The Impact of Jak1/Jak2 Inhibitor Ruxolitinib on the Spleen Size and Symptom Burden in Myeloproliferative Diseases

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ABSTRACT

Ruxolitinib as a JAK1 and JAK2 inhibitor drug has recently been approved for the treatment of patients with high- or intermediate-risk myelofibrosis with symptomatic splenomegaly. Clinical development of ruxolitinib has currently focused on the Ph* negative myeloproliferative neoplastic disorders (MPN). The aim of this study is to assess the impact of ruxolitinib treatment on the clinical course of Ph* negative myeloproliferative disorders. Forty-three patients who were under ruxolitinib treatment and followed-up between years 1987-2015 in Hacettepe University Medical School Hematology Clinic and Ondokuz Mayis University Hematology Clinic with myeloproliferative disease without Philadephia chromosome translocation were retrospectively analyzed. The constitutional symptoms were decreased in 97% of patients after ruxolitinib treatment. The mean spleen sizes before and after ruxolitinib treatment were 229±35 versus 202±31 mm, respectively (p< 0.001). In this study, we observed a reduction in spleen size after ruxolitinib treatment in Turkish patients with MPN and this reduction was statistically significant. Moreover, nearly all of the MPN patients' constitutional symptoms were improved. Those observations are concordant with other geographical MPN data obtained from different countries. Further experimental and clinical studies into the efficacy and safety of ruxolitinib in patients with MPN are necessary to elucidate its role in special subgroups of MPN patients, such as patients undergoing hematopoietic stem cell transplantation and the patients with vascular disorders such as hepatoportal thrombosis.

Keywords: Ruxolitinib, Spleen size, Symptom burden, Myeloproliferative diseases

ÖZET

Myeloproliferatif Hastalıklarda Jak1/Jak2 İnhibitörü Ruksolitinib'in Dalak Boyutu ve Hastalık Semptomları Üzerindeki Etkisi

Ruksolitinib, semptomatik splenomegalisi olan orta ve yüksek riskli myelofibrosis hastalarının tedavisinde kullanımı onaylanmış bir JAK1 ve JAK2 inhibitörüdür. Ruksolitinibin günümüzdeki klinik gelişimi Ph* negatif miyeloproliferatif neoplastik hastalıklar (MNH) üzerine odaklanmıştır. Bu çalışmanın amacı, ruksolitinib tedavisinin Ph* negative MNH'ın klinik seyri üzerindeki etkisini araştırmaktır. Ruksolitinib tedavisi alan ve Hacettepe Üniversitesi Tıp Fakültesi Hematoloji Kliniği ve Ondokuz Mayıs Üniversitesi Hematoloji Kliniği'nde 1987-2015 yılları arasında takip edilen toplam 43 filadelfiya kromozom translokasyonu negatif miyeloproliferatif neoplazi hastası geriye dönük olarak analiz edilmiştir. Hastaların %97'sinde ruksolitinib tedavisi sonrası konstitüsyonel semptomlarda azalma saptanmıştır. Ruksolitinib tedavisi öncesi ve sonrası ortalama dalak boyutu, sırasıyla 229±35 mm'ye karşı 202±31 mm olarak saptanmıştır (p< 0.001). Biz bu çalışmada, ruksolitinib tedavisi alan miyeloproliferatif neoplazi hastalarında dalak boyutlarında istatistiksel olarak anlamlı bir küçülme saptadık. Ayrıca, çalışmaya katılan hastaların tamamına yakınında konsitusyonel semptomlarda ruksolitinib tedavisi sonrası azalma saptandı. Bu veriler farklı ülkelerde ve coğrafi bölgelerde yapılmış olan diğer araştırmalarla uyumludur. Hematopoietik kök hücre nakli ve hepatoportal tromboz gibi myeloproliferatif hastalıkların alt gruplarında, ruksolitinibin etkinlik ve güvenilirliğini araştırmayı hedefleyen klinik ve deneysel çalışmaların gelecekte yapılmasına ihtiyaç vardır.

