Clinical Impact of a Humanized CCR4 Antibody (Mogamulizumab) in 14 Patients with Aggressive Adult T-cell Leukemia-lymphoma Treated at a Single Institution During a Three-year Period (2012-2014)

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Abstract

Objective  We elucidated the effectiveness of a humanized CCR4 antibody (mogamulizumab) on adult T-cell leukemia-lymphoma (ATL), which typically has a poor outcome.

Methods  We retrospectively analyzed 14 patients with aggressive ATL who had been treated at our institution with weekly cycles of mogamulizumab for eight weeks from 2012-2014.

Results  The patients (median age: 63 years old) were classified as having acute- (n=10) or lymphoma-type (n=4) ATL. The prior treatment regimens consisted of CHOP, VCAP-AMP-VECP, DeVIC and CHASE, with an average of two courses (range: 1-4). The prior disease responses were partial remission (n=3) and progressive disease (n=11). The treatment was administered in the primary refractory setting (n=8), for relapse (n=2), or as bridging therapy before hematopoietic stem cell transplantation (n=4). The overall response rates were 64% and 43% after four and eight cycles (or after the final cycles), respectively. The median overall survival (OS), OS rate at six months and OS rate at 12 months were 66 days, 41.7% and 20.8%, respectively. All of the patients with acute-type ATL who showed a response to treatment had an early response. Notably, six of the 14 ATL patients showed somewhat prolonged survival (>100 days). However, 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. The adverse effects were tolerable, and included lymphopenia, cytomegalovirus infection and skin rash.

Conclusion  Mogamulizumab therapy resulted in an early and high remission rate and somewhat prolonged survival in patients with refractory ATL. However, the duration of remission was short, and there was early relapse and disease progression. This study may show the current impact of mogamulizumab in clinical practice.

Key words: adult T-cell leukemia-lymphoma, mogamulizumab, refractory ATL, early and high remission, survival, relapse and progression

(Intern Med 55: 1439-1445, 2016)
(DOI: 10.2169/internalmedicine.55.6312)
Introduction

Adult T-cell leukemia-lymphoma (ATL) is caused by the clonal proliferation of human T-cell leukemia virus type 1 (HTLV-1)-infected CD4 T cells (1, 2). Approximately 2-5% of HTLV-1 carriers develop ATL after a latent period that can last for decades, although the mechanism underlying leukemogenesis has not yet been clarified (3). In general, acute- and lymphoma-type ATL progress rapidly, and the outcomes are generally poor, with death occurring within six to 12 months (4). The disease was first described by Uchiyama in 1977, and remarkable progress in the understanding and treatment of the disease was made following the development of Shimoyama diagnostic criteria in 1991. Thereafter, clinical reports by the Japan Clinical Oncology Group-Lymphoma Study Group were published in 2001 and 2007, and treatment recommendations were developed by the International Consensus Meeting of ATL researchers in 2009 (1, 4-10). Moreover, hematopoietic stem cell transplantation (HSCT) resulted in an improvement of the overall survival (OS) rate at three years to 30-40% (11-15).

Despite these remarkable advances, the mortality statistics from the Ministry of Health, Labour and Welfare of Japan show that approximately 1,000 people die annually from ATL, a statistic that has remained unchanged for at least the past decade (16). A retrospective study performed at our institution yielded similar findings (17).

The findings of recent studies showed that CC chemokine receptor 4 (CCR4) is expressed on normal T helper type 27 and regulatory T cells, and in certain types of T cell neoplasms, including ATL and peripheral T cell lymphoma (PTCL). Ishida et al. recently conducted a study that showed that a newly developed humanized CCR4 antibody (mogamulizumab) was effective against ATL in a phase-2 trial (18). Based on those findings, CCR4 antibody therapy is currently available for use in patients with refractory ATL in Japan (18).

In the present study, we report the clinical impact of mogamulizumab treatment on 14 patients with aggressive ATL who were treated at Miyazaki Prefectural Miyazaki Hospital over the last three years.

Materials and Methods

A total of 45 patients were diagnosed with ATL at Miyazaki Prefectural Miyazaki Hospital from January 1, 2012 to November 20, 2014.

According to Shimoyama’s criteria for the diagnosis of ATL, which are based on clinical features and prognostic factors (4), we classified the 45 cases of aggressive ATL into acute- (27 cases), or lymphoma-type ATL (18 cases).

