Clinical Features, Pathological Features, and Treatment Outcomes of 22 Patients with Aggressive Adult T-cell Leukemia-lymphoma Treated with a Humanized CCR4 Antibody (Mogamulizumab) at a Single Institution during a 6-year Period (2012-2018)

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Abstract:
Objective To elucidate the clinical impact of humanized CCR4 antibody (mogamulizumab) on adult T-cell leukemia-lymphoma (ATL), we retrospectively analyzed the clinical and pathological features and treatment outcomes of aggressive ATL.
Methods Twenty-two patients (median age: 65 years) with aggressive ATL (acute- [n=16] or lymphoma-type [n=6]) had their characteristics analyzed. All cases were treated with mogamulizumab at our institution from 2012 to 2018. In addition, we subjected 14 specimens of ATL to histological, immunological, and genetic analyses.
Results Regarding the patient outcomes, the overall response rates were 68.1% and 31.8% after 4 and 8 courses (or after the final courses), respectively. The median overall survival (OS) was 95.5 days, while the OS rates at 6 and 12 months were 31.5% and 21.1%, respectively. Concerning patient pathological characteristics, 6 of the 14 patients examined (42.9%) had CCR4 mutations. Regarding the clinicopathological findings related to the mogamulizumab response, notably, the cases with somatic CCR4 mutation tended to have a poorer response (16.7%) than those with wild-type CCR4 (62.5%) after 4 cycles of mogamulizumab. Furthermore, the CCR4 global score tended to be higher in the responder cases than in the non-responder cases.
Conclusion The present findings suggest that the CCR4 expression may be related to the mogamulizumab response, although no other significant predictive markers were identified in this study. Further studies will be needed in order to identify more markers related to the mogamulizumab response.

Key words: ATL, mogamulizumab, somatic CCR4 mutation, NS mutation and FS mutation, overall response rate, overall survival

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Introduction

Adult T-cell leukemia-lymphoma (ATL) is a T-cell neoplasm induced by human T-cell leukemia virus type I (HTLV-I) (1-4). For a quarter of a century, the discovery and establishment of the clinical entity of ATL, its pathogenesis, and remarkable progress in its treatment, including chemotherapy and allogeneic hematopoietic stem cell transplantation (allo-HSCT), have been achieved worldwide thanks to skilled research pioneers and clinicians (1-18). However, despite remarkable advances in the pathogenesis and treatment of ATL, the prognosis remains poor.

A newly developed humanized CCR4 antibody (mogamulizumab) was recently reported to be effective for ATL as a molecular-targeted therapy. A phase 2 trial, post-marketing surveillance of mogamulizumab, and case-series reports in clinical practice have confirmed the safety and adverse effects of the drug for ATL treatment (19-26). The mechanism of action of mogamulizumab on ATL involves antibody-dependent cellular cytotoxicity and natural killer cells (27).

In addition, mogamulizumab has also been reported to be effective in immunotherapy via immune check-point inhibition by increasing the numbers of cytotoxic T-cells under conditions of depletion of effector-type regulatory T-cells (Tregs) (28). Gain-of-function mutations in somatic CCR4 in ATL have recently been reported from the viewpoint of conditions (19). Before the administration of mogamulizumab, we confirmed the expression of CCR4 on ATL cells by flow cytometry or an immunohistochemical analysis in all of the ATL patients. Cases 1-14 were described in our previous report (23).

Adverse events (AEs) were evaluated using the National Cancer Institute Common Terminology Criteria for AEs, version 3.0, according to a phase II trial.

Tissue specimens, histology, and immunohistochemistry

Pathological analyses

Fourteen samples, including 1 skin, 2 bone marrow, and 11 lymph nodes lesions (LNS), were available for the pathological analyses. Tissue samples were fixed in 10% formalin, embedded in paraffin, cut into 2-μm-thick sections, and stained with hematoxylin and eosin (H & E) (32, 33). After the histological assessment, a tissue microarray was created containing the 14 samples in a formalin-fixed paraffin block, with each sample placed in a 2-mm (diameter) area. These tissue microarray specimen slides were prepared according to a previous study. Formalin-fixed paraffin sections were used for immunoperoxidase studies performed using the avidin-biotin-peroxidase complex method. The following monoclonal antibodies were used: anti-CCR4 (Poteliego test: Kyowa Medex, Tokyo, Japan), anti-Fox P3 (SP97; Abcam, Tokyo, Japan), anti-PD-1 (NAT 105; Abcam), and anti-human leukocyte antigen (HLA) class I ABC antibody (EMR 1161 (2); Abcam). For the immunohistochemical analysis, CCR4-immunolabelled sections were also evaluated semiquantitatively using a scoring scale based on the extent and intensity of staining (30). The extent and intensity scores were then multiplied to yield a unique global score, range 0-
Table 1. Patient and disease characteristics in ATL cases.

