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Multicenter phase II study of bendamustine for relapsed or refractory indolent B-cell non-Hodgkin lymphoma and mantle cell lymphoma

Ken Ohmachi,[1] Kiyoshi Ando,[1,11] Michinori Ogura,[2] Toshiki Uchida,[2] Kuniaki Itoh,[3] Nobuko Kubota,[3] Kenichi Ishizawa,[4] Joji Yamamoto,[4] Takashi Watanabe,[5] Naokuni Uike,[6] Ilseung Choi,[6] Yasuhito Terui,[7] Kensuke Usuki,[8] Hirokazu Nagai,[9] Nobuhiko Uoshima[10] and Kensei Tobinai[5]; The Japanese Bendamustine Lymphoma Study Group

[1]Division of Hematology/Oncology, Department of Internal Medicine, Tokai University School of Medicine, Kanagawa; [2]Department of Hematology and Oncology, Nagoya Daini Red Cross Hospital, Nagoya; [3]Division of Oncology and Hematology, National Cancer Center Hospital East; [4]Department of Hematology and Rheumatology, Tohoku University Hospital, Sendai; [5]Hematology and Stem Cell Transplantation Division, National Cancer Center Hospital, Tokyo; [6]Department of Hematology, National Kyushu Cancer Center, Fukuoka; [7]Division of Medical Oncology and Hematology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo; [8]Division of Hematology, NTT Medical Center Tokyo, Tokyo; [9]Clinical Research Center, National Hospital Organization, Nagoya Medical Center, Nagoya; [10]Department of Internal Medicine, Hematology, Matsushita Memorial Hospital, Moriguchi, Japan

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Bendamustine is a unique cytotoxic agent that has demonstrated efficacy in the treatment of indolent B-cell non-Hodgkin lymphomas (B-NHLs). In this multicenter phase II trial, the efficacy and safety of bendamustine were evaluated in Japanese patients with relapsed or refractory indolent B-NHL or mantle-cell lymphoma (MCL). Patients received bendamustine (120 mg/m^2) on days 1–2 of a 21-day cycle, for up to six cycles. The primary endpoint was the overall response rate (ORR) as assessed by an extramural committee according to International Workshop Response Criteria (IWRC). Secondary endpoints included complete response (CR) rate, ORR according to Revised Response Criteria (revised RC), progression-free survival (PFS), and safety. Fifty-eight patients with indolent B-NHL and 11 with MCL were enrolled. By IWRC, bendamustine produced an ORR of 91% (95% confidence interval [CI], 82–97%; 90% and 100% in patients with indolent B-NHL and MCL, respectively), with a CR rate of 67% (95% CI, 54–78%). ORR and CR rates according to revised RC were 93% (95% CI, 84–98%) and 57% (95% CI, 44–68%), respectively. After a median follow-up of 12.6 months, median PFS had not been reached. Estimated PFS rates at 1 year were 70% and 90% among indolent B-NHL and MCL patients, respectively. Bendamustine was generally well tolerated. Reversible myelosuppression, including grade 3/4 leukopenia (65%) and neutropenia (72%), was the most clinically significant toxicity observed. Common non-hematologic toxicities included mild gastrointestinal events and fatigue. These results demonstrate the high efficacy and tolerability of single-agent bendamustine in relapsed patients with indolent B-NHL or MCL histologies. (ClinicalTrials.gov ID: NCT00612183). (*Cancer Sci* 2010; 101: 2059–2064)

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoid malignancies, comprising 3% to 5% of all malignancies in the USA, Japan, and worldwide.[1–3] A total of 65 980 new cases and 19 500 deaths due to NHL are estimated for 2009 in the USA,[2] with similar incidence and mortality rates in Japan.[3]

Indolent B-cell non-Hodgkin lymphomas (B-NHLs), including follicular lymphomas, are less aggressive than other NHL subtypes; however, they are generally considered incurable due to their relapsing nature.[4,5] Front-line therapy with a regimen of cyclophosphamide, doxorubicin, vincristine, and prednisolone in combination (CHOP) plus rituximab produces high response rates in these patients and has improved progression-free survival (PFS) and overall survival compared with chemotherapy alone.[6–9] These improvements notwithstanding, most patients relapse and many become refractory to chemotherapy and rituximab. Effective second-line therapies are needed, especially those that do not exhibit cross-resistance with chemotherapy or rituximab.

Mantle cell lymphoma (MCL) is a relatively aggressive subtype of B-NHL, associated with poor responsiveness to treatment and shortened survival, that occurs in 3% to 8% of NHL patients.[10–14] Limited effective therapies are available for this population, particularly for relapsed patients.

Bendamustine is a unique cytotoxic agent with a multifaceted mechanism of action.[15] Structurally, it includes both a mechlorethamine group and a benzimidazole ring, intended to confer properties of both alkylators and purine analogs.[16] Bendamustine acts by directly damaging DNA as well as inducing apoptosis and mitotic catastrophe.[15,17,18] Importantly, bendamustine shows a distinct pattern of activity and a lack of cross-resistance with other alkylating agents.[15,19]

Single-agent bendamustine has demonstrated efficacy in patients with relapsed, rituximab-refractory B-NHL in two North American trials. In a phase II trial by Friedberg *et al.*[20] bendamustine produced a response in 47 (80%) of 59 assessable patients with indolent B-NHL, with a median response duration of 9.0 months. Results from the subsequent single-arm pivotal trial indicated a response rate of 75% in rituximab-refractory indolent B-NHL patients with a median response duration of 9.2 months.[21] Based on the results of these trials, bendamustine was approved in the USA and Canada for the treatment of indolent B-NHL that has progressed during or within 6 months of treatment with rituximab or a rituximab-based regimen. The objective of the present trial was to determine the safety and efficacy of bendamustine in Japanese patients with previously treated indolent B-NHL or MCL.

Materials and Methods

Study design and objectives. This multicenter, open-label, single-arm, phase II clinical study was designed to determine the antitumor effect and safety of bendamustine in patients with relapsed or refractory indolent B-NHL or MCL. The primary endpoint was the overall response rate (ORR), defined as the

[11]To whom correspondence should be addressed.
E-mail: andok@keyaki.cc.u-tokai.ac.jp

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proportion of patients achieving a partial remission (PR) or better, according to International Workshop Response Criteria (IWRC) for NHL.[24] Secondary endpoints included the complete response (CR) rate, the ORR according to the Revised Response Criteria for Malignant Lymphoma (revised RC),[25] PFS, and safety. This study was performed in compliance with the ethical principles provided by the Helsinki Declaration and the Japanese Pharmaceutical Affairs Act. The protocol was approved by the institutional review board of each participating institution.

Eligibility. Patients aged 20 to 75 years were eligible if they had previously treated, histopathologically confirmed indolent B-NHL or MCL[22] that failed to respond to, or relapsed after, prior therapy. There was no maximum number of allowed prior therapies. Patients were required to have a measurable lesion >1.5 cm in one dimension, an Eastern Cooperative Oncology Group performance status[23] of 0 or 1, and a life expectancy ≥3 months. Adequate hematologic (neutrophils ≥1500/μL and platelets ≥100 000/μL), renal (serum creatinine <1.5 × the upper limit of the normal [ULN] at each study institution), hepatic (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] <2.5 × ULN; total bilirubin <1.5 × ULN), and respiratory and cardiovascular (arterial oxygen partial pressure ≥65 mmHg; no abnormal electrocardiogram findings in need of treatment) function were required. Patients could have no carry-over effect of prior therapy, with a required 4-week wash-out period (at least 3 months for antibody therapy). Patients were excluded if they had an apparent infection (including viral infection), other serious medical disorder, infiltration of lymphoma to the central nervous system, or an active malignancy other than lymphoma. Patients were required to provide written informed consent.

