A case of associated refractory acute graft-versus-host disease following umbilical cord blood transplantation in an adult T-cell leukemia/lymphoma patient pretreated with mogamulizumab

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Introduction

Adult T cell leukemia/lymphoma (ATLL) is an aggressive peripheral T-cell neoplasm. Humanized anti-CC chemokine receptor 4 monoclonal antibody (mogamulizumab) has been shown to be effective for relapsed/refractory ATLL. However, the effects of mogamulizumab application before allogeneic stem cell transplantation are uncertain. Here, we present an ATLL patient who was administered mogamulizumab and suffered from refractory acute graft-versus-host disease (GVHD) following umbilical cord blood transplantation (UCBT). This was accompanied by delayed reconstitution and a long-lasting reduction of regulatory T cells (Tregs). We suggest that this attenuation of Tregs influenced the clinical course of the severe/refractory GVHD following UCBT in a patient pretreated with mogamulizumab therapy. (Journal of Hematopoietic Cell Transplantation 4(2): 52–56, 2015.)

CC chemokine receptor 4 (CCR4), designated mogamulizumab, recently became available for this purpose. CCR4 is a chemokine receptor expressed on helper T cells, regulatory T cells (Tregs), and certain types of T-cell neoplasms, such as ATLL. With an increased binding affinity to the Fc-gamma receptor on effector cells, this drug markedly enhances antibody-dependent cell-mediated cytotoxicity (ADCC) against ATLL cells expressing CCR4. In a phase II clinical trial for relapsed ATLL, objective responses were noted in 13 of 26 evaluable patients, including eight complete responses.

Although mogamulizumab is a promising therapeutic alternative for patients with relapsed/refractory ATLL, there is some apprehension regarding treating patients with mogamulizumab before allogeneic hematopoietic stem cell transplantation (allo-HSCT). The fear is that it might affect regulatory T cell (Treg) reconstitution because these cells also express CCR4. Fewer circulating Tregs cause severe graft-versus-host disease (GVHD) after allo-HSCT because these cells have an...
indispensable role in the maintenance of immune tolerance.8

Here, we present a case of an ATLL patient pretreated with mogamulizumab who suffered refractory GVHD after umbilical cord blood transplantation (UCBT). As an underlying mechanism for this refractory GVHD, we demonstrate the possible involvement of delayed reconstitution of Tregs. This is the first report of refractory GVHD accompanied by delayed reconstitution of Tregs after allo-HSCT in a patient pretreated with mogamulizumab.

Materials and methods

Patient

A 62-year-old Japanese woman presented with abnormal peripheral blood lymphocytes in August 2010. Laboratory data were as follows: white blood cells, 13,300/μL with 27% abnormal lymphocytes; lactate dehydrogenase (LDH), 241 IU/L; and corrected serum calcium, 10.5 mg/dL. No lymph nodes were palpable, and computed tomography (CT) scans showed no hepatosplenomegaly. Based on laboratory findings, she was diagnosed with indolent ATLL (smoldering type). In February 2012, she suffered from severe watery diarrhea with elevated abnormal lymphocyte count. Laboratory data were as follows: white blood cells, 9,400/μL (34.5% abnormal lymphocytes with lobulated nuclei); lactate dehydrogenase (LDH), 402 IU/L; and corrected serum calcium, 12.0 mg/dL. CT scans revealed swollen mesenteric lymph nodes, and hepatosplenomegaly. She was diagnosed with acute-type ATLL with duodenal involvement and initially treated with multi-agent chemotherapy (modified LSG15 regimen) consisting of VCAP, AMP, and VECP. However, this regimen was not effective. ATLL cells in the biopsied specimens of the duodenum were positive for CCR4 by immunohistochemistry. Therefore, in June 2012 we started intravenous mogamulizumab at 1.0 mg/kg once a week (Figure 1). The patient received a total of 8 cycles of mogamulizumab treatment. Watery diarrhea improved remarkably after the first cycle. Simultaneously, ATLL cells began to disappear from the peripheral blood. Complete remission was achieved after three cycles of mogamulizumab treatment. She had skin rashes after 8 cycles, but these improved with antihistamines and a topical corticosteroid.

