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Safety and effectiveness of mogamulizumab in relapsed or refractory adult T-cell leukemia-lymphoma

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Abstract

Objective: This prospective, observational, postmarketing surveillance was conducted to evaluate the safety and effectiveness of mogamulizumab, an anti-CC chemokine receptor 4 (CCR4) monoclonal antibody, in patients with CCR4-positive, relapsed or refractory (r/r) adult T-cell leukemia-lymphoma (ATL) in Japan.

Method: All patients were scheduled to receive intravenous infusions of mogamulizumab 1.0 mg/kg once weekly for 8 weeks, alone or in combination with other modalities.

Results: In the safety analysis population comprising 572 patients, mogamulizumab therapy was started between May 29, 2012, and April 30, 2013, and adverse drug reactions (ADRs) were reported in 73.4% (38.6% serious cases) of patients. The most common ADRs were skin disorders (33.2% [10.8% serious cases]), infusion-related reactions (30.1% [4.7% serious cases]), and infections (22.0% [14.7% serious cases]). In the effectiveness analysis population comprising 523 patients, the best overall response rate and the response rate at the end of therapy were 57.9% and 42.0%, respectively. The median overall survival was 5.5 months. Safety and effectiveness results were similar between patients aged ≥70 and <70 years.

Conclusion: This postmarketing surveillance confirmed the safety and effectiveness of mogamulizumab for the treatment of patients with r/r ATL, including elderly patients, in clinical practice.

KEYWORDS

ATL, elderly patients, mogamulizumab, postmarketing surveillance, relapsed or refractory

1 | INTRODUCTION

Adult T-cell leukemia-lymphoma (ATL) is a rare type of non-Hodgkin lymphoma caused by human T-lymphotropic virus type 1 (HTLV-1).[1,2] ATL can be subdivided into acute, lymphoma, chronic, and smoldering subtypes based on the clinical characteristics, prognostic factors, and natural history of the disease.[3] Chronic-type ATL is further classified into favorable and unfavorable subtypes based on the presence or absence of one or more unfavorable prognostic factors including serum lactate dehydrogenase (LDH), albumin, and blood urea nitrogen levels. Patients with acute-, lymphoma-, and unfavorable chronic-type ATL are categorized as patients with aggressive ATL, while those with favorable chronic-type ATL and those with smoldering-type ATL are characterized as patients with indolent ATL.[4]

Patients with acute- and lymphoma-type ATL, which are the major subtypes of ATL, accounting for approximately 80% of patients with ATL, have poor clinical outcome with 4-year overall survival (OS) rates of 11% and 16%, respectively.[5] Intensive chemotherapy is generally administered as first-line treatment for patients with aggressive ATL; however, allogeneic hematopoietic stem cell transplantation (HSCT) is thought to be the only potentially curable therapeutic option, provided the patient is deemed eligible.[5,6] A recent nationwide survey in Japan revealed that the median age at diagnosis of ATL was 67.5 years,[7] which has been increasing over the past few decades, indicating that HTLV-1-infected individuals tended to be of an older age.[7,8] Since most patients with ATL aged 70 years or older are ineligible not only for allogeneic HSCT[5,9] but also for dose-intensified cytotoxic chemotherapy, therapeutic options for patients with ATL aged ≥70 years are limited.

In 2012, mogamulizumab, a defucosylated humanized anti-CC chemokine receptor 4 (CCR4) monoclonal antibody, was first approved for the treatment of CCR4-positive relapsed or refractory (r/r) ATL in Japan,[10,11] following which this postmarketing all-case surveillance study was initiated to evaluate its safety and effectiveness in clinical practice in Japan. The surveillance was mandated by the Pharmaceuticals and Medical Devices Agency in Japan, and data were collected prospectively from all patients who started mogamulizumab therapy during 1-year period after the launch. Preliminary safety information from the surveillance has been published in a previous report,[12] and the surveillance was completed in 2018, enrolling more than 500 patients with r/r ATL who were treated with mogamulizumab. Here, we report response rates, survival, and prognostic factors results from the postmarketing surveillance, together with the subset data of elderly patients with ATL in addition to updated safety information.