Treatment. Bendamustine 120 mg/m^2 was administered by intravenous infusion over 60 min on days 1 and 2 every 21 days for up to six treatment cycles. Hospitalization was required during days 1–3 of cycle 1; subsequent treatment was allowed on an outpatient basis at the discretion of the investigator. Computed tomography (CT) examination was performed at enrollment, during the third and last cycles, and 3 months after the last cycle. When available, positron emission tomography (PET) examination was performed at enrollment and during the last cycle. Hematologic and biochemical laboratory tests were performed at study entry and at 1, 2, and 3 weeks after administration of each cycle. Before beginning each treatment cycle, recovery of neutrophil and platelet counts (to ≥1000/μL and ≥75 000/μL, respectively) and the absence of grade ≥3 toxicities was required. Dose reductions to 90 mg/m^2 were performed in patients with grade 4 neutropenia persisting for ≥1 week despite treatment with granulocyte colony-stimulating factor (G-CSF), febrile neutropenia (grade ≥3 neutropenia, accompanied by a fever of ≥38.5 C) persisting for 3 days or longer, platelet count <10 000/μL or hemorrhagic tendency requiring platelet transfusion, or other grade 3/4 toxicities at the discretion of the investigator. In the case of toxicity recurrence, the dose was reduced to 60 mg/m^2. Further recurrence of toxicity at 60 mg/m^2 resulted in discontinuation of treatment.

The use of prophylactic antiemetics and antibiotics for prevention of opportunistic infection was recommended. The use of G-CSF was permitted during cycles 2 through 6, as well as during cycle 1 when grade ≥3 neutropenia was confirmed. Prophylaxis for tumor lysis syndrome (e.g. allopurinol) was recommended in patients with high tumor burden.

Assessment. Response was assessed after the third and last cycles of treatment by an extramural committee according to the IWRC,[24] as well as by the revised RC.[25] Patients were classified by best tumor response: CR (disappearance of all evidence of disease), unconfirmed CR (CRu; a CR with indeterminate bone marrow histology or a more than 75% decrease from baseline in the sum of the products of the greatest perpendicular diameters [SPD] of all the measurable lesions but with a residual mass; used in IWRC only), partial response (PR; a more than 50% decrease from baseline in the SPD of all the measured lesions, no increase in size of any other lesions, and no new lesions), stable disease (failure to achieve a PR, but without disease progression), or progressive disease (any new lesions or an increase by ≥50% of a previously involved site from nadir). PFS was determined at 3 months after completion of the last cycle, with additional assessments performed every 3 months during the study. PFS was calculated as the time from study enrollment to either disease progression (including relapse and exacerbation) or death from any cause.

Adverse events were reported according to the Common Terminology Criteria for Adverse Events version 3.0.[26] Serious

Table 1. Patient demographics and baseline characteristics

	Indolent B-NHL (*n* = 58)	MCL (*n* = 11)
Age, years		
Median	58.5	70
Range	33–75	59–75
Sex, *n*		
Male	33	7
Female	25	4
ECOG performance status, *n*		
0	52	7
1	6	4
Diagnosis (WHO classification), *n*		
Small lymphocytic lymphoma	3	
Lymphoplasmacytic lymphoma	1	
Splenic marginal zone B-cell lymphoma	0	
MALT lymphoma	1	
Nodal marginal zone B-cell lymphoma	1	
Follicular lymphoma	52	
Mantle cell lymphoma		11
Stage at diagnosis, *n*		
Stage I or II	7	4
Stage III	21	1
Stage IV	29	6
Unknown	1	0
Risk category, *n*†		
Low risk	30	2
Intermediate risk	13	8
High risk	15	1
Prior treatment, *n*		
Chemotherapy	56	11
Purine analogs	20	4
Rituximab	55	11
Ibritumomab tiuxetan	2	0
Radiotherapy	7	2
Corticosteroids alone	3	0
Other	8	4
Number of prior regimens		
Median	2	4
Range	1–9	1–16
Time since last treatment, months		
Median	13.4	6.6
Range	1.1–29.5	1.1–35.8

†Risk categories were determined using the Follicular Lymphoma International Prognostic Index (FLIPI) for patients with indolent B-cell non-Hodgkin lymphoma (NHL) and International Prognostic Index (IPI) for patients with mantle cell lymphoma (MCL). ECOG, Eastern Cooperative Oncology Group; MALT, mucosa-associated lymphoid tissue; WHO, World Health Organization.

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adverse events were also recorded; these were defined as events that led to death or disability, were life-threatening, required hospitalization, caused congenital anomaly, or resulted in medically significant conditions.

Statistical analyses. The sample size was calculated based on an expected and threshold ORR of 55% and 35% in patients with indolent B-NHL and 40% and 15% in patients with MCL, respectively. The ORR was calculated as the proportion of treated patients who achieved a PR or better, along with a 95% confidence interval (CI). The CR rate was calculated as the proportion of treated patients who achieved a CR or CRu, along with a 95% CI. PFS was assessed by the Kaplan–Meier method, with a 95% CI based on Greenwood confidence bounds.

Results

Patients. Fifty-eight patients with indolent B-NHL and 11 patients with MCL were enrolled. Patient demographics and baseline characteristics are summarized in Table 1. Among patients with indolent B-NHL, histologies included follicular (n = 52), small lymphocytic (n = 3), and one each lymphoplasmacytic, nodal marginal zone, and mucosa-associated lymphoid tissue lymphomas. The median number of prior regimens administered was two (range, 1–9) in patients with indolent B-NHL and four (range, 1–16) in patients with MCL. Thirty-seven (64%) patients with indolent B-NHL and six (55%) patients with MCL were known to be responsive to their last prior therapy.

Disposition. All enrolled patients received treatment with bendamustine and were included in both efficacy and safety analyses (Table 2). Fifty (72%; 41 with B-cell NHL and nine with MCL) patients completed the planned treatment of three or more cycles of bendamustine. The median number of cycles administered was five (range, 1–6). All 19 early discontinuations were due to adverse events, mainly myelosuppression, including neutropenia (9), neutropenia/leukopenia (3), thrombocytopenia (2), leukopenia (1), pneumonia (1), fatigue/nausea (1), anorexia/nausea/vomiting (1), and fever/vomiting/increased ALT/AST (1).

Efficacy. Bendamustine produced an ORR of 91% according to the IWRC, with a CR rate (CR plus CRu) of 67% (Table 2). Among patients with indolent B-NHL, the ORR was 90%, including a CR/CRu rate of 66%. All 11 MCL patients responded to bendamustine (100%), with eight patients achieving a CR/CRu (73%). Results were similar using the revised RC, with an ORR of 93% and a CR rate of 57% (Table 3). Among 57 patients who underwent both CT and PET examinations, the evaluation of overall response according to IWRC and the revised RC did not agree in nine patients (seven of 47 with indolent B-NHL and two of 10 with MCL).

In patients with indolent B-NHL, ORR by Follicular Lymphoma International Prognostic Index (FLIPI)[27] risk category was 97% (29 of 30) in low-risk, 92% (12 of 13) in intermediate-risk, and 73% (11 of 15) in high-risk patients (P = 0.041). Response rates were similar by disease stage, number of prior therapy regimens, or response to most recent prior therapy. In patients who received fewer than three cycles of bendamustine, the ORR was 74% (95% CI, 49–91%), compared with 98% (95% CI, 89–100%) in patients who received three or more cycles (Table 4).

After a median follow-up of 12.6 months (range, 1.3–17.9 months), disease progression was observed in 21 patients, 19 with indolent B-NHL, and two with MCL; median PFS had not yet been reached (Fig. 1). Estimated PFS rates at 1 year were 74% in the overall population, 70% in patients with indolent B-NHL, and 90% in patients with MCL.

Safety. The main toxicity observed with bendamustine treatment was reversible myelosuppression, including grade 3/4 neutropenia (72%), leukopenia (65%), and thrombocytopenia (16%) (Table 5). Twenty-seven (39%) patients received growth factor support, two patients received platelet transfusions, and one patient received a transfusion of packed red blood cells.

