Original Article

# Is Ruxolitinib an Effective and Safe Therapy for Chronic Myeloproliferative Diseases?

# Ruksolitinib Kronik Miyeloproliferatif Hastalık için Etkili ve Güvenli Bir Tedavi mi?

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**ABSTRACT**

**Introduction:** Polycythemia vera (PSV), essential thrombocytosis (ET), and primary myelofibrosis (PMF) are BCR/ABL negative chronic myeloproliferative neoplasms (CMPNs). As a result of abnormal clonal proliferation of hematopoietic cells, these disorders have a higher risk of thrombosis, bleeding, leukemic transformation, and worsening in quality of life. While stem cell transplantation is the sole curative option for CMPNs, symptomatic therapies gain importance. The purpose of this study is to assess the results of patients with CMPNs treated with ruxolitinib at our center.

**Methods:** The data from eighteen patients (six patients with PSV and twelve patients with PMF) who were treated with ruxolitinib at our center between January 2013 and January 2022 were analyzed in this retrospective cohort study.

**Results:** Six PSV patients who received ruxolitinib were included in the study. Three patients with splenomegaly previous to ruxolitinib, had a response of spleen volume, median of 6 months. There were no hematological or non-hematological adverse effects, thrombolytic or cardiovascular complications, or leukemic transformation throughout a median of 6 (range 2-52) months of ruxolitinib treatment.

Twelve patients with PMF used ruxolitinib were included in the study. Spleen volume response was observed in six patients (50%) at a median follow-up of 12 months, while symptomatic response was observed in nine patients (75%) during a median of 15.5 months of ruxolitinib treatment. Any thrombolytic or cardiovascular complications were observed.

**Discussion and Conclusion:** Ruxolitinib is an appropriate and safe treatment option for patients who are not candidates for hematopoietic stem cell transplantation.

**Keywords:** ruxolitinib, myelofibrosis, Polycythemia vera, JAK2 V617F, spleen

**ÖZET**

**Giriş ve Amaç:** Polisitemi vera (PSV), esansiyel trombositoz (ET) ve primer miyelofibroz (PMF), BCR/ABL negatif olan kronik miyeloproliferatif hastalıklardır (KMPH). Bu hastalıklarda hematopoietik hücrelerde anormal klonal proliferasyon sonucu artmış tromboz, kanama, lösemik transformasyon riski yanı sıra hayat kalitesinde bozulmalar görülmektedir. Hastalıkların tedavisinde kök hücre nakli tek küratif seçenek iken semptomatik tedaviler ön plana çıkmaktadır. Bu çalışmada amaç, merkezimizde ruksolitinib ile tedavi edilen KMPH hastalarının sonuçlarını değerlendirmektir.

**Yöntem ve Gereçler:** Bu retrospektif kohort çalışmada Ocak 2013 ile Ocak 2022 tarihleri arasında merkezimizde ruksolitinib ile tedavi edilen 18 hastanın (altı hasta PSV ve on iki hasta PMF) verileri analiz edildi.

**Bulgular:** Ruksolitinib alan altı PSV hastası çalışmaya alındı. Ruksolitinib öncesinde splenomegalisi olan üç hastada, ortanca 6 aylık tedavi süresince dalak hacmi yanıtı gözlendi. Ortanca 6 aylık (2-52

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aralığında) ruksolitinib tedavisi boyunca hematolojik veya hematolojik olmayan yan etkiler, trombolitik veya kardiyovasküler komplikasyonlar veya lösemik transformasyon görülmedi.
PMF tanısı ile ruksolitinib kullanan on iki hasta çalışmaya dahil edildi. Altı hastada (%50) ortanca 12 aylık takipte dalak hacmi yanıtı gözlenirken, dokuz hastada (%75) medyan 15,5 aylık ruksolitinib tedavisi sırasında semptomatik yanıt alındığı gözlendi. Trombolitik veya kardiyovasküler komplikasyon gözlenmedi.
**Tartışma ve Sonuç:** Hematopoietik kök hücre nakli için aday olmayan hastalarda ruksolitinib uygun ve güvenli bir tedavi seçeneğidir.