**Clinical characteristics (n=22)**

| Characteristic | Value       |
|----------------|-------------|
| Age median (range) | 65 (46-80) |
| Sex Male (%) | 8 (36) |
| Subtype Lymphoma | 6 |
| Acute | 16 |
| sATL-PI Low | 0 |
| Intermediate | 13 |
| High | 9 |
| Median numbers of prior regimens including allo-SCT (range) | 1 (1-3) |
| Allo-SCT (%) | 1 (5) |
| Clinical status prior mogamulizumab PR | 3 |
| PD | 19 |
| Response after 4 cycles of mogamulizumab CR | 8 |
| PR | 7 |
| SD | 2 |
| PD | 5 |
| Best over all response during mogamulizumab CR | 8 |
| PR | 7 |
| SD | 2 |
| PD | 5 |

**Pathological findings (n=14)**

| Finding | Value       |
|---------|-------------|
| CD3, positive (%) | 13 (93) |
| CD4, positive (%) | 11 (79) |
| CD8, positive (%) | 2 (14) |
| FOXP3, positive (%) | 5 (36) |
| CCR4, positive (%) | 12 (86) |
| CCR4 global score, average (range) | 6.5 (0-12) |
| HLA class1, positive (%) | 10 (71) |
| HLA class2, positive (%) | 6 (43) |
| PDL1, positive in neoplastic cells (%) | 2 (14) |
| PDL1, positive in microenvironment (%) | 7 (50) |
| PD-1 positive TIL, counts/HPF average (range) | 3.8 (0-20) |

sATL-PI: simplified Adult T-cell leukemia/lymphoma prognostic index, SCT: stem cell transplantation, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, TIL: tumor-infiltrating lymphocyte

Mutation analyses for CCR4

We extracted tumor DNA from the available 14 tissue samples using the GeneRead DNA FFPE Kit (QIAGEN, Tokyo, Japan) following the manufacturer’s protocol. According to our previous report, the primer sets used for the polymerase chain reaction (PCR) analysis and sequencing analyses were the same (30). Mutation analyses were performed, and Sanger sequencing was applied to detect mutations in the 14 ATL case samples, as previously reported (30).

Statistical analyses

The Kaplan-Meier method was used to estimate the probabilities of surviving after mogamulizumab treatment (overall survival [OS]). The OS was defined as the time from the first day of mogamulizumab administration to the day of death or last follow-up. We excluded the patients who underwent allo-HSCT after mogamulizumab therapy from the survival analysis (Supplemental Table 1). Fisher’s exact test was used to examine the CCR4 mutation and treatment response for mogamulizumab, yielding statistical significance at p <0.05.
Results

Clinical characteristics of ATL patients

The clinical characteristics of the ATL cases are summarized in Table 1. The patients (median age: 65 years old) were classified as having acute (n=16) or lymphoma-type (n=6) ATL. Previous treatment regimens included CHOP, VCAP-AMP-VECP, DeVIC, CHASE, THP-COP, and GDP, and the analyzed patients had received a median of 1 regimen (range: 1-3). Previous disease responses to treatments were partial remission (n=3) and progressive disease (n=19). The overall response rate (ORR), OS, and adverse effects in the present study were consistent with our previous report. The ORRs were 68.1% and 31.8% after 4 and 8 courses (or after the final courses), respectively. The median OS rates at 6 and at 12 months were 31.5% and 21.1%, respectively. All of the patients with acute-type ATL who showed a response to treatment had an early response. Notably, 12 of the 22 ATL patients showed a somewhat prolonged survival (>100 days). Relapse or disease progression in the peripheral blood, central nervous system, lymph nodes, skin, and/or bone occurred within a relatively short period after treatment in some of the analyzed cases. Four cases maintained a CR status with a median survival time of 2.5 years, although 2 of them underwent allo-HSCT after mogamulizumab treatment (Supplemental Table 1). The adverse effects were tolerable and included lymphopenia, cytomegalovirus infection, and skin rash.

