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H. 知的財産権の出願・登録状況
（予定を含む）

1. 特許取得

該当なし

2. 実用新案登録

該当なし

3. その他

該当なし

III. 研究成果の刊行一覧

別紙４

研究成果の刊行に関する一覧表

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IV. 研究成果の刊行物・別冊

Cancer Science
The official journal of the Japanese Cancer Association JCA

Case Report

Stevens–Johnson Syndrome associated with mogamulizumab treatment of adult T-cell leukemia/lymphoma

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We report an adult T-cell leukemia/lymphoma patient suffering from Stevens–Johnson Syndrome (SJS) during mogamulizumab (humanized anti-CCR4 monoclonal antibody) treatment. There was a durable significant reduction of the $CD4^+CD25^{high}FOXP3^+$ regulatory T (Treg) cell subset in the patient's PBMC, and the affected inflamed skin almost completely lacked FOXP3-positive cells. This implies an association between reduction of the Treg subset by mogamulizimab and occurrence of SJS. The present case should contribute not only to our understanding of human pathology resulting from therapeutic depletion of Treg cells, but also alert us to the possibility of immune-related severe adverse events such as SJS when using mogamulizumab. We are currently conducting a clinical trial of mogamulizumab for CCR4-negative solid cancers (UMIN000010050), specifically aiming to deplete Treg cells. (*Cancer Sci* 2013; 104: 647–650)

Adult T-cell leukemia/lymphoma (ATL) is an aggressive peripheral T-cell neoplasm caused by HTLV-1. The disease is resistant to conventional chemotherapeutic agents, and has a very poor prognosis.[1] Mogamulizumab (KW-0761) is a defucosylated humanized monoclonal antibody targeting CC chemokine receptor 4 (CCR4).[2] A phase I clinical trial for relapsed CCR4-positive peripheral T-cell neoplasms, including ATL, and a phase II study for relapsed ATL have been conducted with mogamulizumab.[3,4] This agent was subsequently approved for the treatment of relapsed or refractory ATL in Japan, the first country in the world to do so, in March 2012. Mogamulizimab went on sale on 29 May 2012. The interim report for the post-marketing surveillance from 29 May to 28 September 2012 revealed skin-related severe adverse events (SAE), as defined by the Medical Dictionary for Regulatory Activities Terminology/Japan, in nine patients. Thus, during only the first 4 months of use, 9 skin-related SAE, including 4 cases of Stevens–Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN) were reported, with 1 SJS/TEN fatality. These skin-related, potentially fatal SAE are certainly a challenge to the free use of this agent and clearly require investigation. Therefore, here we report an informative ATL patient suffering from SJS on mogamulizumab treatment, focusing on the reduction of the regulatory T (Treg) cell subset ($CD4^+CD25^{high}FOXP3^+$) caused by the antibody.

Case Report

A 71-year old woman was admitted due to elevation of her lymphocyte count. She had been diagnosed as suffering from acute-type ATL nearly 5 months prior to admission. She had received VCAP-AMP-VECP chemotherapy[5] followed by oral sobuzoxane in another hospital, and achieved a transient partial remission. We started mogamulizumab to treat the flare-up of ATL disease (Fig. 1). Grade 1 skin eruptions appeared around her neck after three antibody infusions. Because we were also giving her antibacterial (ciprofloxacin hydrochloride), fungal (itraconazole), pneumocystic (sulfamethoxazole-trimethoprim) and viral (aciclovir) prophylaxes in addition to stomach medicine (lansoprazole), we judged the skin event to be due to drug eruption caused by one of these concomitant drugs. Therefore, we stopped all five, but continued with mogamulizumab. Despite their discontinuation and treatment with topical steroids, the skin rashes continued to worsen. We started the patient on 30 mg oral prednisolone, which improved the skin symptoms. The patient was then able to complete the eight planned infusions, and oral prednisolone was tapered off. She was discharged from hospital 8 days after her eighth infusion (day 65), and thereafter seen as an outpatient. However, she had to be readmitted as an emergency patient at day 75 because of fulminant skin rashes. These included erythemas, scale-like plaques, vesicles, blisters and erosions over many areas of the body. Her lips were swollen and oral mucosa was erosive (Fig. 2a). Skin biopsy revealed marked liquefaction, degeneration and perivascular inflammation with dominant CD8-positive cells but almost complete lack of FOXP3-positive cells (Fig. 2b). We diagnosed her as a SJS, and immediately started steroid pulse therapy (methylprednisolone 500 mg/day ×3 days), followed by oral prednisolone. Her skin and mucosal lesions improved gradually, and became inactive. At the same time, her general condition improved. Thus, we again tapered the steroid dose, and she was discharged at day 144. However, she had to come back yet again as an emergency patient on day 151 for the same reason as before, with fulminant skin rashes. We prescribed her mini-steroid pulse therapy (methylprednisolone 125 mg/day ×1 day), followed by oral prednisolone. Once more, her skin lesions improved gradually. Over this whole period, complete ATL remission was maintained by mogamulizumab. The HTLV-1 provirus load in PBMC pre-treatment, and at days 121 and 162 was 750.1, 0.0 (under the limit of detection) and 0.8 copies/1000 cells, respectively. These post-treatment values are strikingly low, considering that median HTLV-1

