more patients at a given dose level exhibited DLT, this dose would be considered to exceed the MTD and the dose escalation would thus be halted. The recommended phase II dose was defined as one dose level below the MTD or the maximum dose level judged to be tolerable. An expanded cohort of three additional newly enrolled patients was also treated at the recommended phase II dose. Patients who relapsed after achieving responses to KW-0761 were allowed to be re-treated with this antibody.

Toxicity Evaluation and Definition of DLT

Patients treated at each dose level were evaluated weekly during therapy and until 4 weeks after the last infusion to assess toxicity. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3. Human anti-KW-0761 antibodies in the plasma of patients were detected by an enzyme-linked immunosorbent assay. The plates were coated with KW-0761 to capture any anti-KW-0761 antibodies, followed by addition of biotinylated KW-0761, and then horseradish peroxidase–labeled avidin. Detection sensitivity of this assay was 5 ng/mL as standard antibody equivalent in plasma.

DLT was defined as an adverse event or a laboratory abnormality that occurred within 28 days after the first infusion, judged to be related to KW-0761 and meeting any of the following criteria: grade 4 hematologic toxicity except lymphopenia, grade 4 symptoms judged to be consistent with an acute infusion reaction/cytokine release syndrome or with tumor lysis

Table 1. Patient Demographic and Clinical Characteristics by Cohort

Characteristic	Cohort and Dosage					
	1: 0.01 mg/kg	2: 0.1 mg/kg	3: 0.5 mg/kg	4: 1.0 mg/kg	Expanded: 1.0 mg/kg	Total
No. of patients	3	4*	3	3	3	16
Median age, years						62
Range	46-68	55-66	60-69	62-64	55-62	46-69
Sex						
Male	2	2	2	0	2	8
Female	1	2	1	3	1	8
Diagnosis						
ATL	2	4	3	2	2	13
PTCL	1 (MF)	0	0	1 (PTCL-NOS)	1 (PTCL-NOS)	3
No. of prior chemotherapy regimens						
1	2	2	2	1	2	9
2	0	0	0	2	0	2
3	1	2	1	0	1	5

Abbreviations: ATL, adult T-cell leukemia-lymphoma; PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; MF, mycosis fungoides.
*One patient enrolled at 0.1 mg/kg was withdrawn due to early progressive disease.

syndrome, and grade 3 nonhematologic toxicities. The independent data monitoring committee evaluated the safety data at all dose levels.

Responses

Responses were evaluated within 2 weeks and again at 4 weeks after the last KW-0761 infusion. The antitumor effects were determined according to criteria described previously.[26,27-29] The overall response (OR) rate included patients with a complete response (CR), CR unconfirmed, or a partial response (PR). Progression-free survival (PFS) was defined from the day of the first KW-0761 infusion until the day of progressive disease (PD) detection or death due to any cause. The tumor response and PFS of each subject were confirmed by the efficacy assessment committee with a central evaluation based on computed tomography imaging.

Pharmacokinetics

Blood was drawn into a heparin-containing tube before and after the infusion in all patients and plasma concentrations of KW-0761 were assessed using an enzyme-linked immunosorbent assay. One blood sample was obtained before each infusion, six during the 0- to 72-hour period after the first or fourth infusion, one immediately after the second or third infusion, and four in the 7 to 28 days after the fourth infusion. The pharmacokinetic parameters of plasma KW-0761 concentrations were calculated by employing a noncompartment model using WINNonlin (Scientific Consulting, Apex, NC) software; plasma maximum (C_{max}) and trough (C_{trough}) drug concentrations after each administration of KW-0761, and the plasma half-life ($t_{1/2}$) and area under the blood concentration time curve ($AUC_{0\text{-}7days}$) after the first and the fourth infusions.

Table 2. Grade 2 or Higher Nonhematologic and Hematologic Adverse Events by Cohort

Adverse Event	Cohort 1 (n = 3)		Cohort 2 (n = 4)		Cohort 3 (n = 3)		Cohort 4 and Expanded (n = 6)	
	Grade 2	Grade 3	Grade 2	Grade 3	Grade 2	Grade 3	Grade 2	Grade 3
Nonhematologic*								
Cardiac arrhythmia and general								
Prolonged QTc	1	—	—	—	—	—	—	—
Vasovagal episode	—	—	—	—	—	—	1†	—
Hypertension	—	—	—	—	—	—	1	—
Hypotension	1†	—	—	—	—	—	—	—
Constitutional symptoms								
Fever	—	—	1†	—	—	—	2 (1†)	—
Dermatology/skin								
Pruritus	—	—	—	—	—	—	1	—
Rash	1	—	—	—	—	—	2	1
Gastrointestinal								
Constipation	1	—	—	—	—	—	—	—
Infection								
Febrile neutropenia	—	—	—	—	—	—	—	1
Herpes zoster‡	—	1	—	—	—	—	—	—
Metabolic								
Alkaline phosphatase	—	—	1†	—	—	—	—	—
ALT	—	—	1	1†	—	—	—	—
AST	—	—	—	1†	—	—	—	—
γ-GTP	—	—	—	1†	—	—	—	—
CRP increased	—	—	—	—	—	—	1†	—
Pain								
Lymph node	—	—	—	—	—	—	1	—
Pulmonary/upper respiratory								
Hypoxemia	—	—	2†	—	—	—	1	—
Syndrome								
Acute infusion reaction/cytokine release	1	—	2	1	1	—	2	—

	Cohort 1 (n = 3)			Cohort 2 (n = 4)			Cohort 3 (n = 3)			Cohort 4 (n = 6)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Hematologic*												
Leukopenia	1	—	—	1	—	—	2	1	—	1	1	—
Lymphopenia§	1	1	—	1	1	1	1	2	—	1	3	2
Neutropenia	1	—	—	1	1	—	—	1	—	1	—	1
Thrombocytopenia	1	—	—	—	—	—	—	—	—	—	—	—
Eosinophilia	1	—	—	—	—	—	—	—	—	—	—	—

Abbreviations: QTc, corrected QT interval; γ-GTP, γ-glutamyl transpeptidase; CRP, C-reactive protein.
*KW-0761–related adverse events.
†Adverse events observed as the acute infusion reaction/cytokine release syndrome.
‡Observed 2.5 months after the last administration.
§Includes abnormal cells and was excluded from the definition of dose-limiting toxicities.

