

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

New Therapies for Polycythemia Vera



Srdan Verstovsek, MD, PhD
Professor
Department of Leukemia
Division of Cancer Medicine
The University of Texas
MD Anderson Cancer Center
Houston, Texas

H&O What is the current standard of care for polycythemia vera (PV)?

SV Overall, PV is considered benign and the primary goal of therapy is not to eliminate disease, but to decrease the risk for blood clotting by controlling the red blood cell counts. Patients are all treated with phlebotomy to lower their red blood cell counts and are usually given aspirin. Patients with a high risk of thrombosis (ie, patients over 60 years old or with a history of blood clots) are usually advised to take cytoreductive medication in order to decrease the risk of thrombosis by strictly controlling red blood cell count and eliminating the need for phlebotomy.

The main goal of therapy is to decrease the hematocrit—a measurement of blood viscosity—to below 45%. In 2013, Marchioli and colleagues published a prospective study in which patients with PV who had a high risk for thrombosis were randomly assigned to have either strict control of hematocrit (below 45%) or not-so-strict control (between 45% and 48%). Patients with strict control of hematocrit had fewer thrombotic events, which led to better survival. This study confirmed the point, which has been made for decades, that strict control of the red blood cell count is important.

In addition to controlling red blood cell count, it is also beneficial to normalize white blood cell or platelet counts, or reduce disease-related symptoms or splenomegaly, each of which may be present in a good proportion of patients.

H&O What are the current therapeutic agents given for PV?

SV The first-line therapy for high-risk patients, as per the guidelines, is either hydroxyurea or interferon. The use of one or the other differs among countries.

Hydroxyurea, which is taken orally, is a chemotherapeutic agent that can be used for decades, though some studies suggest that it may increase the risk of PV transforming into acute myeloid leukemia. Approximately 75% to 80% of patients have very good control of their red blood cell counts with hydroxyurea. Among them, however, many do not have good control of white blood cells, platelets, symptoms, or spleen size. It is clear, however, that up to 20% to 25% of patients do not respond well to or are intolerant of hydroxyurea (mucocutaneous ulcers are the leading toxicity), and require a different therapy.

By contrast, interferon is a biological agent injected 3 to 5 times a week. It can be as effective as hydroxyurea, but it more often causes side effects, such as low-grade fevers, night sweats, flu-type symptoms, long-term myelosuppression, hair loss, autoimmune diseases, and depression. Within a year, approximately one-third of patients discontinue use because of side effects. Novel preparations of interferon (ie, long-acting interferons) that are given as an injection every week or two, appear to be much better tolerated, leading to improved response rates (greater than 90%). Some patients also have a significant decrease in the disease burden (ie, elimination of *JAK2*-mutated cells

in the blood), an effect not seen with hydroxyurea. Thus, this drug may affect the disease biology.

Though there are pros and cons for each medication, hydroxyurea is used by most hematologists as the standard first-line therapy in the United States.

H&O What is given to patients who do not respond well to first-line therapy?

SV For patients who do not respond well to or are intolerant of hydroxyurea, another therapy is needed. One may consider interferon, as discussed, but it has problematic side effects that prevent its widespread use. This is particularly the case with older patients, whose tolerance of interferon is low. Long-acting interferons, although better tolerated, are difficult to obtain in the United States. Other chemotherapeutic agents can be used, such as busulfan; however, the sequential use of 2 chemotherapies increases the risk of transformation to acute myeloid leukemia. A different therapy was sorely needed, and in December 2014, ruxolitinib (Jakafi, Incyte Pharmaceuticals) was approved for patients who do not respond to or are intolerant of hydroxyurea.

H&O Can you describe the mechanism of action for ruxolitinib?