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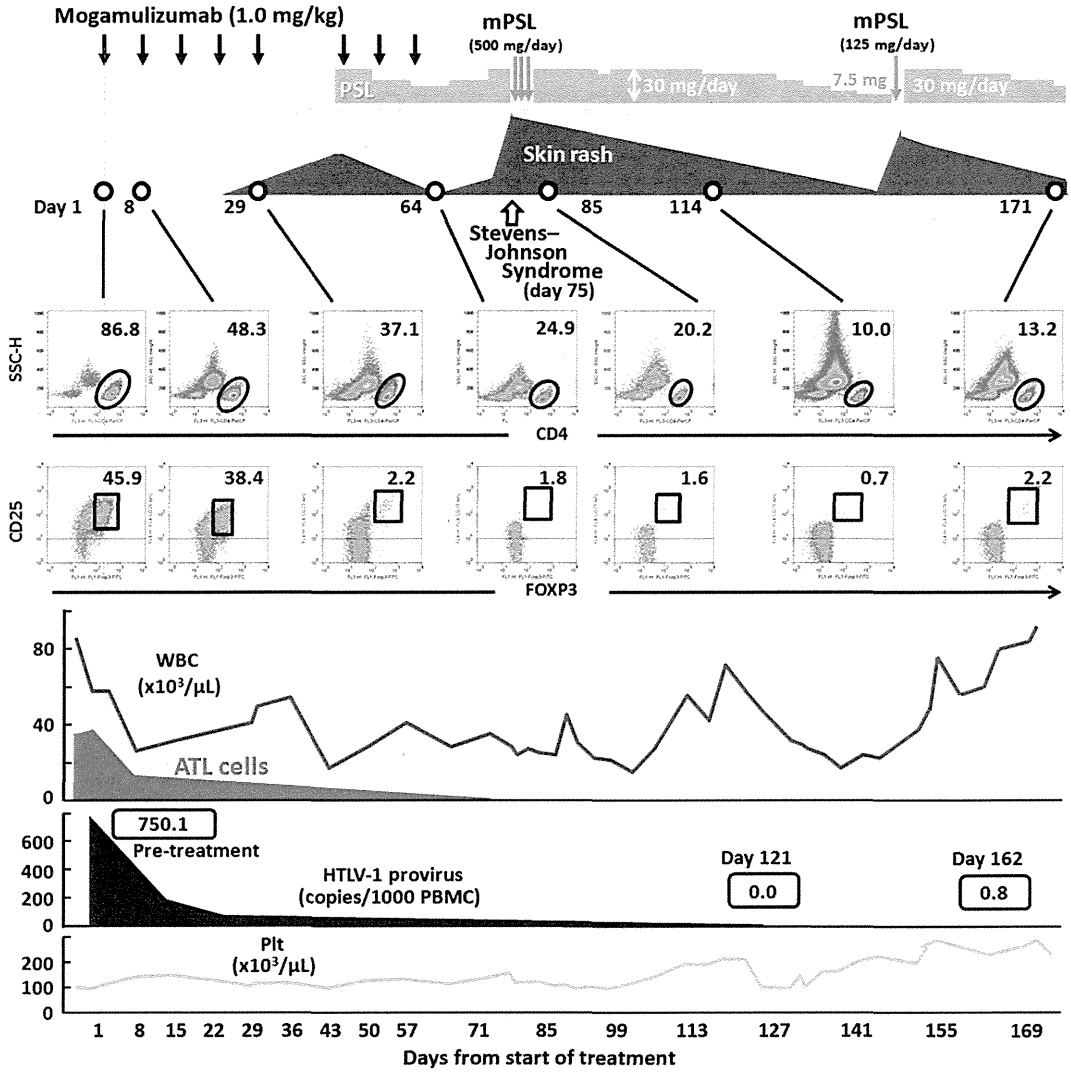

Fig. 1. Clinical course of an ATL patient receiving mogamulizumab monotherapy. ATL; adult T-cell leukemia/lymphoma; mPSL, methylprednisolone; Plt, platelet PSL; prednisolone; WBC, white blood cell.

load in asymptomatic carriers reported by other investigators is 18.0 copies/1000 cells.[6]

We also analyzed CD4, CD25 and FOXP3 expression by PBMC during and after antibody treatment (Fig. 1, middle panels). Before treatment, the majority of the patient's PBMC consisted of CD4-positive and CD25-positive ATL cells. Just before the 5th antibody infusion (day 29), around the time when her skin rash first appeared, the proportion of $CD25^{high}$-$FOXP3^{+}/CD4^{+}$ cells was markedly reduced, to 2.2%. This is low even compared to healthy individuals ($CD25^{high}$-$FOXP3^{+}/CD4^{+}$ cells, mean 3.3%, median 3.3%, range 2.6–4.4%) (Fig. 3). Around the time of SJS onset, the proportion of cells in the Treg subset was further reduced. The proportion of $CD25^{high}FOXP3^{+}/CD4^{+}$ cells at days 64, 85 and 114 was 1.8%, 1.6% and 0.7%, respectively. The striking reduction of the Treg subset persisted until 4 months after the last of the eight antibody infusions (day 171).

Discussion

Drugs often induce adverse cutaneous reactions of varying severity, ranging from simple uncomplicated eruptions to potentially fatal eruptions, such as SJS and TEN, within the spectrum of severe adverse reactions affecting skin and mucosa. Although many factors that might cause variability in the clinical course of such adverse reactions have been suggested, it remains unknown which factors are predominantly involved in these processes. The most prevalent severe drug eruptions are thought to be mediated by drug-reactive T-cells,[7] although we also need to be aware of the alternative view that severe drug eruptions are due to a dysregulated immune system. In this regard, an effect mediated by Treg cells is a likely candidate in severe drug eruptions. Indeed, it is reported that Treg cells can prevent experimentally-induced epidermal injury mimicking TEN in an animal model.[8] Furthermore, Takahashi *et al.* (2009) report that Treg cell function is profoundly impaired in patients with TEN.[9] Consistent with these reports, a marked reduction of the Treg subset was observed in the present case.