2 | PATIENTS AND METHODS

2.1 | Study design, patients, and treatment

This prospective, observational, postmarketing all-case surveillance study (Clinical trial registry number: UMIN000025368) has been conducted from the launch on May 29, 2012 at 294 sites in Japan in accordance with the Good Postmarketing Study Practice (https://www.pmda.go.jp/english/safety/outline/0001.html), the ordinance of the Ministry of Health, Labour and Welfare No. 171., which requires neither acquisition of informed consent from patients nor ethics committee approval at participating sites. The study protocol was reviewed by the Pharmaceuticals and Medical Devices Agency in Japan, and written consent was obtained from each participating site for this publication.

Data were collected from all patients for whom mogamulizumab treatment was initiated before May 1, 2013, as daily clinical practice, and who had planned to be received intravenous infusions of mogamulizumab 1.0 mg/kg once weekly for 8 weeks, the approved dosing schedule in Japan, alone or in combination with other modalities. Patients were observed for 24 weeks after the last dose of mogamulizumab. All data were locked on March 29, 2018.

2.2 | Safety and effectiveness evaluation

The surveillance had five priority survey items for adverse events and adverse drug reactions (ADRs)-infusion-related reactions (IRRs; Medical Dictionary for Regulatory Activities/Japanese version [MedDRA/J] Preferred Term), skin disorders (MedDRA/J System Organ Class), infections (MedDRA/J System Organ Class), immune system disorders (MedDRA/J System Organ Class), and tumor lysis syndrome (TLS; MedDRA/J Preferred Term), which were determined as items to be collected intensively regardless of presence or absence of events, based on safety information from clinical studies.[10,11] Excluding these five items, all other adverse events and ADRs throughout the treatment and follow-up period were reported voluntarily if events occurred. All events were recorded according to the MedDRA/J terminology, version 20.1 and were evaluated as "serious" or "non-serious" per the International Conference on Harmonization guideline E2D. Here, we report events shown as ADRs. The best overall response during mogamulizumab therapy and response at the end of mogamulizumab therapy were assessed by the attending physician according to the response criteria used in the phase 2 study in patients with relapsed ATL in Japan.[6,11]

2.3 | Statistical analyses

The OS curve was estimated by the Kaplan-Meier method from the first dosing of mogamulizumab to the last follow-up date or death due to any cause. Univariate and multivariate logistic regression analyses were performed to assess whether PS, age, serum albumin level, corrected serum calcium level, serum LDH level, and ATL subtype associated the 31-week mortality using SAS software, version 9.3 (SAS Institute, Inc, Cary, NC, USA). The significant level of all tests was $P < 0.05$ by two-side test. These six factors were selected since they were reported to be independent prognostic factors for patients with acute- and lymphoma-type ATL at diagnosis[3,13,14] and were available in this surveillance.

Safety and response rate analyses were performed on the safety and effectiveness analysis populations, respectively. Survival was analyzed for the effectiveness analysis population, after excluding patients lost to follow-up after the last dosing of mogamulizumab. Univariate and multivariate analyses were performed for patients with information on all six prognostic factors and clinical outcome (alive/dead) at 31 weeks from the first dosing of mogamulizumab in the effectiveness analysis population.

3 | RESULTS

3.1 | Patient disposition and characteristics

Patient disposition is shown in Figure 1. Data were collected from 577 of 597 patients, and 572 patients were included in the safety analysis population after excluding four unevaluable patients (three due to double enrollment and one due to no administration of mogamulizumab) and one patient from a study site that did not provide consent for this

