Jakafi (Ruxolitinib): First FDA-Approved Medication for the Treatment of Patients with Polycythemia Vera

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Similar to myelofibrosis and essential thrombocythemia, polycythemia vera is a Philadelphia chromosome–negative myeloproliferative neoplasm.[1] Polycythemia vera is characterized by the clonal stem-cell proliferation of red blood cells, white blood cells, and platelets.[2,3] Increased red blood cell mass results in the hyperviscosity of the blood, an increased risk for thrombosis, poor quality of life, and a shortened life expectancy.[4]

Polycythemia vera is a rare condition. The incidence rate of polycythemia vera for all races and ethnicities is higher among men than among women: approximately 2.8 per 100,000 men and approximately 1.3 per 100,000 women.[3] Based on several small studies, approximately 22 in 100,000 individuals are affected by polycythemia vera.[3] The condition is typically diagnosed in older adults aged 60 to 65 years, and is uncommon in younger people aged <30 years.[3]

Approximately 96% of patients with polycythemia vera have a mutation of the Janus-associated kinase (*JAK*) *2* gene.[5] In the polycythemia vera progenitor cells, *JAK2* is directly involved in the intracellular signaling that occurs after exposure to specific cytokines.[5,6]

The course of the disease varies.[3] Some patients with polycythemia vera have few symptoms, and the condition is discovered only after blood work is performed during a periodic health examination. In others, the signs, symptoms, and complications result from the high red blood cell count and platelet count.[3] In addition, polycythemia vera evolves to postpolycythemia vera myelofibrosis in up to 10% of patients by year 10.[7]

Transformation to acute myeloid leukemia has been observed in up to 15% of patients with polycythemia vera after 10 years of the disease.[8]

The symptoms of polycythemia vera are primarily related to thrombi that result from increased blood viscosity and high platelet counts. The thrombotic complications are divided into microvascular and macrovascular complications. The microvascular complications result from thrombi in small blood vessels and can cause a variety of signs and symptoms, including headaches, dizziness, and paresthesia (**Table 1**).[9] The macrovascular complications, often referred to as major thrombotic events, are serious events that are secondary to thrombi in large arteries or veins, including myocardial infarction (Table 1).[10]

Cardiovascular events are the primary cause of mortality in patients with polycythemia vera, accounting for 45% of deaths.[11] Other major causes of death in this patient population include solid tumors (20%) and hematologic transformations (13%).[11]

Although polycythemia vera is incurable, it can be managed effectively for long periods.[3] The treatment of patients with polycythemia vera is designed to reduce the hematocrit and platelet concentrations, control polycythemia vera symptoms, decrease the risk for thrombotic events and other complications, and avoid leukemic transformation.[3,12,13]

The need for treatment is determined after assessing the patient's risk status, based on age and thrombosis history. Patients aged >60 years or those with a history of thrombosis have high-risk polycythemia vera, whereas younger patients aged <60 years or those with no history of thrombosis have low-risk disease.[3,13] Patients with low-risk polycythemia vera are often phlebotomized and receive low-dose aspirin. Conversely, patients with high-

Table 1 Thrombotic Complications in Polycythemia Vera

Microvascular complications
Erythromelalgia
Headache
Dizziness
Visual disturbances
Paresthesia
Transient ischemic attack
Macrovascular complications
Arterial thrombotic events
Myocardial infarction
Unstable angina
Stroke
Peripheral arterial occlusion
Venous thrombotic events
Deep vein thrombosis
Pulmonary embolism
Intra-abdominal vein thrombosis
Cerebral vein thrombosis

Sources: Michiels JJ, et al. *Semin Thromb Hemost*. 2006;32:174-207; Falanga A, Marchetti M. *Hematology Am Soc Hematol Educ Program*. 2012;2012:571-581; Marchioli R, et al. *J Clin Oncol*. 2005;23:2224-2232.

risk disease require medical therapy to lower their hematocrit concentration permanently (ie, <45% in men and <42% in women), eliminate the need for phlebotomy, and decrease the risk for clotting.[3,13]

Cytoreductive therapy is recommended to control red blood cell volume in patients for whom phlebotomy is poorly tolerated, in patients with a high thrombotic risk, and in those with symptomatic splenomegaly.[3] Among the available cytoreductive medication options, hydroxyurea is currently the treatment of choice for patients with polycythemia vera who are older than 40 years.[12-14] Although it effectively improves myelosuppression and reduces the risk for thrombosis compared with phlebotomy alone, hydroxyurea's utility is limited by its risk for secondary leukemia.[14,15]

