SHORT COMMUNICATION

Cutaneous Adverse Reaction to Mogamulizumab May Indicate Favourable Prognosis in Adult T-cell Leukaemia-lymphoma

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A novel defucosylated humanized monoclonal antibody against the CC chemokine receptor 4 (CCR4), mogamulizumab exhibits strong effects in relapsed adult T-cell leukaemia-lymphoma (ATL) patients (1). The frequent development of skin rash, has been reported with mogamulizumab use (63%) (1). Remarkably, patients with grade 2 or higher cutaneous adverse reactions (CARs) have shown better clinical responses to mogamulizumab than those with grade 1 or no CAR (1). In our previous study of 5 patients with ATL treated with mogamulizumab, 2 patients who achieved complete remission (CR) without CAR experienced ATL relapse very soon after treatment. On the other hand, none of the patients with CAR relapsed during a follow-up period of over 9 months (2). We report here the results of a study with a larger number of patients, in which we assess the influence of CAR on outcome.

CASE REPORTS AND METHODS

This study was approved by the human research ethics committee of our hospital and prior written informed consent was obtained from participants. We analysed 34 patients with ATL who started treatment with mogamulizumab at our hospital from March 2007 to May 2015. We excluded 8 patients who received allogeneic haematopoietic stem cell transplantation (allo-HSCT) because allo-HSCT was thought to affect the prognosis of the patients. In the remaining 26 patients, all CARs occurred after the 4th cycle of mogamulizumab treatment. To avoid the influence of treatment cycles on the prognosis, we re-analysed 18 patients who received more than 4 cycles of treatment. Their diagnoses, treatments, laboratory findings, therapeutic results, and CARs were obtained from their clinical records. Response to mogamulizumab was recorded according to the modified response criteria for ATL (3). The response of the cutaneous lesions was evaluated by physician global assessment, taking into consideration erythema, induration, papules, and nodules. The severity of CAR was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. The patients' clinical profiles are shown in Table I and Table SI[1]. Patient characteristics and treatment effects were compared using the χ^2 test for categorical data and the Mann-Whitney U test for continuous or ordinal data. Overall survival (OS) and progression-free survival (PFS) were defined as the time from the start of mogamulizumab treatment to death and disease progression, respectively. OS was estimated using the Kaplan–Meier method and compared using the log-rank test. Statistical analyses were performed using

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Table I. *Characteristics and treatment of cutaneous adverse reactions*

Case/ Grade	Onset	Symptom	Treatment
1/G4	2 months after 8th cycle	Erythroderma	Oral prednisolone 25 mg
2/G4	1 week after 4th cycle	EM, TEN	Methylprednisolone pulse
3/G3	1 month after 5th cycle	Erythroderma	Topical steroid
4/G3	1 week after 7th cycle	Erythroderma	Oral prednisolone 30 mg
5/G2	1 week after 5th cycle	EM	Oral prednisolone 30 mg
6/G2	6 weeks after 4th cycle	EM	Topical steroid
7/G1	After 8th cycle	EN	None

EM: erythema multiforme, TEN: toxic epidermal necrolysis, EN: erythema nodosum; G: severity grade of CAR.

Graphpad Prism 5 software (Graphpad Software Inc.). *p*-values <0.05 were considered statistically significant.

RESULTS

Patient ages ranged from 55 to 83 years (median age 66.5 years). Eighteen of 26 patients received 4 or more cycles of mogamulizumab treatment. Infusion reactions developed in 15/26 patients.

Seven patients experienced CARs. All these 7 patients had received 4 or more cycles of mogamulizumab treatment (median 7 cycles). Three of the 7 patients presented with generalized erythroderma, 3 with widespread exudative erythema, and one with painful subcutaneous erythematous nodules. One patient (case 2), with generalized erythema, eventually developed toxic epidermal necrolysis (TEN). The severity of CAR was grade 1 in one patient, grade 2 in 2 patients, grade 3 in 2 patients, and grade 4 in 2 patients. CAR diagnosed as grade 2 or higher was treated with topical or oral corticosteroids. The patient who experienced TEN was treated with methylprednisolone pulse therapy. CAR appeared after more than 4 cycles of mogamulizumab treatment. One patient (case 1) experienced CAR 2 months after the last administration of mogamulizumab (Table I).