The selection of the patients for mogamulizumab therapy was based on the following criteria: those with disease that was refractory to the initial treatment, those who required salvage therapy, and those who showed difficulty in continu-
### Table.
The Clinical Features and Treatment Outcomes of 14 ATL Cases Treated with Mogamulizumab.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>ATL diagnosis</th>
<th>Prior treatments</th>
<th>Response</th>
<th>Mogamulizumab administration</th>
<th>Response after 4 cycles</th>
<th>Response after 8 cycles or final cycles</th>
<th>Relapse or progression sites after mogamulizumab</th>
<th>The days of the relapse or progression (days)</th>
<th>Adverse effects (hematological AEs)</th>
<th>Adverse effects (non-hematological AEs)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>70</td>
<td>F</td>
<td>Acute type</td>
<td>VCAP-AMP-V-VECP (1) CHOP (2)</td>
<td>PD</td>
<td>(8) CR (PB:CR)</td>
<td>CR</td>
<td></td>
<td>CNS relapse</td>
<td>52</td>
<td>Lymphopenia (grade 3)</td>
<td>-</td>
<td>Death 66 days</td>
</tr>
<tr>
<td>Case 2</td>
<td>48</td>
<td>F</td>
<td>Acute type</td>
<td>CHOP (3)</td>
<td>PD</td>
<td>(6) PR (PB:PR)</td>
<td>PD (PB relapse)</td>
<td></td>
<td></td>
<td>29</td>
<td>-</td>
<td>-</td>
<td>Death 36 days</td>
</tr>
<tr>
<td>Case 3</td>
<td>74</td>
<td>F</td>
<td>Acute type</td>
<td>CHOP (1)</td>
<td>PD</td>
<td>(8) CR (PB:CR)</td>
<td>CR (PB:CR)</td>
<td></td>
<td>Skin relapse</td>
<td>120</td>
<td>Lymphopenia (grade 3)</td>
<td>-</td>
<td>Death 360 days</td>
</tr>
<tr>
<td>Case 4</td>
<td>61</td>
<td>F</td>
<td>Acute type</td>
<td>CHOP (3) DeVIC (1)</td>
<td>PD</td>
<td>(4) PD (bone tumor progression)</td>
<td>PD</td>
<td></td>
<td>Bone tumor progression</td>
<td>22</td>
<td>-</td>
<td>-</td>
<td>Death 41 days</td>
</tr>
<tr>
<td>Case 5</td>
<td>80</td>
<td>M</td>
<td>Lymphoma type</td>
<td>CHOP (1) DeVIC (1) CHASE (1)</td>
<td>PD</td>
<td>(4) PD (LNS progression)</td>
<td>PD</td>
<td></td>
<td>LNS progression</td>
<td>22</td>
<td>-</td>
<td>-</td>
<td>Death 49 days</td>
</tr>
<tr>
<td>Case 6</td>
<td>79</td>
<td>M</td>
<td>Lymphoma type</td>
<td>CHOP (1) DeVIC (1) CHASE (1)</td>
<td>PD</td>
<td>(4) PD (LNS progression)</td>
<td>PD</td>
<td></td>
<td>LNS progression</td>
<td>22</td>
<td>-</td>
<td>-</td>
<td>Death 55 days</td>
</tr>
<tr>
<td>Case 7</td>
<td>67</td>
<td>F</td>
<td>Acute type</td>
<td>CHOP (3)</td>
<td>PD</td>
<td>(6) PR (PB:CR, LN:PR)</td>
<td>PD</td>
<td></td>
<td>LNS progression</td>
<td>36</td>
<td>Lymphopenia (grade 3)</td>
<td>-</td>
<td>Death 46 days</td>
</tr>
<tr>
<td>Case 8</td>
<td>72</td>
<td>M</td>
<td>Lymphoma type</td>
<td>CHOP (3)</td>
<td>PD</td>
<td>(8) CR</td>
<td>CR</td>
<td></td>
<td>-</td>
<td>63</td>
<td>-</td>
<td>Leukocytopenia (grade 2)</td>
<td>Alive 418 days</td>
</tr>
<tr>
<td>Case 9</td>
<td>63</td>
<td>F</td>
<td>Lymphoma type</td>
<td>CHOP (1)</td>
<td>PD</td>
<td>(8) SD (LNS, skin)</td>
<td>SD (LNS, skin)</td>
<td></td>
<td>-</td>
<td>63</td>
<td>-</td>
<td>CMV infection</td>
<td>Alive 177 days</td>
</tr>
<tr>
<td>Case 10</td>
<td>55</td>
<td>M</td>
<td>Acute type</td>
<td>VCAP-AMP-V-VECP (2) CHOP (2) DeVIC (1)</td>
<td>PD</td>
<td>(8) SD (LNS)</td>
<td>PD (LNS)</td>
<td></td>
<td>LNS progression</td>
<td>49</td>
<td>-</td>
<td>-</td>
<td>Alive 145 days</td>
</tr>
<tr>
<td>Case 11</td>
<td>63</td>
<td>F</td>
<td>Acute type</td>
<td>VCAP-AMP-V-VECP (3) DeVIC (1)</td>
<td>PD</td>
<td>(8) PR (PB:CR, LNS:PR)</td>
<td>PD (LNS, CNS progression)</td>
<td></td>
<td>LNS, CNS progression</td>
<td>49</td>
<td>-</td>
<td>-</td>
<td>Death 129 days</td>
</tr>
<tr>
<td>Case 12</td>
<td>51</td>
<td>M</td>
<td>Acute type</td>
<td>VCAP-AMP-V-VECP (1)</td>
<td>PR</td>
<td>(4) CR (PB:CR, LNS:CR)</td>
<td>CR</td>
<td></td>
<td>-</td>
<td>-</td>
<td>Lymphopenia (grade 3)</td>
<td>CMV infection, Skin rash</td>
<td>Alive 29 days</td>
</tr>
<tr>
<td>Case 13</td>
<td>46</td>
<td>F</td>
<td>Acute type</td>
<td>VCAP-AMP-V-VECP (1)</td>
<td>PR</td>
<td>(4) CR (PB:CR, LNS:CR)</td>
<td>CR</td>
<td></td>
<td>-</td>
<td>-</td>
<td>Lymphopenia (grade 2)</td>
<td>Skin rash</td>
<td>Alive 22 days</td>
</tr>
<tr>
<td>Case 14</td>
<td>54</td>
<td>M</td>
<td>Acute type</td>
<td>VCAP-AMP-V-VECP (1)</td>
<td>PR</td>
<td>(8) CR (PB:CR)</td>
<td>CR (PB:CR)</td>
<td></td>
<td>-</td>
<td>-</td>
<td>Lymphopenia (grade 2)</td>
<td>-</td>
<td>Alive 209 days</td>
</tr>
</tbody>
</table>