Common non-hematologic adverse events included nausea (86%), fatigue (62%), and anorexia (61%), and were mainly grade 1/2 in severity (Table 6). Seventeen infections of any grade were observed in 11 patients (16%); grade 3 infection was observed in five patients (7%; one each febrile neutropenia, pneumonia, upper airway infection, varicella/herpes zoster, and

Table 2. Objective response to bendamustine treatment, by IWRC

Disease type	n	Response by IWRC, n (%)†				CR/CRu,% (95% CI)	ORR, % (95% CI)
		CR	CRu	PR	SD		
All	69	27 (39)	19 (28)	17 (25)	6 (9)	67 (54–78)	91 (82–97)
Indolent B-NHL	58	20 (34)	18 (31)	14 (24)	6 (10)	66 (52–78)	90 (79–96)
Follicular	52	19 (37)	17 (33)	11 (21)	5 (10)	69	90
Small lymphocytic	3	0	1 (33)	1 (33)	1 (33)	33	67
Lymphoplasmacytic	1	0	0	1 (100)	0	0	100
MALT	1	0	0	1 (100)	0	0	100
Nodal marginal zone	1	1 (100)	0	0	0	100	100
MCL	11	7 (64)	1 (9)	3 (27)	0	73 (39–94)	100 (72–100)

†International Workshop Response Criteria (IWRC) for NHL.[24] CI, confidence interval; CR, complete response; CRu, unconfirmed CR; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; PR, partial response; SD, stable disease.

Table 3. Objective response to bendamustine treatment, by revised RC

Disease type	n	Response by revised RC, n (%)†				CR, % (95% CI)	ORR, % (95% CI)
		CR	PR	SD	PD		
All	69	39 (57)	25 (36)	4 (6)	1 (1)	57 (44–68)	93 (84–98)
Indolent B-NHL	58	31 (53)	22 (38)	4 (7)	1 (2)	53 (40–67)	91 (81–97)
MCL	11	8 (73)	3 (27)	0	0	73 (39–94)	100 (72–100)

†Revised Response Criteria for Malignant Lymphomas (revised RC).[25] CI, confidence interval; CR, complete response, MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; PD, progressive disease; PR, partial response; SD, stable disease.

Table 4. Objective response to bendamustine treatment, by number of treatment cycles

Cycles of bendamustine	*n*	Response by IWRC, *n* (%)†				CR/CRu, % (95% CI)	ORR, % (95% CI)
		CR	CRu	PR	SD		
≥3 cycles							
All	50	25 (50)	13 (26)	11 (22)	1 (2)	76 (62–87)	98 (89–100)
Indolent B-NHL	41	19 (46)	12 (29)	9 (22)	1 (2)	76 (60–88)	98 (87–100)
MCL	9	6 (67)	1 (11)	2 (22)	0	78 (40–97)	100 (66–100)
<3 cycles							
All	19	2 (11)	6 (32)	6 (32)	5 (26)	42 (20–67)	74 (49–91)
Indolent B-NHL	17	1 (6)	6 (35)	5 (29)	5 (29)	41 (18–67)	71 (44–90)
MCL	2	1 (50)	0	1 (50)	0	50 (1–99)	100 (16–100)

†International Workshop Response Criteria (IWRC) for NHL.[24] CI, confidence interval; CR, complete response, CRu, unconfirmed CR; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; ORR, overall response rate; PR, partial response; SD, stable disease.

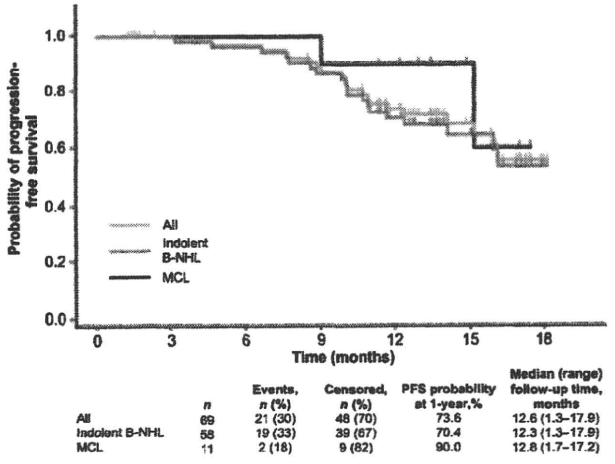

Fig. 1. Kaplan–Meier analysis of progression-free survival (PFS) in patients with relapsed indolent B-cell non-Hodgkin lymphoma (NHL) and mantle cell lymphoma (MCL) who were treated with bendamustine.

viral pharyngitis), and no grade 4 infection was observed. Twenty adverse events in 11 patients were considered serious and required hospitalization. All serious adverse events were resolved with or without treatment. There were no deaths attributed to bendamustine treatment.

Dose reductions or delays were not necessary for most patients. In 11 patients (19%), the bendamustine dose was reduced from 120 mg/m^2 to 90 mg/m^2; in two additional patients (3%), the dose was reduced from 120 mg/m^2 to 90 mg/m^2 and then reduced again to 60 mg/m^2. The mean dose intensity administered was 70.14 ± 8.78 mg/m^2/week, which is equivalent to a mean relative dose intensity of 88% ± 11%. During cycles 2 through 5, treatment was delayed in 47 (21%) of 219 cycles administered. No increase in the length of treatment delays was observed at later cycles; mean intervals between the start of treatment cycles ranged from 22.8 ± 3.9 days (between the first and second cycles) and 25.0 ± 5.3 days (between the fifth and sixth cycles).

Discussion

Bendamustine produced high response rates and durable responses in both indolent B-NHL and MCL patients. Our results in patients with indolent B-NHL complement previous studies of bendamustine in relapsed indolent B-NHL. The 91%

Table 5. Hematologic toxicity in bendamustine-treated patients, by grade† (*n* = 69)

Event	Patients affected, *n*					
	Grade, *n*				All grades *n* (%)	Grade 3/4 *n* (%)
	1	2	3	4		
Leukopenia	5	17	37	8	67 (97)	45 (65)
Neutropenia	2	10	17	33	62 (90)	50 (72)
Thrombocytopenia	31	10	7	4	52 (75)	11 (16)
Anemia	25	17	2	2	46 (67)	4 (6)

†As graded by Common Terminology Criteria for Adverse Events, version 3.0.[26]

ORR (by IWRC) observed in this study compares favorably with the 75–80% ORR observed in the two North American trials.[20,21] Differences in patient population may account for the higher response rates observed in our study because patients were required to be rituximab refractory or intolerant in the North American studies. In patients with MCL, the observed response rate of 100% in our trial was particularly encouraging. A high response rate in MCL patients was also observed with bendamustine plus rituximab in a North American phase II trial.[28] Although the number of MCL patients treated in both trials was small, bendamustine appears to be at least as effective in these patients as in those with indolent B-NHL, providing a valuable treatment option in a population that typically demonstrates poor response rates.

The responses were durable in both subtypes, and the median PFS was not reached after a median follow-up of 12.6 months. The proportion of MCL patients estimated to be progression free at 1 year was similar to that in patients with indolent B-NHL, even though the MCL population was more heavily pretreated.

We assessed patient response using both the IWRC and the revised RC in order to incorporate PET findings into our assessment while allowing for accurate comparison of our data with historical data. The ORRs assessed using the two sets of criteria were very similar, although the CR rate tended to be lower with the revised RC, possibly due to the elimination of the CRu category in the revised criteria. Overall, the results from either method were in general agreement, and the discrepancies did not affect efficacy conclusions.

In subgroup analyses, we found that patients who completed three or more cycles of treatment had higher response rates than patients who received fewer than three treatment cycles. Conversely, dose reductions did not appear to adversely affect treatment outcome because all 11 patients who underwent dose reductions responded to treatment. Based on these results, it

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Table 6. Non-hematologic toxicity in bendamustine-treated patients, by grade† (n = 69)

Event‡	Patients affected, n					
	Grade, n				All grades n (%)	Grade 3/4 n (%)
	1	2	3	4		
Nausea	37	22	0	0	59 (86)	0
Fatigue	35	8	0	0	43 (62)	0
Anorexia	27	13	2	0	42 (61)	2 (3)
Constipation	26	6	0	0	32 (46)	0
Rash	10	21	1	0	32 (46)	1 (1)
Vomiting	14	12	3	0	29 (42)	3 (4)
Weight loss	17	6	1	0	24 (35)	1 (1)
Fever	15	6	0	0	21 (30)	0
Phlebitis	12	7	2	0	21 (30)	2 (3)
Vascular pain	20	0	0	0	20 (29)	0
Injection site reaction	15	3	0	0	18 (26)	0
Dysgeusia	14	3	0	0	17 (25)	0
Diarrhea	11	5	0	0	16 (23)	0
Headache	14	2	0	0	16 (23)	0
Other skin reaction (redness)	12	1	0	0	13 (19)	0
Oral mucositis	10	2	0	0	12 (17)	0
Gastric discomfort	8	3	0	0	11 (16)	0
Infection§	5	1	5	0	11 (16)	5 (7)
Candida stomatitis	1	1	0	0	2 (3)	0
Febrile neutropenia	0	0	1	0	1 (1)	1 (1)
Herpes	3	1	0	0	4 (6)	0
Pneumonia	0	0	1	0	1 (1)	1 (1)
Upper airway infection	0	0	1	0	1 (1)	1 (1)
Varicella/herpes zoster	1	1	1	0	3 (4)	1 (1)
Viral pharyngitis	0	0	1	0	1 (1)	1 (1)
Other infection	1	0	0	0	1 (1)	0

