Clinical factors to predict outcome following mogamulizumab in adult T-cell leukemia-lymphoma

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Running head
Prognostic factors after mogamulizumab in ATL

Original article

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Abstract

Adult T-cell leukemia-lymphoma (ATL) is a distinct T-cell malignancy caused by human T-cell leukemia virus type-1; the prognosis is very poor. Mogamulizumab (Moga), an antibody drug for CC chemokine receptor type 4, has been introduced for the treatment of ATL. However, the prognosis of relapsed or refractory ATL remains poor and the characteristics of patients who derive clinical benefit from treatment with Moga remain poorly understood. We analyzed the associations of clinical factors with the outcome after Moga treatment. Forty-five patients treated with Moga monotherapy were evaluated. The median age of the patients was 69 years, and 40% were female. The median overall survival (OS) time was 17.6 months and the two-year OS rate was 43.2%. Number of prior therapies and response to prior therapy were predictive clinical features in univariate analysis for OS. Performance status, corrected serum calcium level, serum lactate dehydrogenase level, Japan Clinical Oncology Group-prognostic index (PI), and simplified ATL-PI at Moga treatment were also associated with the prognosis after Moga monotherapy. Improved understanding of the clinical factors predicting the prognosis after Moga may contribute to improved treatment strategies for ATL.

Keywords

ATL, mogamulizumab, prognostic factors

1. Introduction

Adult T-cell leukemia-lymphoma (ATL) is a distinct T-cell malignancy caused by human T-cell leukemia virus type I that is divided into four clinical subtypes [1]. Intensive chemotherapy has been introduced for the treatment of aggressive ATL (acute and lymphoma types); however, the progression-free survival (PFS) at one year is only 28% and most patients experience recurrence or relapse after initial treatment [2]. In relapsed or refractory ATL, the prognosis is extremely poor, with a median survival time (MST) for the overall survival (OS) of less than 4 months after the first salvage therapy with conventional treatments [3].

C-C chemokine receptor type 4 (CCR4) is expressed in about 90% of ATL patients; thus, an antibody targeting CCR4, mogamulizumab (Moga), has been developed as a humanized antibody drug [4,5]. The efficacy of Moga monotherapy for relapsed aggressive ATL was evaluated in a phase II clinical trial, with an overall response rate (ORR) and MST for OS after Moga of 50% and 13 months, respectively, which resulted in the approval of Moga monotherapy for relapsed or refractory ATL in Japan in May 2012 [6].

Several retrospective clinical studies reported improved outcome following Moga therapy in relapsed or refractory ATL [7-9]. However, the median OS after Moga therapy was only approximately 4–5 months, a prognosis improvement that seemed insufficient. If the patients with poor predicted outcome could be identified before Moga treatment, combination with chemotherapy or other treatment strategies such as lenalidomide, which has been approved in Japan for relapsed or refractory ATL, might be treatment options [10]. Thus, an analysis of the clinical factors predicting the outcome after Moga is necessary in order to identify which patients could benefit from Moga-containing treatment. For untreated ATL, several prognostic indexes (PIs) were proposed before the Moga era, which were based on factors assessed at initial diagnosis; i.e., the Japan Clinical Oncology Group (JCOG)-PI or ATL-PI [11,12]. However, the factors or PIs to predict the prognosis have not been fully evaluated in relapsed or refractory ATL because the prognosis is very poor in most patients.

We retrospectively analyzed the results of Moga monotherapy for relapsed or refractory ATL patients in three institutions in Nagasaki prefecture, evaluated the efficacy of Moga monotherapy, and assessed the relationship of the clinical factors and prognosis

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after Moga treatment.

2. Materials and methods

A total of 55 patients with relapsed or refractory ATL were treated with Moga monotherapy at three institutions in Nagasaki prefecture: Nagasaki University Hospital, National Hospital Organization Nagasaki Medical Center, and Sasebo City General Hospital, from June 2012 to December 2015. Patients who received allogeneic hematopoietic stem cell transplantation (allo-HSCT) before (n = 8) or after (n = 2) Moga treatment were excluded from this study because allo-HSCT has significant impacts on the prognosis of ATL. As a result, 45 patients were enrolled in this study and were followed through December 2016 (Figure 1). The expression of CCR4 in ATL cells was confirmed before Moga treatment by flow cytometry or immunohistochemical analysis in all patients. The subtypes of the patients at initial treatments were classified according to Shimoyama's classification [1].

The patients received Moga (1.0 mg/kg) once per week, with eight doses planned if the treatment was effective and tolerable. The response to the treatment was

evaluated according to previously described response criteria [13,14]. The best response

was evaluated regardless of duration in this study. The complication with skin rash was

assessed to evaluate the association with the treatment outcome and the highest grade

during the entire course of Moga therapy was recorded according to the National Cancer

Institute Common Terminology Criteria for adverse events, version 4.0. The median

observation time for the censored cases was 29.1 months (range: 3.0 to 51.2). This

retrospective observational study used existing data and was approved by the ethics

committee of each institution, who waived the requirement for written informed consent.

Statistical analysis

The OS was defined as the period from the date of the first dose of Moga to the

date of death or the last follow-up. The PFS was defined as the period from the date of the

first dose of Moga to the date of progression, relapse or death, whichever occurred first.

The time to next treatment (TTNT) was defined as the period from the date of the first

dose of Moga to the initiation of the next treatment or death, whichever occurred first.