Pathological characteristics of ATL patients

To elucidate the poor outcome of ATL, we investigated 14 specimens (13 LNS and 1 skin) of ATL classified as having acute- (n=9) or lymphoma-type (n=5) ATL using histological, immunological, and genetic analyses. The somatic CCR4 mutation sites of ATL cases are shown in Fig. 1A. Six of the 14 analyzed patients (42.9%) had somatic CCR4 mutations (nonsense [NS] in 4 cases and frame shift [FS] in 2 cases). The mutated site of CCR4 was point 6 in all cases (Fig. 1A and Supplementary Table 2). Case 3 had NS mutations at both Y331 and Q336. As Case 14 had a silent muta-
In the immunohistochemical studies, the expression patterns of several antigens were consistent with those in previous reports (Table 1) (32, 33). We previously found that CCR4 mutations, especially NS mutations of CCR4, were related to the expression (30). Indeed, the CCR4 expression in cases with NS tended to be lower than in the cases with

**Clinicopathological findings related to mogamulizumab response**

CCR4 mutations have been reported to be predictive markers of the mogamulizumab response (31). However, the OS was not significantly different between the cases with somatic CCR4 mutations and those with wild-type CCR4 in the present study (Fig. 2A). In addition, stratification by the CCR4 mutation status did not reflect the clinical course (Fig. 2B). Notably, cases with somatic CCR4 mutations tended to have a poorer response (16.7%) than those with wild-type CCR4 (62.5%) after 4 cycles of mogamulizumab (Fig. 2C). In our study, the best overall response was consistent with the treatment response after 4 courses of mogamulizumab, but almost all relapsed later.

In order to analyze the predictive markers related to the mogamulizumab response, we retrospectively compared the clinical laboratory findings, histological findings, and somatic CCR4 mutation between the responders (CR + PR) and non-responders (SD + progressive disease [PD]) (Table 2). Although the difference was not significant, the CCR4 global score tended to be higher in the responders than in the non-responders, suggesting that the intensity and proportion of the CCR4 expression may be related to the response. Notably, 1 case (Case 14) that did not express CCR4 (10% of tumor cells) showed a CR after mogamulizumab and remained alive without disease.

**Discussion**

In the present study, we analyzed the clinicopathological findings, including the CCR4 mutations, in ATL cases treated with mogamulizumab therapy. The best overall response rate was 68% in the current study, with 2 of the analyzed cases living without any disease for more than 3 years. These findings were consistent with those of a phase II study showing a 50% response rate with acceptable toxicity profiles (19). The CCR4 expression may be related to the mogamulizumab response, but no other significant predictive markers were identified in the current study.

We showed that CCR4 mutations did not act as predictive markers in the current study. Given that the identified CCR4 mutations were consistent with those noted in previous reports, including our own (29-31, 34), these mutations are considered gain-of-function mutations. Our previous study showed that the prognosis in ATL cases with an FS mutation of CCR4 was significantly poorer than in other cases without mogamulizumab treatment (30). The current results suggest that this mutation may provide certain benefits under mogamulizumab therapy, as previously reported (31), as the FS mutation seemed to have no adverse effect on the prognosis. However, the prominent predictive impact of

Figure 2. A) Kaplan-Meier plot of the overall survival among acute and lymphoma ATL cases, stratified by the presence of a CCR4 mutation. B) Kaplan-Meier plot of the overall survival among acute and lymphoma ATL cases, stratified by the CCR4 status. C) The examination of the relationship between the clinical response to mogamulizumab and the CCR4 status. The difference was analyzed by Fisher’s exact test.
**Table 2. Clinicopathological and Genomic Findings Based on the Clinical Responses to Mogamulizumab.**