In all 26 patients, the overall response rate (ORR) was 50% (CR in 9 patients, partial remission (PR) in 4 patients). The ORR for the patients with CAR was 86% (CR in 6/7 patients). In contrast, the ORR for the 19 patients without CAR was 37% (CR in 3 patients, PR in 4 patients). Among the 18 patients who received 4 or more treatment cycles, the ORR was 61% (CR in 9 patients, PR in 2 patients). This corresponded to 86%

in the patients with CAR (CR in 6/7 patients) and 45% in the 11 patients without CAR (CR in 3 patients, PR in 2 patients).

In all 26 patients, the PFS and OS rates of the patients with CAR ($n=7$) were significantly superior to the rates of those without CAR ($n=19$) ($p=0.001$, Fig. 1A and $p=0.009$, Fig. 1B, respectively). In the 18 patients who received 4 or more cycles of mogamulizumab, the PFS of the patients with CAR ($n=7$) was also significantly superior to that of those without CAR ($n=11$) ($p=0.0018$, Fig. 1C) and the OS of the patients with CAR was possibly better than that of those without CAR ($p=0.0587$, Fig. 1D).

In the univariate analysis, various factors, such as age, sex, treatment cycles, number of previous treatment regimens, serum lactate dehydrogenase and soluble interleukin-2 receptor levels at the start of treatment, and responses to mogamulizumab were not significantly different between patients with and without CAR (Table SII[1]).

DISCUSSION

CCR4 is often expressed on tumour cells in T-cell lymphomas, such as mycosis fungoides, peripheral T-cell lymphoma, and ATL (4). It has been reported that CCR4 positivity is significantly associated with skin involvement in ATL, and that it is an unfavourable prognostic factor (5). The effect of mogamulizumab, is exerted via antibody-dependent cellular cytotoxicity (ADCC) in ATL cells (6).

CCR4 is also expressed on the surface of regulatory T-lymphocytes (Tregs); therefore, mogamulizumab also depletes $CCR4^+$ Tregs (7–9). In addition, $CD8^+$ T-cells were reported to increase after the administration of mogamulizumab (9).

We recently reported that the biopsy specimen taken from an area of CARs showed spongiosis in the epidermis, liquefactive degeneration of basal cells, and heavy lymphocyte infiltration in the upper dermis. These lymphocytes were $CD3^+ 8^+$ T cells (2, 7, 8), positive for granzyme B, perforin, and TIA-1 (2). Similar changes were observed in this study (data not shown).

It has been suggested that the reduction in $CCR4^+$ Tregs promotes the increase in the levels of the cytotoxic T lymphocytes (CTLs) (2, 8), which may also exert an anti-tumour effect. It has been suggested that CAR is associated with a good clinical response because mogamulizumab is cytotoxic to tumour cells, not only via ADCC, but also through the induction of $CD8^+$ CTLs.