One patient was included in a clinical trial of a novel drug after disease progression after

Moga treatment and was censored at the time of the treatment with the novel drug in the analysis of the OS. The Kaplan-Meier method was used to estimate the probability of the OS and PFS and log-rank tests were used to compare OS and PFS between groups. Differences between the groups were compared using chi-square tests. All analyses were performed using Prism 6 software. P-values <0.05 were considered statistically significant.

3. Results

Patient characteristics

A total of 45 patients were evaluated. The clinical subtypes of ATL at initial treatment included acute type (32 patients), lymphoma (7 patients), chronic (4 patients), and smoldering (2 patients). All of the patients with chronic type had poor prognostic factors, including increased serum lactate dehydrogenase (LDH), increased blood urea nitrogen, or lowered serum albumin levels. The patients with smoldering type had severe skin lesions and received systemic chemotherapy as determined by each physician. The basic characteristics of the patients at Moga treatment are summarized in Table 1. The

median age of the patients was 69 years and 22 (49%) were ≥70 years. Eighteen (40%) of

the patients were female. The European Clinical Oncology Group (ECOG) performance

status (PS) was 2–4 in 16 patients (36%). The median interval period from the initial

treatment to Moga treatments was 6.9 months (range: 1.0–127.0), the median interval

period from prior treatments to Moga treatments was 1.6 months (range: 0.1–98.3), and

the median number of prior therapies was 1 (range, 1–5). Thirty-two patients had

responded (complete response [CR] or partial response [PR]) to the prior therapies, while

13 were non-responders (stable disease [SD] or progressive disease [PD]).

Outcome of Moga monotherapy

In this study, a median of five Moga doses was administered in all patients.

Twenty-six patients did not complete the Moga treatment; the reasons for the

discontinuation of the treatment included the progression of ATL (20 patients), skin

eruption (three patients), infection (one patient), liver dysfunction (one patient), and

patient's preference (one patient). The best responses to Moga monotherapy included CR

(eight patients, 18%), PR (12 patients, 27%), SD (four patients, 8%), and PD (21 patients,

47%), with an overall response rate (ORR, the rates of CR and PR) of 44%. Among the responders, 14 of the 20 patients experienced ATL relapse or recurrence within the follow-up period. According to the disease sites, the ORR was 85% (CR 75% and PR 10%) in the peripheral blood, 45% (CR 20% and PR 25%) in lymph nodes, 58% (CR 29% and PR 29%) in skin lesions, and 45% (CR 30% and PR 15%) in other extranodal lesions.

The survival after Moga therapy is shown in Figure 2. The median PFS duration was 2.1 months (range: 0.1–41.1) and the two-year PFS rate was 13.2% (Figure 2A). The median OS duration was 17.6 months (range: 0.1–51.2) and the two-year OS rate was 43.2% (Figure 2B). The median TTNT duration was 3.2 months (range: 0.1–51.2), and the two-year TTNT rate was 17.0% (data not shown). The OS was significantly better in those who responded to Moga monotherapy (CR/PR) than that in the non-responders (NC/PD); the MST for OS and the two-year OS rate were not reached and were 77.9% in responders, and 6.5 months and 16.9% in non-responders, respectively (p <0.0001). The clinical factors at Moga monotherapy were evaluated for an association with the OS in univariate analysis in order to identify the predictive factors of the outcome; the results are shown in Table 2 and Figure 3. The number of prior therapies

(1 vs. ≥1) and response to prior therapy (CR/PR vs. SD/PD) were significant clinical

features (Figure 3A, B). When the clinical factors included in the JCOG-PI or simplified

ATL-PI were evaluated at Moga treatment, poor ECOG PS (PS 2–4) and elevated

corrected calcium level (≥11 mg/dL) were significant poor prognostic factors (Figure 3C,

D). Patients with low serum albumin (<3.5g/dL) level, increased soluble interleukin 2

receptor (IL2R) level (≥20,000 U/mL), and advanced clinical stage (3–4) tended to have a

worse prognosis, although the differences were not statistically significant. Elevated

LDH level (≥ the upper limit of normal) was also a significant factor for poor prognosis

(Figure 3E). Old age (≥70 years) showed no effects on the OS after Moga monotherapy,

although the patients' basic characteristics showed some difference between the patients

aged ≥70 years and those aged ≤70 years; those with elevated LDH were significantly

lesser in patients aged <70 years than in patients aged ≥70 years (Supplementary Table 1).

When JCOG-PI and simplified ATL-PI were evaluated at Moga treatment, both PIs could

predict the prognosis after Moga monotherapy (Figure 3F, G). The risks of these PIs

evaluated at diagnosis of ATL were not significantly associated with the prognosis after

Moga treatment (data not shown). The number of prior therapies (1 vs. ≥1) was also

significantly associated with better outcomes in the response analysis (hazard ratio [HR]

8.31, 95% confidence interval [CI] 1.58–43.6, p = 0.009), PFS (HR 2.29, 95% CI

1.45–7.00, p = 0.007), and TTNT (HR 2.05, 95% CI 1.14–5.25, p = 0.025) after Moga

treatment. In the TTNT analysis, ECOG PS (0,1 vs. 2-4, HR 1.92, 95% CI 1.05–4.51, p =

0.040) and JCOG-PI (moderate vs. high, HR 2.04, 95% CI 1.17–4.63, p = 0.019) were

also significantly associated with the outcome. In the analysis of responses and PFS, no

other factors were significantly associated with the outcome.

