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Evaluation of Short-Term Ruxolitinib Tapering Strategy Before Allogeneic Stem Cell Transplantation for Primary Myelofibrosis Through the Transition of Serum Cytokines and Growth Factors

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Ruxolitinib (Ruxo), a Janus kinase (JAK) 1/2 inhibitor, has recently been launched for treatment of myelofibrosis (MF)[1]; however, safety of the discontinuation of Ruxo before allogeneic hematopoietic stem cell transplantation (allo-HSCT) for MF is still controversial.[2-5]

We conducted a pilot study in patients with MF treated with Ruxo prior to allo-HSCT. Ruxolitinib was tapered off 24 hours before administration of reduced intensity conditioning regimen consisted of fludarabine (180 mg/m^2), intravenous busulfan (9.6 mg/kg), and 4 Gy total body irradiation. Graft-versus-host disease prophylaxis is a combination of tacrolimus and short-term methotrexate. Serum samples were collected to measure levels of IL-1β, IL-6, IL-8, IL-12, soluble IL-2 receptor (sIL-2R), tumor necrosis factor-α, monocyte chemotactic protein-1, vascular endothelial growth factor (VEGF), and fibroblast growth factors basic, which were known to be upregulated in patients with MF,[6,7] by enzyme-linked immunosorbent assay. This study (UMIN000019421) was approved by the institutional ethics board.

Two patients were enrolled in this study. Case 1 was a 64-year-old man with primary MF with JAK2 V617F mutation and disease status at the administration of Ruxo was Intermediate-2 risk as Dynamic International Prognostic Scoring System (DIPSS)[8] and high risk as DIPSS plus.[9] Ruxolitinib was administered at a maximum dose of 20 mg/d for 2 months until peripheral blood stem cell transplantation from HLA 8/8 match related donor. Case 2 was a 68-year-old woman with primary MF with JAK2 V617F mutation. Disease status was intermediate-1 risk as DIPSS and intermediate-2 risk as DIPSS plus. Ruxolitinib was given at a maximum dose of 20 mg/d for 4 months until bone marrow transplantation from HLA 8/8 matched unrelated donor. In both patients, Ruxo treatment improved splenomegaly without severe complications and no disease progression or withdrawal symptom developed after the discontinuation of Ruxo and during allo-HSCT (Figure 1). Both patients achieved engraftment with complete donor chimerism by day 28 after allo-HSCT.

Serum levels of VEGF, IL-6 and sIL-2R were decreased after the administration of Ruxo. Serum levels of IL-6, and sIL-2R were significantly increased after the discontinuation of Ruxo, and further increased after allo-HSCT. On the other hands, serum level of VEGF was also slightly increased after the discontinuation of Ruxo; however, the elevation was temporary and showed a stable transition during allo-HSCT, consistent with the disease status of MF (Figure 1). Serum levels of monocyte chemotactic protein-1 and IL-8 were not changed before and after the administration of Ruxo but were increased during allo-HSCT, and the transition of serum levels of other cytokines and a growth factor did not show any consistent tendency during allo-HSCT.

This preliminary study suggested that our Ruxo tapering strategy is safe without causing disease progression or withdrawal symptom despite of the elevation of serum levels of cytokines and a growth factor. A recent study reported that proinflammatory parameters including IL-6 and sIL-2R decreased significantly after the initiation of Ruxo.[10] Immediate administration of the conditioning regimen after the discontinuation of Ruxo may inhibit a hyperactivation of immune cells subsequently caused by upregulation of cytokines including IL-6 or sIL-2R. Serum levels of VEGF might reflect disease status of MF possibly unaffected by

Received 5 May 2016. Revision requested 17 May 2016.

Accepted 19 May 2016.

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The authors declare no funding or conflicts of interest.

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ISSN: 2373-8731

Transplantation Direct 2016;2: e95; doi: 10.1097/TXD.0000000000000607
Published online 22 July 2016.

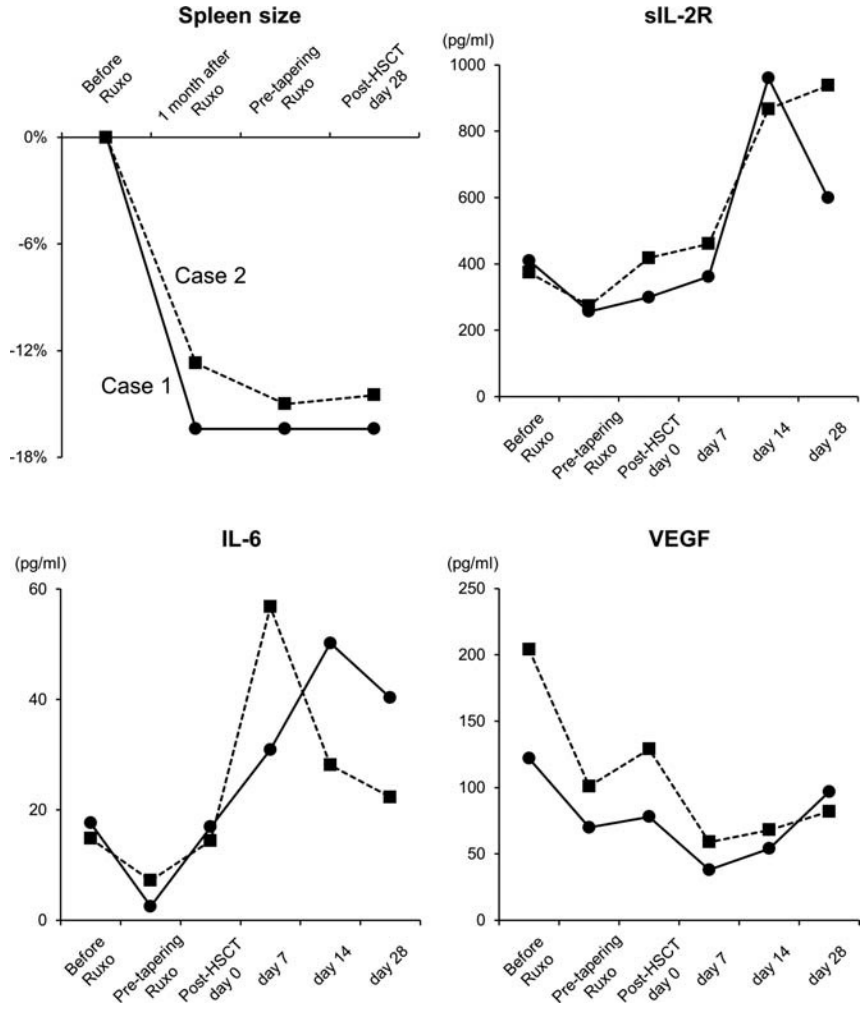

FIGURE 1. Transition of spleen size, IL-6, sIL-2R, and VEGF before and after the start of Ruxo and during allo-HSCT.

engraftment or GVHD during allo-HSCT, although these results need to be validated in a larger study.

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