| Clinical characteristics (n=22) | Reponder group (CR+PR) | Non-Responder group (SD+PD) | p value |
|-------------------------------|------------------------|----------------------------|---------|
| Age Median (range) | 67 (46-79) | 63 (53-80) | 0.48 |
| Sex | | | |
| Male (%) | 5 (33) | 3 (43) | 0.334 |
| Subtype | | | 0.648 |
| Lymphoma | 3 | 3 | |
| Acute | 12 | 4 | |
| sATL-PI | | | 0.523 |
| Low | 0 | 0 | |
| Intermediate | 8 | 5 | |
| High | 7 | 2 | |
| Clinical status prior mogamulizumab | | | |
| PR | 3 | 0 | |
| PD | 12 | 7 | |

| Pathological characteristics (n=14) | (n=8) | (n=6) | |
| CD3, positive (%) | 7 (88) | 6 (100) | 1 |
| CD4, positive (%) | 6 (75) | 5 (83) | 1 |
| CD8, positive (%) | 2 (25) | 0 (0) | 0.473 |
| FOXP3, positive (%) | 3 (38) | 2 (33) | 1 |
| CCR4, positive (%) | 7 (86) | 5 (83) | 1 |
| CCR4 global score, average (range) | 8.4 (1-12) | 4.2 (0-12) | 0.099 |
| HLA class1, positive (%) | 6 (75) | 4 (67) | 1 |
| HLA class2, positive (%) | 3 (38) | 3 (50) | 1 |
| PDL1, positive in neoplastic cells (%) | 1 (13) | 1 (17) | 1 |
| PDL1, positive in microenvironment (%) | 4 (50) | 3 (50) | 1 |
| PD-L1 positive TIL, counts/HPF average (range) | 1.9 (0-10) | 6.4 (0-20) | 0.156 |
| CCR4 mutation | 2 (25) | 4 (67) | 0.277 |

**CCR4** mutations identified in the previous study (31) was not found in our analysis. It is well recognized that complete remission rates of mogamulizumab therapy vary among target lesions, being high in peripheral blood and low in lymph nodes (19). All of the cases analyzed in the current study had lymph node lesions, and two of the CCR4-mutated cases showed PD at the lymph node lesions after four cycles of mogamulizumab treatment. This finding may indicate that tumors in lymph nodes are not sensitive to mogamulizumab, even in cases with **CCR4** mutations. It is therefore speculated that the patient background, especially the tumor involvement sites, may differ between the previous (31) and current studies. We believe that the full impact of **CCR4** mutations on the mogamulizumab response is still unclear, and further studies should be performed.

The CCR4 expression may also reflect the response, as responders to mogamulizumab tended to show a higher CCR4 global score than non-responders. Although our previous data showed that cases with NS mutations had higher CCR4 global scores than other cases (30), such differences were not detected in the present study (Fig. 1B). Other studies have also revealed that CCR4 mutations cause impaired internalization of CCR4, leading to a sustained CCR4 expression (29, 34). Indeed, one case (case 21) with an NS mutation (Q336) lacked CCR4 expression in the LNS of our immunohistochemistry study, even though CCR4 expression was detected in the peripheral blood by a flowcytometric analysis; no such cases were detected in our previous study (30). Another case with NS mutations (Y331 and Q336) had CCR4 expression, but the expression was quite low. In line with the findings of a previous study (19), those cases showed PD only in the lymph node lesions during mogamulizumab treatment. Umino et al. previously found that clonal evolution of ATL occurred in lymph nodes, and a fraction of these clones was detected in the peripheral blood according to a genomic analysis (35). The current case also suggests a difference in the clones between the lymph nodes and peripheral blood. In order to clarify the utility of CCR4 mutations as a predictive marker concerning the response to mogamulizumab treatment, multiple samples from identical cases and a detailed analysis of CCR4 mutations should be performed in the future.

Of note, we detected one case (case 14) without **CCR4** mutation that showed a good response to mogamulizumab, although the case had low levels of CCR4, HLA-I, HLA-II, and tumor infiltrating lymphocytes. Mogamulizumab exerts antibody-dependent cellular cytotoxicity on ATL cells (36), but the current results suggest that other mechanisms may...
underlie the anti-ATL effect of mogamulizumab.

In conclusion, no apparent predictive markers for mogamulizumab sensitivity were identified, although 68% of the relapsed ATL cases showed a response. Further studies will be needed in order to identify more markers related to the mogamulizumab response. Our current results also suggest the importance of preparing several validation cohorts to determine the definite impacts of genomic alterations on the clinical courses and molecular aspects.

The authors state that they have no Conflict of Interest (COI).

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