RESULTS

Patient Characteristics

Sixteen patients (13 ATL, two PTCL-NOS, one mycosis fungoides) were enrolled in this phase I study (Table 1). Patients characteristics both at first presentation and at study entry are listed in Appendix Table A1 (online only). Four patients were enrolled in cohort 2 because one participant (203) withdrew due to PD after receiving the first infusion. The other 15 patients completed the planned treatment. All 16 enrolled patients were evaluated for toxicity and response on an intent-to-treat basis.

Adverse Events and Nonhematologic Toxicities

All adverse events grade 2 are listed in Table 2.

The grade 3 nonhematologic toxicities were herpes zoster, skin rash, febrile neutropenia, elevations of ALT, AST, and γ-glutamyl transpeptidase (γ-GTP), and acute infusion/cytokine release syndrome (n = 1, each). All other toxicities observed were grade 2, and there were no grade 4 or grade 5 nonhematologic toxicities. Among the grade 3 toxicities, increases liver transaminases and γ-GTP were judged to be infusion-related toxicity. Neither the frequency nor the severity of toxicities increased with dose escalation. None of our patients had detectable human anti-KW-0761 antibody. Recovery from toxicities was observed in all cases.

Hematologic Toxicities

Lymphopenia occurred in 14 (88%) of the 16 patients: grade 2 or grade 3 in 11 and grade 4 in three. Grade 4 neutropenia, which developed in one patient, was associated with a febrile episode. Other hematologic toxicities were leukopenia, thrombocytopenia, and eosinophilia. These hematologic toxicities, which were grade 3, occurred at all the dose levels, but were transient. Recovery to normal or baseline levels was eventually seen in all cases.

Infusion-Related Toxicities

As presented in Table 2, seven (44%) of the 16 patients exhibited grade 2 acute infusion reaction or cytokine release syndrome. In six cases, the severity was grade 2, and in one grade 3. Overall, 14 patients (88%) had such events with a severity of at least grade 1. These adverse events occurred primarily at the first infusion, then became less frequent with subsequent treatments. The common infusion-related events were vasovagal episodes, hypotension, fever, hypoxemia, and elevations of alkaline phosphatase, C-reactive protein (CRP), liver transaminases, and γ-GTP. None of the patients required interruption of antibody infusion due to these toxicities.

Only one patient (201) who developed grade 2 infusion-related toxicities needed steroid administration for his infusion reactions. He was given one dose of 100 mg hydrocortisone with symptomatic improvement. The remaining patients did not need steroids.

Dose Escalation and DLT

In cohort 1, no DLT was observed during the DLT observation period, although one patient (102) developed grade 3 herpes zoster 2.5 months after the last infusion. This adverse event was treated with topical dressing by ointment and acyclovir and resolved in 1 week. Another patient (103) in cohort 1 showed a grade 3 increase in liver transaminase due to hepatitis B virus reactivation (grade 2) 6 months after the last infusion. At the onset, this patient was receiving the second course of KW-0761 because of PD after achieving PR with the first course, according to the protocol. This event resolved with the antiviral drug entecavir. This event was not judged to represent DLT by the independent data monitoring committee. In cohort 2, one patient (203) showed grade 3 liver function impairment. The event was not, however, considered to represent DLT, instead being judged to be an acute infusion reaction and cytokine syndrome toxicity. Patients in cohorts 3 and 4 developed neither grade 3 nonhematologic or grade 4 hematologic toxicities, nor acute infusion reaction and cytokine syndrome toxicities. Therefore, the MTD was not reached by cohort 4 and the maximum dose of 1.0 mg/kg was thus selected as the dose for the expanded cohort. In the expanded cohort, one patient (412) exhibited grade 4 neutropenia and grade 3 skin rash and febrile neutropenia (Appendix Fig A1, online only), possibly related to KW-0761 treatment. In total, one of the six patients at the 1.0 mg/kg dose level showed a DLT. Taking all data into account, the recommended phase II dose was determined to be 1.0 mg/kg.

Pharmacokinetics

KW-0761 exhibited dose-proportional pharmacokinetics. The plasma C_{max} and C_{trough} as well as the $AUC_{0\text{-}7days}$ increased dose and frequency dependently, as presented in Figure 1 and Table 3. At 1.0 mg/kg, the mean values (standard deviation [SD]) of C_{max}, C_{trough}, and $AUC_{0\text{-}7days}$ after the first infusion were 21,758 3,495 ng/mL, 7,544 3,009 ng/mL, and 1,879,383 464,447 ng hours/mL, respectively, while the corresponding values after the fourth infusion were 41,374 5,317 ng/mL, 19,637 3,826 ng/mL, and 4,224,459 533,158 ng hours/mL. The $t_{1/2}$ was prolonged at the 0.5 and 1.0 mg/kg dose levels as compared with lower doses. The mean value SD of $t_{1/2}$ after the fourth infusion at 1.0 mg/kg was 438 76 hours (18.3 3.2 days). There were no significant correlations between any of the pharmacokinetic parameters and either the clinical response to treatment or adverse events.