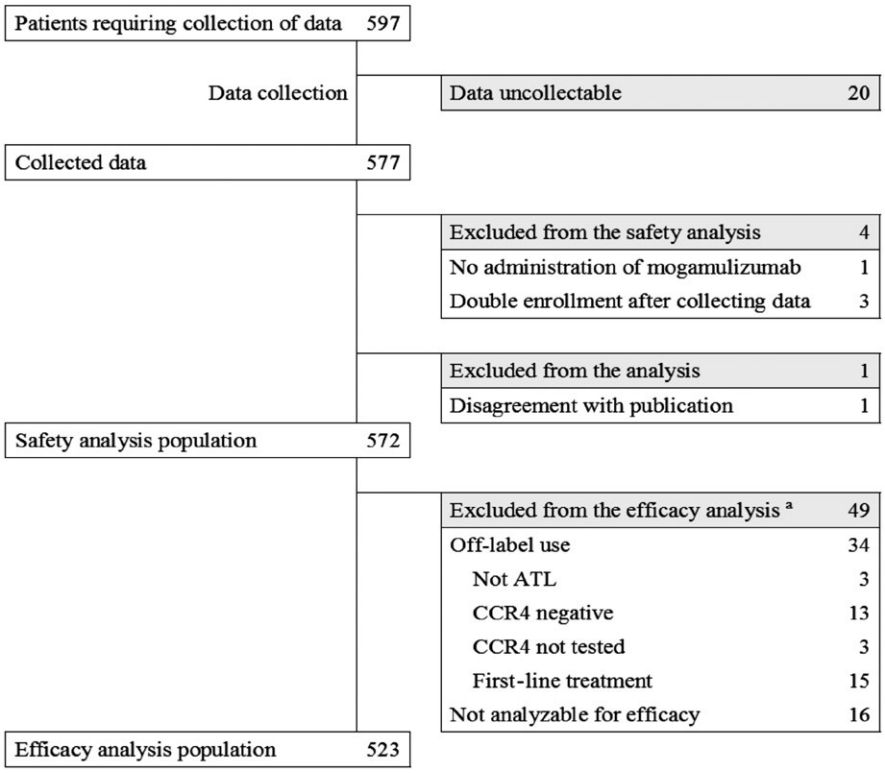

FIGURE 1 Patient disposition. [a]One patient had two reasons for exclusion. ATL, adult T-cell leukemia-lymphoma; CCR4, CC chemokine receptor 4

publication. Of the 572 patients, 523 were included in the effectiveness analysis after excluding 49 patients due to either off-label use or unanalyzable data for effectiveness or both.

Table 1 shows the characteristics of the safety analysis population. The majority of patients (93.8%) were of acute or lymphoma subtype, and in 30.8% of patients, mogamulizumab was used in combination with other modalities, mainly cytotoxic agents.

The median age of patients was 67.0 years, with patients aged ≥70 years accounting for 41.6% of the population. Following mogamulizumab treatment, 49 patients (8.6%) underwent allogeneic HSCT, of which 47 were aged <70 years. The median interval between the last mogamulizumab treatment and the HSCT was 36 days (range 6-191 days).

In the safety analysis population, the mean number of mogamulizumab administrations was 5.4, and 60% of patients did not complete all eight courses of mogamulizumab therapy, mainly due to disease progression (52.5%) and adverse events (37.0%).

3.2 | ADRs

As shown in Table 2, 73.4% and 38.6% of patients were reported to experience at least one ADR and serious ADR, respectively. Of the 572 patients, ADRs in 42 patients (7.3%) resulted in death that was attributable to mostly infections (3.1% [18/572]) and graft vs host disease (GVHD; 1.2% [7/572]).

Overall frequencies for IRRs, skin disorders, infections, immune system disorders, and TLS were 30.1%, 33.2%, 22.0%, 4.7%, and 2.8%, respectively, with frequencies of serious events of 4.7%, 10.8%, 14.7%, 4.4%, and 1.2%, respectively. The most common ADRs were skin disorders (33.2%), IRRs (30.1%), and infections (22.0%), of which infections (14.7%) and skin disorders (10.8%) were the most common serious ADRs.

