

## Mogamulizumab for adult T-cell leukemia/lymphoma expressing atypical phenotype CD4-/CD8+/CCR4+

Hiroshi Ureshino<sup>1</sup>, Natsuko Komiya<sup>1</sup>, Eizaburo Sueoka<sup>2</sup>, Shinya Kimura<sup>2,\*</sup>, Masaharu Miyahara<sup>1</sup>

<sup>1</sup> Department of Internal Medicine, Karatsu Red Cross Hospital, Saga, Japan

<sup>2</sup> Department of Internal Medicine, Saga University, Saga, Japan

### Corresponding Author & Address:

Shinya Kimura\*

Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan. TEL: +81-952-34-2353, FAX: +81-952-34-2017, Email: [shkimu@cc.saga-u.ac.jp](mailto:shkimu@cc.saga-u.ac.jp)

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### ABSTRACT

Adult T-cell leukemia/lymphoma (ATL) cells are generally CD4+, CD8- and CCR4+. A 76-year-old man was diagnosed with a rare case of CD4-/CD8+ ATL in 2013. He was initially treated with the THP-COP regimen. The number of ATL cells in lymph nodes and peripheral blood (PB) and the level of soluble interleukin-2 receptor (sIL-2R) were decreased initially after chemotherapy but increased within 3 months and hypercalcemia appeared. Thus, the patient was diagnosed with ATL progression. Since CCR4 expression in CD4-/CD8+ ATL cells was confirmed by flow cytometry, the patient was treated with the newly developed CCR4 antibody mogamulizumab. Treatment significantly eradicated ATL cells in PB. To our knowledge, this is the first case of CD4- ATL treated with mogamulizumab.

### INTRODUCTION

Adult T-cell leukemia/lymphoma (ATL) is an aggressive type of peripheral T-cell neoplasm associated with human T-cell lymphotropic virus type I (HTLV-I). ATL usually shows resistance to conventional chemotherapy, resulting in poor prognosis. ATL is most frequently associated with a mature CD4+/CD8- T-cell phenotype; however, rare cases of an unusual immunophenotype characterized by CD4-/CD8+ cells have been reported. This atypical ATL phenotype has an even poorer prognosis [1]. CC chemokine receptor 4 (CCR4) is one of the chemokine receptors

expressed on helper T-cells of the Th2 subtype, regulatory T-cells (T-regs) and effector/memory T-cells. CCR4 is expressed on tumor cells in most patients with ATL and is associated with poor prognosis [2]. Mogamulizumab is a newly developed humanized anti-CCR4 monoclonal antibody that demonstrated clinical antitumor efficacy in patients with relapsed ATL [3]. We herein report the effect of mogamulizumab in a rare case of CD4-/CD8+/CCR4+ ATL.

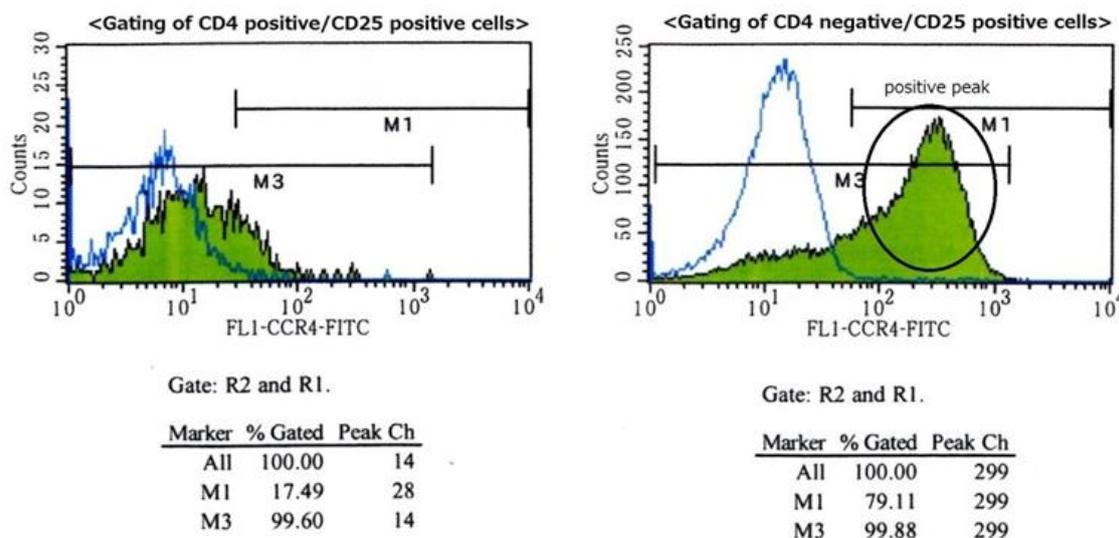
### CASE REPORT

A 76-year-old Japanese male presented with chronic hepatitis B and post-operative aortic valve

stenosis. He had received entecavir for his chronic hepatitis B. Abnormal PB lymphocytes were detected in January 2012. The patient had systemic lymph node swelling and examinations revealed a number of nucleated lymphocytes, so called flower cells, in PB, monoclonal integration of HTLV-I proviral DNA and hypercalcemia, leading to the diagnosis of acute ATL. Flow cytometry demonstrated that the phenotype of the ATL cells was atypical since they lacked CD4 expression but were positive for CD8 (CD4-/CD8+). As other features, ATL cells expressed CD2 and CD3 and did not express CD5 and CD7. The patient was treated with the cyclophosphamide, epirubicin, vincristine, prednisolone (THP-COP) regimen. Chemotherapy shrank lymph nodes significantly, brought ATL cells in PB below the detection threshold, and rapidly decreased the sIL-2R level.