Complications with skin rash and prognosis after Moga

Skin rash has been reported as an important complication and as a clinical feature

associated with better prognosis after Moga treatment [9,15,16]. In this study, skin rash of

all grades occurred in 15 patients (33%), including grades 3–4 in four patients (9%). In 9

out of 15 patients, ATL-related skin lesions were not found by the skin biopsies, whereas

in the remaining six patients, skin rashes were clinically diagnosed as Moga-related,

based on the clinical courses and features of rashes, without performing the skin biopsy.

The OS after Moga treatment was significantly better in the patients with skin rash

complications compared to that in those without skin rash (Figure 4A. complication vs.

no complication, hazard ratio [HR] 0.29, 95% confidence interval (CI) 0.16–0.74, p =

0.006). The complication of skin rash was also associated with the number of the Moga

doses; skin rash was observed in 13 of 25 patients (52%) treated with ≥5 doses of Moga,

compared to only two of 20 patients (10%) treated with ≤5 doses of Moga (≥5 doses vs.

<5 doses, HR 0.10, 95%CI 0.02–0.54, p = 0.004). In addition, the number of Moga doses

was also associated with the outcome; the OS was better in the patients treated with ≥5

doses of Moga than that in those treated with <5 doses (≥5 doses vs. <5 doses, HR 0.24,

95%CI 0.07–0.38, p <0.0001). When the OS was compared in patients who received ≥5

doses of Moga to avoid the bias of Moga doses, the difference in the prognosis was not

statistically significant in patients who developed a skin rash complication compared

with that in the patients who did not, although those with a skin rash tended to show a

better prognosis (Figure 4B. complication vs. no complication HR 0.49, 95%CI 0.15–1.6,

p = 0.24). Comparison of the background of the patients treated ≥5 doses of Moga

revealed that those with skin rash tended to have a worse risk at Moga treatment, such as

PS 2–4, and poor risk in JCOG-PI, compared to the risk among those without skin rash

(Supplementary Table 2). Analysis of patients treated with ≥4 doses of Moga, as in a previous study, revealed a non-significant difference in OS between the patients complicated with skin rash and those not complicated (HR 0.425, 95%CI 0.165–1.174, p = 0.104)[9].

4. Discussion

This study detected several clinical factors as possible prognostic factors for relapsed or refractory ATL treated with Moga monotherapy. The number of prior therapies and the response to prior therapy were identified as predictive clinical features of OS in Moga treatment, suggesting that Moga might be more effective in earlier stages of treatment and in sensitive patients to prior chemotherapies. Some of the clinical factors included in the JCOG-PI or simplified ATL-PI were also identified as predictive markers for the OS and the risk of these PIs also predicted the prognosis after Moga treatment. However, the impact of older age, an important prognostic factor in conventional chemotherapies, was not shown in this and a previous study [9,12]. Thus, treatment with Moga might improve prognosis, especially in elderly ATL patients.

Low serum albumin level (<3.5g/dL), and increased sIL2R level (>10,000

U/mL) were significantly associated with poor prognosis in a previous study [9]. Patients

with these factors also tended to have a worse prognosis in this study, but the difference

was not statistically significant. The small number of patients might partially explain the

difference in findings between these studies, in addition to differences in the backgrounds

of the enrolled patients; for example, patients treated with allo-HSCT were excluded in

this study but were included in the previous study.

The clinical factors detected in our study might be useful for understanding the

results of Moga treatment and the backgrounds of treated patients. The median OS after

Moga treatment (including in combination with chemotherapy) reported in a previous

study was 4.0 months, and shorter than that in the present study. This might be due to

differences in patient backgrounds. The previous study included more patients that had

received two or more regimens prior to Moga therapy and with PS 2–4 at Moga treatment

(42% and 53%, respectively) compared to our study (31% and 36%, respectively).

The association between skin rash and better prognosis after Moga has been

reported previously [9,15]. In this study, the frequency of complication with skin rash

similar to those in previous reports, and there was a statistically significant difference between patients complicated with skin rash and who were not in the analysis of all patients. However, the difference was not significant in the analysis of patients treated with ≥5 doses of Moga. The small number of patients and difference in patient backgrounds might have affected the results. However, the complication of skin rash was associated with the number of Moga doses and the number of Moga doses was also associated with the prognosis after Moga in the present and in previous studies [8,16]. Thus, various biases should be considered in the analysis of the association between skin rash and outcome after Moga treatment and further studies on this issue are warranted, including those on the mechanism of skin rash and the anti-tumor effect of Moga.

This retrospective study had a limited study population and might have included various biases. The sample size was too small to perform multivariate analysis and whether the clinical factors detected in this study were independent prognostic factors was not assessed. Patients treated with allo-HSCT or with a combination of Moga and chemotherapies were not included in this study. Thus, further studies are required to confirm the predictive factors detected in this study, which include these situations.

However, the results of this study provide important information to improve future ATL treatment strategies.

In conclusion, a better prognosis after Moga monotherapy was shown among patients who had responded to prior therapy and those in earlier stages of ATL treatment. The clinical factors at Moga treatment, such as ECOG PS, corrected serum calcium level, and LDH level, as well as JCOG-PI and simplified ATL-PI, could predict the prognosis after Moga monotherapy. Evaluation of these factors at salvage therapy might be helpful to make clinical decisions regarding treatment in patients with relapsed or refractory ATL.

Compliance with ethical standards

Conflict of interest

The authors have no conflict of interest to declare.

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Figure Legends

Figure 1. Patient flowchart

Figure 2. Survival curve after mogamulizumab therapy in all patients (n = 45).

a PFS. The median PFS was 2.1 months and the two-year PFS rate was 13.2%.

b OS. The median OS was 17.6 months and the two-year OS rate was 43.2%.