Among 27 patients (4.7%) who had serious IRR, six patients were eventually discontinued the treatment of mogamulizumab. Skin disorders were mostly rash and erythema, and severe ones such as Stevens–Johnson syndrome and toxic dermal necrosis were reported in 0.7% (4/572) of patients each. The median time from the first administration of mogamulizumab and median number of mogamulizumab infusion to event onset were 35.5 days (range 1-230) and 5 infusions (range 1-11), respectively. The median time to resolved/resolving status in skin disorders was 36.5 days (range 2-1555). Skin disorders were more frequent in patients who received ≥8 infusions of mogamulizumab compared with those who received <8 infusions (50.2% [115/229] vs 21.9% [75/343], respectively). Infections included mainly cytomegalovirus (CMV) infection or viremia in 8.2% (5.4% serious cases), pneumonia in 4.0% (3.3%), and sepsis in 2.3% (1.9%) of patients. Other than these, CMV end-organ diseases such as CMV chorioretinitis, CMV enterocolitis, and CMV pneumonia were reported in 0.3% (2/572), 0.5% (3/572), and 0.3% (2/572) of patients, respectively. Of the 27 patients (25 serious cases) categorized as having immune system disorders, 25 patients (22 serious cases) were reported to have GVHD.

When these frequencies were stratified by ages of ≥70 and <70 years, no particular item was predominantly observed in the

TABLE 1 Patient characteristics (safety analysis population)

Characteristic	N	%
Total	572	100.0
Sex		
Male	307	53.7
Female	265	46.3
Age (Median 67 y)		
<70 y	334	58.4
≥70 y	238	41.6
Primary disease (ATL)	569	99.5
ATL subtype (Shimoyama's classification (Shimoyama 1991))		
Acute type	339	59.6
Lymphoma type	195	34.3
Chronic type with unfavorable prognostic factors	12	2.1
Chronic type without unfavorable prognostic factors	10	1.8
Smoldering type	9	1.6
ECOG PS		
0-1	383	67.0
2-4	187	32.7
CCR4 test, Yes	569	99.5
CCR4 expression, Positive	556	97.7
Number of prior therapies		
0	15	2.6
1	342	59.8
≥2	214	37.4
Combination therapy		
No	396	69.2
Yes	176	30.8
Type[a]		
CHOP including modified therapy	42	23.9
Oral chemotherapy[b]	35	19.9
Intrathecal therapy	27	15.3
Corticosteroid monotherapy	24	13.6
VCAP/AMP/VECP including modified therapy	21	11.9
Radiotherapy	20	11.4
EPOCH including modified therapy	10	5.7
Other	30	17.0
Allogeneic HSCT after mogamulizumab therapy		
No	523	91.4
Yes	49	8.6
Number of mogamulizumab administrations (Mean 5.4)		
<8	343	60.0
8	222	38.8
>8	7	1.2

ATL, adult T-cell leukemia-lymphoma; CCR4, CC chemokine receptor 4; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone regimen; ECOG PS, Eastern Cooperative Oncology Group performance status; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin regimen; HSCT, hematopoietic stem cell transplantation; VCAP/AMP/VECP, vincristine, cyclophosphamide, doxorubicin, and prednisone/doxorubicin, ranimustine, and prednisone/vindesine, etoposide, carboplatin, and prednisone regimen.

[a]Some patients received more than one type of treatment in combination with mogamulizumab.

[b]Sobuzoxane, etoposide, etc, as mono- or combination therapy.

TABLE 2 Adverse drug reactions

	Overall		≥70 y		<70 y	
ADRs[a]	N	%	N	%	N	%
Total	572	100	238	100	334	100
Overall (Any)	420	73.4	180	75.6	240	71.9
IRRs	172	30.1	68	28.6	104	31.1
Skin disorders	190	33.2	83	34.9	107	32.0
Infections	126	22.0	56	23.5	70	21.0
Cytomegalovirus infection or viremia	47	8.2	16	6.7	31	9.3
Pneumonia	23	4.0	11	4.6	12	3.6
Sepsis	13	2.3	7	2.9	6	1.8
Immune system disorders	27	4.7	1	0.4	26	7.8
GVHD	25	4.4	1	0.4	24	7.2
TLS	16	2.8	8	3.4	8	2.4
Serious[b] (Any)	221	38.6	88	37.0	133	39.8
IRRs	27	4.7	12	5.0	15	4.5
Skin disorders	62	10.8	31	13.0	31	9.3
Infections	84	14.7	35	14.7	49	14.7
Cytomegalovirus infection or viremia	31	5.4	10	4.2	21	6.3
Pneumonia	19	3.3	10	4.2	9	2.7
Sepsis	11	1.9	6	2.5	5	1.5
Immune system disorders	25	4.4	1	0.4	24	7.2
GVHD	22	3.8	1	0.4	21	6.3
TLS	7	1.2	2	0.8	5	1.5