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Patients who are intolerant of or are resistant to hydroxyurea can be effectively managed with pegylated interferon (IFN)-alpha or with busulfan.[16] A 2011 article recommends the use of IFN-alpha for the treatment of patients with polycythemia vera aged <65 years, and the use of busulfan in older patients, although no other evidence is available to validate this recommendation.[16]

Table 2 RESPONSE: Patients with Polycythemia Vera Reaching Primary and Key Secondary End Points

Patients achieving primary/secondary end points	Ruxolitinib, N (%) (N = 110)	Best available therapy, N (%) (N = 112)	*P* value
Response[a] at week 32	23 (21)	1 (<1)	<.001
Durable response[a] at week 48	21 (19)	1 (<1)	<.001
Complete hematologic remission[b] at week 32	26 (24)	10 (9)	.003
Hematocrit control at week 32	66 (60)	22 (20)	—
Spleen volume reduction ≥35% from baseline at week 32	42 (38)	1 (<1)	—

[a]Defined as hematocrit control and a ≥35% reduction from baseline in spleen volume at week 32.

[b]Defined as hematocrit control, platelet count ≤400 × 10^9/L, and white blood cell count ≤10 × 10^9/L at week 32.

Sources: Jakafi (ruxolitinib) tablets prescribing information; December 2014; Vannucchi AM, et al. *N Engl J Med*. 2015;372:426-435.

Data regarding the economic burden of polycythemia vera and other myeloproliferative neoplasms are sparse. However, a study presented at the 2011 annual meeting of the American Society of Hematology demonstrated that the medical costs for patients with myeloproliferative neoplasms are significant and are up to 6 times higher than the medical costs incurred by patients with other noncancer conditions.[17] The investigators assessed the medical costs of more than 25,000 patients with myeloproliferative neoplasms using claims data from approximately 100 US-based payers. Patients with myelofibrosis incurred the highest total annual costs, averaging $34,690, with outpatient costs accounting for the majority of the costs. The total medical costs for patients with essential thrombocythemia averaged $19,672, and $11,927 for patients with polycythemia vera.[17]

Ruxolitinib First Therapy Approved by the FDA for Polycythemia Vera

On December 4, 2014, the US Food and Drug Administration (FDA) approved ruxolitinib (Jakafi; Incyte Corporation), an oral kinase inhibitor, for the treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.[18,19] Ruxolitinib is the first drug approved by the FDA for the treatment of polycythemia vera.[18]

"The approval of Jakafi for polycythemia vera underscores the importance of developing drugs matched to our increasing knowledge of the mechanisms of diseases," said Richard Pazdur, MD, Director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research. "The trial used to evaluate Jakafi confirmed clinically meaningful reductions in spleen size and the need for phlebotomies to control the disease."[18]

The FDA approved ruxolitinib under its priority review program, because the medication demonstrated the potential to provide significant improvement in safety or efficacy over the other available therapy for polycythemia vera at the time its application was submitted. In addition, ruxolitinib received an orphan drug designation.[18]

Polycythemia vera is the second indication for ruxolitinib. Ruxolitinib was first approved by the FDA in November 2011 for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, postpolycythemia vera myelofibrosis, and postessential thrombocythemia myelofibrosis.[18,20]

Mechanism of Action

Polycythemia vera is associated with dysregulated JAK1 and JAK2 signaling. Ruxolitinib inhibits JAK1 and JAK2; these kinases mediate the signaling of cytokines and growth factors that are important for hematopoiesis and for immune function. JAK signaling involves the recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors, as well as the activation and the subsequent localization of STATs to the cell nucleus. This process results in the modulation of gene expression.[19]

Dosing and Administration

The starting dose of ruxolitinib is 10 mg taken orally twice daily with or without food. The doses of ruxolitinib can be altered based on the drug's safety and efficacy.[19] The drug labeling provides detailed recommendations for dose reduction and dose reinitiation after interruption of treatment with ruxolitinib.[19]

