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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

Souichi Shiratori, MD, PhD,1,2 Takahiro Tateno, MD,1 Shinichi Ito, MD,1 Yutaka Tsutsumi, MD, PhD,1 and Takanori Teshima2

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/m²), 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)9 and high risk as DIPSS plus.8 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

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

REFERENCES