In August 2012, she underwent UCBT after conditioning with fludarabine (30 mg/m² on days −7 to −4), melphalan (70 mg/m² on days −3 and −2), and total body irradiation (4 Gy fractionated in 2 doses on day −1). The cord blood graft contained 3.23 × 10⁷/kg of mononuclear cells and 0.83 × 10⁵/kg of CD34-positive cells. Post-transplant GVHD prophylaxis was with 0.03 mg/kg/day of tacrolimus and 15 mg/kg/day of mycophenolate mofetil (MMF). Eleven days after UCBT, she developed skin rash; acute GVHD (aGVHD) of the skin (grade II) was diagnosed by biopsy and treated with 1 mg/kg of methylprednisolone (mPSL). Although mPSL was decreased as the skin aGVHD improved, it had to be started again at a dose of 1 mg/kg because of watery diarrhea, which was diag-
nosed as gut aGVHD (grade II) by biopsy specimens of colorectal mucosa on day 31. Thereafter, mPSL could not be tapered due to exacerbation of skin (stage 2) (day 55) and gut (stage 3) (day 75) aGVHD, which was confirmed by esophagogastroduodenoscopy and biopsy. After day 100 post-UCBT, we could finally reduce the mPSL dose without aGVHD aggravation; however, she developed sepsis and thrombotic microangiopathy, which proved fatal. Complete remission of ATLL had been sustained until that time.

Flow cytometric analysis

We analyzed CD4, CD25, and Forkhead box protein 3 (FoxP3) expression on peripheral blood mononuclear cells (PBMC) after UCBT. Protocol-specified immunophenotypic analyses were performed by flow cytometry as described previously.9 Tregs were defined as CD4+CD25+FoxP3+ cells as shown in Figure 2. Briefly, 1 × 10⁶ PBMCs were incubated with fluorophore-conjugated monoclonal antibodies, anti-CD4 PerCP (clone SK3, BD Biosciences, San Diego, CA), and anti-CD25 APC (clone 2A3, BD Biosciences). Stained PBMCs were treated with fixation/permeabilization buffer (eBioscience, San Diego, CA) and then incubated with anti-human FoxP3 PE (clone PCH101, eBioscience). Cell analysis was performed with the FACS Calibur system (BD Biosciences).

Measurement of plasma mogamulizumab concentrations

The concentration of mogamulizumab in the patient’s serum was measured by Kyowa Hakko Kirin Co., Ltd. (Tokyo, Japan) using their enzyme-linked immunosorbent assay system.

Results

Measurement of Tregs population and plasma mogamulizumab concentrations

As shown in Figure 3, the proportions of CD4+CD25+ FoxP3+ Tregs among CD4+ T cells at day 11, 31, 46, 78, and 112 post-UCBT were 2.80, 2.47, 1.28, 2.14, and 10.2% (0.16, 0.37, 0.92, 0.99, and 4.7/μL), respectively, compared to 5.2 ± 0.9% in 9 healthy controls. Plasma mogamulizumab concentrations were measured by ELISA (Figure 3). They were 3350.4, 368.6, 310.1, 71.2, 21.7, and 5.0 ng/mL at day -27, 5, 13, 25, 41, and 73 post-UCBT, respectively.

Discussion

Tregs are a subset of T cells defined by coexpression of CD4, CD25, and transcription factor FoxP3, which suppress autoreactive lymphocytes, and control innate and adaptive immune responses.10 These cells might be affected by the anti-CCR4 antibody mogamulizumab, because CCR4 is
expressed not only on ATLL cells but also on Tregs. A reduction of Tregs after mogamulizumab treatment has indeed been reported in a case of ATLL. However, the decreased number of CD4+25+FoxP3+ cells after mogamulizumab treatment may not be a unique feature of Tregs because these lymphocyte subsets potentially including ATLL cells that have the same surface markers as Tregs. This requires careful consideration.