Responses

Five (31%; 95% CI, 11% to 59%) of the 16 enrolled patients achieved objective responses, including two (13%) with CR and three (19%) with PR (Table 4). The two patients achieving CR had acute-type ATL and their CR status was maintained until the last follow-up (12 and 3 months) without subsequent therapy. Two other acute-type

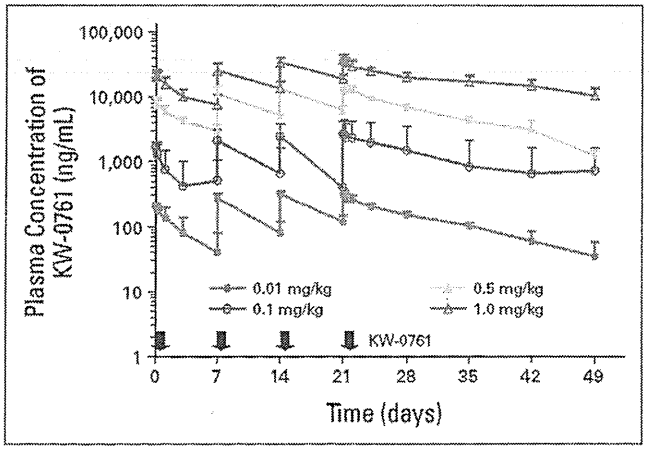

Fig 1. Mean KW-0761 plasma concentration profile by cohort; bar indicates upper limit of standard deviation.

Table 3. Mean Value of Pharmacokinetic Parameters of KW-0761 by Cohort

Dose (mg/kg) by Frequency	No.	C_{max} (ng/mL)		C_{trough} (ng/mL)		$AUC_{0\text{-}7\ days}$ (ng hours/mL)		$t_{1/2}$ (hours)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.01	3								
4th		323.7	56.7	151.6	12.4	34,301	4,455	244	117
0.1	3								
4th		2,806.7	1,664.5	1,515.2	1,873.4	327,212	322,031	201	196
0.5	3								
4th		15,161.2	872.0	6,824.7	872.9	1,615,135	143,225	332	122
1	6								
1st		21,758.0	3,495.4	7,544.2	3,008.8	1,879,383	464,447	133	111*
4th		41,373.7	5,316.6	19,636.7	3,825.7	4,224,459	533,158	438	76

Abbreviations: C_{max}, plasma maximum; C_{trough}, plasma trough; AUC, area under the curve; $t_{1/2}$, terminal half-life; SD, standard deviation.
*n = 2.

ATL and one PTCL-NOS patient showed PR, and one of these three patients maintained PR until the last follow-up (6 months). The median progression-free survival was 46 days although some patients remain progression free at last follow-up.

Clinical response was observed even at 0.01 mg/kg (Table 4). It is noteworthy that tumor cells disappeared rapidly from peripheral blood in most patients after KW-0761 infusion, as documented in patient 204 (Fig 2). Two other representative cases are also shown in Appendix Figures A1 and A2 (online only). These patients had ATL (102) and PTCL-NOS (401) and had previously been treated with VCAP plus AMP plus VECP and CHOP, respectively. The ATL patient (102) showed systemic skin involvement of ATL cells, and a lytic bone lesion. This patient received KW-0761 once a week for 4 weeks by intravenous infusion at 0.01 mg/kg, and 3 weeks later, his skin and bone lesions were assessed as stable disease according to the response criteria. Subsequently, both lesions gradually diminished in size, and by 1 year after treatment, the disease had completely disappeared, and this patient was categorized as showing CR. His CR status was maintained until the last follow-up (Appendix Fig A2, online only). The PTCL-NOS patient (401) had an enlarged inguinal lymph node and lymphoma cell involvement in peripheral blood and the skin. This patient received KW-0761 once a week for 4 weeks by intravenous

Table 4. Summary of Clinical Response of Each Patient

Patient No. by Cohort	Sex	Age (years)	Disease	No. of infusions	Response				PFS (days)
					PB	Skin	LN*	OR	
1									
101	M	46	MF tumor stage	4	—	PD	SD	PD	29
102	M	60	ATL acute	4	—	SD	—	SD→ CR†	617+
103	F	68	ATL acute	4	CR	—	CR	PR‡	85
2									
201	M	55	ATL acute	4	CR	PR	SD	SD	50
202	F	66	ATL acute	4	PR	—	SD	SD	36
203	M	66	ATL acute	1	—	—	SD	PD‡	8
204	F	57	ATL acute	4	CR	CR	—	CR	379+
3									
301	M	60	ATL acute	4	—	PD	—	PD	36
302	M	64	ATL acute	4	—	—	PD	PD	29
303	F	69	ATL lymphoma	4	—	—	SD	PD‡	29
4									
401	F	64	PTCL-NOS	4	CR	CR	PR	PR	198+
402	F	62	ATL acute	4	CR	CR	PR	PR	64
403	F	64	ATL lymphoma	4	—	—	SD	SD	43
Expanded									
411	M	55	ATL acute	4	—	PD	—	PD	28
412	M	62	ATL acute	4	CR	—	—	CR	107+
413	F	58	PTCL-NOS	4	—	—	SD	SD	110+

Abbreviations: PB, peripheral blood; LN, lymph node; PFS, progression-free survival; OR, overall response; M, male; MF, mycosis fungoides; PD, progressive disease; SD, stable disease; F, female; ATL, adult T-cell leukemia-lymphoma; CR, complete response; PR, partial response; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified.
*Target lesions among measurable enlarged lymph nodes and tumor nodules in extranodal organs.
†The diseases had disappeared by 1 year after treatment and 102 was categorized as showing CR.
‡Patients had nontarget lesions (nonincrease on 103, increase on 203) and new tumor legions (303).

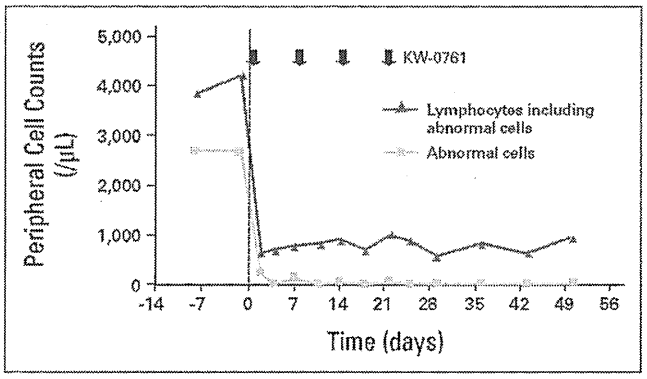

Fig 2. Response to KW-0761 in a representative patient (204). The time course of lymphocytes and adult T-cell leukemia-lymphoma (ATL) cells in peripheral blood of a patient with acute-type ATL treated with 0.1 mg/kg KW-0761 is shown.

infusion at 1.0 mg/kg. Lymphoma cells rapidly decreased after the first infusion and had completely disappeared before the second infusion. The skin lesions also resolved completely after the last infusion, while the lymph node remained somewhat enlarged, indicating PR in this case. The PR status was maintained for at least 6 months until the last follow-up (Appendix Fig A3, online only).