Clinical Trials

The approval of ruxolitinib for the treatment of patients with polycythemia vera was based on a randomized, open-label, active-controlled phase 3 clinical trial known as the RESPONSE trial.[18,19,21] In this clinical trial, ruxolitinib (10 mg twice daily) was compared with best available care in patients with polycythemia vera who had unacceptable side effects from or who had an inadequate response to hydroxyurea.[19,21]

The primary end point of the RESPONSE study included hematocrit control and a spleen volume reduction of ≥35% by week 32.[19,21] The secondary end points included the proportion of randomized patients who reached the primary end point and maintained their response 48 weeks after randomization, and the proportion of patients who reached complete hematologic remission at week 32.[19,21]

A total of 222 phlebotomy-dependent patients with splenomegaly received ruxolitinib (N = 110) or best available therapy (N = 112), which was determined by the investigators on an individualized basis[19,21]; patients in the best available therapy group typically received hydroxyurea, IFN-alpha, or no medication.[21] The doses of ruxolitinib were individualized based on tolerability and efficacy, with a maximum dose of 25 mg twice daily.[19,21]

The majority of patients in the RESPONSE trial had been diagnosed with polycythemia vera for 8 years or longer (range, 0.5-36 years).[21] Approximately 95% of patients had the *JAK2* V617F mutation.[21] The patients' median age was 61 years (range, 33-90 years), with 30% of patients aged >65 years.[19,21] Overall, 66% of patients were male.[19] The median spleen volume was 1272 cm^3 (range, 254 cm^3-5147 cm^3), and the median palpable spleen length below the costal margin was 7 cm.[19,21]

Table 3 RESPONSE: Treatment Emergent Adverse Events in ≥6% of Patients Receiving Ruxolitinib Up to Week 32

	Patients receiving ruxolitinib (N = 110)		Patients receiving best available therapy (N = 111)	
Adverse events	All grades,[a] %	Grade 3-4,[a] %	All grades,[a] %	Grade 3-4,[a] %
Headache	16	<1	19	<1
Abdominal pain[b]	15	<1	15	<1
Diarrhea	15	0	7	<1
Dizziness + vertigo	15	0	13	0
Fatigue	15	0	15	3
Pruritus	14	<1	23	4
Dyspnea[c]	13	3	4	0
Muscle spasms	12	<1	5	0
Nasopharyngitis	9	0	8	0
Constipation	8	0	3	0
Cough	8	0	5	0
Edema + peripheral edema	8	0	7	0
Arthralgia	7	0	6	<1
Asthenia	7	0	11	2
Epistaxis	6	0	3	0
Herpes zoster + postherpetic neuralgia	6	<1	0	0
Nausea	6	0	4	0

[a]National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.
[b]Including lower and upper abdominal pain.
[c]Including dyspnea exertional.
Source: Jakafi (ruxolitinib) tablets prescribing information; December 2014.

As shown in **Table 2**, 21% of patients who received ruxolitinib reached the primary end point compared with <1% of patients who received best available therapy.[19,21] The majority (77%) of patients in the ruxolitinib group reached at least 1 component of the primary end point by week 32.[21]

The results of the secondary end point analyses also favored ruxolitinib.[19,21] The likelihood that the response to therapy was maintained 48 weeks after randomization was higher in patients who received ruxolitinib compared with patients who received best available therapy. In addition, a significantly larger proportion of patients who received ruxolitinib reached complete hematologic remission at week 32 compared with patients who received best available therapy.[19,21]

Safety

The safety of ruxolitinib has been assessed in 617 patients who participated in 1 of 6 clinical trials.[19] The median duration of follow-up was 10.9 months.[19] This cohort included 110 patients with polycythemia vera whose disease was resistant to or who were intolerant of hydroxyurea in the RESPONSE clinical trial[19]; in this study, the most frequent adverse drug reaction was anemia.[19]

Table 3 lists the most common nonhematologic treatment-emergent adverse events that occurred up to week 32 in the RESPONSE trial, which included headaches, abdominal pain, and diarrhea.[19] Other clinically important treatment-emergent adverse events that were noted in <6% of patients who received ruxolitinib were weight gain, hypertension, and urinary tract infections.[19] Of the patients who received ruxolitinib in the RESPONSE trial, 4% discontinued the use of the drug as a result of adverse events.[19]

Ruxolitinib has no contraindications.