were classified as having either a partial remission (PR) (3) or progressive disease (PD) (11) prior to mogamulizumab administration. The majority of patients (11/14) had refractory disease after initial or salvage chemotherapy. Mogamulizumab treatment was administered in the primary refractory setting (n=8), for relapse after complete remission (CR) (n=2) or as bridging therapy before HSCT (n=4). The patients were treated with an average of six courses of mogamulizumab (range: 4-8).

**Treatment outcomes of the ATL patients treated with mogamulizumab**

The treatment outcomes of the 14 ATL patients treated with mogamulizumab are shown in Table. Laboratory findings such as the WBC counts, abnormal lymphocyte counts, lactic dehydrogenase levels and sIL-2R levels are shown in Fig. 1. A statistically significant reduction in the abnormal lymphocyte count was found after four courses of mogamulizumab treatment. The laboratory findings in the peripheral blood (PB) during the first week of mogamulizumab therapy are shown in Fig. 1. Surprisingly, of the seven patients who responded after eight cycles of treatment, six showed a dramatic reduction in leukocytes and abnormal lymphocyte numbers in the PB within the first seven days (Fig. 2).

Regarding the treatment response, after four cycles of mogamulizumab, six patients were in CR, three in PR, two showed stable disease (SD) and three showed PD, resulting in a response rate of 64% (9/14). After eight cycles (or the final cycle), six patients showed a CR, none showed a PR, one showed SD and seven showed PD, giving a response rate of 43% (6/14).

The median OS, OS rate at six months and OS rate at 12 months were 66 days, 41.7% and 20.8%, respectively (Fig. 3). Of the eight patients with primary refractory disease at the start of treatment, one survived to the end of the study; of the two patients with relapse after CR, one survived; and of the four who received mogamulizumab treatment as bridging therapy before HSCT, all survived. Two of the four patients who received mogamulizumab as a bridging therapy underwent HSCT after the therapy. Two patients (cases 9 and 14) underwent HSCT at 177 days and 209 days, respectively, after mogamulizumab therapy. After HSCT, one of these patients (case 14) developed acute graft-versus-host disease (GVHD) (grade 2), but the other patient (case 9) did not. The other two patients (cases 12 and 13) were scheduled to receive hematopoietic stem cells from an unrelated (non-sibling) bone-marrow-transplant donor in the future.