ADRs, adverse drug reactions; GVHD, graft versus host disease; IRRs, infusion-related reactions; TLS, tumor lysis syndrome.
[a]According to the Medical Dictionary for Regulatory Activities/Japanese version terminology, version 20.1.
[b]Following the International Conference on Harmonization guideline E2D.

elderly population. Seemingly, GVHD was reported more in the younger patients, given that, of the 49 patients who received allogeneic HSCT after mogamulizmab therapy, 47 patients (95.9%) were aged <70 years in the surveillance. Of these 49 patients, 50.0% (1/2) of patients aged ≥70 years and 42.6% (20/47) of patients aged <70 years experienced GVHD. Of patients experienced GVHD stratified by ages of ≥70 and <70 years, the median interval period between the last mogamulizumab treatment and the HSCT was 27 and 39 days (range 6-144), respectively.

3.3 | Response

The reported response rates are shown in Table 3. The overall best response rate (complete, uncertified complete, or partial remission) during mogamulizumab therapy and the response rate at the end of therapy were 57.9% and 42.0%, respectively. The best response rates according to disease sites were 82.0% for blood, 55.9% for skin, 45.5% for lymph nodes, 47.9% for liver, 42.3% for spleen, and 38.2% for others. The response rate was highest in blood, followed by skin. A similar trend was observed in the response rates by site at the end of mogamulizumab therapy. For blood lesion, with a best response rate of 82.0% and response rate after therapy of 69.8%, 58.7% (196/334) and 50.6% (169/334) of responders were reported to achieve complete response (CR), respectively. For skin lesion, with a best response rate of 55.9% and response rate after therapy of 40.6%, 26.5% (45/170) and 24.1% (41/170) of responders were reported to achieve CR, respectively. Among patients aged ≥70 vs <70 years, the best response rates were 57.9% vs 57.8%, respectively, and the response rates at the end of therapy were 45.3% vs 39.5%, respectively. Importantly, response rates in the elderly population aged ≥70 years did not tend to be inferior to those in the younger population aged <70 years.

3.4 | Survival

Survival analysis was performed for 500 patients after excluding 23 patients lost to follow-up from the effectiveness analysis population of 523 patients. Events, any death, were observed in 260 (55.0%) out

TABLE 3 Response rate

Age	N	Best response rate during mogamulizumab therapy		Response rate at the end of mogamulizumab therapy	
		N	%	N	%
Overall	523	302	57.9[a]	219	42.0[a]
Disease site					
Blood	334	274	82.0	233	69.8
Skin	170	95	55.9	69	40.6
Lymph nodes	308	140	45.5	102	33.1
Liver	73	35	47.9	24	32.9
Spleen	71	30	42.3	24	33.8
Others	77	29	38.2[a]	20	26.0
Age					
≥70 y	214	124	57.9	97	45.3
<70 y	309	178	57.8[a]	122	39.6[a]

[a]One patient whose response results were not available were excluded from the denominato.

of 473 patients, excluding 27 censored cases due to changing hospitals during the 6-month interval from the first dosing of mogamulizumab. As indicated in Figure 2, the median OS was 5.5 months (95% confidence interval [CI], 4.8-6.4), and when stratified by age, the median OS was 5.5 months in both subgroups of patients aged ≥70 (95% CI, 4.4-7.2) and <70 years (95% CI, 4.5-7.4). The surveillance included 49 patients, with two patients aged ≥70 years and 47 patients aged <70 years who received allogeneic HSCT after mogamulizumab therapy. Their median OS was 7.4 months (95% CI, 5.2-9.9) from the first dosing of mogamulizumab.

