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Author(s)	Shiratori, Souichi; Tateno, Takahiro; Ito, Shinichi; Tsutsumi, Yutaka; Teshima, Takanori
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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-1 β , IL-6, IL-8, IL-12, soluble IL-2 receptor (sIL-2R), tumor necrosis factor- α , monocyte chemoattractant 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 chemoattractant 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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¹ Department of Hematology, Hakodate Municipal Hospital, Hakodate, Hokkaido, Japan.

² Department of Hematology, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan.

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Correspondence: Souichi Shiratori, MD, PhD, Department of Hematology, Hokkaido University Graduate School of Medicine, W7, N15, Kita-ku, Sapporo, Hokkaido, 060-8638, Japan. (s.shiratori@med.hokudai.ac.jp).

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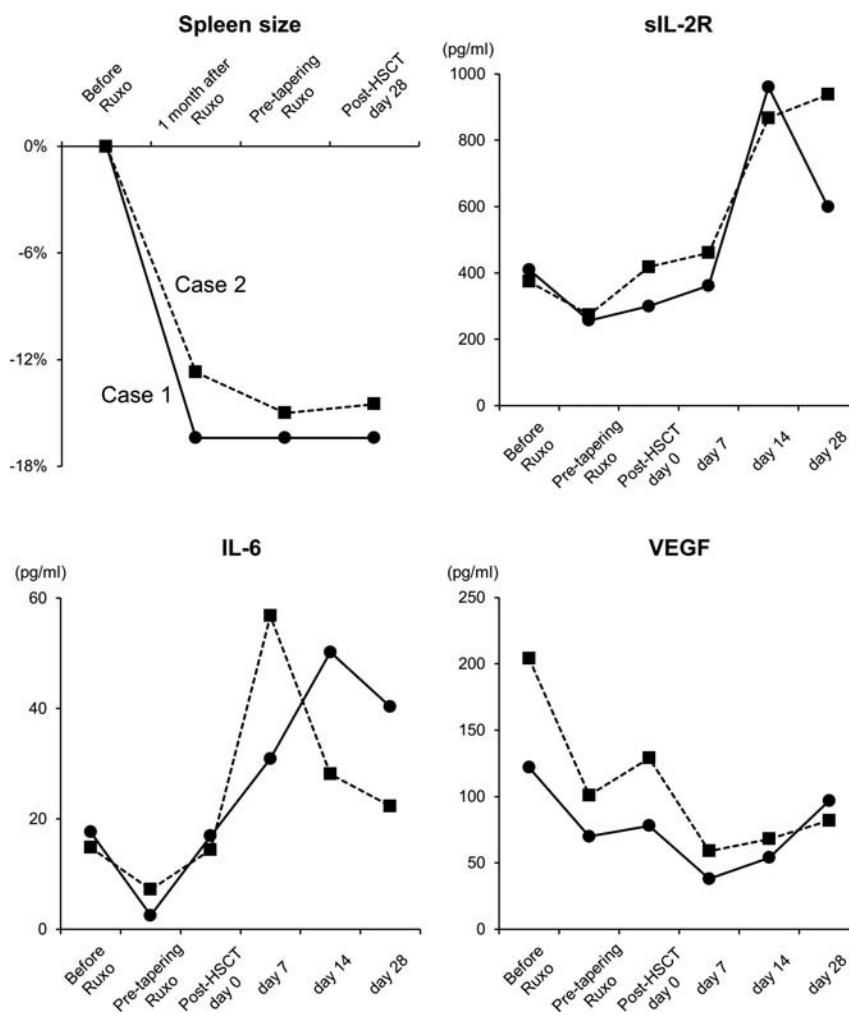


FIGURE 1. Transition of spleen size, IL-6, sIL-2R, and VEGF before and after the start of Ruxo and during allo-HSCT.

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

REFERENCES

- Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med*. 2012; 366:787.
- Robin M, Francois S, Huynh A, et al. Ruxolitinib before allogeneic hematopoietic stem cell transplantation (HSCT) in patients with myelofibrosis: a preliminary descriptive report of the JAK ALLO Study, a phase II trial sponsored by Goelams-FIM in collaboration with the Sfgmtc. *Blood*. 2013; 122:306.
- Jaekel N, Behre G, Behning A, et al. Allogeneic hematopoietic cell transplantation for myelofibrosis in patients pretreated with the JAK1 and JAK2 inhibitor ruxolitinib. *Bone Marrow Transplant*. 2014;49:179.
- Stübig T, Alchalby H, Ditschkowski M, et al. JAK inhibition with ruxolitinib as pretreatment for allogeneic stem cell transplantation in primary or post-ET/PV myelofibrosis. *Leukemia*. 2014;28:1736–1738.
- Shanavas M, Popat U, Michaelis LC, et al. Outcomes of allogeneic hematopoietic cell transplantation in patients with myelofibrosis with prior exposure to janus kinase 1/2 inhibitors. *Biol Blood Marrow Transplant*. 2016; 22:432–440.
- Tefferi A, Vaidya R, Caramazza D, et al. Circulating interleukin (IL)-8, IL-2R, IL-12, and IL-15 levels are independently prognostic in primary myelofibrosis: a comprehensive cytokine profiling study. *J Clin Oncol*. 2011;29:1356.
- Hasselbalch HC. The role of cytokines in the initiation and progression of myelofibrosis. *Cytokine Growth Factor Rev*. 2013;24:133.
- Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). *Blood*. 2010;115:1703–1708.
- Gangat N, Caramazza D, Vaidya R, et al. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. *J Clin Oncol*. 2011;29:392–397.
- Zeiser R, Burchert A, Lengerke C, et al. Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. *Leukemia*. 2015;29:2062–2068.