PFS: progression free survival, *OS:* overall survival

Figure 3. OS after Moga treatment according to clinical factors.

a Number of prior therapies. 1 vs. >1 (n = 31, MST 29.7 months, and two-year OS rate 57.1% vs. n = 14, MST 5.4 months, and two-year OS rate 14.3%).

b Response to prior therapy. CR/PR vs. SD/PD (n = 32, MST 28.5 months, and two-year OS rate 56.3% vs. n = 13, MST 6.2 months, and two-year OS rate 10.3%).

c PS. 0–1 vs. 2–4 (n=29, MST 28.5 months, and two-year OS rate 56.5% vs. n = 16, MST 6.2 months, and two-year OS rate 15.9%).

d Ca. ≤11 vs. >11 (n = 39, MST 19.7 months, and two-year OS rate 48.9% vs. n = 6, MST 3.6 months, and two-year OS rate 0%).

e LDH. ≤ ULN vs. >ULN (n = 13, MST 29.7 months, and two-year OS rate 69.2% vs. n = 32, MST 10.2 months, and two-year OS rate 31.6%).

f JCOG-PI at Moga treatment. Moderate vs. poor (n = 26, MST 29.7 months, and two-year OS rate 64.7% vs. n = 19, MST 6.2 months, and two-year OS rate 13.0%).

g simplified ATL-PI at Moga treatment. Low vs. intermediate vs. high (n = 12, MST 34.4 months, and two-year OS rate 75.0% vs. n = 22, MST 12.7 months, and two-year OS rate 38.6% vs. n = 10, MST 6.2 months, and two-year OS rate 17.5%).

OS, overall survival; *Moga,* mogamulizumab; *MST,* median survival time; *CR,* complete response; *PR,* partial response; *SD,* stable disease; *PD,* progressive disease; *PS,* performance status; *Ca,* corrected calcium; *LDH,* lactate dehydrogenase, *ULN,* upper limit of normal; *JCOG-PI,* Japan Clinical Oncology Group-prognostic index; *ATL-PI,* adult T-cell leukemia-lymphoma prognostic index

Figure 4. Overall survival after mogamulizumab treatment according to skin rash complication.

a OS in patients complicated with skin rash vs. without skin rash (n = 15, MST not reached, and two-year OS rate 70.2% vs. n = 30, MST 8.0 months, and two-year OS rate 31.3%).

b OS in patients who received ≥5 doses of Moga complicated with skin rash vs. without skin rash (n = 13, MST not reached, and two-year OS rate 64.7%, vs. n = 12, MST 28.5 months, and two-year OS rate 54.5%).

OS, overall survival; *MST,* median survival time; *Moga,* mogamulizumab; *Skin rash (+),* complicated with skin rash; *Skin rash (-),* not complicated with skin rash

Table 1. Patient characteristics at mogamulizumab treatment

Characteristics (n=45)	
Age	
Median (range), years	69 (43-89)
Sex	
Female, n (%)	18 (40)
ECOG PS	
0-1, n (%)	29 (64)
2-4, n (%)	16 (36)
WBC count	
Median (range), x 10^9/L	5.94 (1.4-121.4)
Abnormal lymphocyte count	
Median (range), %	4.0 (0-97)
Platelet count	
Median (range), x 10^9/L	130 (11-331)
Corrected calcium (mg/dL)	
<11 mg/dL, n (%)	39 (87)
≥11 mg/dL, n (%)	6 (13)
Serum albumin (g/dL)	
≥3.5 g/dL, n (%)	30 (67)
<3.5 g/dL, n (%)	15 (33)
LDH	
≤upper limit of normal, n (%)	13 (29)
>upper limit of normal, n (%)	32 (71)
sIL2R	
<20,000 U/ml, n (%)	34 (77)
≥20,000 U/ml, n (%)	10 (23)
Interval from initial therapy to mogamulizumab	
Median (range), months	6.9 (1.0-127.0)
Interval from prior therapy to mogamulizumab	
Median (range), months	1.6 (0.1-98.3)
Prior lines of therapy	
Median (range), n	1 (1-5)
Best response to prior therapy	
CR, n (%)	8 (18)
PR, n (%)	24 (53)
SD, n (%)	6 (13)
PD, n (%)	7 (16)

ECOG PS European Clinical Oncology Group performance status, *WBC* white blood

cells, *LDH* lactate dehydrogenase, *sIL2R* soluble interleukin 2 receptor, *CR* complete

response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Table 2. Overall survival after mogamulizumab and clinical factors

Factors	Patients, n	Median OS (month)	HR (95% CI)	p value
Age (year)				
<70	23	19.7	0.897	0.779
≥70	22	12.7	(0.421-1.91)	
ECOG PS				
0-1	29	28.5	2.511	0.013
2-4	16	6.2	(1.294-7.538)	
Clinical stage				
1-2	4	not reached	3.902	0.148
3-4	41	12.7	(0.748-7.027)	
Corrected calcium (mg/dL)				
<11	39	19.7	3.876	0.003
≥11	6	3.6	(2.455-66.42)	
Serum albumin (g/dL)				
≥3.5	30	25.1	1.885	0.102
<3.5	15	10.2	(0.871-5.122)	
LDH				
≤upper limit of normal	13	29.7	2.502	0.035
>upper limit of normal	2	10.2	(1.087-5.122)	
sIL2R (U/mL)*				
<20,000	34	25.1	2.289	0.052
≥20,000	10	6.9	(0.9995-9.247)	
JCOG-PI				
Moderate	26	29.7	3.273	0.001
Poor	19	6.2	(1.828-9.876)	
ATL-PI*				
Low	12	34.4		0.028
Intermediate	22	12.7		
High	10	6.2		
Interval from initial therapy to Moga (months)				
<12	28	20.6	1.454	0.335
≥12	17	8.0	(0.665-3.344)	
Interval from proior therapy to Moga (months)				
≤1	17	6.8	0.599	0.184
>1	28	25.1	(0.248-1.304)	
Number of prior therapies				
1	1	29.7	3.787	0.0002
≥2	14	5.4	(2.445-16.30)	
Response to prior therapy				
CR/PR	32	28.5	2.737	0.007
SD/PD	13	6.2	(1.459-9.597)	