SV Ruxolitinib inhibits Janus kinase 2 (JAK2), a non-receptor tyrosine kinase involved in the production of new blood cells. Typically when we lose blood, our bodies make growth factors that activate the JAK-STAT pathway in bone marrow cells to signal for new blood cell production. In PV, mutations that lead to hyperactivity of the JAK-STAT pathway cause uncontrolled growth of blood cells. Most commonly, the mutation is in the *JAK2* gene: approximately 95% of patients specifically have a *JAK2* V617F mutation. Some patients (3%-4%) have a different point mutation in the same gene, called a *JAK2* exon 12 mutation. Other infrequent mutations have been found in the calreticulin gene and the *Lnk* gene (*Sh2b3*). Therefore, the therapeutic aim is to inhibit the JAK-STAT pathway with a drug that is not specific for a single mutation, and this is what ruxolitinib achieves.

H&O Could you describe the clinical trial for ruxolitinib?

SV The randomized open-label trial, published recently by Vannucchi and colleagues, enrolled patients resistant to or intolerant of hydroxyurea. Treatment in this trial had 2 primary endpoints: (1) to eliminate the need for phlebotomy by strict control of hematocrit and (2) to achieve a 35% reduction in spleen size (measured by

magnetic resonance imaging of spleen volume). Based on the primary composite endpoint of these 2 factors, the study found a significant difference between the ruxolitinib group and the standard therapy group, which then led to approval of the drug. The primary composite endpoint was achieved by 21% of patients treated with ruxolitinib and 1% of patients treated with standard therapy. Specifically, 60% of patients with ruxolitinib vs 20% of patients with standard therapy had controlled hematocrit, and 38% vs 1%, respectively, had the required decrease in spleen volume.

There were also secondary endpoints to determine how many patients had complete hematologic remission; those were statistically different between the 2 groups as well (24% of patients with ruxolitinib vs 9% with standard therapy). The study also examined the symptoms associated with PV (ie, itching, night sweats, burning in the skin, headaches, abdominal pain from the spleen, fatigue, and weakness) and found that those also significantly improved with ruxolitinib treatment.

H&O What are the side effects and toxicities of ruxolitinib?

SV Occasionally, patients developed anemia or thrombocytopenia due to excess suppression of the JAK-STAT pathway. However, this was easily fixed by lowering the dose, and no one discontinued therapy because of anemia or thrombocytopenia. The standard starting dosage of ruxolitinib in PV is 10 mg twice a day, and a majority of the patients required a dosage increase; only a small percentage required a decrease.

A small percentage of patients treated with ruxolitinib also developed herpes zoster. This is because the JAK-STAT pathway is associated with the immune system, and inhibition with ruxolitinib may alter the function of the T cells and natural killer cells, which are important in defense against atypical infections, such as the herpes virus. Awareness about possible atypical infections, although rare, is important, because these patients may be taking ruxolitinib for decades.

In the assessment of adverse events, the study also found a possible benefit of ruxolitinib. Safety studies typically measure the occurrence of thrombotic events. In the observation period of 32 weeks, the study found only 1 thrombotic event in patients receiving ruxolitinib vs 6 events in patients receiving standard therapy, which suggests that control of the blood cell counts with ruxolitinib leads to a decrease in the risk of thrombosis. This is just an observation; the study was not statistically powered to determine significance for that endpoint. However, this is an interesting finding that could be assessed in future studies.

H&O Are any other JAK inhibitors in clinical trials for PV?

SV Yes; 10 different JAK inhibitors have been tested in myeloproliferative neoplasms, which include PV, myelofibrosis, and essential thrombocythemia. In the past, a JAK inhibitor called CEP-701 was tested in PV, but the drug was not very efficacious because of poor tolerance. Currently, a study in PV is underway with another JAK2 inhibitor called momelotinib; this is an open-label phase 2 study.

H&O Could you describe any other promising drugs currently in clinical trials for PV?

SV A preparation of long-acting interferon called peginterferon α -2a, given weekly, is currently in clinical trials. This drug is being tested in a randomized trial vs hydroxyurea in newly diagnosed patients with PV (NCT01258856), and in an open-label phase 2 trial for previously treated patients with PV (NCT01259817). In Europe, another new long-acting interferon given every 2 weeks is being tested in a phase 3 study comparing it with hydroxyurea in newly diagnosed and previously treated patients with PV (NCT01949805).