DISCUSSION

KW-0761 is a first-in-class therapeutic antibody targeting CCR4. In addition, this phase I study was the first clinical trial to examine the safety and efficacy of this next-generation defucosylated therapeutic antibody against hematologic malignancies. In humans, however, up to 15% of IgG does not contain fucose, and its physiological importance has yet to be fully elucidated,[30,31] although defucosylated antibodies markedly enhanced ADCC due to increased binding affinity to the Fcγ receptor on effector cells in vitro and in a mouse model.[21,22]

In this study, one patient showed DLT (grade 3 skin rash and febrile neutropenia; grade 4 neutropenia) at the 1.0 mg/kg dose in the expanded cohort. These toxicities were judged to possibly be related to KW-0761, although a causal association with trimethoprim/sulfamethoxazole could not be excluded. Further safety assessment is needed to determine whether KW-0761 itself might directly cause these toxicities. All other toxicities and symptoms including infusion reactions were mild to moderate and easily managed. The incidence and severity of infusion-related toxicity were the highest at the first infusion, diminishing with subsequent infusions, as has been observed with other antibody therapies.[32,33] The other important adverse event was viral reactivation. Hepatitis B virus reactivation and varicella-zoster virus infection were observed. These episodes might be related to a reduction in the number of CCR4-expressing cells caused by KW-0761 infusion, resulting in an alteration of the immune balance. Alterations in the proportions of each T-cell subset including Treg cells, due to this treatment, are currently being evaluated in detail in an ongoing phase II study.

Although the number of patients was small, it would be noteworthy that objective responses were achieved in 31% of patients, with 13% of CR. This is a particularly promising result since the response rate of relapsed patients with ATL to conventional chemotherapy with a single agent is reportedly extremely low.[6,34-36] Clinical responses were observed even at 0.01 mg/kg, which is approximately 1/1,000 of the rituximab dose. The clinical effect observed at the 0.01 mg/kg dose of KW-0761 would be consistent with this defucosylated mAb markedly enhancing ADCC.[22-24]

Pharmacokinetic analyses of KW-0761 revealed plasma C_{max}, C_{trough}, and $AUC_{0\text{-}7days}$ for both the first and the fourth infusion increased as the dose was increased. The $t_{1/2}$ after the fourth administration at 1.0 mg/kg was almost 18 days, which is nearly equal to the $t_{1/2}$ of circulating endogeneous human IgG,[37] indicating good stability of KW-0761 in the human body. In addition, in this study, no anti-KW-0761 antibody was detected, suggesting that the antigenicity of this novel defucosylated mAb agent was not therapeutically problematic. The C_{trough} level of 10 g/mL was achieved after the fourth infusion of KW-0761 at 1.0 mg/kg. The in vitro study using primary ATL cells from patients demonstrated profound autologous ADCC mediated by 10 g/mL KW-0761,[17] suggesting that an antibody concentration sufficient to exert ADCC against primary leukemia/lymphoma cells can be achieved clinically at this dose.

Increased Treg cells in the tumor microenvironment are thought to play an important role in tumor escape from host immunity in several different types of cancer.[38] Emerging recent evidence has demonstrated that the presence of Treg cells among tumor infiltrating lymphocytes is the main obstacle to successful tumor immunotherapy. Therefore, depletion of Treg cells around tumors is a potentially promising strategy for boosting tumor-associated antigen-specific immunity.[19,38-41] We previously reported that chimeric anti-CCR4 mAb actually depleted CD4-positive, CCR4-positive, and forkhead box protein P3–positive Treg cells both in vitro[17,41] and in vivo in a murine model.[21] The unexpected long-term CR in one patient (102) after stable disease at the 0.01 mg/kg dose of KW-0761 might be related to such a KW-0761-induced Treg reduction, resulting in enhancing the tumor immunity against ATL cells. However, there is no direct evidence for this and further studies are needed to assess the validity of this concept.

In summary, the results of this phase I trial show that KW-0761 infusion is tolerated at all dose levels tested in patients with relapsed CCR4-positive PTCL, including ATL and PTCL-NOS. This preliminary evidence of antitumor activity, in addition to the good tolerability and reasonable pharmacokinetics of KW-0761, warrants further investigation including a single-agent phase II study at the 1.0 mg/kg dose level and combination studies with conventional chemotherapeutic agents in patients with ATL and PTCL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Shiro Akinaga, Kyowa Hakko Kirin Co Ltd (C) **Consultant or Advisory Role:** Michinori Ogura, Kyowa Hakko Kirin Co Ltd (C) **Stock Ownership:** None **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

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ATL

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ATL

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はじめに

成人T細胞白血病・リンパ腫（ATL）は1977年に内山・高月らにより提唱された疾患概念であり，成人に好発し，特徴的な細胞形態を有するT細胞性白血病として記載された[1]。この時既に，患者の出生地が九州に偏在していたことからウイルスなどの病原体の関与が推測されている。1981年には三好らが臍帯血とATL患者の白血病細胞を共培養することにより細胞株を樹立した[2]。1981年にGalloらが皮膚T細胞性白血病リンパ腫患者の腫瘍細胞からレトロウイルスhuman T-cell leukemia virus type I/human T-lymphotropic virus type I（HTLV-1）と命名した[3]。このアフリカ系患者は後日，ATLであったことが判明している。1982年には日沼らがATL患者の白血病細胞を増殖因子添加で短期培養すると細胞表面に特異的な抗原が出現し，これが患者血清と反応することを報告した[4]。1984年には吉田らがHTLV-1の全塩基配列である約9,000ベースを同定した[5]。田島らとBlattnerらは，それぞれ九州とジャマイカではHTLV-1キャリアの頻度が高いことなど，疫学的に重要な知見を見出した[6,7]。HTLV-1がATLの病因ウイルスであることが示された後には，本疾患の多様性が明らかとなり，1992年に下山らは，臨床病態の特徴と予後の差から，急性型，リンパ腫型，慢性型，くすぶり型からなるATLの病型分類を提唱した[8]。