*Sufficient data were not available in one patient

ECOG PS European Clinical Oncology Group performance status, *LDH* lactate

dehydrogenase, *sIL2R* soluble interleukin 2 receptor, *JCOG-PI* Japan Clinical Oncology

Group-prognostic index, *ATL-PI* adult T-cell leukemia-lymphoma prognostic index,

Moga mogamulizumab, *CR* complete response, *PR* partial response, *SD* stable disease,

PD progressive disease, *OS* overall survival, *HR* hazard ratio
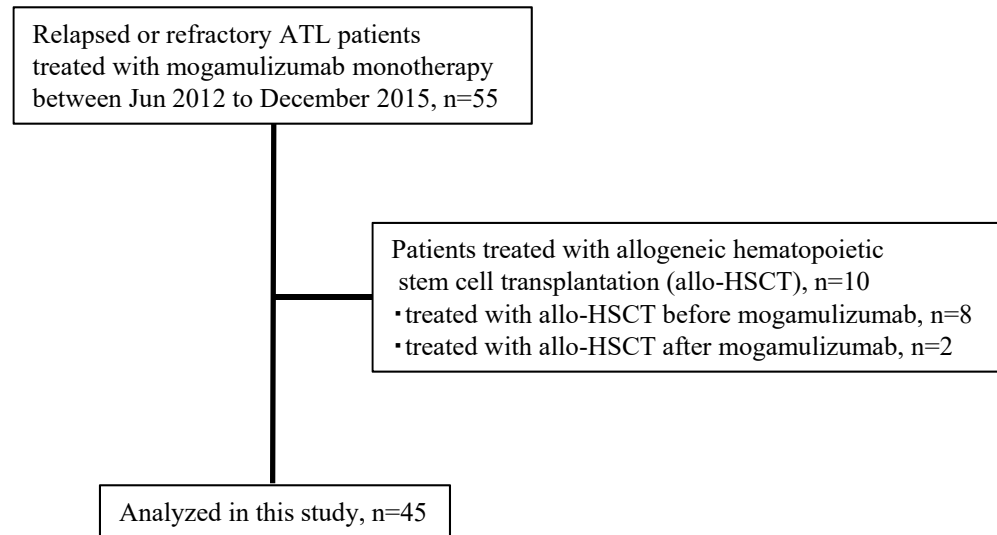
Figure 1. Patient flowchart