Consequently, six (cases 3, 8, 9, 10, 11, and 14) of the 14 ATL patients survived for more than 100 days. Four (case 3, 8, 10 and 11) of these six patients were treated only with mogamulizumab. The remaining two patients were treated with mogamulizumab combined with HSCT. To exclude the effect of HSCT (cases 9 and 14), we calculated the survival rates based on the survival of these two patients before...
Cases 1 and 3) showed a relapse at 52 days and 120 days after the mogamulizumab therapy, two of the six patients with a CR (cases 1 who responded (CR or PR) after four cycles of mogamulizumab therapy (Table). Among the nine ATL patients the time to relapse and progression during or after mogamulizumab therapy. We therefore examined HSCT.

The adverse events (AEs) are shown in Table. AEs occurred in approximately 57.1% (8/14) of the 14 patients. The hematological AEs were lymphopenia (six cases) and leukocytopenia (one case). The non-hematological AEs were skin rash (two cases). No infusion reactions were observed or were prevented because of the premedication with prednisolone. Among the various AEs, CMV infection (two cases) and skin rash (two cases) necessitated testing for AEs during the follow-up examinations. CMV antigens were detected in the PB of two patients (cases 2, 7, and 11) developed PD within seven weeks (on day 29, 36, and 49, respectively) after the first cycle of mogamulizumab therapy. Relapse or progression occurred in the PB (one site), central nervous system (CNS; two sites), lymph nodes (LNs; five sites), skin (one site) and bone (one site). Increased tumor formation was observed at the site of relapse or progression. Among the patients who responded, 86% (6/7) cleared the disease from the PB site and 14% (1/7) cleared it from nodal and extranodal sites (Table). Surprisingly, after the disappearance of abnormal lymphocytes in the acute ATL patients, the ATL cells in the PB remained in CR despite relapse at another site (Table).
Discussion

Remarkable advances in ATL treatment (1-15) have been obtained, but have not led to a reduction in the annual death toll (16). Our retrospective study of 81 patients with aggressive-type ATL conducted over seven years clearly showed that the OS of ATL patients is poor because of the advanced age of the patients at the time of diagnosis, with a high proportion of patients receiving only palliative therapy, and a small proportion of long-term survivors receiving chemotherapy and HSCT (17). To improve the survival rates, it is essential to clarify the effectiveness of the newly-developed mogamulizumab treatment under real-world conditions. In a study of relapsed/refractory ATL, Taniguchi et al. reported that conventional treatments were of very limited utility (19). The study looked at 81 ATL patients who were initially treated with chemotherapy, radiation or HSCT, followed by chemotherapy, radiation, HSCT or donor lymphocyte infusion as salvage therapy (19). The median survival time was only 3.9 months (19). In a phase II trial that included 26 ATL patients, Ishida et al. observed a 50% overall response rate (13 of 26 patients), with a median progression-free survival and OS of 5.2 and 13.7 months, respectively (18).

In the present retrospective study, we described the clinical characteristics and treatment outcomes of ATL patients treated with mogamulizumab in Miyazaki Prefecture. Our results were as follows: (i) an early response and OS equivalent to those in Ishida’s phase II study; (ii) an early response and disappearance of abnormal lymphocytes in the PB in acute-type ATL; (iii) ATL patients with relatively prolonged survival (over 100 days); (iv) tolerable side effects, including lymphopenia, leukocytopenia, CMV infection and skin rash and (v) early relapse and disease progression during or after mogamulizumab therapy with a tendency toward tumor formation or CNS infiltration. Consequently, our results clearly show that mogamulizumab therapy may be effective, feasible and safe for refractory ATL patients under real-world conditions. Our findings are strong enough that we feel confident in drawing these conclusions despite the small number of ATL patients and the fact that this study was a single-institution retrospective analysis.

The major advantages of this treatment regimen were as follows: (i) an early response and disappearance of abnormal lymphocytes from the PB was observed in patients with acute-type ATL and (ii) several ATL patients (six cases: nos. 3, 8, 9, 10, 11, and 14) survived for more than 100 days. These clinical findings clearly showed that in our study, mogamulizumab therapy led to an early and high remission rate and a relatively prolonged survival in several patients with refractory ATL who showed tolerable AEs in the real-world situation.