In the present study, a relationship was shown between CAR and clinical response or good prognosis. Since CAR may progress to a more severe form, such as TEN, careful follow-up is recommended for several months after treatment. Because this is a retrospective study, there may be bias in the result. For example, patients who responded well to mogamulizumab treatment had a better chance of receiving more cycles of treatment. Treatments for CAR, such as systemic corticosteroids, may have affected the survival of patients. Finally, a longer use of mogamulizumab may itself be a risk factor for CAR. Further studies using multivariate analyses with a larger sample population are warranted.
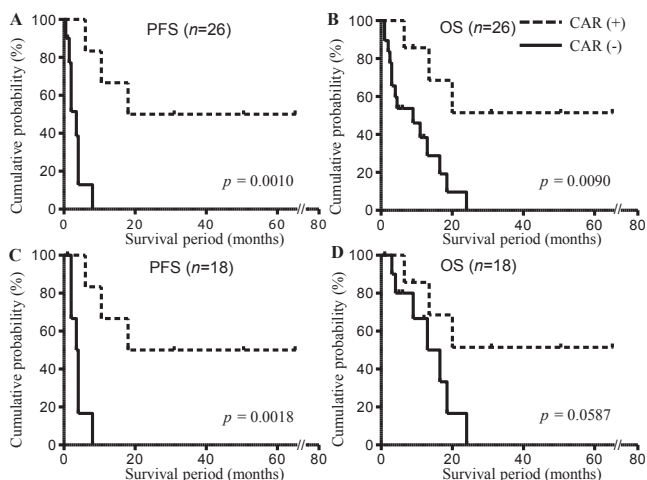
Fig. 1. Progression-free survival (PFS) (A, C) and overall survival (OS) (B, D) in patients with or without cutaneous adverse reactions (CARs). A and B show the results in all patients ($n=26$). C and D show patients who received ≥4 cycles of mogamulizumab ($n=18$).

REFERENCES

1. Ishida T, Joh T, Uike N, Yamamoto K, Utsunomiya A, Yoshida S, et al. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. J Clin Oncol 2012; 30: 837–842.
2. Yonekura K, Kanzaki T, Gunshin K, Kawakami N, Takatsuka Y, Nakano N, et al. Effect of anti-CCR4 monoclonal antibody (mogamulizumab) on adult T-cell leukemia-lymphoma (ATL): cutaneous adverse reactions may predict the prognosis. J Dermatol 2014; 41: 239–244.
3. Tsukasaki K, Hermine O, Bazarbachi A, Ratner L, Ramos JC, Harrington W Jr., et al. Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: a proposal from an international consensus meeting. J Clin Oncol 2009; 27: 453–459.
4. Ishida T, Inagaki H, Utsunomiya A, Takatsuka Y, Komatsu H, Iida S, et al. CXC chemokine receptor 3 and CC chemokine receptor 4 expression in T-cell and NK-cell lymphomas with special reference to clinicopathological significance for peripheral T-cell lymphoma, unspecified. Clin Cancer Res 2004; 10: 5494–5500.
5. Ishida T, Utsunomiya A, Iida S, Inagaki H, Takatsuka Y,

Kusumoto S, et al. Clinical significance of CCR4 expression in adult T-cell leukemia/lymphoma: its close association with skin involvement and unfavorable outcome. Clin Cancer Res 2003; 9: 3625–3634.

6. Ishii T, Ishida T, Utsunomiya A, Inagaki A, Yano H, Komatsu H, et al. Defucosylated humanized anti-CCR4 monoclonal antibody KW-0761 as a novel immunotherapeutic agent for adult T-cell leukemia/lymphoma. Clin Cancer Res 2010; 16: 1520–1531.

7. Ishida T, Ito A, Sato F, Kusumoto S, Iida S, Inagaki H, et al. Stevens-Johnson syndrome associated with mogamulizumab treatment of adult T-cell leukemia/lymphoma. Cancer Sci 2013; 104: 647–650.

8. Honda T, Hishizawa M, Kataoka TR, Ohmori K, Takaori-Kondo A, Miyachi Y, et al. Stevens-Johnson syndrome associated with mogamulizumab-induced deficiency of regulatory T cells in an adult T-cell leukaemia patient. Acta Derm Venereol 2015; 95: 606–607.

9. Ni X, Jorgensen JL, Goswami M, Challagundla P, Decker WK, Kim YH, et al. Reduction of regulatory T cells by Mogamulizumab, a defucosylated anti-CC chemokine receptor 4 antibody, in patients with aggressive/refractory mycosis fungoides and Sézary syndrome. Clin Cancer Res 2015; 21: 274–285.