Mogamulizumab is the first therapeutic agent targeting CCR4, which is expressed on Treg cells,[10,11] to receive marketing approval anywhere in the world. The reduction of the Treg subset seen here was not specific to the present case, but is commonly observed in ATL patients receiving mogamulizumab. In fact, skin rashes were observed as a frequent non-hematologic adverse event (AE) (63%), mostly occurring

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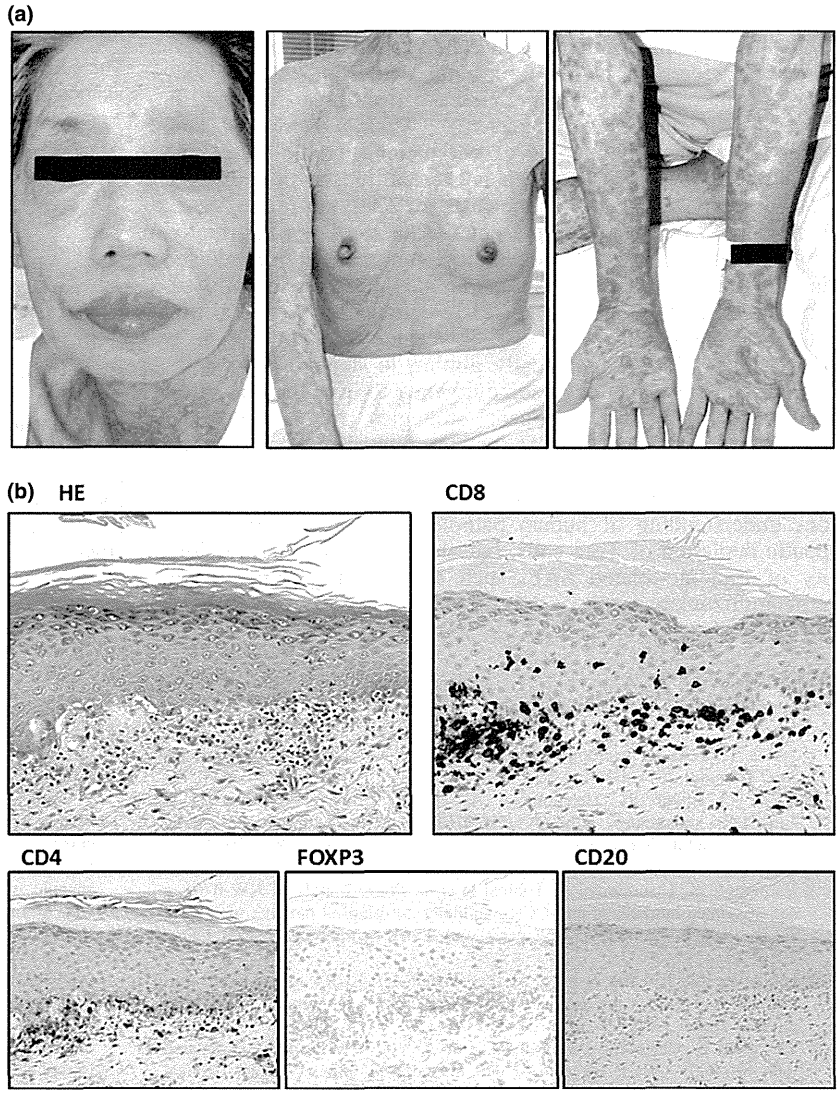
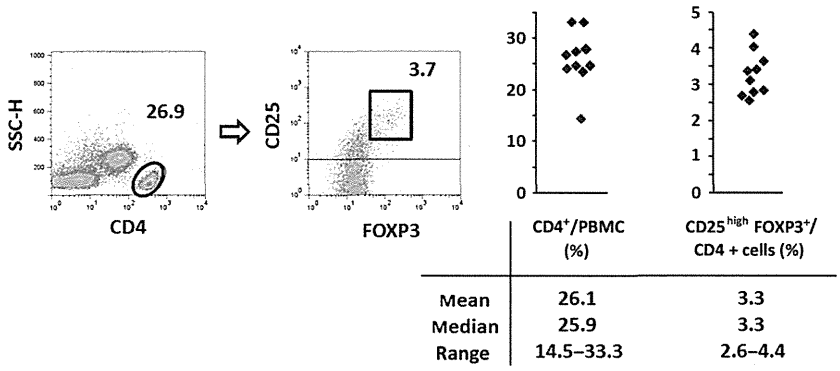


Fig. 2. (a) Macroscopic observations of the patient's skin on the day she was diagnosed with Stevens–Johnson Syndrome. (b) Corresponding skin biopsy showing liquefaction, degeneration and perivascular inflammation with dominant CD8-positive cells but almost no FOXP3-positive cells.



	$CD4^+$/PBMC (%)	$CD25^{high}$ $FOXP3^+$/ CD4 + cells (%)
Mean	26.1	3.3
Median	25.9	3.3
Range	14.5–33.3	2.6–4.4

Fig. 3. $CD4^+CD25^{high}FOXP3^+$ regulatory T cells in PBMC from healthy volunteers (n = 10).

after the fourth or subsequent infusions in the phase II study.[4] The present case was one of these patients. It has been reported that alterations in $CD4^+CD25^+FOXP3^+$ Treg cell frequencies and/or function may contribute to various types of autoimmune diseases.[12] Because the CCR4 molecule aids lymphocyte skin-specific homing,[13] it is not unexpected that skin rashes, which could be an immune-related AE, will be frequently observed in ATL patients receiving mogamulizumab. Because it is an urgent issue to identify which factors determine the severity of immune-related skin disorders associated with mogamulizumab treatment, further investigation on this matter are clearly warranted.

However, reduction of Treg cells is a promising strategy for boosting antitumor immunity in cancer patients, because these cells are increased in the tumor microenvironment and may play an important role in tumor escape from host immunity in several different types of cancer.[14,15] Thus, reduction of Treg cells by mogamulizumab in cancer patients would have both potential benefits leading to enhanced antitumor immunity, but also pose risks of autoimmune disease. The skin-related SAE, including SJS/TEN, are representative of the latter. Currently, several clinical trials of mogamulizumab are being conducted worldwide, not only for ATL, but also other types of lymphoma. In addition, we are currently conducting a clinical trial of mogamulizumab for CCR4-negative solid cancers (UMIN000010050), specifically aiming to deplete Treg cells. Therefore, it is a matter of some urgency to establish the safest and most effective treatment strategies for using mogamulizumab not only in ATL patients but also other types of cancer, to maximize benefit and minimize risk.