The major disadvantages of this treatment regimen are early relapse and disease progression during or after mogamulizumab treatment. These are serious issues. In our study, the early relapse after a CR in two patients (at 52 days and 120 days after the initial cycle) and early disease progression after a PR in three patients (at 29 days, 36 days and 49 days after the initial cycle) during and after mogamulizumab therapy necessitated testing for relapse and disease progression in follow-up examinations. Moreover, the relapse and progression sites (the LNs, skin or bone) tended to correspond to tumor formation and CNS infiltration. In particular, two patients (cases 1 and 11) showed a rapid clinical course of CNS infiltration. In a pharmacokinetic study of mogamulizumab tissue distribution in a cynomolgus monkey model reported by Kyowa Hakko Kirin Co., Ltd. (data not published), mogamulizumab did not diffuse across the CNS barrier. Thus, the combination of mogamulizumab therapy and prophylactic intrathecal chemotherapy, such as methotrexate therapy, may be needed to prevent CNS infiltration in patients with ATL. Consequently, the combination of mogamulizumab therapy with other treatments may be necessary to prevent the early relapse and early disease pro-

Figure 4. The clinical course of a skin rash after mogamulizumab treatment (case 13). A skin rash developed after four cycles of mogamulizumab. Initially, the patient was treated with prednisolone (PSL) ointments on the back and lower extremities. After three days, the patient developed a fever and the rash spread to the chest, arms and head. After taking a skin biopsy, we administered a pulse of methyl PSL. The skin specimen revealed the proliferation of CD3+8+ T cells, consistent with a drug eruption. The PSL was tapered as the rash improved, and it eventually resolved.

two different patients (cases 12 and 13). The representative photograph of the skin rashes is shown in Fig. 4. For patient 13, the rash developed after four cycles of mogamulizumab. Initially, the patient was treated with prednisolone ointments on the back and lower extremities. However, three days after developing the skin rash, the patient developed a fever and the rash spread to the chest, arms, and head. Thus, after performing a skin biopsy, we administered methylprednisolone pulse therapy. The skin specimen revealed the proliferation of CD3+8+ T cells consistent with a drug eruption. The prednisolone dose was tapered as the rash improved and eventually resolved.

The clinic of four cycles of mogamulizumab was eventually resolved. The nisolone dose was tapered as the skin rash improved and followed by chemotherapy, radiation, HSCT or donor lymph.
gression. Recently, Jo et al. reported that mogamulizumab plus VCAP-AMP-VECP therapy had an excellent response rate and progression-free survival rate (20).

Another disadvantage of mogamulizumab therapy is the development of AEs such as lymphopenia, leukocytopenia, CMV infection and skin rash. However, these AEs were tolerated and controlled. Of note, a skin rash was detected in two out of 14 cases. Ishida et al. reported that a skin rash occurred in approximately 52% (±14/27) of ATL patients in a phase II trial (18). In our study, we found that a skin biopsy and prompt prednisolone therapy in cooperation with a dermatologist were important for effectively treating the rash. The previous skin rashes reported after mogamulizumab treatment varied from mild to severe (21, 22). Ishida et al. reported a case of Steven-Johnson syndrome associated with mogamulizumab treatment for ATL (21), and Yonekura et al. suggested that adverse cutaneous reactions may predict the outcomes based on the effects of the anti-CCR4 monoclonal antibody on ATL (22). More research is needed to clarify the clinical importance of a skin rash. Furthermore, one of the two patients who received mogamulizumab as bridging therapy following HSCT developed acute GVHD (grade 2). More research is needed to determine the impact of mogamulizumab on the development of GVHD after HSCT and its relationship to the clinical outcomes.

In conclusion, in our study, mogamulizumab therapy led to an early and high remission rate and a relatively prolonged survival in patients with refractory ATL who showed tolerable AEs in the real-world setting. However, the short duration of remission and early relapse and disease progression were serious problems. These results should be taken into consideration when determining whether to use mogamulizumab-based treatments for ATL in clinical practice. A randomized study and longer follow-up periods are necessary to determine the specific sub-groups of ATL patients who would benefit the most from treatment with mogamulizumab and to elucidate the pathogenic and treatment effects of this therapeutic modality.

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

Acknowledgement

We thank Ms. Sakurai, Ms. Kiyoyama, Ms. Kugimiya and Ms. Nakamura for carefully examining the bone marrow specimens.

References