However, the number of ATL cells in PB and the level of sIL-2R increased within 3 months of chemotherapy and hypercalcemia appeared again. Thus, the patient was diagnosed with progression of ATL. During progression, the PB white blood cell count reached  $1.503 \times 10^{10}$  cells/L including  $4.844 \times 10^9$  cells/L of ATL cells, hemoglobin reached 11.8mg/dL, and the platelet count reached  $11.2 \times 10^{10}/L$ . Biochemistry showed lactate dehydrogenase levels at 308 IU/L, blood urea nitrogen at 35.7 mg/dL, serum creatinine at 1.83 mg/dL, serum calcium at 10.6 mg/dL, and sIL-2R at 42,600U/mL. Flow cytometry analysis demonstrated that the percentage of CD4+/CD25+ cells had not increased since the ATL diagnosis, but that the percentage of CD8+/CD25+ cells had (Fig. 1).

Figure 1. Phenotype of ATL cells

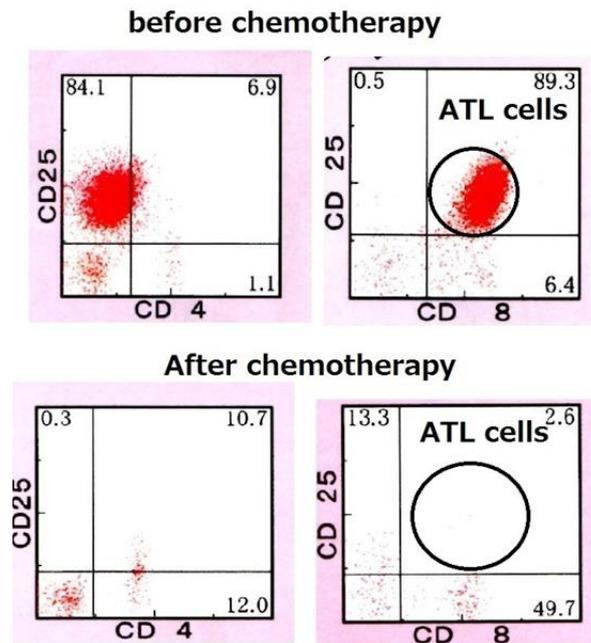


(A) Flow cytometry of peripheral blood before administration of mogamulizumab. The percentage of CD8+/CD25+ cells among ATL cells was high. (B) After administration of mogamulizumab, the percentage of CD8+/CD25+ cells decreased significantly.

To confirm the association of HTLV-1 with the abnormal CD4-/CD8+ lymphocytes, Separated CD4+cells and CD8+cells by flow cytometry, is performed each culture, HTLV-1 copy numbers were measured in each cell subset. The CD4+ subset had only 25.3 copies of HTLV-1 per 1000 PB mononuclear cells (PBMCs), while the CD8+ subset had 708.3 copies per 1000 PBMCs, indicating that HTLV-1 infected mainly CD4-/CD8+ lymphocytes. This CD4-/CD8+ population expressed CCR4 (Fig. 2). Thus, the patient was treated with mogamulizumab. After administration of

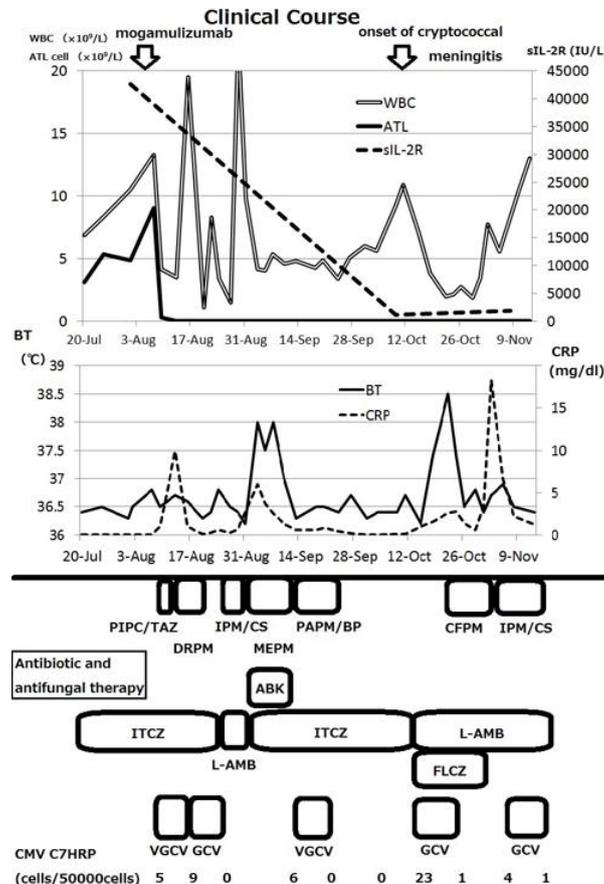
mogamulizumab, ATL cells disappeared in PB and the level of sIL-2R decreased immediately (Fig. 3). At day 42 after chemotherapy with mogamulizumab, the patient suffered from hearing loss, weakness, paralysis of the lower limbs and dementia. He was diagnosed with cryptococcal meningitis by magnetic resonance imaging and cerebrospinal fluid examination. Although he was treated with antifungal drugs, he died 10 months after the onset of ATL. ATL cells were never observed after treatment with mogamulizumab.