**Anahtar Kelimeler:** ruksolitinib, myelofibrozis, Polisitemia vera, JAK2 V617F, dalak

## Introduction

Polycythemia vera (PSV), essential thrombocytosis (ET), and primer myelofibrosis (PMF) are chronic myeloproliferative diseases (MPN) that are BCR/ABL negative. Polycythemia vera is a BCR/ABL negative chronic MPN characterized by abnormal clonal proliferation of hematopoietic cells, which results in elevated peripheral blood cells, increased thrombotic and hemorrhagic events, and the possibility of disease progression to PMF or acute myeloid leukemia (AML) [1]. Hydroxyurea (HU) is the first line of cytoreductive treatment [2]. If a patient is intolerant or non-responsive to HU and experiences an unexpected side effect, ruxolitinib is considered a second-line treatment [2]. The RESPONSE and RESPONSE-2 clinical trials demonstrated ruxolitinib's safety and efficacy in PSV patients [3, 4].

Primary myelofibrosis is a type of MPN characterized by bone marrow fibrosis, cytopenias, constitutional symptoms, hepatosplenomegaly, and/or extramedullary hematopoiesis [5]. Among the MPNs, PMF has the worst prognosis, with patients at risk of early death from disease progression, leukemic transformation, thrombohemorrhagic complications, and infections [5]. All PMF patients should aim to minimize their symptoms and improve their quality of life. Agents such as HU and ruxolitinib are used to treat symptoms and splenomegaly in patients who are not candidates for hematopoietic stem cell transplantation (HSCT). The first-line treatment for MF-related splenomegaly is HU [5]. Ruxolitinib is an effective treatment for HU-resistant or intolerant PMF patients who have constitutional symptoms and splenomegaly. The COMFORT-1 and COMFORT-2 clinical trials demonstrated the safety and efficacy of ruxolitinib.

Ruxolitinib is recommended as a second-line treatment for PSV and PMF at our institution. We aimed to evaluate the characteristics and outcomes of MPN patients treated with ruxolitinib at our institution.

## Methods

This retrospective cohort study examined data from patients with PSV and PMF treated at our center between January 2013 and January 2022, were analyzed. We evaluated the eighteen patients (six with PSV and twelve with PMF) who were treated with ruxolitinib. Manual file records and electronic medical record systems were used to obtain clinical information from patients. The demographics, comorbidities, disease diagnosis date, disease type, disease risk groups, therapy and response, last control date, and survival status of all patients were documented. The 2016 WHO classification was used for diagnosis [6].

The local human research ethics committee approved this study. All procedures performed in studies involving human participants were under the national research committee’s ethicalstandards and with the 1964 Helsinki Declaration and its later amendments or comparableethical standards. The study was carried out with the permission of the Ethics Committee of Ankara Onology hospital (24.08.2022 /Decision number: 2022.08/1981).

 

Table 1. Characteristics of patients with PSV who were treated with ruxolitinib

| Parameters | N =6, (%) |
|---|---|
| Age, median (range min-max), years | 63 (59-72) |
| Gender (M/F) | 2 (33.3) / 4 (66.7) |
| JAK2 V617F, allele burden, median (range min-max), % | 35 (20-67) |
| Splenomegaly | 3 (50) |
| Duration between the initiation of ruxolitinib treatment and the diagnosis of the disease, median (min-max), months | 30.5 (8-74) |
| Duration of ruxolitinib therapy, median (min-max), months | 6 (2-52) |
| Disease duration, median (min-max), months | 55 (10-82) |

*PSV; polycythemia vera, M; male, F; female*

Statistical Analysis

The SPSS software (Version 25.0; Armonk, NY: IBM Corp.) was used for statistical analysis. The numerical variables were presented as medians (min-max), while the categorical variables were presented as ratios. Disease duration was calculated as the time defined as the period between the date of PSV or PMF diagnosis and the date of last follow-up or death from any cause.

**Results**

Polycythemia vera

Between January 2000 and January 2022, 80 PSV patients were diagnosed, but only six of them received ruxolitinib treatment and were included in the study. The average age of the patients was 63 years (range 59-73 years). JAK2 V617F and cytogenetic abnormalities were tested in all patients. The JAK2 V617F mutation was found in all the patients, and the median allele load was 37%. (range 20-67%). They didn't have any cytogenetic abnormalities or extra mutations like calreticulin (CALR) or myeloproliferative leukemia (MPL).

In the bone marrow examination, four patients (66%) had grade 2/3 fibrosis. Half of the patients had splenomegaly at the time of presentation. Table 1 summarizes the characteristics of PSV patients treated with ruxolitinib.

In the six patients treated with ruxolitinib as a second-line treatment, the median duration was 30.5 (range 8-74) months between starting ruxolitinib and disease diagnosis. The reasons for changing to ruxolitinib as a second-line treatment were oral ulcers (two patients) after HU, symptomatic splenomegaly (two patients), and HU-intolerant patients (two patients).