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┌─────────────────────────────────────┐
│ Relapsed or refractory ATL patients  │
│ treated with mogamulizumab monotherapy│
│ between Jun 2012 to December 2015, n=55│
└─────────────────────────────────────┘
        │
        │     ┌──────────────────────────────────────────────────┐
        │     │ Patients treated with allogeneic hematopoietic     │
        ├─────│  stem cell transplantation (allo-HSCT), n=10       │
        │     │ ・treated with allo-HSCT before mogamulizumab, n=8  │
        │     │ ・treated with allo-HSCT after mogamulizumab, n=2   │
        │     └──────────────────────────────────────────────────┘
        │
┌───────────────────────────┐
│ Analyzed in this study, n=45│
└───────────────────────────┘
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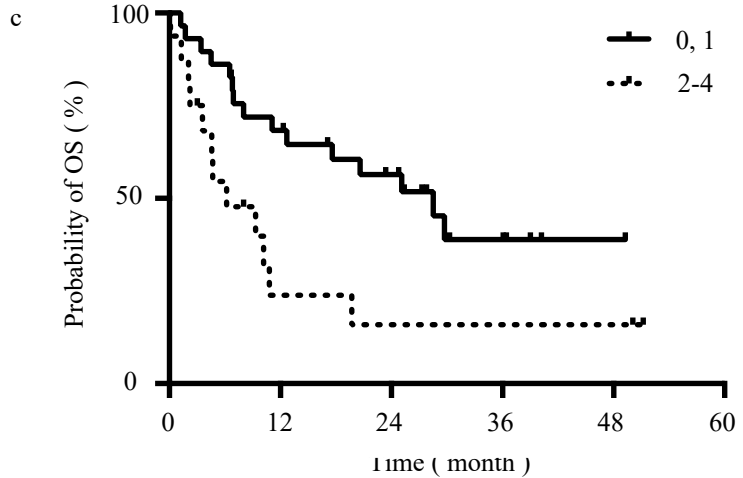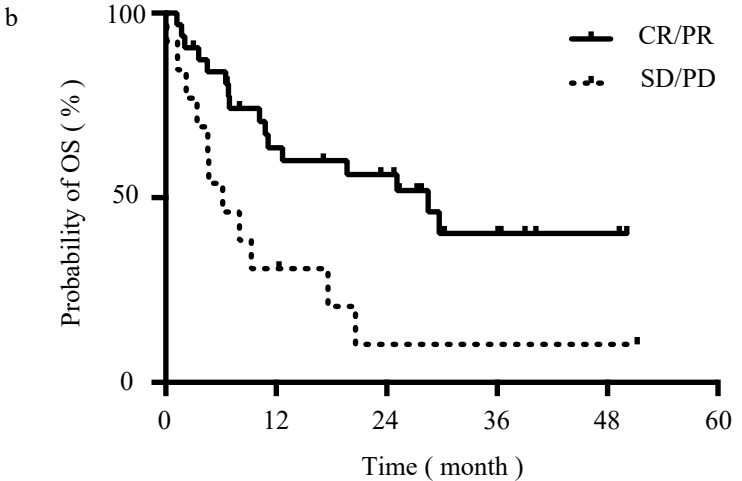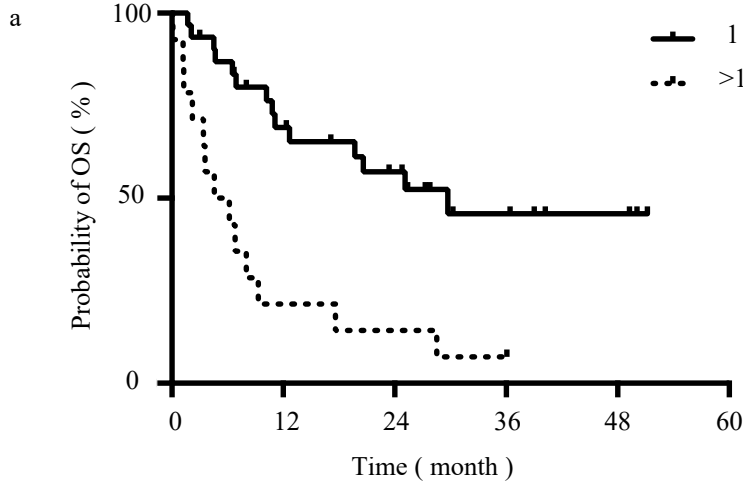Figure 2. Survival curve after mogamulizumab in all patients (n=45) .
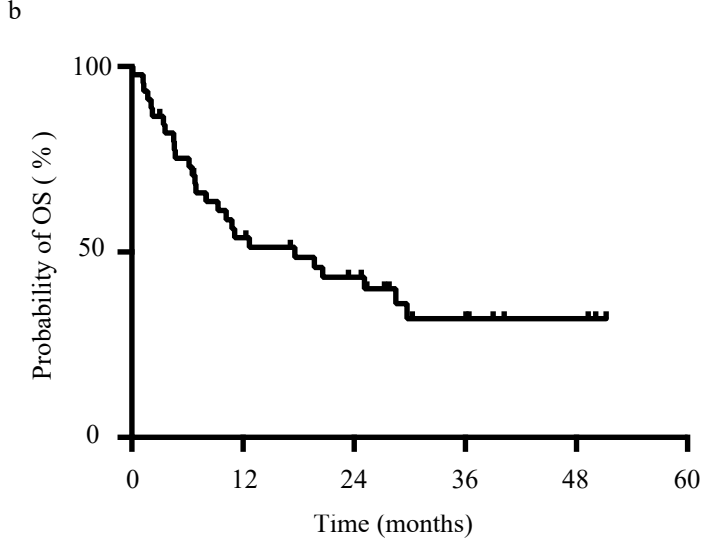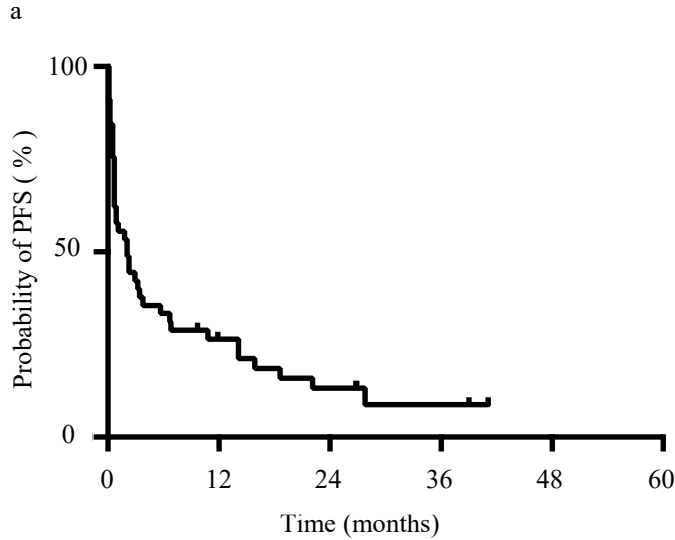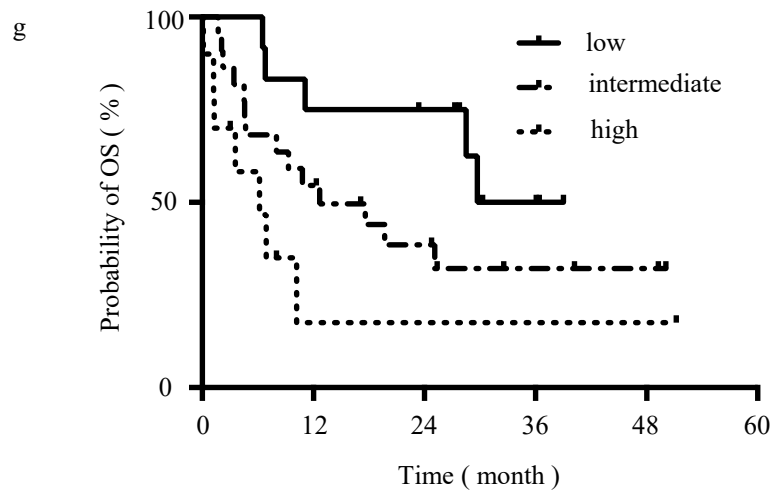
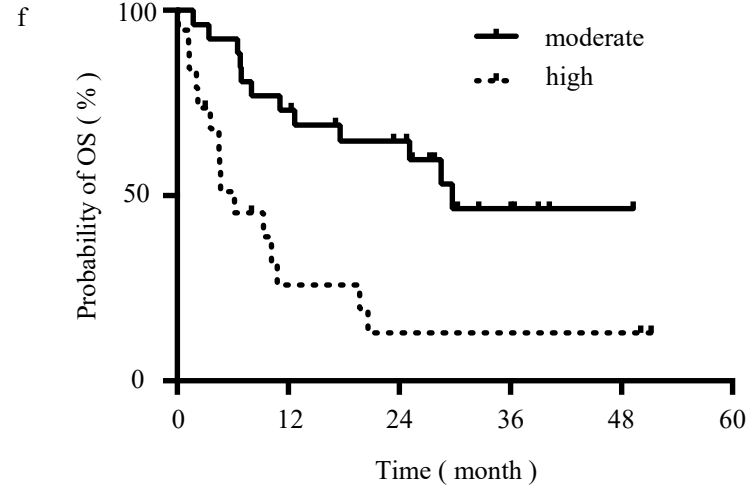Figure 3. OSafter Moga treatment according to clinical factors.
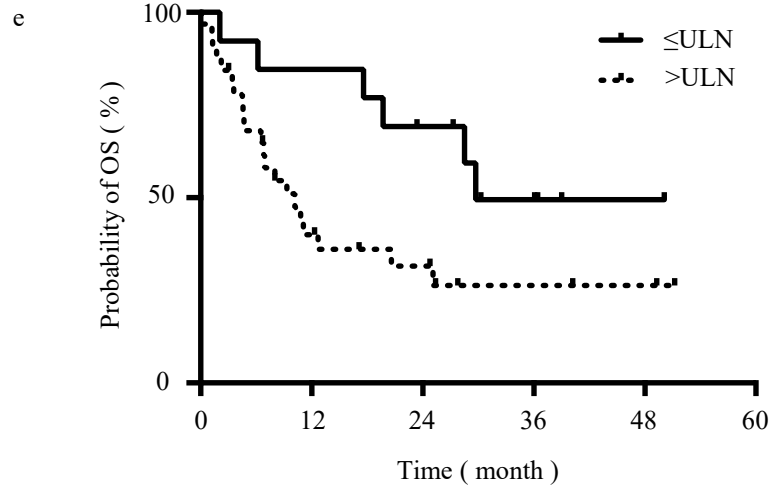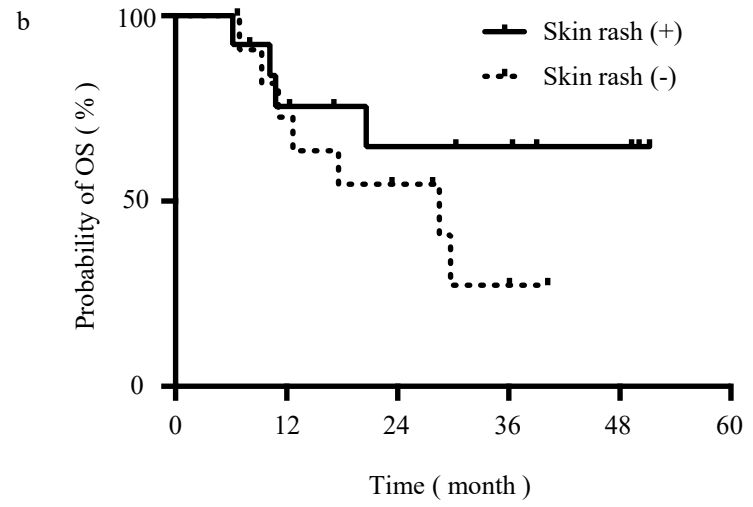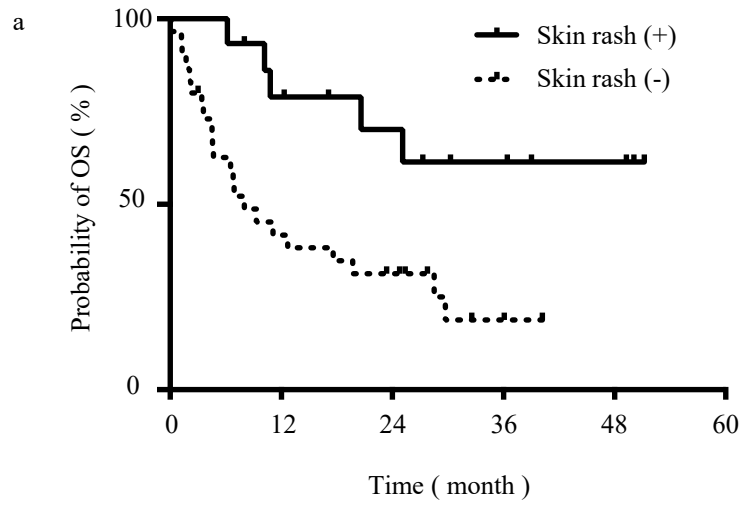
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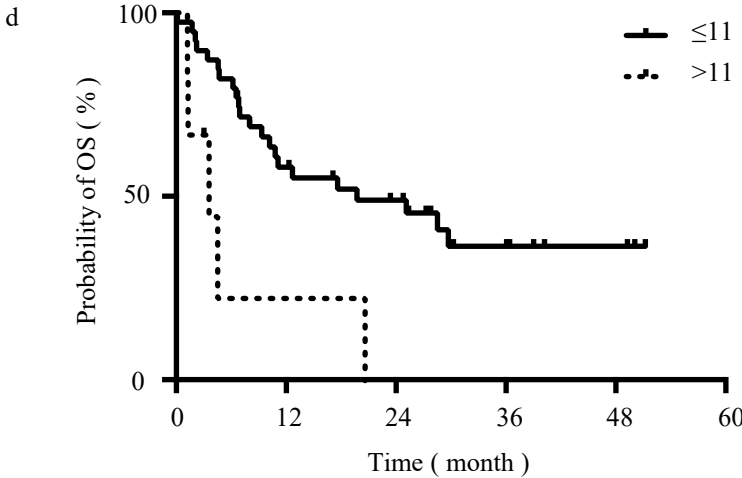
Figure 4. Overall survival after mogamulizumab by skin rash.