†As graded by Common Terminology Criteria for Adverse Events, version 3.0.[26] ‡Events occurring in ≥15% of patients. §Indicates the number of patients developing any infection, at the greatest severity; totals do not sum because more than one type of infection could occur per patient.

might be reasonable that dose reductions be performed when necessary to allow continuation of treatment. Neither the extent of previous therapy (<3 or ≥3 prior therapies, or 1, 2, or 3 + prior therapies) nor the refractoriness of patients to prior therapy affected response rates. The distinct mechanism of action of bendamustine may partly explain its low cross-resistance in heavily pretreated or refractory patients.

Reversible myelosuppression was the primary adverse event associated with bendamustine and was the reason given most frequently for discontinuation of treatment. Tumor lysis syndrome was not observed in this study. Few serious adverse events occurred, and all were resolved with or without treatment. No secondary malignancies were observed during the study period (median follow-up of 12.6 months). Gastrointestinal events were common, but were typically mild in severity. The majority of adverse events that occurred were manageable with supportive care and dose reductions, and most patients were able to continue to receive bendamustine without delays or dose reductions. The toxicity of bendamustine did not appear to be additive, with no increase in treatment delays noted with subsequent treatment cycles.

In conclusion, the results of this study support the use of bendamustine in relapsed indolent B-NHL and show promising results for single-agent bendamustine in relapsed MCL. Ongoing studies of bendamustine in combination with rituximab will further clarify the role of this distinct alkylator in both relapsed and newly diagnosed patients.

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Disclosure Statement

The authors have no conflict of interest.

Abbreviations

CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisolone
CI	confidence interval
CR	complete response
CRu	unconfirmed CR
CT	Computed tomography
ECOG	Eastern Cooperative Oncology Group
FLIPI	Follicular Lymphoma International Prognostic Index
G-CSF	granulocyte colony-stimulating factor
IPI	International Prognostic Index
IWRC	International Workshop Response Criteria
MALT	mucosa-associated lymphoid tissue
MCL	mantle cell lymphoma
NHL	non-Hodgkin lymphoma
ORR	overall response rate
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PR	partial response
SD	stable disease
SPD	sum of the products of the greatest perpendicular diameters
ULN	upper limit of the normal
WHO	World Health Organization.

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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

Kazuhito Yamamoto, Atae Utsunomiya, Kensei Tobinai, Kunihiro Tsukasaki, Naokuni Uike, Kimiharu Uozumi, Kazunari Yamaguchi, Yasuaki Yamada, Shuichi Hanada, Kazuo Tamura, Shigeo Nakamura, Hiroshi Inagaki, Koichi Ohshima, Hitoshi Kiyoi, Takashi Ishida, Kouji Matsushima, Shiro Akinaga, Michinori Ogura, Masao Tomonaga, and Ryuzo Ueda

From Department of Hematology and Cell Therapy, Aichi Cancer Center; Department of Clinical Pathophysiology and Department of Infectious Diseases, Nagoya University Graduate School of Medicine; Department of Hematology and Oncology, Nagoya Daini Red Cross Hospital, Nagoya; Department of Clinical Pathology and Department of Medical Oncology and Immunology, Nagoya City University Graduate School of Medical Sciences, Nagaya; Department of Hematology, Imamura Bun-in Hospital; Department of Internal Medicine, National Hospital Organization Kagoshima Medical Center; Department of Hematology and Immunology, Kagoshima University Hospital, Kagoshima; Hematology and Stem Cell Transplantation Division, National Cancer Center Hospital; Department of Safety Research on Blood and Biologics, National Institute of Infectious Diseases; Department of Molecular Preventive Medicine, Graduate School of Medicine, The University of Tokyo; Kyowa Hakko Kirin Co Ltd, Tokyo; Department of Hematology and Molecular Medicine Unit and Department of Laboratory Medicine, Nagasaki University Graduate School of Biomedical Science, Nagasaki; Department of Hematology, National Kyushu Cancer Center; The Department of Medicine, Division of Medical Oncology, Infectious Disease, and Endocrinology, School of Medicine, Fukuoka University, Fukuoka; and the Department of Pathophysiology, Kurume University School of Medicine, Kurume, Japan.

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Corresponding author: Kazuhito Yamamoto, MD, PhD, Department of Hematology and Cell Therapy, Aichi Cancer Center, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi 464-8681, Japan; e-mail: kyamamoto@aichi-cc.jp.

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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					Total
	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	
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

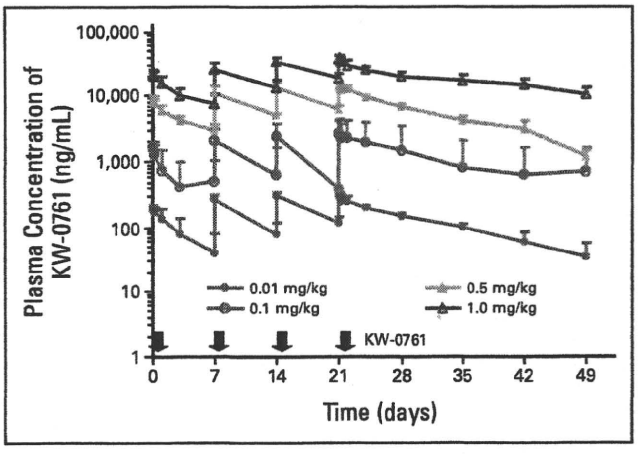

Fig 1. Mean KW-0761 plasma concentration profile by cohort: bar indicates upper limit of standard deviation.

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		15,181.2	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).

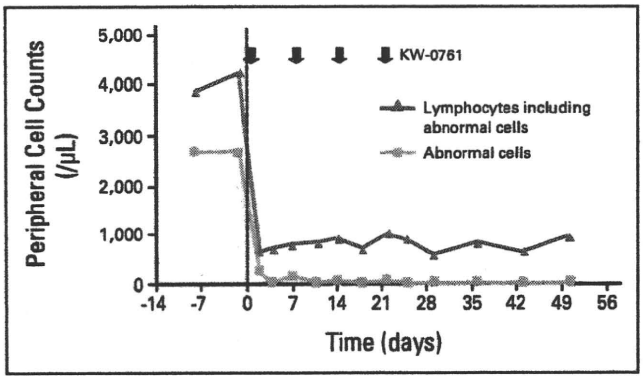

Fig 2. Response to KW-0761 in a representative patient (204). The time course of lymphocytes and adult T-cell leukemia-lymphoma (ATL) cells in peripheral blood of a patient with acute-type ATL treated with 0.1 mg/kg KW-0761 is shown.

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 μg/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 μg/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.