Ruxolitinib is the first medication to receive FDA approval for the treatment of patients with polycythemia vera. This medication demonstrated superior efficacy in controlling hematocrit levels, reducing spleen size, and improving disease-related symptoms.

Warnings and Precautions

Thrombocytopenia, anemia, and neutropenia. Thrombocytopenia, anemia, and neutropenia can occur after treatment with ruxolitinib. Thrombocytopenia should be managed by reducing the dose of ruxolitinib or by temporarily interrupting its use; platelet transfusions may be required. If anemia occurs, blood transfusions and/or dose modification of ruxolitinib may be necessary. Severe neutropenia is generally reversible after the discontinuation of ruxolitinib therapy. Patients should undergo a complete blood count before starting treatment with ruxolitinib, followed by every 2 to 4 weeks until the doses are stabilized.[19]

Risk for infection. Ruxolitinib has been associated with serious bacterial, mycobacterial, fungal, and viral infections. Ruxolitinib therapy should not be started until active serious infections have resolved. Patients who receive ruxolitinib should be observed for the signs and symptoms of infection and should be managed promptly.[19]

Tuberculosis has been reported in patients who received ruxolitinib. Patients should be evaluated for tuberculosis risk before starting ruxolitinib therapy. Patients at high risk for tuberculosis should be tested for latent infection. If evidence of active or latent tuberculosis is found, a physician with expertise in the treatment of tuberculosis should be consulted before starting ruxolitinib therapy. The decision to continue ruxolitinib therapy while active tuberculosis is being treated should be based on the overall risk–benefit determination.[19]

Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib in the treatment of patients with myelofibrosis. The use of ruxolitinib therapy should be discontinued if PML is suspected.[19]

Patients who receive ruxolitinib should be advised about the early signs and symptoms of herpes zoster and should seek treatment if it is suspected.[19]

Symptom exacerbation after ruxolitinib discontinuation. Symptoms associated with myeloproliferative neoplasms may return to pretreatment levels approximately 1 week after ruxolitinib therapy is discontinued.[19] If symptoms occur, patients should be evaluated and treated for any intercurrent illness; in addition, restarting ruxolitinib therapy or increasing its dose should be considered.[19] Patients should not interrupt or discontinue ruxolitinib therapy without consulting their physician. If therapy is stopped for reasons other than thrombocytopenia, the dose of ruxolitinib should be tapered.[19]

Nonmelanoma skin cancer. Skin cancers, including basal-cell, squamous-cell, and Merkel-cell carcinoma, have occurred in patients receiving ruxolitinib. Therefore, the skin should be examined periodically while taking ruxolitinib.[19]

Use in Specific Populations

Pregnancy. Ruxolitinib is a pregnancy category C teratogen; there are no adequate and well-controlled studies with ruxolitinib in pregnant women. Ruxolitinib should only be used during pregnancy if the potential benefit outweighs the potential risk to the fetus.[19]

Nursing mothers. It is not known whether the components of ruxolitinib are present in human breast milk. Nursing or ruxolitinib should be discontinued on the basis of the importance of ruxolitinib to the mother.[19]

Pediatric use. The safety and efficacy of ruxolitinib have not been established in patients aged <18 years.[19]

Geriatric use. Overall, 52% of patients with myelofibrosis in clinical studies of ruxolitinib were aged ≥65 years. No overall differences in safety or efficacy were observed between older and younger patients.[19]

Renal impairment. The dose of ruxolitinib should be reduced in patients with moderate or severe renal impairment, or in patients with end-stage renal disease (ESRD) who are on dialysis. Ruxolitinib should not be used by patients with ESRD who are not on dialysis.[19]

Hepatic impairment. A dose reduction is recommended in patients with hepatic impairment; ruxolitinib

should be started at 5 mg twice daily in patients with mild, moderate, or severe hepatic impairment.[19]

Conclusion

Ruxolitinib is the first medication to receive FDA approval for the treatment of patients with polycythemia vera. This medication demonstrated superior efficacy in controlling hematocrit levels, reducing spleen size, and improving disease-related symptoms in a randomized clinical trial that compared oral ruxolitinib with best available therapies, including hydroxyurea, for the treatment of patients with polycythemia vera. By contrast, best available therapies offered little to no benefit.