In summary, the present case should contribute not only to our understanding of human pathology resulting from therapeutic depletion of Treg cells, but also alert us to the possibility of immune-related SAE, such as SJS/TEN, when using mogamulizumab.

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ORIGINAL REPORT

Multicenter Phase II Study of Mogamulizumab (KW-0761), a Defucosylated Anti-CC Chemokine Receptor 4 Antibody, in Patients With Relapsed Peripheral T-Cell Lymphoma and Cutaneous T-Cell Lymphoma

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ABSTRACT

Purpose
CC chemokine receptor 4 (CCR4) is expressed by peripheral T-cell lymphomas (PTCLs) and is associated with poor outcomes. Mogamulizumab (KW-0761) is a defucosylated humanized anti-CCR4 antibody engineered to exert potent antibody-dependent cellular cytotoxicity. This multicenter phase II study evaluated the efficacy and safety of mogamulizumab in patients with relapsed PTCL and cutaneous T-cell lymphoma (CTCL).

Patients and Methods
Mogamulizumab (1.0 mg/kg) was administered intravenously once per week for 8 weeks to patients with relapsed CCR4-positive PTCL or CTCL. The primary end point was the overall response rate, and the secondary end points included safety, progression-free survival (PFS), and overall survival (OS).

Results
A total of 38 patients were enrolled, and 37 patients received mogamulizumab. Objective responses were noted for 13 of 37 patients (35%; 95% CI, 20% to 53%), including five patients (14%) with complete response. The median PFS was 3.0 months (95% CI, 1.6 to 4.9 months), and the median OS was not calculated. The mean maximum and trough mogamulizumab concentrations (± standard deviation) after the eighth infusion were 45.9 ± 9.3 and 29.0 ± 13.3 μg/mL, respectively. The most common adverse events were hematologic events, pyrexia, and skin disorders, all of which were reversible and manageable.

Conclusion
Mogamulizumab exhibited clinically meaningful antitumor activity in patients with relapsed PTCL and CTCL, with an acceptable toxicity profile. Further investigation of mogamulizumab for treatment of T-cell lymphoma is warranted.

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INTRODUCTION

Mature T/natural killer (NK)-cell neoplasms comprise approximately 20 subclassified heterogeneous groups of non-Hodgkin lymphomas (NHLs) that account for approximately 10% of NHLs in Western countries[1-3] and approximately 25% of NHLs in Japan.[4,5] Mature T/NK-cell neoplasms are largely subdivided into peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL), and different treatment strategies are used for each of these entities.[1,6]

According to the WHO classification, PTCL includes peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large-cell lymphoma (ALCL).[1-3] Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and CHOP-like regimens have been widely used as the standard first-line treatment for patients with PTCL.[7,8] With the exception of those patients with anaplastic lymphoma kinase-positive ALCL, the efficacy of these combination therapies is unsatisfactory because those who achieve remission eventually experience relapse and poor outcomes.[3,9] Several agents have been approved by the US Food and Drug Administration for the treatment of relapsed or refractory (Rel/Ref) PTCL: pralatrexate, romidepsin for Rel/Ref PTCL, and brentuximab vedotin for Rel/Ref ALCL. The overall response rates

(ORRs) were reported to be 29% and 25% for PTCL and 86% for ALCL, respectively.[10-12]

CTCL can be classified as mycosis fungoides (MF), Sézary syndrome, or cutaneous ALCL. The majority of cases of CTCL in Japan consist of MF.[13] The therapeutic approaches and outcomes for these conditions are primarily dependent on disease stage.[6,7,14] Patients with advanced stage CTCL who relapse after systemic chemotherapies and those with transformed MF have particularly poor outcomes.[15,16] Recently, the US Food and Drug Administration approved agents for Rel/Ref CTCL treatment, including vorinostat, denileukin diftitox, and romidepsin, with ORRs of 30%, 30%, and 34%, respectively.[17-19] However, there are few treatment options or approved agents for CTCL in Japan, partly because of its low prevalence here.[5,12,13]

CC chemokine receptor 4 (CCR4) is a marker for type 2 helper T cells or regulatory T (Treg) cells and is expressed on tumor cells in approximately 30% to 65% of patients with PTCL.[20,21] CCR4-positive patients (eg, in the PTCL-NOS subgroup) have a shorter survival time when compared with CCR4-negative patients.[21-23] Further, CCR4 expression increases with advancing disease stage in patients with MF/Sézary syndrome.[24]

Mogamulizumab (KW-0761) is a humanized anti-CCR4 monoclonal antibody with a defucosylated Fc region that enhances antibody-dependent cellular cytotoxicity.[25,26] In vitro antibody-dependent cellular cytotoxicity assay and in vivo studies in a humanized mouse model revealed that mogamulizumab exhibited potent antitumor activity against T-cell lymphoma cell lines and against primary CTCL cells from patients.[26-28]

In a phase I study of patients with relapsed adult T-cell leukemia-lymphoma (ATL) and PTCL/CTCL, mogamulizumab was well tolerated up to a dose of 1.0 mg/kg. An ORR of 31% (five of 16) was obtained, including one partial response (PR) among three patients with PTCL/CTCL.[29] Mogamulizumab yielded an ORR of 50% (13 of 26) for relapsed CCR4-positive ATL in a subsequent phase II study.[30] In the United States, a phase I/II study for patients with Rel/Ref CTCL revealed that mogamulizumab was well tolerated with an ORR of 37% (14 of 38, 8% complete response [CR], 29% PR) and a median PFS of 341 days.[31]

The present report describes the results of a multicenter phase II study in Japan that was designed to assess the efficacy and safety of mogamulizumab in patients with relapsed CCR4-positive PTCL or CTCL.