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AUTHOR CONTRIBUTIONS

Conception and design: Kazuhito Yamamoto, Atae Utsunomiya, Kensei Tobinai, Kunihiro Tsukasaki, Naokuni Uike, Kimiharu Uozumi, Takashi Ishida, Kouji Matsushima, Shiro Akinaga, Michinori Ogura, Masao Tomonaga, Ryuzo Ueda

Financial support: Shiro Akinaga

Provision of study materials or patients: Kazuhito Yamamoto, Atae Utsunomiya, Kensei Tobinai, Kunihiro Tsukasaki, Naokuni Uike, Kimiharu Uozumi

Collection and assembly of data: Kazuhito Yamamoto, Atae Utsunomiya, Kensei Tobinai, Kunihiro Tsukasaki, Naokuni Uike, Kimiharu Uozumi

Data analysis and interpretation: Kazunari Yamaguchi, Yasuaki Yamada, Shuichi Hanada, Kazuo Tamura, Shigeo Nakamura, Hiroshi Inagaki, Koichi Ohshima, Hitoshi Kiyoi, Takashi Ishida, Michinori Ogura

Manuscript writing: Kazuhito Yamamoto, Kensei Tobinai, Takashi Ishida, Shiro Akinaga, Ryuzo Ueda

Final approval of manuscript: Kazuhito Yamamoto, Atae Utsunomiya, Kensei Tobinai, Kunihiro Tsukasaki, Naokuni Uike, Kimiharu Uozumi, Kazunari Yamaguchi, Yasuaki Yamada, Shuichi Hanada, Kazuo Tamura, Shigeo Nakamura, Hiroshi Inagaki, Koichi Ohshima, Hitoshi Kiyoi, Takashi Ishida, Kouji Matsushima, Shiro Akinaga, Michinori Ogura, Masao Tomonaga, Ryuzo Ueda

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Long-term study of indolent adult T-cell leukemia-lymphoma

Yumi Takasaki, Masako Iwanaga, Yoshitaka Imaizumi, Masayuki Tawara, Tatsuro Joh, Tomoko Kohno, Yasuaki Yamada, Shimeru Kamihira, Schuichi Ikeda, Yasushi Miyazaki, Masao Tomonaga and Kunihiro Tsukasaki

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Long-term study of indolent adult T-cell leukemia-lymphoma

Yumi Takasaki,[1,2] Masako Iwanaga,[2,3] Yoshitaka Imaizumi,[2] Masayuki Tawara,[1,2] Tatsuro Joh,[1,2] Tomoko Kohno,[4] Yasuaki Yamada,[5] Shimeru Kamihira,[5] Schuichi Ikeda,[6] Yasushi Miyazaki,[2] Masao Tomonaga,[1] and Kunihiro Tsukasaki[2]

[1]Third Department of Internal Medicine, Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki; [2]Department of Molecular Medicine and Hematology, Molecular Medicine Unit, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki; [3]Department of Nutritional Health, Faculty of Wellness Studies, Kwassui Women's College, Nagasaki; [4]Division of Cytokine Signaling, Department of Molecular Microbiology and Immunology and [5]Department of Laboratory Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki; and [6]Department of Hematology, Hirado Municipal Hospital, Nagasaki, Japan

The long-term prognosis of indolent adult T-cell leukemia-lymphoma (ATL) is not clearly elucidated. From 1974 to 2003, newly diagnosed indolent ATL in 90 patients (65 chronic type and 25 smoldering type) was analyzed. The median survival time was 4.1 years; 12 patients remained alive for more than 10 years, 44 progressed to acute ATL, and 63 patients died. The estimated 5-, 10-, and 15-year survival rates were 47.2%, 25.4%, and 14.1%, respectively, with no plateau in the survival curve. Although most patients were treated with watchful waiting, 12 patients were treated with chemotherapy. Kaplan-Meier analyses showed that advanced performance status (PS), neutrophilia, high concentration of lactate dehydrogenase, more than 3 extranodal lesions, more than 4 total involved lesions, and receiving chemotherapy were unfavorable prognostic factors for survival. Multivariate Cox analysis showed that advanced PS was a borderline significant independent factor in poor survival (hazard ratio, 2.1, 95% confidence interval, 1.0-4.6; $P = .06$), but it was not a factor when analysis was limited to patients who had not received chemotherapy. The prognosis of indolent ATL in this study was poorer than expected. These findings suggest that even patients with indolent ATL should be carefully observed in clinical practice. Further studies are required to develop treatments for indolent ATL. (*Blood.* 2010;115(22):4337-4343)

Introduction

Adult T-cell leukemia-lymphoma (ATL) is a peripheral T-lymphocytic malignancy associated with human T-cell lymphotropic virus type 1 (HTLV-1).[1] ATL has been classified into 4 clinical subtypes: acute, lymphoma, chronic, and smoldering.[2] In general, acute and lymphoma types of ATL have a extremely poor prognosis despite advances in chemotherapy and allogenic hematopoietic stem cell transplantation[3-5] because of multidrug resistance, a large tumor burden with multiorgan failure, hypercalcemia, and/or frequent infectious complications associated with a T-cell immunodeficiency. A previous study, in which Japanese patients with ATL were followed for a maximum duration of 7 years, reported that the 4-year survival rates for acute, lymphoma, chronic, and smoldering type were 5.0%, 5.7%, 26.9%, and 62.8%, respectively, with the median survival time (MST) of 6.2 months, 10.2 months, 24.3 months, and not yet reached, respectively.[2] Therefore, the chronic and smoldering subtypes of ATL are considered indolent and are usually managed with watchful waiting until disease progression to acute crisis, similar to the management of chronic lymphoid leukemia or smoldering myeloma. However, the follow-up duration of the previous Japanese study was too short for indolent ATL to evaluate the overall risk of progression to acute or lymphoma types (ie, aggressive ATL). A recent Brazilian study, in which patients with ATL were followed for a maximum duration of 14 years, reported that the MST of chronic and smoldering types were 18 months and 58 months, respectively, and the overall survival (OS) rates were less than 20% in both types.[6] Their results suggest that the long-term prognosis of indolent ATL might be worse than expected.

The long-term prognosis of Japanese patients with indolent ATL has not been well evaluated so far. Prognostic factors for patients with indolent ATL are also unclear. In the present study, we investigated the long-term outcome of 90 patients with indolent ATL. The purposes of this study were to estimate the 5-, 10-, and 15-year survival rates for indolent ATL and to evaluate the prognostic factors.

Methods

Patients

We evaluated a total of 90 patients with indolent ATL (25 smoldering type and 65 chronic type) who were newly diagnosed at the Nagasaki University Hospital between July 1974 and December 2003. The distribution of patients by year of diagnosis in decades (1974-1983, 1984-1993, and 1994-2003) are presented in Table 1. The cutoff date for analysis was December 2008. The diagnosis of ATL was based on clinical features, histologically and/or cytologically proven mature T-cell malignancy, the presence of anti–HTLV-1 antibody, and monoclonal integration of HTLV-1 proviral DNA into tumor cells as described previously.[2,7-9] The subtypes of ATL were classified according to criteria established by the Lymphoma Study Group of Japan Clinical Oncology Group.[2] Clinical data included date of diagnosis, complications at diagnosis, therapy regimens if applicable, date of death, cause of death, and date of latest contact. This retrospective, nonrandomized, observational study that used existing data

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Table 1. Distribution of patients in 3 decades from 1974 to 2003

Year	Total no. of patients	No. of smoldering type (% of total)	No. of chronic type (% of total)
1974-1983	19	2 (10.5)	17 (89.5)
1984-1993	35	7 (20.0)	28 (80.0)
1994-2003	36	16 (44.4)	20 (55.6)
Total for all years	90	25 (27.8)	65 (72.2)

was granted an exemption from the institutional review board and waived the requirement for written informed consent.

Clinical factors and definitions

Age was dichotomized into 2 groups: 60 years or older and younger than 60 years. Performance status (PS) was based on the 5-grade scale of the World Health Organization. Complications at diagnosis were dichotomized into present and absent. Leukocytosis was defined as white blood cell count of 12×10^9/L or greater with the median value as cutoff level. Lymphocytosis was defined as a total lymphocyte count of 6.5×10^9/L or greater with the median value as cutoff level. Neutrophilia was defined as a neutrophil count of 7.5×10^9/L or greater.[10] Eosinophilia was defined as an eosinophil count of 0.4×10^9/L greater.[11] Lactate dehydrogenase (LDH) and blood urea nitrogen (BUN) were dichotomized into normal and elevated concentrations.[12] Albumin was dichotomized into concentrations of 40.0 g/L (4.0 g/dL) or greater and less than 40.0 g/L (4.0 g/dL).[2] Potential prognostic factors (PPFs) for chronic ATL were defined as those with at least one of the following 3 factors: low serum albumin, high LDH, or high BUN according to previous reports.[13,14] Tumor lesions were evaluated as the number of lymph node lesions, number of extranodal lesions, and number of total involved lesions. Extranodal lesions were defined as follows: bone marrow (BM) involvement as the presence of more than 5% typical ATL cells on a BM smear or detection of their infiltration in a BM biopsy specimen; skin involvement as the presence of ATL infiltration in a skin biopsy specimen or as the clinically presence of typical types of skin lesions such as tumors, nodules, erythema, and papules, if biopsy was impossible; lung involvement as lesions with ATL cell infiltration in a transbronchial lung biopsy specimen or in bronchoalveolar lavage fluid; liver involvement as hepatomegaly determined by any imaging tests or liver biopsy if done; spleen involvement as splenomegaly on any imaging test. All patients had peripheral blood involvement. Both lymph node and extranodal tumor lesions were determined according to Ann Arbor classification.[2] The number of total involved lesions was defined as the sum of lymph node lesions and extranodal lesions.[2] Factors used in analyses were listed in Table 2.