3.5 | Univariate and multivariate analyses of prognostic factors

A correlation analysis confirmed that there were no mutual correlations between the sets of variables (data not shown), that is, patients aged ≥70 years were not prone to have poorer PS and more unfavorable laboratory results than patients aged <70 years, and no association existed between survival time and age as a continuous variable (data not shown).

As shown in Table 4, univariate analysis identified PS of 2-4, serum albumin <3.5 g/dL, corrected serum calcium ≥2.75 mmol/L, and serum LDH between >240 and <720 IU/L or serum LDH ≥720 IU/L as statistically significant factors associated with poor prognosis ($P < 0.001$), whereas multivariate analysis identified PS of 2-4 (odds ratio [OR], 3.27; 95% CI, 1.68-6.74; $P < 0.001$), serum LDH between >240 and <720 IU/L (OR, 2.63; 95% CI, 1.52-4.57; $P < 0.001$), and serum LDH ≥720 IU/L (OR, 7.24; 95% CI, 2.84-21.73; $P < 0.001$) as factors associated with poor prognosis. Neither univariate nor multivariate analyses identified age ≥70 years as a prognostic factor.

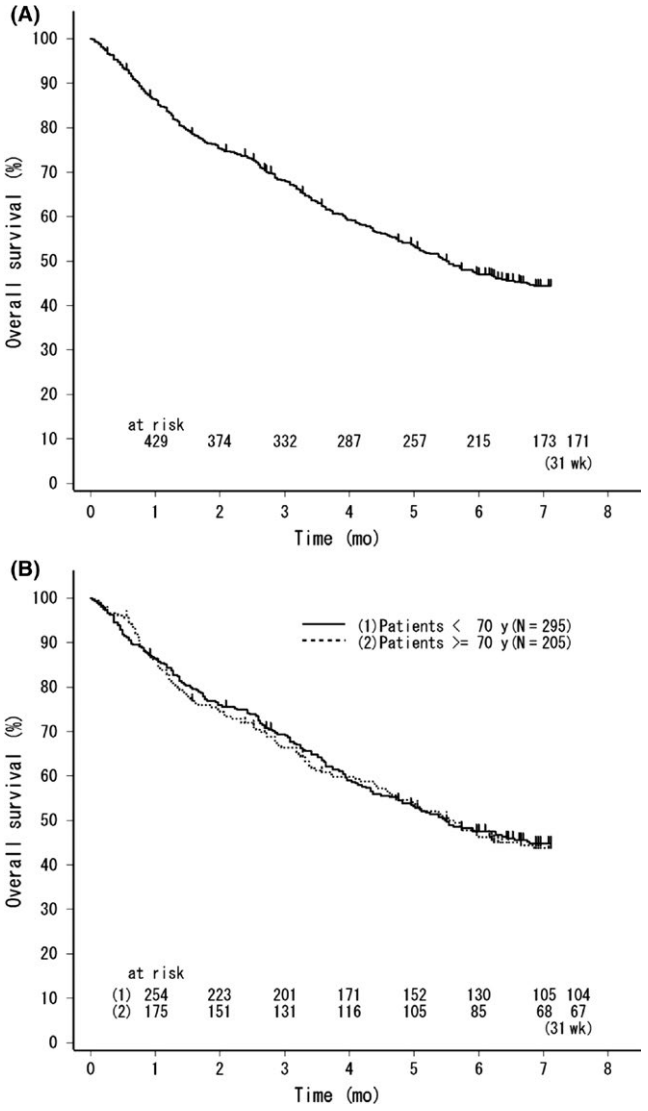

FIGURE 2 Survival curves from the first dosing of mogamulizumab estimated by Kaplan-Meier method. (A) Overall survival curve with a median survival of 5.5 mo, (B) Survival curves stratified by ages <70 and ≥70 y with a median survival of 5.5 mo in both populations