PATIENTS AND METHODS

Study Design and Treatment

This was a multicenter, single-arm phase II study conducted at 15 Japanese centers. At least 35 patients were required to detect a lower limit of the 95% CI that exceeded the 5% threshold, and the expected ORR for mogamulizumab was 25% with a statistical power of 90%.[10,29]

All patients gave written informed consent before enrollment. Patients received intravenous infusions of 1.0 mg/kg mogamulizumab once per week for 8 weeks. Dose modification of mogamulizumab was not allowed. Oral antihistamine and acetaminophen were given before each dose of mogamulizumab as premedication.[29,30] A systemic corticosteroid (hydrocortisone 100 mg intravenously) was also administered before the first dose of mogamulizumab to prevent an infusion reaction. The same dose of hydrocortisone was administered before the second and subsequent administrations at the investigators' discretion. The plasma concentrations of mogamulizumab and antimogamulizumab antibodies in plasma were determined by using enzyme-linked immunosorbent assays.[29,30] Blood samples were collected from all patients who received at least one dose of mogamulizumab at times determined by the protocol for pharmacokinetic analyses. Maximum plasma mogamulizumab concentration and trough concentration parameters were calculated from 0 to 7 days after the eight doses. T-cell subsets and NK cell distribution were also investigated by flow cytometry during and after mogamulizumab treatment. This study was conducted in accordance with the Declaration of Helsinki and in compliance with Good Clinical Practices. The protocol was approved by the institutional review board at each participating institution.

Patients

Patients who were ≥ 20 years of age and who had CCR4-positive PTCL or CTCL with relapse after their last systemic chemotherapy were eligible for participation. Patients who were refractory to their most recent therapy were not eligible for this study. Histopathological subtypes were assessed and reclassified by the Independent Pathology Review Committee according to the 2008 WHO classification.[1] CCR4 expression was determined by immunohistochemistry by using an anti-CCR4 monoclonal antibody (KM2160) and was confirmed by central review, as described previously.[29] In brief, CCR4 expression was classified according to the proportion of stained tumor cells (negative, < 10%; 1+, 10% to <25%; 2+, 25% to < 50%; 3+, ≥ 50%). Staging of nodal/extranodal and/or cutaneous lesions was performed if the lesions met the following requirements: nodal and extranodal lesions were > 1.5 cm in measurable length on cross-sectional computed tomography images, cutaneous lesions were identifiable on visual inspection, and peripheral blood abnormal lymphocyte count was ≥ 1,000/μL and comprised ≥ 5% of total leukocytes. All patients were required to have an Eastern Cooperative Oncology Group performance status of 0 to 2. Other notable eligibility criteria regarding laboratory values were as follows: neutrophil count ≥ 1,500/μL, platelet count ≥ 50,000/μL, hemoglobin level ≥ 8.0 g/dL, AST level ≤ 2.5× the upper limit of normal (ULN), ALT level ≤ 2.5× the ULN, total bilirubin level ≤ 1.5× the ULN, and serum creatinine level ≤ 1.5× the ULN. Patients were excluded if they had any severe complications, such as CNS involvement or a bulky lymphoma mass requiring emergent radiotherapy, a history of allogeneic stem-cell transplantation, active concurrent cancers, an active infection, or positivity for hepatitis B virus DNA, hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus antibody.

Efficacy and Safety Assessment

The primary objective was to assess the best overall response, and the secondary objectives included assessments of the best response according to disease site, progression-free survival (PFS), and overall survival (OS). Efficacy was evaluated by the Independent Efficacy Assessment Committee according to modified response criteria based on the International Working Group Criteria.[32,33] Cutaneous lesions were evaluated by using the modified Severity Weighted Assessment Tool.[34] In addition, treatment efficacy in patients with CTCL was evaluated by using a Global Response Score.[35] Responses were assessed after the fourth and eighth mogamulizumab infusions and at 2 and 4 months after the end of treatment. Treatment was discontinued if progressive disease (PD) was evident. PD and survival were monitored until at least 4 months after the completion of dosing. For safety evaluations, adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for AEs, version 4.0.

Statistical Analysis

PFS and OS were analyzed by using the Kaplan-Meier method. PFS was defined as the time from the first dose of mogamulizumab to progression, relapse, or death by any cause (whichever occurred first). OS was measured from the day of the first dose to death by any cause.

RESULTS

Patient Characteristics

Sixty-five patients were screened, and 64 biopsy specimens were histologically confirmed as PTCL or CTCL by the Independent Pathology Review Committee. In total, 50 (78%) of the 64 screened

patients were CCR4-positive. Of these, 38 eligible patients were enrolled in the study and 37 received at least one infusion of mogamulizumab. One patient withdrew because of an infectious complication before dosing. Patient characteristics, histopathology subtypes, and previous systemic therapies are shown in Table 1.

Table 1. Baseline Patient Demographic and Clinical Characteristics

Characteristic*	Patients (N = 37)		Patients With PTCL (n = 29)		Patients With CTCL (n = 8)	
	No.	%	No.	%	No.	%
Age, years						
Median	64		67		50	
Range	33-80		33-80		36-70	
≥ 65	18	49	17	59	1	13
Sex						
Male	23	62	20	69	3	38
Female	14	38	9	31	5	63
ECOG performance status						
0	24	65	19	66	5	63
1	12	32	10	34	2	25
2	1	3	0	0	1	13
Elevated LDH level†	21	57	18	62	3	38
Bone marrow involvement	7	19	7	24	0	0
No. of previous systemic regimens						
Median	2		2		3	
Range	1-6		1-5		1-6	
1	14	38	13	45	1	13
2	15	41	12	41	3	38
≥ 3	8	22	4	14	4	50
Types of systemic therapy						
Chemotherapy	37	100	29	100	8	100
CHOP/CHOP-like regimen	36	97	29	100	7	88
DeVIC	6	16	4	14	2	25
CHASE	5	14	5	17	0	0
Single-agent therapy	5	14	0	0	5	63
Other	10	27	10	34	0	0
Auto-PBSCT	3	8	3	10	0	0
Radiotherapy	9	24	5	17	4	50
Intensity of CCR4 expression‡						
1+	6	16	4	14	2	25
2+	6	16	4	14	2	25
3+	25	68	21	72	4	50
Histopathology by central review						
PTCL-NOS	16	43	16	55		
AITL	12	32	12	41		
ALCL, ALK negative	1	3	1	4		
MF	7	19			7	88
c-ALCL	1	3			1	13

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; c-ALCL, cutaneous anaplastic large-cell lymphoma; CHASE, cyclophosphamide, cytosine arabinoside, etoposide, and dexamethasone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CTCL, cutaneous T-cell lymphoma; DeVIC, dexamethasone, etoposide, ifosfamide, and carboplatin; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MF, mycosis fungoides; NOS, not otherwise specified; PBSCT, peripheral-blood stem-cell transplantation; PTCL, peripheral T-cell lymphoma.