There were no hematological or non-hematological adverse effects, thrombolytic or cardiovascular complications, or leukemic transformation throughout a median of 6 (range 2-52) months of ruxolitinib treatment. After a median of 6 months, three patients with splenomegaly prior to ruxolitinib had normal spleen volume (range 3-12 months). Only one patient had transformed myelofibrosis after 14 months of ruxolitinib treatment.

Myelofibrosis

Between January 2000 and January 2022, twelve patients were diagnosed with PMF and treated with ruxolitinib. The patients' median age was 68 years (range 25-80 years), with eight (66.7%) females. All cases were evaluated for JAK2 V617F, CALR, and MPL mutations as well as cytogenetic abnormalities.

 

Table 2. Characteristics of patients with PMF who were treated with ruxolitinib

| Parameters | N = 12, (%) |
|---|---|
| Age, median (range min-max), years | 68 (25-80) |
| Gender (M/F) | 4 (33.3) / 8 (66.7) |
| Genetic mutations,<br>JAK2 V617F mutation<br>CALR mutation<br>MPL mutation<br>Triple negative | <br>8 (66.7)<br>1 (8.3)<br>0<br>2 (16.7) |
| JAK2 V617F, allele burden, median (range min-max), % | 80 (22-91) |
| Bone marrow fibrosis,<br>Grade 2/3<br>Grade 3/3 | <br>10 (83.3)<br>2 (16.7) |
| Risk stratification, median (min-max)<br>MIPSS-70<br>DIPSS-plus | <br>5 (2-7)<br>1 (0-1) |
| Splenomegaly | 12 (100) |
| Duration between starting ruxolitinib and disease diagnosis, median (min-max), months | 16.5 (8-74) |
| Duration of ruxolitinib therapy, median (min-max), months | 12.5 (5-60) |
| Disease duration, median (min-max), months | 48.5 (7-214) |

*PMF; primary myelofibrosis, M; male, F; female, CALR; Calreticulin, MPL; myeloproliferative leukemia*

The JAK2 V617F mutation was found in eight patients (66.7%), with a median allele load of 80% (range 22-91%). Two (16.7%) of the patients had triple-negative disease. None of them had any cytogenetic abnormalities. Technical difficulties limited the evaluation of high molecular risk (HMR) mutations. In risk stratification, the median MIPSS-70 was 5 (2-7), while the DIPSS-plus was 1 (0-1). Four patients experienced ET and one had PSV before being diagnosed with PML. At the time of presentation, all the patients had splenomegaly. Table 2 summarizes the characteristics of PMF patients treated with ruxolitinib.

Because of HU resistance, nine (75%) patients received ruxolitinib as a second-line treatment. Ruxolitinib was used as first-line therapy in three patients. The median time between initiating ruxolitinib and disease diagnosis was 16.5 (range 8-74) months. Six patients (50%) had a response to decreased spleen volume (median 12 (6-24) months) and nine patients (75%) had a symptomatic response during a median of 15.5 (range 5-60) months of ruxolitinib treatment.

Three patients (25%) discontinued treatment; one suffered skin ulcers, one had disease progression with increased spleen volume, and one had AML transformation. One patient had thrombocytopenia during a median of 12.5 (range 5-60) months of ruxolitinib treatment, which was resolved by lowering the ruxolitinib dose. There were no thrombolytic or cardiovascular complications to report. Only one female patient transformed AML after 13 months of treatment with ruxolitinib. The patient had a long disease

 

duration (191 months), post-ET PMF, grade 2/3 fibrosis in the bone marrow, a negative JAK2 mutation, and a positive CALR mutation. Two patients died during therapy from unrelated causes of the disease.

**Discussion**

Polycythemia vera (PSV) is a condition characterized by clonal proliferation of hematopoietic cells, which results in elevated red blood cells, increased thrombotic events, and can progress to fibrosis or leukemia. The treatment's goal is to avoid thrombotic events and fibrotic/leukemic change while also improving quality of life. Ruxolitinib is used as a second-line treatment in HU-intolerant or nonresponder patients. Ruxolitinib was found to be safe and effective in PSV patients with and without splenomegaly in the RESPONSE and RESPONSE 2 clinical trials.

In our study, six patients with PSV who were intolerant or refractory to HU were treated with ruxolitinib. Three patients who had splenomegaly before ruxolitinib had normal spleen volume after a median of 6 months (range 3-12 months).