Statistical analysis

OS was defined as the time from the date of first diagnosis to the date of death or the latest contact with the patient. Survival curves were estimated using the Kaplan-Meier method and were compared using the generalized Wilcoxon test. MST was estimated as the time point at which the Kaplan-Meier survival curves crossed 50%. Time to transformation was calculated as the time from the date of the first diagnosis to the date of transformation into the aggressive type (acute or lymphoma type). Univariate and multivariate Cox regression analyses were applied to evaluate prognostic factors for survival. The effects of clinical parameters were evaluated as hazard ratios (HRs) and their 95% confidence intervals (95% CIs). All statistical analyses were performed using SAS software (Version 9.1; SAS Japan Institute). All tests were 2-tailed, and the statistical significance level was set at .05.

Results

Baseline characteristics

The median value of white blood cell count, lymphocyte count, neutrophil count, and eosinophil count was 11.5×10^9/L (range, $3.9\text{-}94.4 \times 10^9$/L), 6.5×10^9/L (range, $0.9\text{-}80.2 \times 10^9$/L), 4.9×10^9/L (range, $1.5\text{-}25.5 \times 10^9$/L), and 0.06×10^9/L (range, $0\text{-}3.0 \times 10^9$/L), respectively. Frequencies of the patients at baseline are summarized in Table 2. Fifty-eight percent of the patients were male, 52% were 60 years or older, and 22% had an advanced PS (2 or more grade). Regarding complications, 35 patients (39%) had some complications at the time of diagnosis, including 13 with chronic pulmonary diseases (10 chronic bronchitis, 2 diffuse panbronchiolitis, and 1 bronchial asthma with chronic bronchitis), 9 with opportunistic infections (3 pneumocystis pneumonia, 2 cryptococcal meningitis, 2 aspergillus pneumonia, 1 cytomegalovirus infection, and 1 pulmonary tuberculosis), 7 with malignancies other than ATL (2 lung cancer, 1 larynx cancer, 1 pharynx cancer, 1 colon cancer, 1 hepatic cell carcinoma, and 1 lip cancer), and 6 with autoimmune diseases (2 infective dermatitis, 1 primary biliary cirrhosis, 1 autoimmune hemolytic anemia, 1 dermatomyositis, and 1 ulcerative colitis). The 6 patients with autoimmune diseases had received a variety of medications as follows: antibiotics for infective dermatitis, ursodeoxycholic acid for primary biliary cirrhosis, prednisolone for autoimmune hemolytic anemia and dermatomyositis, and sulfasalazine for ulcerative colitis. Concerning the hematologic factors, 43 patients (48%) had leukocytosis, 45 (50%) had lymphocytosis, 17 (19%) had neutrophilia, and 17 (19%) had eosinophilia. Regarding the laboratory factors, 28 patients (31%) had a high LDH level (greater than the normal limit). Only 5 of 87 patients (6%) had an abnormal BUN level; 34 of 88 patients (39%) had a low albumin level. Forty-seven patients (55%) had more than 1 of the 3 unfavorable prognostic factors.

Twenty-four patients (27%) had more than 2 involved lymph node lesions. Regarding the extranodal lesions, skin involvement was observed in 46 patients (51%), liver involvement in 15 (17%), spleen involvement in 6 (7%), and pulmonary involvement in 1 (1%). Of the 64 patients who had BM examined, the involvement was observed in 16 patients (25%; data not shown). Twenty percent of the patients (n = 18) had more than 3 extranodal lesions. Regarding the number of total involved lesions (extranodal lesions plus lymph node lesions), more than 4 involved lesions were observed in 24 patients (27%), 2 or 3 involved lesions in 42 patients (46%), and only 1 involved lesion in 24 patients (27%).

Prognosis

Among 90 patients with indolent ATL, 63 (70%) died, with a median duration of follow-up of 4.1 years (range, 8 days to 17.6 years). The estimated 5-, 10-, and 15-year survival rates were 47.2% (95% CI, 36.1%-57.5%), 25.4% (95% CI, 15.3%-36.8%), and 14.1% (95% CI, 6.2%-25.3%), respectively, with an MST of 4.1 years (95% CI, 2.9-6.3 years; Figure 1A). No plateaus were observed in the survival curves for OS. Of the 27 survivors, 12 were alive for more than 10 years. Of the 63 patients who died, 41 (65.1%) died of acute ATL after transformation, 5 (7.9%) died of severe chronic ATL, 11 (17.5%) died of other diseases (3 malignancies other than ATL, 2 chronic pulmonary diseases, 2 opportunistic infections, 2 autoimmune diseases, 1 cardiac failure, and 1 myocardial infarction), 2 died of transplantation-related complications, and 4 died of unknown cause. No significant difference in OS was observed between patients who died of ATL and patients who died of other causes (data not shown). Among 90 patients, 44 (49%) progressed to aggressive ATL (all were acute types), among those, 41 (93%) died. The median time to transformation was 18.8 months (range, 0.3 months to 17.6 years).