*Of the 38 patients enrolled, 37 received at least one infusion of mogamulizumab.

†Elevated LDH level: higher LDH level than upper limit of the normal range.

‡The denominator used for the intensity of CC chemokine receptor 4 (CCR4) expression is based on subjects who were positive for CCR4 by immunohistochemistry.

Of the 37 patients who received mogamulizumab, 25 (68%) completed the planned course of eight infusions. Nine patients (24%) discontinued treatment because of PD, and three patients (8%) due to serious AEs.

Efficacy

The ORR for the 37 treated patients was 35% (13 of 37; 95% CI, 20% to 53%), and 14% of patients (five of 37) achieved a CR, of which one was unconfirmed (Table 2). Reponses (CR/PR) were observed in at least one patient with each subtype of disease, but the ORR differed between subtypes. The ORR was 34% (10 of 29; 95% CI, 18% to 54%) in patients with PTCL (three of 16 for PTCL-NOS, six of 12 for AITL, and one of one for ALCL, anaplastic lymphoma kinase-negative) and 38% (three of eight; 95% CI, 9% to 76%) in those with CTCL (two of seven for MF and one of one for cutaneous ALCL). In addition, ORR in patients with CTCL was 50% (four of eight; 95% CI, 16% to 84%) according to the Global Response Score.

Total ORR did not significantly correlate with CCR4 expression level, patient age, or the number of previous chemotherapy regimens. The response rates for lymph node and cutaneous lesions were 33% (11 of 33) and 58% (seven of 12), respectively.

The median PFS was 3.0 months (95% CI, 1.6 to 4.9 months) for the entire population and 2.0 months for patients with PTCL. Although the median OS was not reached for the entire population at the

Table 2. Best Response (N = 37)

Parameter	No. of Patients	No. of Patients With Best Response				Response Rate (%)*
		CR/CRu	PR	SD	PD	
Overall response	37	5	8	13	11	35
Histopathology by central review						
PTCL	29	5†	5	9	10	34
PTCL-NOS	16	1	2	6	7	19
AITL	12	3	3	3	3	50
ALCL, ALK negative	1	1†	0	0	0	100
CTCL	8	0	3	4	1	38
MF	7	0	2	4	1	29
c-ALCL	1	0	1	0	0	100
Age, years						
< 65	19	1†	6	7	5	37
≥ 65	18	4	2	6	6	33
Intensity of CCR4 expression						
1+	6	1	1	3	1	33
2+	6	1	2	2	1	50
3+	25	3†	5	8	9	32
No. of previous systemic regimens						
1	14	3	3	6	2	43
2	15	1	1	6	7	13
≥ 3	8	1†	4	1	2	63

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; c-ALCL, cutaneous anaplastic large-cell lymphoma; CCR4, CC chemokine receptor 4; CR, complete response/complete remission; CRu, uncertain complete response/uncertain complete remission; CTCL, cutaneous T-cell lymphoma; MF, mycosis fungoides; NOS, not otherwise specified; PD, progressive disease; PR, partial response/partial remission; PTCL, peripheral T-cell lymphoma; SD, stable disease.

*Response rate (%): 100 × number of responders/number of subjects in each category included in the efficacy analysis set.

†Among the patients who showed CR/CRu, one showed CRu.