4 | DISCUSSION

The safety profile reported in this surveillance study was similar to that reported in our preliminary report[12] and in previous clinical trials.[10,11,15] IRRs, skin disorders, and infections which were collected as mandatory items were the most common ADRs, and the frequencies for the first two events were less than those reported in the clinical study of patients with relapsed ATL using the same administration schedule of mogamulizumab as used in this surveillance.[11] Less frequent IRRs may be attributed to differences in the monitoring system between the clinical surveillance studies, use of corticosteroids as premedication and antiemetics, and combination with corticosteroid-containing chemotherapy in this surveillance study. Skin disorders are one of the characteristic toxicities of mogamulizumab. An exploratory analysis to determine factors inducing skin

TABLE 4 Prognostic factors

			Univariate analysis				Multivariate analysis (full model)			
Factors	**Variables**	**N**	**Odds ratio**	**95% CI**		***P*-value**	**Odds ratio**	**95% CI**		***P*-value**
Overall	—	367	—	—	—	—	—	—	—	—
PS	0-1	232	1.00				1.00			
	2-4	135	5.23	2.93	9.91	<0.001*	3.27	1.68	6.74	<0.001*
Age	<70 y	221	1.00				1.00			
	≥70 y	146	1.00	0.63	1.59	0.986	0.77	0.45	1.32	0.350
Serum albumin	≥3.5 g/dL	160	1.00				1.00			
	<3.5 g/dL	207	3.60	2.25	5.85	<0.001*	1.73	1.00	3.02	0.052
Corrected serum calcium	<2.75 mmol/L	308	1.00				1.00			
	≥2.75 mmol/L	59	4.64	2.03	12.93	0.001*	2.43	0.98	7.12	0.075
LDH[a]	≤240 IU/L	93	1.00				1.00			
	>240 IU/L, <720 IU/L	199	3.16	1.89	5.31	<0.001*	2.63	1.52	4.57	<0.001*
	≥720 IU/L	75	13.66	5.65	39.60	<0.001*	7.24	2.84	21.73	<0.001*
Subtype	Acute	233	1.00							
	Lymphoma	121	0.92	0.57	1.52	0.753	1.14	0.66	2.01	0.635
	Unfavorable chronic	8	0.36	0.09	1.45	0.162	0.66	0.15	2.86	0.592

CI, confidence interval; LDH, lactate dehydrogenase; PS, performance status.
[a]Used 240 IU/L as the normal upper limit of LDH.
*Statistically significant.

disorders was performed for various backgrounds, and body mass index, ATL subtype, PS, concomitant use of non-anticancer products, and the number of mogamulizumab infusion were statistically associated with the incidence of skin disorders (data not shown). However, except for the number of mogamulizumab infusion described in the previous report,[12] the other factors were not reliable predictors of skin disorders. Skin disorders were late-onset toxicities with a median time to onset of 35.5 days and a maximum time to onset of 230 days. Hence, patients should be monitored carefully not only during mogamulizumab therapy but also after completion of the therapy. In phase 1 and 2 studies of mogamulizumab monotherapy,[10,11,16] CMV infection or viremia, pneumonia, and sepsis were reported in 2.5%, 1.3%, and none of the patients, respectively, while in this surveillance, the incidence was relatively higher (8.2%, 4.0%, and 2.3% of patients, respectively). The differences in incidences may be partly due to the inclusion of patients with longer follow-up time, poor condition or patients who received combination therapy in this surveillance. The incidences of overall and serious ADRs were similar between patients aged ≥70 and <70 years in this surveillance.