1984年と1985年にGessainらと納らはカリブ諸島と鹿児島とでそれぞれ独自に，成人に発症し特異的な臨床病態を有する痙性麻痺患者が抗HTLV-1抗体陽性であったことから，HTLV-1 associated myelopathy / tropical spastic paraparesis（MAM/TSP）を第2のHTLV-1関連疾患として提唱した[9,10]。1992年には久留米の望月らが成人のブドウ膜炎患者では抗HTLV-1抗体陽性率が高く，抗体陽性例ではブドウ膜炎の臨床病態に特徴があることからHTLV-1 associated uveitis（HAU）を提唱した[11]。ATL，HAM，HAUはその臨床病態とHTLV-1を用いた疫学調査とから確立した疾患概念である。HTLV-1は，感染T細胞が腫瘍化することによりATLを，感染T細胞が関与して免疫学的に脊髄またはブドウ膜を傷害することによりそれぞれHAMまたはHAUを発症する。しかしそれぞれの疾患の頻度はHTLV-1キャリアの数%以下であることから，その発症にはHTLV-1感染に加えていくつかの要因が必要であると推測されている。その他，感染性皮膚炎，シェーグレン症候群とHTLV-1との関連も報告されている[12,13]。HTLV-1/ATLに関する優れた総説がこれまでにあるが[14~17]，本稿ではATLの発症から治療までについて概説する。

HTLV-1の構造

ヒトの成熟Tリンパ球に感染するレトロウイルスの3種であるHTLV-1，HTLV-2とhuman immunodeficiency virus（HIV: 当初はHTLV-3と呼ばれた）は塩基配列で相同性を有するが，HTLV-1でのこの相同性はむしろサルに感染するsimian lymphotropic virusとの間で高いことから，人猿共通の祖先ウイルスの存在が示唆されている[15]。HTLV-1の亜種としてはCosmopolitan type，Zairian type，Melanesian typeなどが知られているが，その変異は数%とHIVにおける変異率と比べて極めて低く，アンデスで数千年前のミイラからもHTLV-1が検出されたことと合わせて，長年にわたり種が保持されてきたウイルスと考えられている[15]。これは，HTLV-1がHIVと異なり，生体内でウイルスをほとんど発現せずに，感染する場合はglucose transporter 1を介したcell to cell infectionであり，ウイルスの増殖は感染細胞のク

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ローナルな増殖によってきたことに関連すると推定されている[18]。AIDS と ATL の発症とそれぞれのウイルスの動態との関連については，以下のように考えることができる。HIV は，宿主の HIV に対する特異的細胞障害性 T リンパ球を含む免疫系を障害した後に自己ウイルスを爆発的に発現，増殖しながら感染した CD4T リンパ球を破壊して AIDS を発症させるのに対し，HTLV-1 は，自己ウイルスを発現せず特異的細胞障害性 T リンパ球からの攻撃を避けながら，感染した CD4T リンパ球をクローナルに増殖させて ATL を発症させる。

他のレトロウイルスと同様に HTLV-1 は，両端に long terminal repeat（LTR）を，内部にウイルスの構成蛋白をコードする gag，pol，env を有するほかに pX と呼ばれる領域を有する（図 1）[15, 19, 20]。この領域がコードする tax，rex などは，trans-activation によりウイルス遺伝子のみならず宿主遺伝子の転写を制御する。これらの宿主遺伝子がコードする蛋白の多くは，HTLV-1 が感染 T 細胞を活性化あるいは腫瘍化するのに重要な役割を果たすと報告されている。しかし前述のように生体内で Tax 蛋白を含む HTLV-1 はほとんど発現しておらず，さらには ATL 細胞の染色体ゲノムへの HTLV-1 プロウイルスの組み込み部位は症例により全くまちまち（random）であることから，HTLV-1 による発がん機構は，マウスやチキンなどで知られているウイルス発がんとは大きく異なると推測されている[15]。最近，HTLV-1 の LTR と pX 領域のマイナス鎖にコードされる HTLV-1 bZIP factor（HBZ）が同定された。HBZ は c-Jun，JunB などの bZIP ドメインを有する転写因子と結合する。HBZ は，tax と異なりすべての ATL 症例で発現されていること，siRNA 解析により ATL 細胞の増殖に関係することが明らかとなり，腫瘍化との関連が解析されつつある[21~23]。

HTLV-1 と ATL の疫学

HTLV-1 の感染経路としては，輸血，性交渉，主に母乳を介した母児感染の 3 つが知られている[14, 15]。HTLV-1 キャリアの生涯における ATL 発症率は数％と推定されているが，多くの悪性腫瘍と同様に女性よりも男性で好発する。稀に成人での臓器移植後あるいは造血器腫瘍に対する輸血後の ATL 発症が報告されているが，大多数の患者は母児感染後に数十年を経て本疾患を発症することが疫学調査で強く示唆されている。日本とジャマイカ，アフリカからの報告を比較すると，ATL の発症頻度や病像の多く（日和見感染症や高 Ca 血症などの合併症，予後など）は同様であるが，一点大きく異なっている。それは平均発症年令であり日本では約 60 歳であるのに対し，ジャマイカ，アフリカでは 40 代と有意に若年で ATL を発症している[14, 15]。前述のようにこれらの地域間で HTLV-1 ゲノムに大差がないことから，HLA などの民族学的要因あるいは環境要因といった宿主側の因子がこの年齢差，すなわち多段階発癌の進展速度の差に関与していることが示唆される。HTLV-1 キャリアにおける ATL の発症危険因子としては，若年での HTLV-1 感染，加齢，男性，喫煙感染性皮膚炎の既往，HTLV-1 抗体高力価，TNFα 遺伝子多型などが報告されている[14, 15, 24~26]。HTLV-1 感染から ATL 発症までは多段階発がんによると考えられるが，約 60 年の潜伏期間を経て数％の保因者に発症することから，統計学的にはお