Recent clinical trials have investigated targeted agents called histone deacetylase (HDAC) inhibitors, which alter gene transcription. These drugs seemed promising because epigenetic control of genetic expression is abnormal in PV. HDAC inhibitors were given alone or in combination with hydroxyurea, and produced some interesting findings. However, tolerance was a major issue.

H&O What is the next step for treatment of PV?

SV So far, the main goal of treatment has been to decrease the risk of thrombosis, and with hydroxyurea, interferon, and ruxolitinib, we can cover most high-risk PV patients who need cytoreductive therapy. However, as with any neoplasms, we ultimately would like to eliminate the disease. Some suggest that this might be possible by combining a JAK inhibitor and a low dose of interferon. In this case, ruxolitinib would provide good control of blood cell counts, spleen volume, and symptoms, and interferon would exert its beneficial effect on the bone marrow and possibly eliminate *JAK2*-mutated cells. This hypothesis is based on the fact that interferon can eliminate *JAK2*-mutated cells in approximately 20% of patients with PV; however, its tolerance over time still

presents a challenge that might be curbed if a lower dose can be used in combination with a JAK inhibitor. Such a study is currently being conducted in Denmark and we are eagerly awaiting the results.

H&O Is there anything else that you would like to add?

SV I think that the development of ruxolitinib is a major breakthrough for patients with PV. This is the first time that any medication has been approved in the United States as a therapy for PV, and it provides a great benefit to patients who do not respond well to or are intolerant of hydroxyurea. This is especially important because these patients have more aggressive disease, a larger spleen, a high risk of thrombosis, and a shorter life expectancy. Ruxolitinib covers this unmet need area very well. I am very happy for these patients, who I often see in the referral center at MD Anderson Cancer Center and who, until recently, did not have good options for therapy.

Suggested Readings

- Alvarez-Larrán A, Pereira A, Cervantes F, et al. Assessment and prognostic value of the European LeukemiaNet criteria for clinicohematologic response, resistance, and intolerance to hydroxyurea in polycythemia vera. *Blood*. 2012;119(6):1363-1369.
- Barbui T, Barosi G, Birgegard G, et al; European LeukemiaNet. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol*. 2011;29(6):761-770.
- Finazzi G, Vannucchi AM, Martinelli V, et al. A phase II study of Givinostat in combination with hydroxycarbamide in patients with polycythemia vera unresponsive to hydroxycarbamide monotherapy. *Br J Haematol*. 2013;161(5):688-694.
- Gisslinger H, Buxhofer-Ausch V, Thaler J, et al. Efficacy and safety of AOP2014/p1101, a novel, investigational mono-pegylated proline-interferon alpha-2b, in patients with polycythemia vera (PV): update on 51 patients from the ongoing phase I/II Pegivera study [ASH abstract 4046]. *Blood*. 2013;112(21).
- Hultcrantz M, Kristinsson SY, Andersson TM, et al. Patterns of survival among patients with myeloproliferative neoplasms diagnosed in Sweden from 1973 to 2008: a population-based study. *J Clin Oncol*. 2012;30(24):2995-3001.
- James C, Ugo V, Le Couédic JP, et al. A unique clonal *JAK2* mutation leading to constitutive signalling causes polycythemia vera. *Nature*. 2005;434(7037):1144-1148.
- Kiladjian JJ, Cassinat B, Chevret S, et al. Pegylated interferon- α -2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. *Blood*. 2008;112(8):3065-3072.
- Marchioli R, Finazzi G, Specchia G, et al; CYTO-PV Collaborative Group. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med*. 2013;368(1):22-33.
- Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med*. 2015;372(5):426-435.
- Verstovsek S, Passamonti F, Rambaldi A, et al. A phase 2 study of ruxolitinib, an oral *JAK1* and *JAK2* inhibitor, in patients with advanced polycythemia vera who are refractory or intolerant to hydroxyurea. *Cancer*. 2014;120(4):513-520.