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Ruxolitinib use in myelofibrosis patients: the single center experience and the relationship between JAK-2 allele burden and Ruxolitinib response

Myelofibrozis hastalarında Ruxolitinib kullanımı: tek merkez deneyimi ve JAK-2 allel yükü ile Ruxolitinib yanıtı arasındaki ilişki

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Abstract

Purpose: Ruxolitinib is an oral JAK-1/2 inhibitor approved for the treatment of splenomegaly and/or constitutional symptoms in intermediate and high-risk myelofibrosis patients. The aim of our study is to evaluate the efficacy and safety of ruxolitinib in primary MF, post-ET MF and post-PV MF patients, to evaluate the relationship between response and JAK-2 allele burden and to compare them with literature data.

Materials and methods: In our single centered and retrospective study, we investigated the data of 30 MF patients diagnosed in our clinic between May 2015 and December 2019. We reported demographic features, laboratory values, and spleen sizes.

Results: 18 patients (60%) with a median age of 67.5 (45-78) had primary myelofibrosis. Spleen sizes decreased significantly 3 and 6 months after treatment. Constitutional symptoms have disappeared in 28 patients (93.3%). No association was found between JAK-2 allele burden and treatment response success.

Conclusion: Ruxolitinib MF is very safe and effective to relieve constitutional symptoms and decrease spleen size. Despite JAK-2 inhibition, no linear relationship was found between JAK-2 allele burden and treatment efficacy.

Key words: Ruxolitinib, efficacy, jak2 mutation, myelofibrosis, response rate.

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Özet

Amaç: Ruksolitinib, intermediate ve yüksek risk myelofibrozis hastalarında splenomegali ve/veya konstitusyonel semptomların tedavisi için onay almış oral olarak kullanılan bir JAK-1/2 inhibitörüdür. Bu çalışmamızda amacımız primer MF, post-ET MF ve post-PV MF hastalarında ruksolitinibin etkinlik ve güvenirliliğini değerlendirmek, JAK-2 allel yüküyle yanıt ilişkisini değerlendirmek ve literatür verileriyle karşılaştırmaktır.

Gereç ve yöntem: Tek merkezli ve retrospektif çalışmamızda kliniğimizde Mayıs 2015 ile Aralık 2019 tarihleri arasında tanı almış 30 MF hastasının verilerini dosyalarından inceledik. Demografik özelliklerini, laboratuvar değerlerini ve dalak boyutlarını kaydettik.

Bulgular: Mediyan yaşları 67,5 (45-78) olan hastaların 18 tanesi (%60) primer myelofibrozis hastasıydı. Ruksolitinib tedavisi sonrası 3.ay ve 6.ayda hastaların dalak boyutlarında anlamlı azalma saptandı. Hastaların 28 tanesinin (%93,3) konstitusyonel semptomları kayboldu. JAK-2 allel yüküyle tedavi yanıt başarısı arasında ilişki saptanmadı.

Tartışma: Ruxolitinib MF tedavisinde hem konstitusyonel semptomları ortadan kaldırmada hem de dalak boyutunda azalma sağlamada oldukça etkin ve güvenlidir. JAK-2 inhibisyonu yapmasına rağmen JAK-2 allel yükü ile tedavi etkinliği arasında ise lineer bir ilişki yoktur.

Anahtar kelimeler: Ruksolitinib, etkinlik, jak2 mutasyonu, myelofibrozis, yanıt oranı.

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Introduction

Chronic myeloproliferative neoplasms (MPN) are a group of bone marrow diseases with molecular abnormalities resulting in uncontrolled cell proliferation, and thus, increased mature cells in peripheral blood [1]. According to the recent classification of the World Health Organization (WHO), polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) are the most common BCR-ABL negative myeloproliferative neoplasms [2]. Myelofibrosis is the most aggressive one in this group [2].

Myelofibrosis, a rare chronic disease, may occur as de novo (primary MF) or as myelofibrotic transformation (post-ET MF or post-PV MF) of other MPNs such as ET or PV [2-4]. MF is clinically characterized by progressive anemia (cytopenias), bone marrow fibrosis and extramedullary hematopoiesis accompanied by splenomegaly and/or hepatomegaly. In addition, constitutional symptoms (fever, night sweats, itching, weight loss, fatigue, bone pain and feeling of early satiety), thromboembolic events and infections may often present in the clinical picture [5, 6]. Besides, there is a risk of acute leukemia transformation in the next stages of the disease [6].