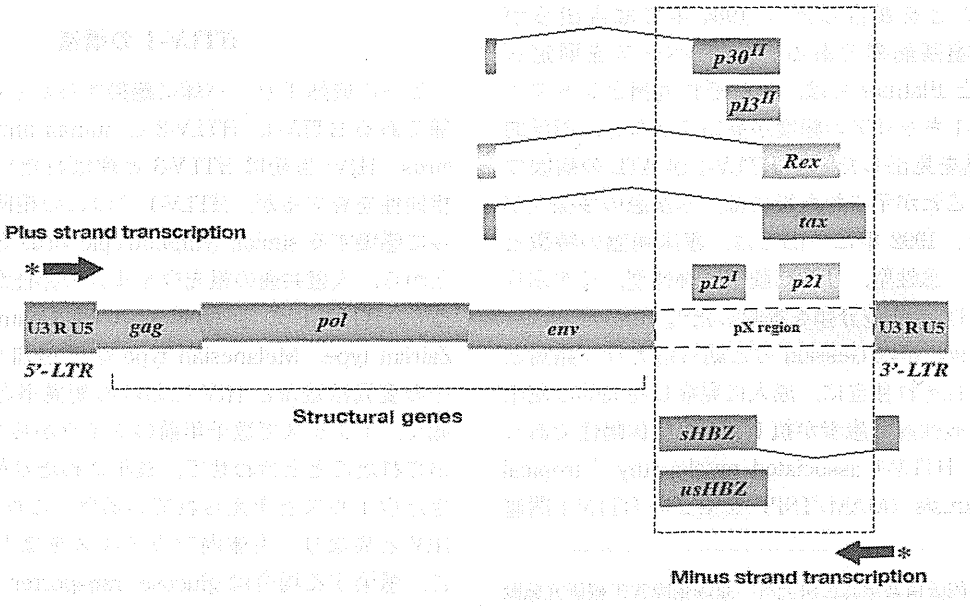


図 1　HTLV-1 の構造（文献 20 より改変引用）

よそ5段階の遺伝子レベルでのイベントを経て発症すると推定されている[27]。その多くは不明だが，くすぶり型/慢性型ATLの急性転化の場合，過半数ではp53，$p15^{INK4B}$，$p16^{INK4A}$などの癌抑制遺伝子の変異がこの時点のイベントであることが報告されている[28,29]。

HTLV-1のendemic areaとしては西南日本の他に，中南米，アフリカが知られている。一方，韓国や中国ではHTLV-1キャリアは極めて稀である。この地域学的および民俗学的偏在性の原因は不明であり，HTLV-1を用いた民族学の研究もなされつつある。一方，限られた地域においてもHTLV-1キャリアの偏在性が知られている。HTLV-1のendemic areaである日本のいくつかの島嶼において，数kmしか離れていない集落ごとに主に高齢の住民の抗体陽性率が約5%から40%と大きく異なっており，HTLV-1の感染様式と交通の便などを含む住民の生活様式とがこれに関与していると考えられる[14,15]。

endemic areaにおいて抗体陽性率は，男性よりも女性に高く，加齢とともに高くなる。これらは，性交渉による水平感染が女性で男性よりも高頻度であり，また加齢と共にリスクが増すためと考えられている。また，高齢者での高陽性率には乳児期の年代の違い（birth cohort effect）も関与する。HTLV-1のendemic areaにおける各年齢層での抗HTLV-1抗体陽性率が，介入試験をしないでも10年以上フォローすると低下傾向にあることがいくつかの地域から報告されており，新生児期を中心とした栄養・環境要因の変化がこれに関与していると推定されている[14,15]。

初回献血者での抗HTLV-1抗体陽性率から推定した全国のHTLV-1キャリアの現状（2006～07年）が報告された[30]。初回献血者（16歳～64歳）119万6千人中3,787人0.317%が陽性（男性0.3%，女性0.34%）であり，肝炎ウイルス感染率よりもやや低かった（HBsAg 0.6%，HBcAb 1.6%，HCVAb 0.5%）。HTLV-1陽性率は30代で0.25%から60代で1.48%までほぼ直線的に上昇しており，HTLV-1キャリア数は若年者を中心に確実に減少した。1988年の同様の解析と比較すると，国内キャリア数とその九州居住率は，それぞれ120万人と61%から108万人と46%へ低下していた。

日本では1980年代に献血時の抗HTLV-1抗体のスクリーニングが開始された後，輸血による感染はほぼ阻止された。HTLV-1のendemic areaの1つである長崎におけるHTLV-1キャリア妊婦への授乳遮断の介入事業・研究では，児の抗体陽転率をそれまでの約20%から約3%と著明に低下できている。約3%の陽転については，経胎盤感染の所見はなく，経産道感染などが推定される。1987年からのこの事業では20年間でキャリア妊婦が約7,000人であったことから，約1,250人のキャリア児の発症予防，さらにはATLの生涯発症率が約5%であることから，約60人のATL発症を予防できたと推定されている[31]。