The best response rate and response rate at the end of therapy were 57.9% and 42.0%, respectively, indicating that, of the 57.9% of responders, approximately 30% experienced disease progression during treatment. To identify the risk factors for such early progression should be future clinical question. Mogamulizumab also showed similar response rates in both patients aged ≥70 and <70 years in this surveillance as well the other approved therapeutic monoclonal antibodies.[17,18]

The median OS in our surveillance was 5.5 months, which was much shorter than the 13.7 months reported in the phase 2 study of mogamulizumab in patients with relapsed ATL.[11] This could possibly be due to the inclusion of patients with poor conditions such as unfavorable laboratory findings, PS of 3-4, and poor response to prior therapy, as this postmarketing surveillance did not have prespecified eligibility criteria for patients unlike the prospective clinical trial. According to retrospective studies analyzing data from clinical practice for patients with r/r ATL who received various treatments, including mogamulizumab, the median OS was reported to be within the range of 3.9-5.4 months,[19-23] which was consistent with our results. Of note, some of the previous publications suggested a survival benefit of mogamulizumab in patients who received mogamulizumab therapy compared with those who did not[19-21] based on the result from the subgroup analyses; however, the sample sizes of the mogamulizumab-treated populations in these studies were small (<100 patients). In addition, some articles have demonstrated that mogamulizumab administration before allogeneic HSCT may be associated with increased risks of severe GVHD. In fact, we observed that 7 patients died of GVHD among 49 patients who received mogamulizumab before allogeneic HSCT. Our previous result had demonstrated that the rate of grade III-IV acute GVHD was 28.6% and might be higher compared with that of HSCT not preceded by mogamulizumab, suggesting the risk of severe GVHD is increased by administering mogamulizumab before allogeneic HSCT in patients with ATL.[12] However, it should be paid attention to be led by a small number of patients who have many background factors.

According to our multivariate analysis, poor PS of 2-4, low serum albumin <3.5 g/dL, high corrected serum calcium ≥2.75 mmol/L, and high LDH >240 IU/L were associated with poor prognosis, with $P < 0.05$ or of borderline significance. These results were consistent with those of previous publications.[3,13,14] However, age was not associated with survival in this surveillance, contradictory to previous reports using cut-off ages of ≤70 and >70 years.[13] This could be due to the influence of other factors not assessed here. Other studies having small sample sizes,[23,24] which performed univariate analysis for the mogamulizumab-treated population with r/r ATL, have also reported that age >65 or ≥70 years was not associated with poor prognosis.

As previously reported,[12] due to the nature of surveillance, data collection for safety was considered to be less frequent and response assessment less objective since they were assessed by an attending physician during clinical practice. Additionally, our observation period, at the longest of 31 weeks from the first dosing of mogamulizumab, might not be sufficiently long to evaluate OS and analyze prognostic factors even though the events occurred in 55% of patients during this period. Despite these limitations, the surveillance, which prospectively enrolled more than 500 patients with rare disease (r/r ATL), is valuable for future treatment development.

In conclusion, in clinical practice, the overall safety profile of mogamulizumab was manageable in most patients and was consistent with previous reports. The best response rate was reported to be over 50% and the median survival was 5.5 months. The safety profile, response, and survival were not different between patients aged ≥70 and <70 years, and age was not associated with prognosis. In clinical practice, mogamulizumab therapy was confirmed to be a feasible option for the treatment of patients with r/r ATL, including the elderly.

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CONFLICT OF INTEREST

KI reports grants and personal fees from Takeda Pharmaceutical; personal fees from Bristol-Myers Squibb, Celgene, Chugai Pharmaceutical, and Kyowa Hakko Kirin. SY, YT, MI, and TT are employees of Kyowa Hakko Kirin. KT reports grants and personal fees from Ono Pharmaceutical, Celgene, Eisai, Takeda, Mundipharma, Janssen, Kyowa Hakko Kirin, and Chugai Pharmaceutical; personal fees from Zenyaku Kogyo, and HUYA Bioscience International; and grants from GlaxoSmithKline, and AbbVie.

AUTHOR CONTRIBUTIONS

YT and MI contributed to the design and conception of the surveillance; KI and KT contributed to data acquisition; and YT and MI contributed to data analysis. All authors were involved in data interpretation, preparation of the manuscript draft, and review of the manuscript, and approved the final version of the manuscript for submission.

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