The pathogenesis of myelofibrosis is complex and hasn't been fully clarified yet. Signal disorder and overactivity in the JAK-STAT pathway are the main accepted theory in the pathogenesis and clinical signs of MF [7, 8]. It is considered that $JAK2^{V617F}$, CALR and MPL are major mutations leading to myelofibrosis [9]. Ruxolitinib is an oral JAK-1 and JAK-2 inhibitor approved for the treatment of intermediate and high-risk myelofibrosis [10, 11]. The studies showed that Ruxolitinib treatment has decreased spleen volume and improved constitutional symptoms [12-14]. Before ruxolitinib, allogeneic stem cell transplant was the only treatment method having potential to reverse fibrosis and provide cure [15, 16].

Our aim in this single-centered study is to evaluate the efficacy and safety of ruxolitinib in primary MF, post-ET MF and post-PV MF patients in real-life practice and to compare them with literature data. However, we plan to study the presence of JAK-2 mutation and whether there is a relationship between the JAK-2 allele burden and the ruxolitinib response.

Materials and methods

Study design

This study is an observational, non-interventional, single-centered and retrospective study to evaluate the effect and side effect profile of ruxolitinib. Patients over 18 years old, diagnosed with primary myelofibrosis (PMF), post polycythemia vera myelofibrosis (post-PVMF) and post essential thrombocythemia myelofibrosis (post-ET MF) between May 2015 and December 2019 were included in the study. At least 3 months use of ruxolitinib treatment was required. Demographic features, laboratory values, spleen sizes measured (on pre-treatment and follow-up visits) by ultrasonography, constitutional symptoms, side effect profile and management were noted. In addition, the presence of JAK-2 mutation and the JAK-2 allele burden were also studied, and the relationship between post-treatment response rates was compared. The risk classification of patients was performed by Dynamic International Prognostic Scoring System (DIPSS) -plus scoring system [17]. Spleen size and constitutional symptoms were evaluated as the most important follow-up criteria. Response was evaluated by the 2013 IWG-MRT/ELN criteria [18].

The hospital management and Antalya Training and Research Hospital Ethics Committee have approved the use of patient data. The study was performed in line with ethical principles of the Helsinki Declaration.

Statistical analysis

Descriptive statistical analysis was performed with the statistical program SPSS software (IBM SPSS Statistics 22, IBM Corporation, Chicago, IL). Changes from baseline or crossover baseline in spleen volume were summarized with descriptive statistics. Continuous variables were expressed as median and ranges, and categorical variables were presented as frequencies and percentages. Spearman correlation test was performed for the relationship between JAK-2 allele burden and treatment response. The P value for statistical significance was set to $p<0.05$.

Results

The median age of 30 patients on ruxolitinib was 67.5 (45-78), they were followed up in our clinic and their files were screened retrospectively. Demographic and clinical characteristics of the patients were presented in Table 1. Seven (23.3%) of these patients were female and 23 (66.7%) were male. 18 (60.0%) patients on ruxolitinib had primary myelofibrosis, 6 (20%) patients had post-ET myelofibrosis and 6 (20%) patients had post-PV myelofibrosis. The most common complaint or sign was cytopenia (10 patients (33.3%)). However, all patients had constitutional symptoms at the treatment initiation. Constitutional symptoms disappeared completely in 23 (66.7%) patients at the end of the first 3 months and 28 (93.3%) at the end of the 6th month. The risk classification of the patients by DIPSS-plus scoring system: 3 patients (10.0%) were in intermediate-1, 20 patients (66.6%) were in intermediate-2 and 7 patients (23.4%) were in high risk group. Ruxolitinib was not initiated in the low-risk patient group.

Table 1. Demographic and clinical features of the patients

Demographic and Clinical Features	n=30 (100)
Median age	**67.5 (45-78)**
Gender Female / Male n (%)	7/23 (23.3/66.7)
Diagnosis n (%)	
PMF	18 (60.0)
Post-PV MF	6 (20.0)
Post-ET MF	6 (20.0)
Complaint-Symptom at Admission	
Thrombocytosis	5 (16.7)
Hb increased	6 (20.0)
Cytopenia	10 (33.3)
Weakness-fatigue	9 (30.0)
Constitutional Symptom	30 (100)
DİPSS plus score	
intermediate-1	3 (10.0)
intermediate-2	20 (66.6)
High Risk	7 (23.4)
Time to Fibrosis Progression (Non-PMF)	47 (4-135)
BM reticulin fibrosis	
Grade 0-1	5 (16.7)
Grade 2-3	25 (83.3)
BM collagen fibrosis	
Grade 0-1	7 (23.3)
Grade 2-3	23 (76.7)
HU treatment	27 (90.0)
HU treatment time; median month	4 (1-73)
Anagrelide treatment	2 (6.7)
Anagrelide treatment time; median month	91.5 (63-120)
Ruxolitinib treatment dose	
2x5 mg	3 (10.0)
2x15 mg	6 (20.0)
2x20 mg	21 (70.0)
Diagnosis-Ruxolitinib initiation median month	23.5 (1-147)
Ruxolitinib treatment time; median month	10 (3-33)