キャリアにおけるATL発症要因については前述の報告があるが，これまで明確に同定されていなかった[14,15,24～26]。JSPFAD（HTLV-1感染者コホート共同研究班）研究では日本全国の拠点病院で2002年から2008年までの期間に1,218例（男性426例，女性792例）の無症候性キャリアが前向きにフォローされた[32]。登録時のキャリアの末梢血HTLV-1ウイルス量はゼロから高い人で55コピー/100末梢血単核球（PBMC）と非常に幅広く，中央値は1.6 copies/100 PBMCであった。登録時のウイルス量は有意に女性よりも男性で高く，（median, 2.10 vs 1.39コピー/100 PBMC）（P<.0001），40歳代と50歳代は40歳未満よりも有意に高かった（それぞれP=.02と.007）。また家族歴にATLがある場合はない場合よりも高かった（中央値，2.32 vs 1.33コピー/100 PBMC）（P=.005）。フォローアップ中に14例がATLを発症したが，これらの症例のベースラインのウイルス量は有意に高かった（range, 4.17～28.58コピー/100 PBMC）。このコホートにおけるATL発症要因について多変量解析したところ，表1に示すリスクファクターが同定された。HAMの家族歴があるキャリアのウイルス

表1 ATL発症のリスクファクター

	単変量解析		多変量解析	
	ハザード比（95% CI）	*P*	ハザード比（95% CI）	*P*
男　性	0.74（0.23～2.37）	.01	0.36（0.12～1.16）	.09
HTLV-1ウイルス量	2.55（1.91～3.41）	<.0001	3.57（2.25～5.88）	<.0001
年齢（40歳以降での5歳ずつの増加）	1.20（0.94～1.53）	.15	1.67（1.12～2.50）	.012
ATLの家族歴	2.88（0.80～8.98）	.11	12.1（2.26～64.7）	.004
初回HTLV-1抗体検査が他の疾患治療中	3.40（1.12～10.28）	.03	4.16（1.37～12.8）	.012

（文献25より改変引用）

量も高い傾向にあったが，ATLへの進展者はいなかった。観察期間が短かったため，とらえることができなかった他の因子や，調査していない未知の因子も関与している可能性もあるが，少なくとも現段階では，登録時のHTLV-1感染細胞率が4 copies/100 PBMC以下のキャリアはATLに進展していなかった。今後はリスクファクターを有するキャリアのATL進展予防法の開発が望まれる。

ATLの臨床病態

HTLV-1プロウイルスが染色体DNAに組み込まれた成熟T細胞が形質転換して，単クローン性に増殖する腫瘍がATLである[14,17]。腫瘍細胞は花弁状の核と凝集したクロマチン構造が特徴的であり，細胞質にアズール顆粒は認めない。また，活性化helper T細胞/regulatory T細胞の細胞形質（CD3，CD4，CD25，CCR4，FoxP3陽性）を有するが，患者の細胞性免疫能は低下していることが多い[33,34]。ATLの臨床病態は多様である。予後因子としては，800例を超える多変量解析で同定された年齢，全身状態，総病変数，高Ca血症，高LDH血症が重要である[35]。予後因子解析と臨床病態の特徴から，ATLは急性型，リンパ腫型，慢性型またはくすぶり型の4型に分類される[8]。その診断アルゴリズムを表2に示すが，急性型は他の病型およびキャリアを除外して診断する。生存期間中央値は急性型6ヶ月，リンパ腫型10ヶ月，慢性型24ヶ月，くすぶり型は3年以上であった。慢性型/くすぶり型では血液，皮膚，肝臓，脾臓，リンパ節などにATL細胞が浸潤するが増殖力は強くないため，病状は無治療でも安定していることが多く，高Ca血症，基準値の2倍を超える高LDH血症や前述の臓器以外への浸潤を認めない。くすぶり型と慢性型の違いは，後者がATL細胞による4,000/μl以上のリンパ球増多を有する点である。急性型/リンパ腫型は消化管，骨，胸水，腹水や中枢神経など，前述以外の主要臓器への浸潤，高Ca血症または基準値の2倍以上の高LDH血症を有する。急性型とリンパ腫型の違いは，前者が2%以上のATL細胞を血液中に認める点である。急性型/リンパ腫型の臨床症状としては，浸潤した臓器障害，高Ca血症，合併した日和見感染症などにより多彩である。慢性型/くすぶり型は検診などでATL細胞を血液中に認めて発見される場合のほか，慢性に経過する紅斑，腫瘤，紅皮症などの皮膚病変，日和見感染症，慢性閉塞性肺疾患，自己免疫性疾患などで診断されることがある。