Anahtar Kelimeler: Ruksolitinib, Dalak boyutu, Konstitusyonel semptomlar, Miyeloproliferatif hastalıklar

INTRODUCTION

The Janus kinase 2 (JAK2) mutations are detected nearly all of the polycytemia vera (PV) cases and nearly half of the essential trombocytosis or primary myelofibrosis cases.[1] JAK2 is a gene found on the short arm of chromosome 9 and it is related with the hypersensitivity of progenitor cells to growth factors in myeloproliferative neoplasia (MPN). JAK1 and JAK2 induced signal transducer and activators of transcription (STATs) leads to the modification of gene expression. Ruxolitinib is a Janus kinase inhibitor which inhibits the dysregulated JAK signaling.[2-4]

Ruxolitinib as a JAK1 and JAK2 inhibitor drug has recently been approved for the treatment of patients with high- or intermediate-risk myelofibrosis (MF) with symptomatic splenomegaly.[5] This approval in MF depends upon two different phase 3 randomized clinical trials (RCT) namely COMFORT-I and COMFORT-II.[6,7] COMFORT-I compared ruxolitinib with placebo in 309 patients with MF, whereas COMFORT-II compared the drug with the best-available therapy (mostly hydroxyurea) in 219 MF patients. Both of the RCTs attained the primary endpoint of > 35% reduction in spleen size, as measured by imaging techniques, at the 24 or 48 weeks of the ruxolitinib treatment initiations.[8-10] Clinical development of ruxolitinib has currently focused on the Ph* negative myeloproliferative neoplastic disorders.

The aim of this study is to assess the impact of ruxolitinib treatment on the clinical course of Ph* negative myeloproliferative disorders. The need of pharmacobiological assessments in addition to the risk profile for ruxolitinib in MPN is required in different patient populations Worldwide.

PATIENTS AND METHODS

All patients who were under ruxolitinib treatment and followed-up between years 1987-2015 in Hacettepe University Medical School Hematology Clinic and Ondokuz Mayis University Hematology Clinic with myeloproliferative disease without Philadephia chromosome translocation were retrospectively analyzed. There were a total of 43 patients. 25 patients were followed-up in Ondokuz Mayis University Hematology Clinic, whereas 18 patients were followed-up in Hacettepe University Medical School Hematology Clinic. All of the ethical considerations were strictly handled in accordance with the Helsinki Declaration. Patients' age of diagnosis, gender, constitutional symptoms, spleen size before and after ruxolitinib treatment and other clinical parameters were noted. All of the Ruxolitinib drugs have been obtained from the official compassionate use program approved by the Turkish health authorities (T.C. Ilac Eczacılık Genel Mudurlugu). Retrospective evaluation of the patient report forms were performed within the file archives of Samsun 19 Mayis University Medical School and Hacettepe University Medical School Hematology Departments.

Statistical Analysis

Statistical Packages for the Social Sciences v20.0 (SPSS Inc., Chicago, Ill., USA) software was used for statistical analyses. Data were given as median (minimum-maximum). Bivariate correlation analysis for categorical and continuous data was performed by Spearman's and Pearson's correlation analysis. A p value below 0.05 was considered as statistically significant.

RESULTS

There were total 43 patients with MPN. Types of MPN among the patients were polycythemia Vera, essential thrombocytosis, myelofibrosis and overlap syndromes in 13, 7, 21 and 2 patients, respectively. The main demographic parameters of participants were given in Table 1. There was no family history of myeloproliferative diseases among participants. Hepatomegaly was detected in 90% of the patients whereas pruritus was present only 47% of the patients. Minor neurological and constitutional symptoms were observed in 48% and 90% of the patients, respectively. There was thrombosis and bleeding history before diagnosis in 11% and 8% of the patients, respectively. Sites of thrombosis before diagnosis were, portal vein thrombosis, deep vein thrombosis, cerebrovascular event in 50%, 25%, 25% of patients, respectively. Sites of bleeding episodes before diagnosis were epistaxis, gingival hemorrhage in 64% and 36% patients, respectively. Antiplatelet, androgen and