Supplementary table 1. Patient characteristics at mogamulizumab treatment by age, <70 years and

≥70 years

Characteristics (n=45)	<70 (n=23)	≥70 (n=22)	HR (95% CI)	P value
Sex				
Male, n (%)	11 (48)	16 (73)	0.344	0.130
Female, n (%)	12 (52)	6 (27)	(0.099-1.194)	
ECOG PS				
0-1, n (%)	14 (61)	15 (68)	0.726	0.758
2-4, n (%)	9 (39)	7 (32)	(0.213-2.477)	
Clinical stage				
1-2, n (%)	1 (4)	3 (14)	0.288	0.346
3-4, n (%)	22 (96)	19 (86)	(0.028-3.01)	
Corrected calcium (mg/dL)				
<11 mg/dL, n (%)	20 (87)	19 (86)	1.053	1.000
≥11 mg/dL, n (%)	3 (13)	3 (14)	(0.189-5.88)	
Serum albumin (g/dL)				
≥3.5 g/dL, n (%)	15 (65)	15 (68)	0.875	1.000
<3.5 g/dL, n (%)	8 (35)	7 (32)	(0.253-3.029)	
LDH				
≤upper limit of normal, n (%)	10 (43)	3 (14)	5.128	0.047
>upper limit of normal, n (%)	13 (57)	19 (86)	(1.182-22.250)	
sIL2R				
<20,000 U/mL, n (%)	16 (73)	18 (82)	0.593	0.721
≥20,000 U/mL, n (%)	6 (27)	4 (18)	(0.141-2.485)	
Interval from initial therapy to mogamulizumab				
<12months	14 (61)	14 (64)	0.887	1.000
≥12months	9 (39)	8 (36)	(0.266-2.972)	
Prior lines of therapy				
1	15 (65)	16 (73)	0.703	0.749
≥2	8 (35)	6 (27)	(0.197-2.508)	
Best response to prior therapy				
CR/PR, n (%)	17 (74)	15 (68)	1.322	0.749
SD/PD, n (%)	6 (26)	7 (32)	(0.363-4.818)	

HR Hazard Ratio, *ECOG PS* European Clinical Oncology Group performance status, *LDH* lactate

dehydrogenase, *sIL2R* soluble interleukin 2 receptor, *CR* complete response, *PR* partial response,

SD stable disease, *PD* progressive disease

Supplementary table 2. Characteristics of the patients treated with ≥5 doses of mogamulizumab by skin rash

	Skin rash		
	(+)	(-)	
Total	13	12	p value
Age (year)			
≥70, n (%)	7 (54)	7 (58)	1.000
ECOG PS			
2-4, n (%)	6 (46)	1 (8)	0.073
Corrected calcium (mg/dL)			
≥11, n(%)	1 (7)	0 (0)	1.000
Serum albumin (g/dL)			
<3.5, n (%)	6 (46)	2 (17)	0.207
LDH			
>upper limit, n (%)	8 (62)	7 (58)	1.000
sIL2R (U/mL)*			
≥20000, n (%)	3 (23)	1 (8)	0.590
JCOG-PI			
Poor, n (%)	7 (54)	1 (8)	0.030
ATL-PI*			
Low, n (%)	3 (25)	6 (50)	0.317
Intermediate, n (%)	5 (42)	5 (42)	
High, n (%)	4 (31)	1 (8)	
Interval from Initial therapy to Moga (months)			
≥12 months, n (%)	2 (15)	6 (50)	0.097
Number of prior therapies			
≥2, n (%)	1 (7)	4 (33)	0.160
Response to prior therapy			
SD/PD, n (%)	4 (31)	2 (17)	0.645

*Sufficient data were not available in one patient

ECOG PS European Clinical Oncology Group performance status, *LDH* lactate dehydrogenase, *sIL2R* soluble interleukin 2 receptor, *JCOG-PI* Japan Clinical Oncology Group-prognostic index, *ATL-PI* adult T-cell leukemia-lymphoma prognostic index, *Moga* mogamulizumab, *SD* stable disease, *PD* progressive disease