This novel kinase inhibitor represents an important new, and the only FDA-approved, option for the treatment of patients with polycythemia vera. Clinical trials continue to explore the potential role of ruxolitinib in myeloproliferative neoplasms, as well as in other hematologic malignancies, such as acute myeloid leukemia and chronic myeloid leukemia, as well as in solid tumors, such as metastatic pancreatic cancer.[22] ■

References

1. Tefferi A, Vardiman JW. Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organization criteria and point-of-care diagnostic algorithms. *Leukemia.* 2008;22:14-22.

2. Spivak JL. Polycythemia vera: myths, mechanisms, and management. *Blood.* 2002;100:4272-4290.

3. Leukemia & Lymphoma Society. Polycythemia vera facts. No. 13. Revised June 2012. www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/mpd/pdf/polycythemiavera.pdf. Accessed March 2, 2015.

4. Kumar C, Purandare AV, Lee FY, Lorenzi MV. Kinase drug discovery approaches in chronic myeloproliferative disorders. *Oncogene.* 2009;28:2305-2313.

5. Passamonti F, Rumi E, Pietra D, et al. Relation between JAK2 (V617F) mutation status, granulocyte activation, and constitutive mobilization of CD34+ cells into peripheral blood in myeloproliferative disorders. *Blood.* 2006; 107:3676-3682.

6. Vannucchi AM, Antonioli E, Guglielmelli P, et al. Clinical correlates of JAK2V617F presence or allele burden in myeloproliferative neoplasms: a critical reappraisal. *Leukemia.* 2008;22:1299-1307.

7. Tefferi A. Essential thrombocythemia, polycythemia vera, and myelofibrosis: current management and the prospect of targeted therapy. *Am J Hematol.* 2008; 83:491-497.

8. Finazzi G, Caruso V, Marchioli R, et al; for the ECLAP Investigators. Acute leukemia in polycythemia vera: an analysis of 1638 patients enrolled in a prospective observational study. *Blood.* 2005;105:2664-2670.

9. Michiels JJ, Berneman Z, Van Bockstaele D, et al. Clinical and laboratory features, pathobiology of platelet-mediated thrombosis and bleeding complications, and the molecular etiology of essential thrombocythemia and polycythemia vera: therapeutic implications. *Semin Thromb Hemost.* 2006;32:174-207.

10. Falanga A, Marchetti M. Thrombotic disease in the myeloproliferative neoplasms. *Hematology Am Soc Hematol Educ Program.* 2012;2012:571-581.

11. Marchioli R, Finazzi G, Landolfi R, et al. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. *J Clin Oncol.* 2005;23:2224-2232.

12. Barbui T, Barosi G, Birgegard G, et al; for the European LeukemiaNet. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol.* 2011;29:761-770.

13. Finazzi G, Barbui T. Evidence and expertise in the management of polycythemia vera and essential thrombocythemia. *Leukemia.* 2008;22:1494-1502.

14. Weinfeld A, Swolin B, Westin J. Acute leukaemia after hydroxyurea therapy in polycythaemia vera and allied disorders: prospective study of efficacy and leukaemogenicity with therapeutic implications. *Eur J Haematol.* 1994;52:134-139.

15. Fruchtman SM, Mack K, Kaplan ME, et al. From efficacy to safety: a Polycythemia Vera Study Group report on hydroxyurea in patients with polycythemia vera. *Semin Hematol.* 1997;34:17-23.

16. Tefferi A. Annual clinical updates in hematological malignancies: a continuing medical education series: polycythemia vera and essential thrombocythemia: 2011 update on diagnosis, risk-stratification, and management. *Am J Hematol.* 2011;86:292-301.

17. Price GL, Pohl GM, Xie J, Walgren RA. A retrospective observational study of annual healthcare costs for patients with forms of myeloproliferative neoplasms (MPN). *Blood (ASH Annual Meeting Abstracts).* 2011;118. Abstract 2060.

18. US Food and Drug Administration. FDA approves Jakafi to treat patients with a chronic type of bone marrow disease: first FDA-approved drug for polycythemia vera. Press release. December 4, 2014. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm425677.htm. Accessed March 2, 2015.

19. Jakafi (ruxolitinib) tablets [prescribing information]. Wilmington, DE: Incyte Corporation; December 2014.

20. US Food and Drug Administration. FDA approves first drug to treat a rare bone marrow disease. Press release. November 16, 2011. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm280102.htm. Accessed March 2, 2015.

21. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med.* 2015; 372:426-435.