Table 1. Essential clinical parameters of the studied patients with myeloproliferative diseases

Parameter	Data
Age	61 (37-79)
Gender (F/M)	16/27
Spleen size before ruxolitinib(mm)	224 (158-307)
Cardiovascular risk (Y/N)(%)	32/68
White blood cell (x10^3/µl)	12.3 (2.7-55.5)
Platelet (x10^3/µl)	385 (42-1920)
Hemoglobin (g/dl)	10 (7-21)
LDH elevation (Y/N)(%)	87/13
Presence of mutation analysis (Y/N)(%)	95/5
JAK-2 mutation (Y/N/borderline)(%)	63/35/2
MPL mutation (Y/N)(%)	22/78
Secondary myelofibrosis (Y/N)(%)	37/63
Red blood cell transfusion history (Y/N)(%)	50/50

Y: Yes; N: No

steroid treatments were present in 91%, 39% and 12% patients, respectively. No patients had history of erythrocyte stimulating agent treatment. Splenectomy was performed only in 6% of the patients. Only two patients had concomitant cancer history. These were cholangiocellular in one patient and gastric cancer in the other patient. Only in one patient, the blast count in bone marrow aspiration was higher than 5%. Leukemic transformation was observed in only one patient. No patients were undergone hematopoietic stem cell transplantation. Conventional cytogenetic analysis was applied in 6 patients. 4 patients had normal karyotype and 2 patients had complex karyotype. 6 patients were lost. Exitus reasons were pneumonia in 2 patients, myocardial infarction, acute respiratory distress syndrome, sepsis and cholangiocellular carcinoma in each other patients. The treatment data were given in Table 2. All patients had first line cytoreductive treatment. Anagrelide was not used as first line treatment agent in our patients. 37% of patients had second line treatment. Hydroxycarbamide was not used as second line treatment agent in our patients. Only one patient had third line treatment and interferon was given to this patient for 15 months. Ruxolitinib treatment details were given in Table 3. 55% of patients were using ruxolitinib with dosage of 40 mg. Ruxolitinib was solely used in 64% patients. In 23% patients it was used with hydroxycarbamide, 7% with hydroxycarbamide +interferon, 3% with anagrelide, 3% with hydroxycarbamide + anagrelide. The mean spleen sizes before and after ruxolitinib treatment were 229±35 mm versus 202±31, respectively (p value<0.001).

Table 3. Ruxolitinib treatment details of the studied patients with myeloproliferative diseases

Treatment details	Data
Ruxolitinib dosage (mg)	40 (10-80)
Duration of ruxolitinib (months)	14 (1-34)
Improvement of constitutional symptoms after ruxolitinib (Y/N) (%)	97/3
Spleen size after ruxolitinib treatment (mm)	201 (140-270)

DISCUSSION

In this study, we observed a reduction in spleen size after ruxolitinib treatment in Turkish patients with MPN and this reduction was statistically significant. Moreover, nearly all of the MPN patients' constitutional symptoms were improved. Those observations are concordant with other geographical MPN data obtained from different countries such as Taiwan[11], Japan[12], Korea[13], Denmark[14], Finland[15], Israel[16], United States[17] and other parts of the World[18].