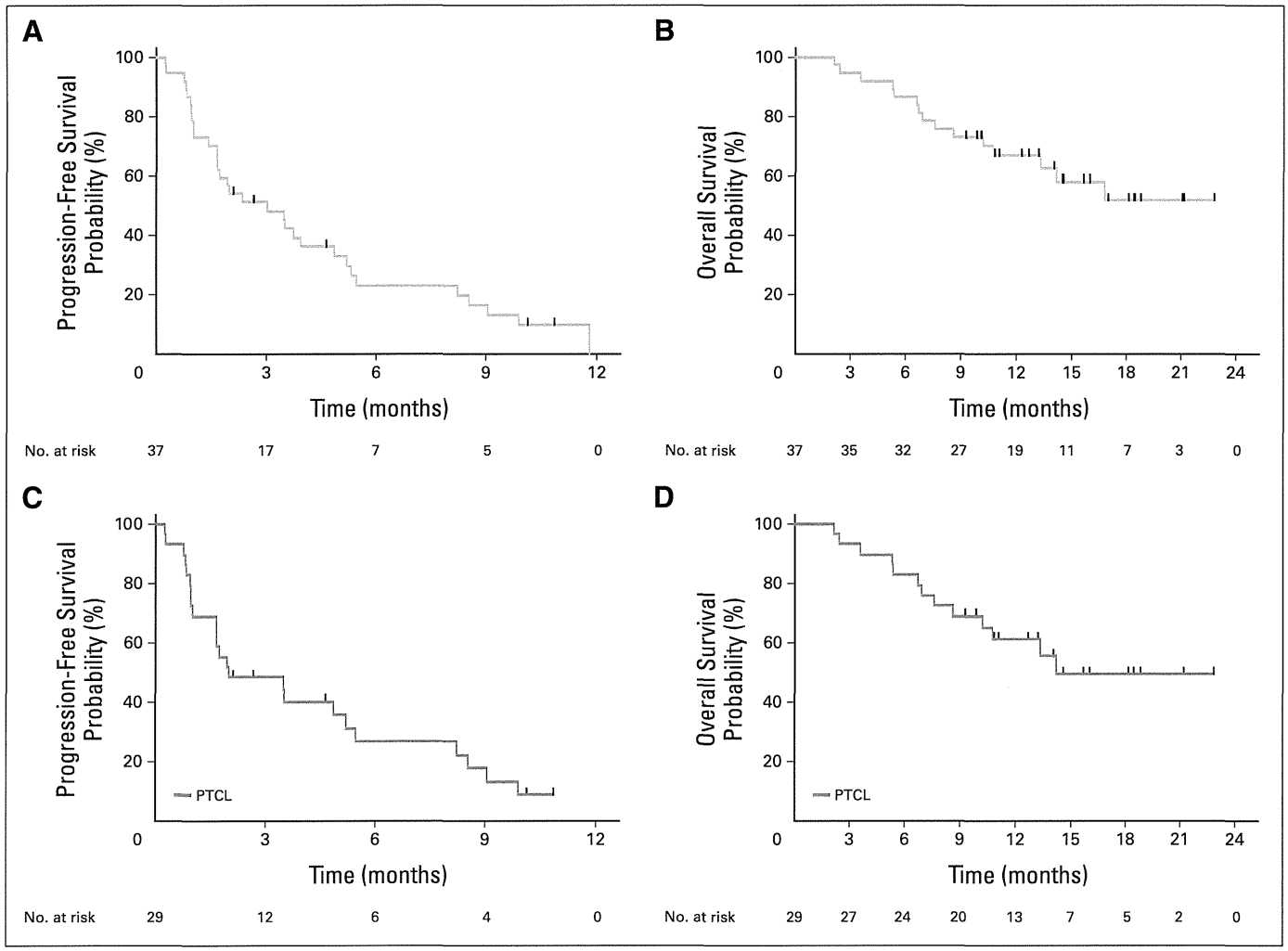

Fig 1. Kaplan-Meier curves of (A) estimated progression-free survival (median, 3.0 months), (B) overall survival (median not reached), (C) progression-free survival in patients with peripheral T-cell lymphoma (PTCL; median, 2.0 months), and (D) overall survival in patients with PTCL (median, 14.2 months).

time of this report, it was 14.2 months for patients with PTCL (Fig 1). Moreover, the median PFS of all 13 responders was 5.5 months, and for PTCL responders (n = 10), it was 8.2 months.

Safety

The most common treatment-related AEs of all grades and treatment-related AEs of grade 3/4 were lymphocytopenia (81%, 73%), neutropenia (38%, 19%), and leukocytopenia (43%, 14%), whereas the most common nonhematologic AE was pyrexia (30%; grade 2 or lower) (Table 3). Lymphocytopenia occurred in 30 patients (81%) and was noted after the first dose in 26 of these patients. For 19 of the patients, lymphocyte counts were $< 800/\mu L$ (grades 2 to 4) before the first dosing. The lymphocyte count ultimately recovered to normal or baseline levels in all patients.

Infusion reaction (24%; grade 2 or lower) occurred primarily at the first infusion, after which it became less frequent, and all patients recovered. No infusion prolongation/interruption was caused by the infusion reaction.

In addition, treatment-related skin disorders were commonly reported (all grades, 51%; grade 3/4, 11%) when grouped according to system organ class. Of the 19 patients who suffered from skin disorder complications, 15 patients experienced improvement, whereas the remaining patients discontinued treatment because of PD or switched to other post treatments. One patient who had a history of psoriasis before the study treatment developed two serious skin disorders (toxicoderma and psoriasis vulgaris) during the study period.

Fifteen serious treatment-related AEs were observed among eight patients (22%); these AEs included grade 3 polymyositis in one patient, grade 2 cytomegalovirus retinitis in two patients, and grade 4 second primary malignancy in one patient with AITL. All patients improved over time, and there were no deaths related to AEs.

Pharmacokinetics and Pharmacodynamics

The mean maximum mogamulizumab concentration and trough mogamulizumab concentration ($\pm$ standard deviation) in plasma after the eighth infusion were 45.9 $\pm$ 9.3 and 29.0 $\pm$ 13.3 μg/mL, respectively. Antimogamulizumab antibodies were not detected after dosing in any patients. These results were consistent with the findings of a previous study of patients with ATL.[30] As an exploratory study, we assessed the effect of mogamulizumab on the number of CD4+/CD25+/Foxp3+ cells (the Treg cell subset) and CD45+/CD16+/CD56+ cells (the NK cell subset). Patients given

Table 3. Treatment-Related Adverse Events (N = 37)

Adverse Event*	All Grades No.	All Grades %	Grade ≥ 3 No.	Grade ≥ 3 %
Hematologic				
Lymphocytopenia	30	81	27	73
Leukocytopenia	16	43	5	14
Thrombocytopenia	14	38	1	3
Neutropenia	14	38	7	19
Anemia	5	14	2	5
Febrile neutropenia	1	3	1	3
Nonhematologic				
Pyrexia	11	30	0	0
Infusion reaction	9	24	0	0
ALT increased	8	22	1	3
ALP increased	8	22	1	3
Hypophosphatemia	6	16	1	3
Hypokalemia	2	5	1	3
Infection	1	3	1	3
Oral candidiasis	1	3	1	3
Pneumonia	1	3	1	3
Herpes esophagitis	1	3	1	3
Polymyositis	1	3	1	3
Second primary malignancy†	1	3	1	3
Skin and subcutaneous tissue disorders (SOC)	19	51	4	11
Rash papular	6	16	1	3
Rash erythematous	5	14	1	3
Psoriasis	2	5	1	3
Rash maculopapular	2	5	1	3
Toxic skin eruption	2	5	1	3

Abbreviations: ALP, alkaline phosphatase; SOC, System Organ Class (according to the Medical Dictionary for Regulatory Activities).
*Treatment-related adverse events that were reported in at least 15% of patients or that were of grade 3-4 severity.
†Diffuse large B-cell lymphoma was reported in one patient with angioimmunoblastic T-cell lymphoma.

mogamulizumab exhibited a profound depletion of the Treg cell subset during treatment, and cell levels had not returned to baseline 4 months after the last dose (Fig A1). Mogamulizumab also caused a modest decrease in the NK cell subset during treatment (data not shown).