Figure 2. CCR4 expression by flow cytometry



Gating of CD4+/CD25+ cells. There was no positive peak, and thus these cells did not express CCR4 (left). Gating of CD4-/CD25+ cells including CD8+/CD25+ cells (ATL cells). There was a positive peak, and thus these cells expressed CCR4 (right).

Figure 3. Clinical course



PIPC/TAZ: piperacillin/tazobactam; DRPM: doripenem; IPM/CS: imipenem/cilastatin; MEPM: meropenem; PAMP/BP: panipenem/ betamipron; CFPM: cefepime; ABK: arbekacin; ITCZ: itraconazole; L-AMB: liposomal amphotericin B; F-FLCZ: fosfluconazole; GCV: ganciclovir; VGCV: valganciclovir.

## DISCUSSION

ATL cells generally expressed CD4+/CD8-/CD25+. However, the presence of ATL indicating the aberrant phenotype has been reported. The incidence of the typical (CD4+/CD8-) phenotype, and the CD8 positive (CD4-/CD8+) phenotypes was 81% and 4%, respectively. Median survival time (MST) of patients with typical phenotypes is 10.2 months, while that of the patients with CD8 positive phenotype is 2.6 months. The prognosis of CD4-/CD8+ ATL is significantly poorer than that of CD4+/CD8- ATL [1]. It was reported that patients with CD4-/CD8+ ATL often suffer from severe infection because of more severe immunodeficiency compared to patients with CD4+/CD8- ATL [4]. The patient in the present case also died of fungal infection.

Mogamulizumab was approved in 2012 for CCR4+ relapsed or refractory ATL with an objective response rate (ORR) of 50%, a progression-free survival (PFS) of 5.7 months, and an overall survival (OS) of 13.7 months [2]. CCR4, a chemokine receptor usually expressed on regulatory T cell (Tregs), Th2 and effector/memory T cells. ATL cells had a function of Tregs and expressed phenotype of CD4+ / CD25+ / FOXP3+ / CCR4+ similar to Tregs [5]. In addition, CCR4 positive ATL had worse prognosis [2].

By the way, we diagnosed this case CCR4 positive by flow cytometry gated of CD4 negative region, but there is nothing that is enough to this study of CD4-/CD8+/CCR4+ ATL that we experienced. However, as of CCR4 + CD8 + T cell Human memory and CD8+ regulatory T cell, CD8+

T cell also expressed CCR4 [6, 7]. In addition, CCR4+ ATL without the typical CD4+/CD8- phenotype also exists in 10% of ATL [2]. Thus, it seems that there is no contradiction for the CD4-/CD8+/CCR4+ ATL cell exists in this way. If CD4-/CD8+ ATL cells work like Tregs as well with CD4+/CD8- ATL cells, CD4-/CD8+ ATL cells suppress the proliferation and differentiation of CD4+ T cells like CD8+ Tregs [7]. Thereby, CD4+ T cells markedly decreased by CD4-/CD8+ ATL cells. CD4-/CD8+ ATL patient becomes strong immunodeficiency state and may tend to short-lived because of the severe infection as of this case and known. Mogamulizumab is especially effective against ATL cells in PB, with a 100% ORR, not against those in lymph nodes. Since the main lesion in the present case was PB, ATL cells disappeared immediately after treatment with mogamulizumab.

To our knowledge, this is the first report of mogamulizumab efficacy in CD4-/CD8+/CCR4+ ATL. CD4-/CD8+ ATL cells also expressed CCR4 like CD4+/CD8- ATL cells, if ATL cells expressed CCR4, effect of mogamulizumab can expect. However, CD4-/CD8+ ATL patients have poor prognosis with many complication such as severe infection. Thus we should do treatment for CD4-/CD8+ ATL while performing the supportive care of CD4+/CD8- ATL or more. This result warrants further investigation of mogamulizumab in atypical ATL.

## CONFLICT OF INTEREST

No authors have any conflict of interest about this study

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