Table 2. Survival by baseline clinical factors

Factors	No. of evaluated (% of total)	No. of deaths (%)*	MST, y	Cumulative probability of survival†		
				5-y survival, % (95% CI)	10-y survival, % (95% CI)	P†
Total	90	63 (70)	4.1	47.2 (36.1-57.5)	25.4 (15.3-36.8)	
Clinical subtype						
Smoldering	25 (28)	17 (68)	2.9	39.4 (19.8-58.6)	25.3 (8.2-47.0)	.36
Chronic	65 (72)	46 (71)	5.3	50.2 (37.0-62.0)	26.3 (14.6-39.5)	
Patient-related factors (n = 90)						
Sex						
Male	52 (58)	34 (65)	4.3	48.1 (33.4-61.3)	24.9 (11.8-40.5)	.99
Female	38 (42)	29 (76)	4.1	46.4 (29.5-61.6)	26.5 (12.0-43.4)	
Age						
60 y or older	46 (52)	32 (70)	3.7	45.5 (30.4-59.4)	29.5 (14.8-45.8)	.18
Younger than 60 y	44 (48)	31 (70)	4.5	49.2 (32.9-63.6)	24.0 (11.2-39.3)	
PS						
0	22 (24)	15 (68)	8.4	75.9 (51.4-89.1)	38.9 (16.8-60.7)	.006
1	49 (54)	33 (67)	3.4	41.5 (26.9-55.5)	22.5 (9.7-38.5)	
2 or 3	19 (22)	15 (79)	1.3	27.9 (10.2-49.0)	13.9 (1.3-41.1)	
Complications at diagnosis (n = 90)						
Absent	55 (61)	37 (67)	5.7	54.1 (39.4-66.7)	25.4 (12.9-40.1)	
Present	35 (39)	26 (74)	3.4	36.6 (20.7-52.8)	28.3 (13.5-45.1)	.06
Malignancies other than ATL	7 (8)	6 (86)	0.8	28.6 (4.1-61.2)	28.6 (4.1-61.2)	
Opportunistic infection	9 (10)	7 (78)	1.2	0	0	
Chronic pulmonary disease	13 (14)	10 (77)	4.1	38.5 (14.1-62.8)	25.6 (5.2-53.4)	
Autoimmune disease	6 (7)	3 (50)	11.4	62.5 (14.2-89.3)	62.5 (14.2-89.3)	
Hematologic factors						
WBC count (n = 90)						
At least 12.0 × 10^9/L	43 (48)	32 (74)	3.4	43.0 (27.6-57.5)	22.3 (9.9-37.8)	.24
Less than 12.0 × 10^9/L	47 (52)	31 (66)	5.3	51.0 (35.1-64.8)	28.5 (13.6-45.2)	
Total lymphocyte count (n = 90)						
At least 6.5 × 10^9/L	45 (50)	35 (78)	3.7	43.3 (28.2-57.5)	17.4 (6.8-32.0)	.34
Less than 6.5 × 10^9/L	45 (50)	28 (62)	5.3	51.4 (35.2-65.4)	36.8 (20.9-52.9)	
Neutrophil counts (n = 89)						
At least 7.5 × 10^9/L	17 (19)	14 (82)	2.3	29.4 (10.7-51.1)	14.7 (1.3-42.9)	.05
Less than 7.5 × 10^9/L	72 (81)	48 (67)	5.3	51.0 (38.3-62.4)	28.4 (16.6-41.3)	
Eosinophil count (n = 89)						
At least 0.4 × 10^9/L	17 (19)	11 (65)	4.0	34.9 (13.0-58.0)	23.2 (4.9-49.4)	.47
Less than 0.4 × 10^9/L	72 (81)	51 (71)	4.5	49.2 (36.8-60.5)	27.4 (16.0-40.1)	
Laboratory factors						
LDH (n = 90)						
Greater than NI	28 (31)	23 (82)	1.5	34.8 (17.3-53.0)	14.9 (3.9-32.7)	.004
Less than or equal to NI	62 (69)	40 (65)	5.4	52.9 (39.2-64.8)	31.8 (18.5-45.9)	
BUN (n = 87)						
Greater than NI	5 (6)	5 (100)	2.0	20.0 (0.8-58.2)	0	.18
Less than or equal to NI	82 (94)	56 (68)	4.5	48.9 (37.2-59.6)	28.4 (17.3-40.6)	
Albumin (n = 88)						
Less than 40.0 g/L	34 (39)	22 (65)	3.4	39.9 (22.4-56.8)	25.6 (8.9-46.4)	.22
At least 40.0 g/L	54 (61)	40 (74)	5.3	52.2 (37.9-64.7)	26.6 (14.3-40.6)	
Potential prognostic factors (n = 87)‡						
At least 1	47 (55)	34 (72)	2.9	38.7 (24.1-53.1)	18.1 (6.5-34.3)	.05
None	40 (45)	27 (68)	5.4	56.1 (39.2-70.0)	35.2 (19.3-51.6)	
Tumor lesions (n = 90)						
No. of lymph node lesions						
2 or more	24 (27)	16 (67)	2.1	37.5 (19.0-56.0)	30.0 (12.1-50.4)	.09
0 or 1	66 (73)	47 (71)	5.3	50.9 (37.5-62.8)	23.6 (12.2-37.2)	
No. of extranodal lesions						
3 or more	18 (20)	14 (78)	1.1	29.4 (10.7-51.1)	19.6 (4.2-43.3)	.005
1 or 2	72 (80)	49 (68)	5.3	51.6 (38.9-62.9)	26.8 (15.2-39.7)	
No. of total involved lesions						
4 or more	24 (27)	16 (67)	1.3	34.8 (16.6-53.7)	26.1 (8.8-47.6)	.03
2 or 3	42 (46)	30 (71)	4.5	49.5 (32.7-64.3)	13.1 (3.5-29.1)	
1	24 (27)	17 (71)	5.4	54.5 (32.1-72.4)	44.1 (22.8-63.5)	
Chemotherapy						
Received	12 (13)	12 (100)	1.4	25.0 (6.0-50.5)	0	.01
Not received	78 (87)	51 (65)	5.3	50.8 (38.6-61.8)	31.3 (19.3-44.0)	

WBC indocates white blood cell count; MST, median survival time (years); and NI, normal index.

*Rate of death in evaluated cases.

†Cumulative probability of survival rate was estimated with the Kaplan-Meier method, and the *P* value was calculated with the generalized Wilcoxon test.

‡PPFs indicate at least 1 of the following 3 factors: low serum albumin, high LDH, or high BUN.[13,14]

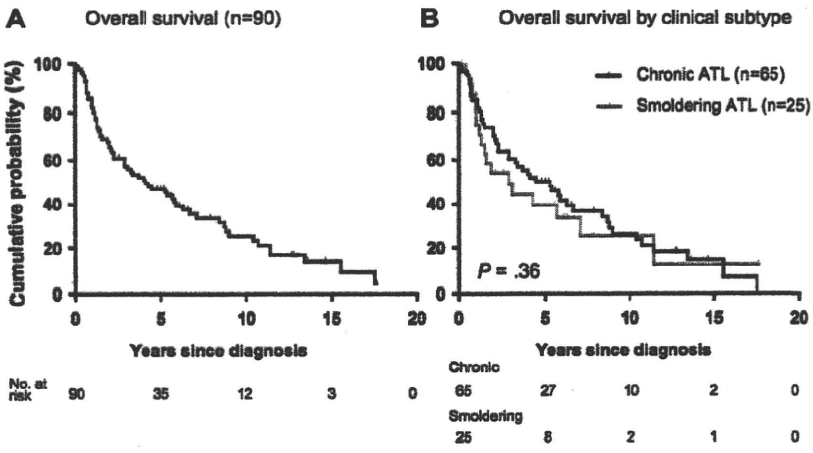

Figure 1. Survival of patients with indolent ATL. (A) For OS (n = 90), the median survival time was 4.1 years (95% CI, 2.9-6.3 years). No plateau was observed in the survival curves for OS. The estimated 5-, 10-, and 15-year survival rates were 47.2% (95% CI, 36.1%-57.5%), 25.4% (95% CI, 15.3%-36.8%), and 14.1% (95% CI, 6.2%-25.3%), respectively. (B) OS by clinical subtype (smoldering type vs chronic type). The estimated 15-year survival rate was 12.7% (95% CI, 1.1%-38.8%) with an MST of 2.9 years for smoldering type and 14.7% (95% CI, 5.7%-27.8%) with an MST of 5.3 years. There was no statistically significant difference ($P = .36$).

Among 25 patients with smoldering ATL, 17 patients (68%) died, and the estimated 15-year survival rate was 12.7% (95% CI, 1.1%-38.8%) with an MST of 2.9 years (95% CI, 1.3-7.1 years). Of the 17 patients who died, 15 died of acute ATL after transformation. Among 65 patients with chronic ATL, 46 (71%) died, and the estimated 15-year survival rate was 14.7% (95% CI, 5.7%-27.8%) with an MST of 5.3 years (95% CI, 2.9-6.7 years). Of the 46 patients who died, 29 died of acute ATL after transformation and 5 died of the disease severity. No statistically significant difference was observed in OS between subtypes ($P = .36$; Figure 1B). The overall estimated 5- and 10-year survival rates of both subtypes are shown in Table 2.

Effects of clinical factors on prognosis

Effects of clinical factors on prognosis were analyzed with the use of all the 90 patients together. Results of prognostic analyses (estimated 5- and 10-year OS rates and MST) with the use of Kaplan-Meier methods are summarized in Table 2. The survival rate was poor for patients with advanced PS ($P = .006$; Figure 2A), neutrophilia ($P = .05$; Figure 2B), and a higher LDH level ($P = .004$; Figure 2C). Patients with at least 1 of 3 PPFs for chronic ATL (a high level of LDH and BUN and a low level of albumin)[13,14] showed a poor survival rate compared with patients without ($P = .05$; Figure 2D). The difference in survival rates between patients with any complications and patients without was marginally significant ($P = .06$). Among patients with any complications, those with malignancies other than ATL or opportunistic infections at diagnosis showed a tendency of poor prognosis, although the number of patients in each category was too small (supplemental Figure 1, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). Although no difference was observed in survival rates between patients with involvement of more than 2 lymph node lesions and patients with less involvement ($P = .09$; Table 2), the survival rate of patients