DISCUSSION

This report described results from a single-arm, open-label multicenter phase II study of mogamulizumab in patients with relapsed CCR4-positive PTCL and CTCL.

Mogamulizumab showed promising antitumor activity, with an ORR of 35% (95% CI, 20% to 53%) and a CR/unconfirmed CR of 14%. These data were consistent with those reported with relapsed ATL.[30] It is notable that all three patients who relapsed after autoperipheral blood stem-cell transplantation responded to mogamulizumab. The total ORR is comparable to that of other US Food and Drug Administration-approved drugs, such as pralatrexate and romidepsin.[10,11] However, the present study differed from previous studies in several important respects. Firstly, the patient population was smaller than in the pralatrexate or romidepsin studies. Secondly, since it has been reported that CCR4 expression correlated with advanced disease,[24] it is important to note that although these two studies enrolled relapsed and refractory patients irrespective of their CCR4 expression status, the present study only recruited relapsed patients who were CCR4-positive. However, almost all patients in the present study had good PS compared with those patients in the previous studies. Thirdly, all patients with MF (n = 7) in the present study had relapsed after systemic chemotherapies and were presumed to have advanced stage disease, because all of these patients exhibited clinical skin tumors. Further, four of these seven patients exhibited clinically abnormal lymph node swelling, which does not usually occur at stages lower than IIB.[14,15]

In future study, PFS may also be improved by a longer continuous dosing schedule, such as a phase I/II study for CTCL.[31]

Although the number of patients was relatively small in the present study, the ORR for the AITL group (50%; six of 12) seemed noteworthy, while appearing relatively low in patients with PTCL-NOS (19%; three of 16). However, the three patients with PTCL-NOS who responded to mogamulizumab achieved durable PFS (9.0, 10.1+, and 10.8+ months; +, censored). Further studies are needed to identify which CCR4-positive T-cell lymphoma patients are most likely to benefit from mogamulizumab therapy.

There was no definite correlation between ORR and patient characteristics, such as age, CCR4 expression level, or number of previous systemic regimens. Although our study only included CCR4-positive patients with PTCL and CTCL, a recent US phase I/II study of mogamulizumab included both CCR4-positive and CCR4-negative patients with CTCL.[31] In that study, mogamulizumab exhibited efficacy irrespective of CCR4 expression (positive or negative) or CCR4 expression level, with a continuous dosing schedule.[31] Further studies are needed to define if CCR4 positivity represents a useful predictive biomarker in either PTCL or CTCL.

CCR4-positivity was confirmed in 78% of the 64 screened patients, a higher rate than previously reported.[20,21] However, it is possible that this variation in CCR4 positivity was due to differences in immunohistochemistry assay sensitivity. In our ongoing CTCL phase III study, our protocol permitted recruitment of both CCR4 positive and negative CTCL patients (NCT01728805). This is because the detection limit of CCR4 positivity may not be yet fully established, and mogamulizumab might have antitumor activity against CCR4-negative tumors through the depletion of CCR4-positive regulatory T cells,[36] thus enhancing pre-existing CD8+ cytolytic T-lymphocytes. Based on the latter new concept, an investigator-initiated trial of mogamulizumab against CCR4-negative solid tumors has been initiated (UMIN000010050).

Most of the AEs associated with mogamulizumab were mild and reversible. One patient suffered from polymyositis, an immune-related serious AE, after seven doses of mogamulizumab. The patient improved after steroid pulse therapy, treatment with tacrolimus hydrate, and continuous rehabilitation. Although drug-induced myositis was a possible cause, the relationship between mogamulizumab and myositis was not determined, even after detailed investigation. In our study, skin rash could also represent an immune-related AE, as other immunotherapies, including ipilimumab and zanolimumab, cause similar skin toxicity.[18,36-38] In addition, this may relate to the antitumor mechanism of mogamulizumab, because CCR4 contributes to skin-specific lymphocyte homing.[39] Indeed, a previous study revealed that patients who developed skin disorders ultimately had better therapeutic responses to treatment.[30] In the present study, of the

13 patients who developed grade 2 to 3 skin disorders, five patients achieved CR/PR. Of the 24 patients who developed grade 1 or no skin disorders, eight patients achieved CR/PR. Hence, no clear correlation between skin disorders and response rate was observed in the present study.

As shown in Figure A1, mogamulizumab caused a significant and persistent reduction in the number of Treg cells. This may be responsible for the increased incidence of skin disorders seen in patients with ATL.[30,40] Skin disorders were observed in 19 patients (51%), with grade 3/4 in four cases (11%). This was lower than the proportion of patients who developed skin disorders (67%, 22% in grade 3/4) in a previous study.[30] One patient (4%) with ATL developed Stevens-Johnson syndrome (SJS)[30] and four patients with ATL developed SJS/toxic epidermal necrolysis in postmarketing surveillance of mogamulizumab[40]; however, no cases of SJS/toxic epidermal necrolysis were observed in the present study. Similarly, four of 21 patients with ATL (19%) developed symptoms consistent with SJS[41] after treatment with pralatrexate, whereas no SJS was observed in patients with PTCL[10] after pralatrexate treatment. The risk of severe skin disorders may therefore be lower in patients with PTCL, compared with patients with ATL.

In conclusion, this phase II study revealed that mogamulizumab had promising efficacy and tolerability in patients with relapsed CCR4-positive PTCL and CTCL. Given its novel mechanism of action and favorable toxicity profile compared with multiagent cytotoxic chemotherapy, we might expect the use of mogamulizumab in combination with other agents. Further preclinical and clinical studies of combination therapy will be needed.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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