Table 2. Treatment types and durations of the studied patients with myeloproliferative diseases

Treatment Type	Data
First line treatment (Hydroxycarbamide/thalidomide/interferon)(%)	94/3/3
Duration for the first line treatment (months)	29 (4-148)
Second line treatment (Interferon/thalidomide/anagrelide)	38/31/31
Duration for the second line treatment (months)	10 (1-92)

Ruxolitinib is a "JAK-STAT signaling pathway inhibitor" targeted drug with predictable pharmacobiological actions.[19] The main function of JAK-STAT signaling pathway is cellular proliferation in health and disease. Ruxolitinib should, thus, be considered as an "anti-proliferative" medicine.[2] Therefore ruxolitinib has the potential to inhibit neoplastic cellular proliferation of MPN and can cause cytopenias due to its "anti-proliferative" effects at any hematopoietic lineage. Current view of ruxolitinib in MPN is dependent upon mainly the disease risk profile of the given MPN entity.[20] However, this risk-only approach is not sufficient and can cause mechanistic, wrong way of decision that ruxolitinib is unnecessary in low-risk MPN at all. Likewise, ruxolitinib may be considered as ineffective, useless, harmful, dangerous in (very) high-risk advanced/terminal MPN due to cytopenias of the drug itself. Ruxolitinib could precipitate anemia, leukopenia, and thrombocytopenia in an already pancytopenic patient with MPN.[2] However, there are some initial clues that ruxolitinib can reverse bone marrow fibrosis in MPN if the patient population (such as hyperproliferative bone marrow with splenomegaly and peripheral cytosis) is carefully selected and long-time exposure to the drug (such as 48 months) would be possible.[21,22] Bone marrow microenvironment may be modulated via ruxolitinib in MPN.[23] Ruxolitinib is also an effective treatment for CALR-positive patients with myelofibrosis.[24]

We have previously proposed that the ideal MPN population that ruxolitinib shall be administered; i.e; hyperproliferative bone marrow with or without fibrosis and peripheral cytosis and organomegaly.[2] MPN disease risk categories of the specific MPN patient populations shall be detected as well as the established Ruxolitinib effects (decreased spleen size, symptom burden). Our present data supported this notion and future trials could be designed to test those hypotheses. Angona and coworkers searched the effects of ruxolitinib on hematopoietic stem cells (HSCs, CD34+ CD38-), hematopoietic progenitor cells (HPCs, CD34+ CD38+) and granulocytes from the patients with JAK2V617F(+) myeloproliferative neoplasms.[25] They indicated that ruxolitinib had clinical benefit in terms of reduction of the spleen size in spite of a minimal effect on the JAK2 V617F mutant allele burden of HSCs and HPCs.[25] Therefore the impact of ruxolitinib on the spleen size and symptom burden in MPN is not restricted with the positivity of JAK2 mutations as of our present MPN patient group. Based on the results of Phase III clinical studies, ruxolitinib provided rapid and durable improvement of myelofibrosis-related splenomegaly and symptoms irrespective of mutation status, and was associated with a survival advantage compared with placebo or best available therapy.[8,26]

The treatment with ruxolitinib alleviates symptom burden and improves quality of life of patients with advanced MPN also without clinically significant splenomegaly.[27] We have also observed symptomatic relief in our patient cohort without enormously enlarged spleen in the present study. The positive effect of ruxolitinib on patient symptoms is not related to reduction of spleen size. On the other hand, hemoglobin changes on ruxolitinib treatment may not be the same prognostic implications as hemoglobin changes that occur as a consequence of myelofibrosis progression. Therefore transient hemoglobin changes during ruxolitinib therapy should not lead to premature interruption or discontinuation.[28] The same logic shall be applied to thrombocytopenia.[29] We observed the positive impact of ruxolitinib on the spleen size and symptom burden in our cytopenic MPN patient group as well.

Further experimental and clinical studies into the efficacy and safety of ruxolitinib in patients with MPN are necessary to elucidate its role in special subgroups of MPN patients, such as patients undergoing hematopoietic stem cell transplantation[30-32] and the patients with vascular disorders such as hepatoportal thrombosis.

Conflict of Interest Statement

The authors of this paper have no conflicts of interest, including specific financial interests, relationships and/ or affiliations relevant to the subject matter or materials included.

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