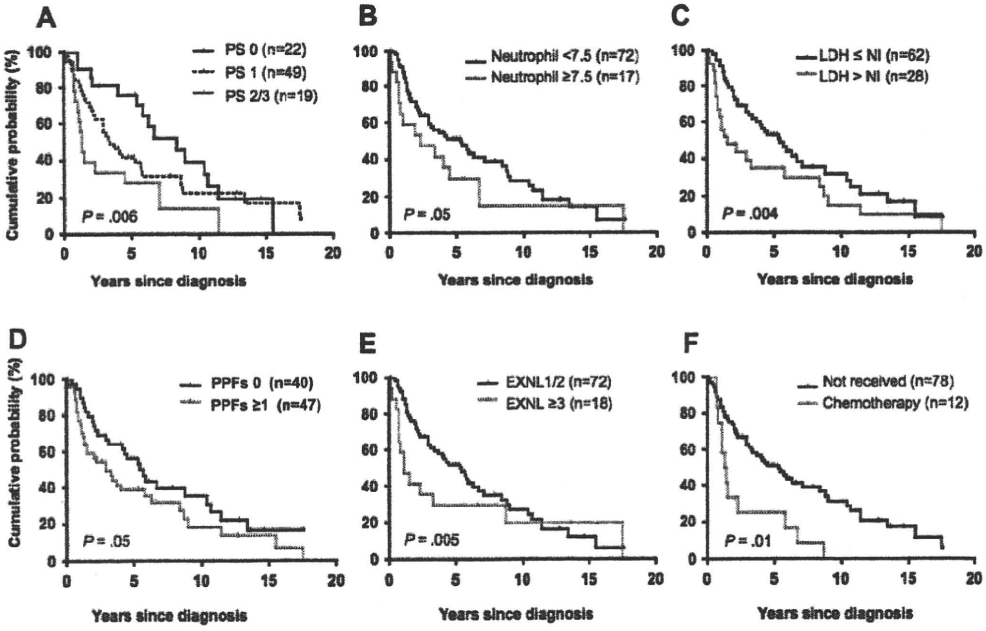

Figure 2. OS by clinical parameters. (A) OS by PS ($P = .006$). (B) OS by neutrophil count ($P = .05$). The unit is $\times 10^9$/L. (C) OS by LDH level ($P = .004$). NI indicates normal index. (D) OS by PPFs for chronic ATL that were defined based on low serum albumin, high LDH, or high BUN according to previous reports[13,14] ($P = .05$). (E) OS by the number of extranodal lesions (EXNL; $P = .005$). (F) OS by treatment states ($P = .01$).

Table 3. Effects of clinical factors on OS in Cox analyses

	All patients (n = 90)						Patients had not received chemotherapy (n = 78)					
	Univariate analysis		Multivariate model A		Multivariate model B		Univariate analysis		Multivariate model C		Multivariate model D	
Clinical factor	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
PS												
0	1		1		1		1		1		1	
1	1.5 (0.8-2.7)	.22	1.4 (0.8-2.8)	.27	1.3 (0.7-2.6)	.37	1.4 (0.7-2.7)	.28	1.6 (0.8-3.1)	.21	1.4 (0.7-2.9)	.30
2 or more	2.5 (1.2-5.2)	.01	2.1 (1.0-4.6)	.06	2.1 (1.0-4.6)	.06	1.7 (0.7-4.0)	.26	1.5 (0.6-3.8)	.39	1.6 (0.6-4.2)	.30
Neutrophil counts												
Less than 7.5 × 10^9/L	1		1		1		1		1		1	
7.5 × 10^9/L or greater	1.6 (0.9-2.9)	.15	1.3 (0.6-2.7)	.45	1.2 (0.6-2.3)	.58	1.3 (0.6-2.7)	.47	1.5 (0.6-3.8)	.43	1.0 (0.5-2.3)	.94
LDH												
Less than or equal to NI	1		1		1		1		1		1	
Greater than NI	1.7 (1.0-2.9)	.04	1.5 (0.8-2.7)	.16	1.5 (0.8-2.6)	.21	1.5 (0.8-2.8)	.19	1.7 (0.9-3.3)	.12	1.6 (0.8-3.1)	.20
No. of extranodal lesions												
0-2	1		1				1		1			
3 or more	1.5 (0.8-2.8)	.16	0.7 (0.3-1.6)	.41			0.9 (0.4-2.2)	.82	0.5 (0.1-1.6)	.22		
No. of total involved lesions												
1	1				1		1				1	
2 or 3	1.2 (0.7-2.2)	.52			0.8 (0.4-1.6)	.52	1.1 (0.6-2.1)	.67			0.9 (0.4-1.7)	.65
4 or more	1.5 (0.7-3.0)	.26			0.9 (0.4-2.1)	.83	1.0 (0.5-2.3)	.96			0.8 (0.3-2.0)	.67
Chemotherapy												
Not received	1		1		1							
Received	2.6 (1.4-5.1)	.003	2.3 (1.1-4.7)	.03	2.0 (1.0-4.2)	.06						

HR indicates hazard ratio; 95% CI, 95% confidence interval; and NI, normal index.

with more than 3 extranodal lesions was significantly poor than the others ($P = .005$; Figure 2E). The survival rate was worse in patients with more than 4 total involvement lesions than in the others (Table 2). Of the extranodal lesions, we additionally examined the effect of skin lesion and BM involvement on survival rates. The survival rate of patients with BM involvement was significantly poor than of patients without ($P = .04$; data not shown), but that of patients with skin involvement was not different from those without ($P = .66$; supplemental Figure 2).

Although most patients in this study had not been treated until their disease progression was similar to B-cell chronic lymphoid leukemia, 12 patients with chronic ATL were treated with chemotherapy immediately after diagnosis because of elevated LDH levels in 8 patients, severe BM involvement in 2 patients, and severe skin involvements in 2 patients. Among them, 2 patients were treated with VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisone)–AMP (doxorubicin, ranimustine, and prednisone)–VECP (vindesine, etoposide, carboplatin, and prednisone),[3] 2 with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), 4 with CHOP-like, 3 with VEPA (vincristine, etoposide, prednisone, and doxorubicin),[15] and 1 with low-dose etoposide. All of these patients died (MST, 1.4 years; 95% CI, 1.1-2.3 years), and their prognosis was very poor compared with patients not treated ($P = .01$; Figure 2F).

On the basis of results from Kaplan-Meier curves and univariate analysis for each factor, we decided to include PS category, dichotomized neutrophil counts, dichotomized LDH category, dichotomized number of extranodal lesions, the number of total involved lesions, and chemotherapy states into multivariate Cox analysis. Model A included PS category, dichotomized neutrophil counts, dichotomized LDH category, dichotomized number of extranodal lesions, and chemotherapy states. Model B included the same factors as model A except for the number of total involved lesions instead of the number of extranodal lesions. This was because, by definition, a factor of the number of total involved lesions included a factor of the number of extranodal lesions. Results were summarized in Table 3. In model A, advanced PS (≥ 2; HR, 2.1; 95% CI, 1.0-4.6; $P = .06$, borderline significance) and chemotherapy states (HR, 2.3; 95% CI, 1.1-4.7; $P = .03$, significance) were correlated with OS, but the remaining factors were not independent prognostic factors after adjustment for covariate factors. To evaluate effects of clinical factors beyond the effect of chemotherapy states on OS, we also performed additional multivariate analyses for patients who were not received chemotherapy (n = 78; model C and model D in Table 3). We found that there was no clinical parameter that associated with OS.

Discussion

In the present study, we investigated for the first time the long-term clinical course of patients with indolent ATL with a maximum duration of follow-up of 17.6 years. We found that the prognosis of indolent ATL was poor with the MST of 4.1 years, and the estimated 15-year OS rates were 14.1% with no plateau in the survival curve. The prognosis observed in the present study was poorer than expected. Our results confirmed a recent long-term Brazilian study,[6] that showed a poor OS of less than 20% for indolent ATL. In the present study, we showed that 65.1% of patients died of acute ATL with a median time to transformation of 18.8 months. This finding suggests that most patients with indolent ATL will eventually die of aggressive ATL during their long-term course of illness. These findings suggest that even patients with indolent ATL should be carefully observed by frequent clinical visits.

The cause of death in patients with indolent ATL has not been well reported so far. In the present study, patients with indolent ATL died of various causes such as malignancies other than ATL,