Table 1. Demographic and clinical features of the patients

Hb gr/dl	10.0 (7.0-14.5)
WBC $10^3/mm^3$	13100 (2400-63800)
PLT $10^3/mm^3$	268000 (44000-730000)
LDH u/l	408 (155-849)
Uric acid mg/dl	6.7 (3.7-12.4)
Hematological side effect n (%)	18 (60.0)
Is Ruxolitinib discontinued? n (%)	6 (20.0)
Is Ruxolitinib dose decreased? n (%)	13 (43.3)
molecular status	
JAK-2^{V617F}-positive n (%)	20 (66.7)
CALR-positive n (%)	1 (3.3)
MPL-positive n (%)	0 (0.0)
Triple negatıve n (%)	9 (30.0)

PMF: Primary myelofibrosis, Post-PV: Post-polycytemia vera, Post-ET: Post-essential thrombocythemia, DIPSS: Dynamic International Prognostic Scoring System, HB: hemoglobin, WBC: White blood cell, PLT: platelet, LDH: Lactate dehydrogenase, BM: Bone marrow, HU: Hydroxyurea, CALR: calreticulin, MPL: myeloproliferative leukemia virus oncogene

12 patients on ruxolitinib treatment were diagnosed with post-ET MF or post-PV MF. The median time to post-ET MF or post-PV MF progression was 47 (4-135) months after ET or PV were diagnosed. The evaluation of bone marrow biopsies showed that 25 (83.3%) patients had grade 2-3 reticulin fibrosis and 23 (76.7%) patients had grade 2-3 collagen fibrosis. 20 (66.7%) patients had JAK-2 mutation, while 9 (30.0%) patients did not have any JAK-2, CALR or MPL mutations. 27 (90.0%) patients had used hydroxyurea before ruxolitinib, while only 2 (6.7%) patients had used anagrelide. None of the patients used ruxolitinib as the first line treatment. The initial ruxolitinib dose was 2x20 mg in 21 (70.0%) patients. Anemia, thrombocytopenia or leukopenia developed in 18 (60.0%) patients during follow-u*p* period. Dose reduction was required in 13 (43.3%) patients due to side effects. Thrombocytopenia was the most common adverse event leading to dose reduction.

When ruxolitinib was initiated, median spleen size measured by ultrasonography (USG) was 210 mm (122-300). In the treatment follow-up, spleen sizes were measured as 180 mm (115-250) at 3rd month and 175 mm (110-270) at 6th month. The change in the spleen size is presented in Figure 1. Spleen size decreased significantly at 3rd and 6th months of ruxolitinib treatment ($X^2(2)=30.692$, $p=0.000$).

Spearman correlation test conducted to determine the relationship between JAK-2 allele burden and response rates at the 3rd and 6th month showed that there is no relationship between the JAK-2 allele burden and the response rate (treatment success) (r=0.192 and 0.218, $p=0.430$ and $p=0.454$). JAK-2 allele burden and response rates were presented in Table 2.

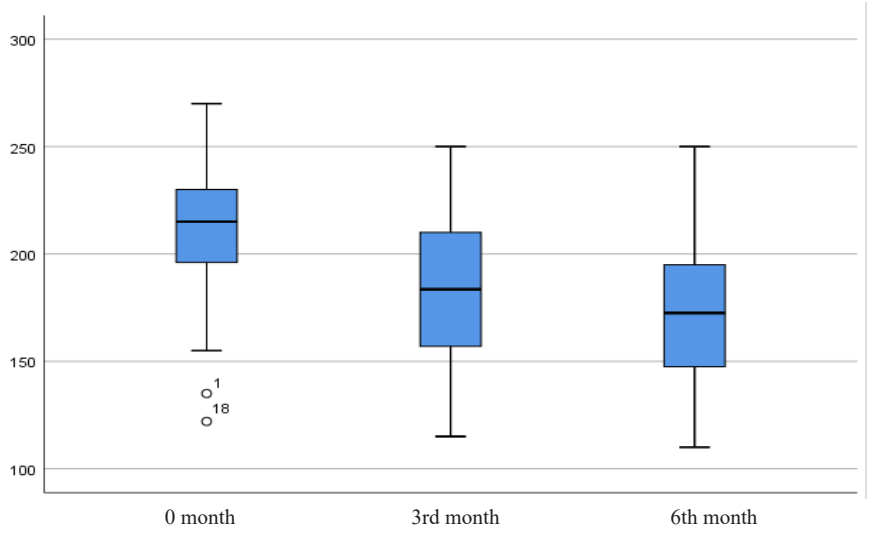

Figure 1. Spleen size in time

Table 2. Comparison of JAK-2 allele burden and Ruxolitinib response rates

Test		N	r	*p*
JAK-2 allele burden	3rd month response rate	19	0.192	0.430
	6th month response rate	14	0.218	0.454

Discussion

Ruxolitinib is a selective JAK-1/2 inhibitor used in the treatment of myelofibrosis (PMF, Post-ET MF and Post-PV MF). The double-blind, placebo-controlled studies proved its safety and efficacy to control splenomegaly and constitutional symptoms [14, 19, 20]. Our study proved its efficacy once again by the significant decrease in spleen size and managing constitutional symptoms. However, its safety was also reported since no adverse event leading to discontinuation was observed.