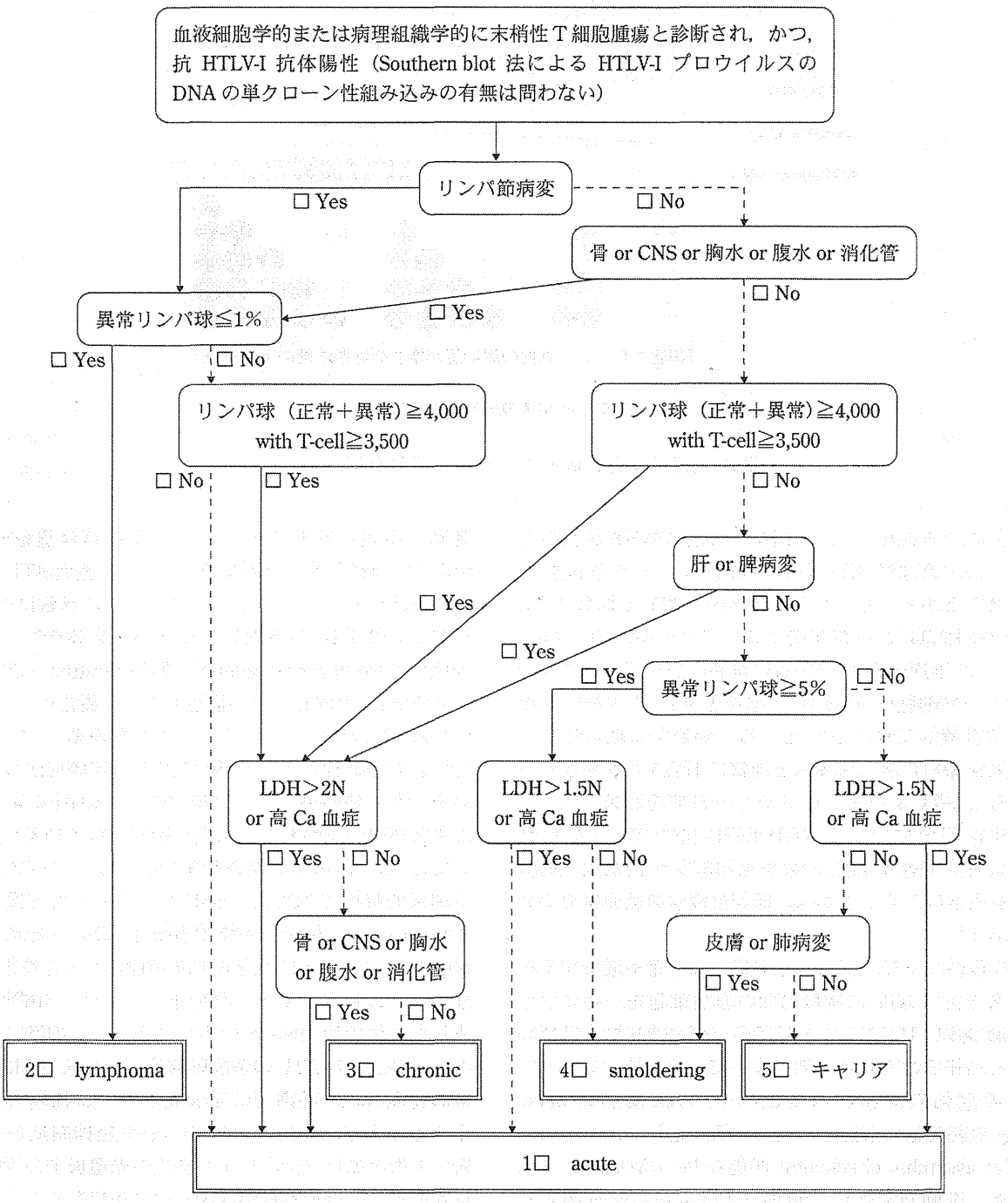
慢性型/くすぶり型ATLの長期予後

慢性型/くすぶり型ATLは急性型/リンパ腫型ATLよりも予後良好であったが，その長期予後の報告はこれまでなかった[8]。当科で1974年以降に診断された初診のくすぶり型25例，慢性型65例を対象とし長期follow upデータを解析し予後と予後因子を検討した[33]。観察期間の中央値は4.0年（0.02～17.5）であった。5年，10年，15年生存率はそれぞれ47%，23%，9%であり，全生存曲線ではプラトーは得られず下に凸の2相性のカーブを描いた。63例（70%）が死亡しており，死因はATL 46例，他病死（重複がんと日和見感染症を多く含む）11例，移植関連死2例，不明4例であった。多くの症例は急性転化するまで無治療で経過観察（Watchful waiting: WW）されたが，12例はLDH高値などのため早期に治療が開始されていた。早期治療開始例は，その他と比べて予後不良であった。WWが選択されることが多いくすぶり型またはLDH高値などの予後不良因子を持たない慢性型（計62例）に限っても，MSTは5.4年であった。全身状態，高LDH血症，総病変数，節外病変数，好中球数増多の有無で予後に差を認めた。同じくWWが治療方針とされる慢性リンパ性白血病と比べて慢性型/くすぶり型ATLの予後は不良であるが，比較的早期に病状が進展する群と，緩やかに進行していく群の存在が生存曲線から示された。

ATLの多段階発がんにおける分子病態

HTLV-1感染から数十年を経て，数%のキャリアに発症するATLの多段階発癌について，図2に現時点で明らかとなっている知見に基づいた模式図を記す[12~14,17~19]。HTLV-1プロウイルスのTリンパ球染色体ゲノムへの組み込み部位特異的にクローンを同定する遺伝子検査法であるサザンブロット法は，約5%の感度で単クローン性のHTLV-1感染細胞集団を検出できるATLの確定診断法である。しかしこの方法ではキャリアとHAM患者の一部でも末梢血で単クローン性が証明される[37,38]。さらには高感度なPCR法による組み込み部位特異的な解析では，検索されたHTLV-1キャリアの全例でオリゴクローナルな感染細胞の増殖を認めた[39]。同様の解析法によると，急性型ATL症例でも末梢血中に白血病由来のメジャーな単クローン以外に，キャリアで検出されたのと同様のオリゴクローナルな感染細胞の増殖を認めた。さらにはキャリアのコホート研究で同定された，ATLを発症した症例についてさかのぼったところ，ATLのクローンは数年ごとの検診でオリゴクローンのうちの一つとして検出され続けていた[40]。以上からHTLV-1感染者は，無症候性キャリアとATL患者とに関わらずオリゴクローナルなHTLV-1感染細胞の増殖を認めること，ATLのクローンはキャリアのオリゴクローンのうちの一つが拡大して出来上がったことが示され

表 2　ATL の臨床病型診断フローチャート



・リンパ球数：正常リンパ球数＋異常リンパ球数
・高 Ca 血症：≧11.0 mg/dl（補正値）
・末梢血中の異常リンパ球が 5%未満で，リンパ節を含め他に病変を持たず LDH≦1.5N かつ高 Ca 血症を認めない症例は Southern blot 法による結果に関わらず，キャリアとして取り扱う。

た。

無症候性キャリアにおけるこの HTLV-1 が感染したオリゴクローンを検討するため，末梢血単核球を用いてインターロイキン 2（IL-2）添加コロニー形成法により HTLV-1 感染 T リンパ球クローンでウイルスを発現させて *in vitro* で増大させたのちに染色体分析を行ったところ，対照（*in vitro* で HTLV-1 に感染させた T リンパ球）と比べて有意に高率に染色体異常を認めたことから，ATL 発症前からキャリアでは HTLV-1 感染細胞が染色体不安定性を持っていることが示された[41]。慢性型 ATL