The RESPONSE study compared ruxolitinib to the best available treatment (BAT) in HU refractor/intolerant patients [3]. The trial results showed that ruxolitinib was superior to BAT in both hematocrit level control and lowering spleen volume [3]. Hematological and non-hematological adverse effects are comparable between the two arms of the trial; however, thrombotic events are more prevalent in the BAT arm [3]. Our patients with or without splenomegaly, received well-tolerated ruxolitinib treatment. During the median of 5.5 months (range 2-52 months) of ruxolitinib treatments, we did not observe any hematological or non-hematological side effects, thrombolytic and cardiovascular complications, or leukemic transformation. Only one female patient transformed myelofibrosis after 14 months of treatment with ruxolitinib. The patient had a long duration of disease (80 months) and splenomegaly, grade ⅔ fibrosis in the bone marrow, and a high JAK2 allele load.

Splenomegaly is found in 30-35% of PSV patients at the time of diagnosis, and it is considered to be associated with progressive disease [2]. These splenomegaly patients are more prone to develop myelofibrosis and AML [2]. Grade 2-3/3 bone marrow fibrosis is reported in 20-51% of PSV patients [7, 8], and these patients are more likely to progress to myelofibrosis [9]. Tefferi et al. demonstrated that the persistence of leukocytosis, fibrosis in the bone marrow at the time of diagnosis, and more than 50% JAK2 allele burden increase the probability of myelofibrosis transformation [10].

The RELIEF study demonstrated that ruxolitinib therapy reduced symptoms in PSV patients [11]. One of our study's shortcomings was that we did not evaluate patients' symptoms. The effects of ruxolitinib therapy on thrombotic events and disease progression to myelofibrosis or AML, have not been clearly demonstrated. A meta-analysis reported that patients on ruxolitinib therapy had fewer thrombotic events, but the difference was not statistically significant [12].

Myelofibrosis is a form of MPN characterized by fibrosis of the bone marrow, cytopenias, constitutional symptoms, hepatosplenomegaly, and/or extramedullary hematopoiesis [5]. Patients with PMF suffer an increased risk of death due to disease progression, leukemic transformation, thrombo-hemorrhagic complications, and infections [5]. All PMF patients should aim to minimize their symptoms and improve their quality of life. Ruxolitinib is an effective treatment for HU-resistant or intolerant PMF patients who have constitutional symptoms and splenomegaly. The COMFORT-1 and COMFORT-2 clinical trials established the safety and efficacy of ruxolitinib in patients with PMF [13, 14].

In our study, twelve patients were diagnosed with PMF and treated with ruxolitinib (nine patients as second-line and three patients as first-line). In the COMFORT-I trial, ruxolitinib was found to be more effective than placebo at 24 weeks in reducing spleen volume and improving the overall symptom

 

score [13]. In the COMFORT-2 trial, ruxolitinib was compared to the best available therapy in high-risk PMF patients; spleen volume reduction was better in the ruxolitinib arm (28% vs. 5%) [14]. During a median of 15.5 months of ruxolitinib treatment, 50% of our patients had a response to decreasing spleen volume, and 75% had a clinical response. Three patients (25%) discontinued treatment; two developed skin ulcers; and one patient had disease progression with increased spleen volume.

The JAK2 V617F mutation was reported in more than half of PMF patients, which is similar to our findings [15]. Another study from our center showed that 25% of all PMF patients had JAK2 mutations [16]. Triple-negative PMF is detected in 8-10% of patients [15], while in our study, we found triple-negative PMF in 16.7% of patients, and we only included patients receiving ruxolitinib. If we investigate all PMF patients, the percentage may be similar to the literature.

The effects of ruxolitinib therapy on thrombotic events and disease progression to myelofibrosis or AML, have not been clearly demonstrated. AML transformation occurs in 3.9% of PMF patients, with the majority of them previously treated with alkylating drugs [17]. High levels of circulating blast (>3%) and thrombocytopenia (<100.000/$mm^3$) are independent risk factors for AML transformation [18]. In our study, one patient (8.3%) developed AML and was treated with HU before ruxolitinib; she had thrombocytopenia but no more than 3% circulating blast.

Therefore, PSV and PMF are diseases that can be treated with ruxolitinib. It is highly effective in relieving symptoms and reducing splenomegaly. In this study, we observed that ruxolitinib was well-tolerated, effective, and had few side effects. The effect of ruxolitinib on AML transformation and thromboembolic events is unclear; a larger series is required. For patients who are not candidates for HSCT, ruxolitinib is an appropriate and safe treatment option.

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