Intracellular tyrosine kinase JAK-2 plays a role in the growth and proliferation of erythropoietin and thrombopoetin receptors [21]. Ruxolitinib may cause selective JAK-1/2 inhibition, leading to anemia and/or thrombocytopenia. Recently developed anemia, thrombocytopenia or leukopenia were observed during treatment in 18 patients included in our study. However, only one patient had severe anemia requiring erythrocyte suspension support. Thrombocytopenia was more moderate and no transfusion support was needed. No complications due to thrombocytopenia have developed. However, dose adjustment was required due to the decreased platelet value in several patients. Besides all these, it has already been found in one study that low-dose ruxolitinib is effective in the treatment of MF [22]. Both anemia and platelet values improved in the next stages of the treatment. Several studies showed that anemia and thrombocytopenia may develop in the early stages of treatment, but this condition improves in the next weeks of the treatment continuation [19, 23, 24].

Rarely leukocytosis or thrombocytosis as well as anemia and thrombocytopenia may develop after hydroxyurea and anagrelide treatments are discontinued and Ruxolitinib treatment is initiated [25]. The control of the blood values is important to prevent thromboembolic complications. However, no standard treatment was determined for these patients. Ruxolitinib is known to provide optimum hematocrit management in patients and reduce the phlebotomy requirement [26]. However,

an additional treatment may be required for leukocytosis and thrombocytosis. In a recent study, it has been shown that ruxolitinib can be used alone or in combination for MF treatment [27]. Platelet level was increased (>1.500.000/ mm^3) in one of our patients after ruxolitinib treatment. Hydroxyurea was combined with Ruxolitinib in this patient. The platelet level was controlled without any adverse events. Several studies showed that successful results have been obtained with the addition of hydroxyurea when ruxolitinib treatment alone could not control leukocytosis and/or thrombocytosis [25]. It contributed to the control of splenomegaly and constitutional symptoms without a serious side effect potential [25].

The change in spleen size was the most important response criterion when examining our patients retrospectively. The relationship between the decrease in spleen size and mean survival has been observed in previous studies [28]. The spleen sizes of our patients at the 3rd and 6th months decreased significantly during the treatment as compared to the baseline dimensions. This has been evaluated as the efficacy of the treatment. In a previous study ruxolitinib was shown led to rapid and sustained reduction in spleen size within the first 6 months [29]. It is known that ruxolitinib treatment may reverse fibrosis in the bone marrow [30]. Extramedullary hematopoiesis improves with the regression of fibrosis and, in conclusion, the spleen size decreases.

Ruxolitinib not only reduces spleen size but also improves the constitutional symptom burden [26]. However higher doses of ruxolitinib were associated with higher spleen response rates, but not with symptom improvement [31]. Low-dose ruxolitinib has been shown to be effective on constitutional symptoms [22]. In several countries, it is approved for use in PMF, Post-ET MF and Post-PV MF patients with splenomegaly and/or symptoms due to the condition. In our two patients, ruxolitinib treatment was initiated for severe constitutional symptoms without splenomegaly. The treatment improved the symptoms of the patients completely.

We found that the efficacy of the JAK-2 inhibitor Ruxolitinib did not increase as the JAK-2 allele burden increased, and we found no linear relationship between the JAK-2 allele burden and efficacy. During Ruxolitinib treatment, it's observed that JAK-2 allele burden was significantly reduced as compared to the best applicable treatment [11, 30]. We consider that it might be the cause of not obtaining the expected increase in efficacy as JAK-2 allele burden increases. On the other hand, ruxolitinib efficacy was not only observed in JAK-2 positive patients but also in other CALR, MPL or triple negative patients.

In conclusion, Ruxolitinib is an effective and safe treatment method in PMF, Post-PV MF and Post-ET MF patients. Ruxolitinib is very effective to relieve constitutional symptoms and decrease spleen size. Despite JAK-2 inhibition, no linear relationship was found between JAK-2 allele burden and treatment efficacy.

Conflict of interest: No conflict of interest was declared by the authors.

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Contributions of the authors to the article

M.G. was the corresponding author who designed and wrote this study. M.G. and E.K. researched the data and contributed to discussion. M.G. and E.K. contributed to the interpretation of the results. Literature data were provided by M.G. and E.K., M.G. and E.K. discussed and approved the final manuscript.