There is some concern that mogamulizumab administered as an induction therapy prior to allo-HSCT might delay the reconstitution of Tregs and cause severe refractory GVHD, because it has been shown that Tregs reduce GVHD severity. In general, Tregs account for approximately 5 to 10% of circulating CD4+ T cells; this normal proportion of Tregs is usually recovered after allo-HSCT within only one month. However, the proportion of Tregs in the patient presented here did not exceed 3% until day 78 after UCBT. During this period, our patient suffered from refractory GVHD. It is hypothesized that one of the causes of the delayed reconstitution of Tregs was the mogamulizumab treatment. However, there is no evidence that the decrease of Tregs caused severe GVHD since we have no data of Tregs before mogamulizumab treatment. Further examination will be needed to prove its relevance.

For mogamulizumab to have this effect of delaying Treg reconstitution, there must still be residual antibody in the patient after stem cell transplantation. To test this, we quantified mogamulizumab in the patient’s frozen serum and found that it could be clearly detected on day 7 post-UCBT at 368.6 ng/mL. This concentration might be sufficient to inhibit Treg reconstitution because even only 10 ng/mL of mogamulizumab was demonstrated to have plateau cytotoxicity on ATLL cells in vitro, although Tregs might be less sensitive to the effects of the antibody than cancer cells. Thereafter, at time points later than 7 days post-UCBT, the concentration of mogamulizumab in the patient’s serum gradually decreased and could no longer be detected on day 73 post-UCBT. After mogamulizumab was no longer present in the blood, the proportion of Tregs increased up to 10.2% at day 112 post-UCBT. At that time, mPSL could be tapered successfully without exacerbation of skin and gut aGVHD.

The concentration of mogamulizumab in serum should be determined for each patient prior to transplantation. However, currently there is no commercial assay system available for this purpose. It may be sufficient to wait a certain time after the last administration of mogamulizumab prior to allo-HSCT. Because mogamulizumab could not be detected 111 days after the last administration (day 73 post-UCBT) in the patient reported here, it may be safer to wait 4 months. Motohashi K et al. showed the time interval between mogamulizumab treatment and allo-HSCT was about 2 months; however, the optimum interval before allogeneic stem cell transplantation is uncertain. We would also suggest that one month is certainly not long enough because our patient received transplantation 38 days after the last administration of mogamulizumab. The number of ATLL cells in our patient was immediately reduced after first mogamulizumab treatment. In the multicenter phase II study, mogamulizumab monotherapy demonstrated significant reduction of CD4+CCR4+ cells and CD4+CD25+FoxP3+ cells after the first mogamulizumab infusion. Determining the optimum number of mogamulizumab administrations before allogeneic stem cell transplantation is a future task.

When she was diagnosed with acute-type ATLL with duodenal involvement, tumor cells were not detected in colonic mucosa, which was confirmed on random biopsy of the colon. Since she developed severe diarrhea, there was the potential for infiltration of ATLL cells to small intestinal mucosa. It would have been better if we had performed a double-balloon enteroscopy earlier for our patient.

In summary, we described the clinical course of a patient with ATLL pretreated with mogamulizumab who later received UCBT. This is the first report associating Treg reconstitution and residual concentrations of mogamulizumab post-transplant as a possible cause of refractory GVHD. Clearly, mogamulizumab is an important therapeutic alternative for ATLL, but a sufficient time interval must be left between the last administration of the antibody and subsequent allo-HSCT in order to prevent delayed Treg reconstitution and severe refractory GVHD.

**Authorship**

AH, SI: wrote the paper, designed research/study, and performed research/study. TS: designed research/study and performed research/study. KO, HH, AT, YK, SI: performed research/study. AF, MK, KT, TH, KM, YS, RT, MK: analyzed data. JK: designed research/study.

**Conflict of interest**

The authors declare that they have no conflicts of interest.
References


