

MEETING HIGHLIGHTS

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Highlights in Polycythemia Vera From the 2016 EHA Congress



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H&O What are the characteristics of polycythemia vera?

SV Polycythemia vera is a myeloproliferative neoplasm (MPN) characterized by an uncontrolled growth of blood cells—most commonly the red cells, but also the white cells and platelets. It is in essence a benign leukemia because the prognosis is good. Patients live close to a normal life expectancy. Most diagnoses occur in people in their 60s. The expectation is for these patients to live approximately 20 more years, which is just a bit shorter than people without the disease. The goal of treatment therefore focuses not on extending survival or eliminating the disease, but on preventing complications associated with too many blood cells that can impact quality of life. Patients have an increased risk of blood clotting.

Polycythemia vera is not common. The incidence is approximately 2.3 per 100,000 people per year. In the United States, there are approximately 7000 new cases each year. It is estimated that 140,000 people are living with polycythemia vera in the United States.

H&O How is polycythemia vera diagnosed?

SV It can be difficult to distinguish polycythemia vera from the other MPNs. There is no single test to diagnose these neoplasms (with the exception of chronic myeloid leukemia).

The World Health Organization published new, modified diagnostic criteria for polycythemia vera earlier this year. There are 3 major criteria. The first is a very high red blood cell count, which is usually identified by elevated levels of hemoglobin or hematocrit. Importantly,

the new guidelines decreased the threshold for the red blood cell count needed for the diagnosis to be made. Levels of hemoglobin should be at least 16.5 g/dL for men and 16.0 g/dL for women. These lower levels provide a better way of recognizing patients. Panmyelosis, which refers to elevation of red cells, white cells, and platelets, is another sign.

The new guidelines also emphasize the need for bone marrow biopsy that shows hypercellularity and abnormalities in megakaryocytes, which is the second major criterion. Previous guidelines had listed bone marrow findings as a minor diagnostic characteristic.

The third major criterion is the presence of a mutation in the Janus kinase 2 (*JAK2*) gene. In 2005, this mutation was discovered in several types of MPNs. Almost all patients with polycythemia vera have a *JAK2* mutation. In 95% of these patients, it is a *JAK2 V617F* mutation. Another mutation is the *JAK2* exon 12 mutation, which is seen in less than 5% of patients.

There is a fourth diagnostic feature, which is minor and not mandatory. Patients usually have a very low level of erythropoietin, a growth factor that increases the production of red blood cells. Shutting down production of erythropoietin is the body's way to compensate for the high levels of red blood cells, which grow without control in polycythemia vera.

H&O What are the signs and symptoms?

SV The signs and symptoms generally stem from too many red blood cells, but can also arise from too many white cells or platelets. The risk of thrombosis is directly associated with increased red blood cells, and therapies are

focused on decreasing them. Symptoms of a blood clot vary according to location, and can include swollen legs and abdominal pain and distention. Patients can have a heart attack or a stroke.

There are many other symptoms linked to the sluggish blood flow seen in patients with polycythemia vera. They include headaches, blurred vision, tingling in the fingers and toes, and erythromelalgia, which is supersensitivity to hot and cold caused by the opening and closing of the small blood vessels in the extremities. One of the typical symptoms of polycythemia vera is pruritus, particularly after a hot bath or shower, when the blood vessels open. In addition, the spleen can enlarge in response to the increased cells in the blood circulation. There can also be some weight loss. Patients can develop B symptoms, such as night sweats, low-grade fevers, chronic pain, and weakness. Fatigue is one of the most important findings, as well.

H&O What are the goals of treatment?

SV In the past, there was a single goal: to reduce the number of red blood cells. Now, there are 4 others: to reduce the number of white cells and platelets, shrink an enlarged spleen, and improve symptoms. Most clinical trials⁴ in polycythemia vera now evaluate how well treatments address all 5 goals. Systemic symptoms will improve by normalizing the blood cell count and decreasing the size of the spleen, if it is enlarged.

H&O What is the first-line treatment?

SV The correlation between increased red blood cells and clotting is clear. Therefore, the standard practice is to first control the red blood cells by phlebotomy to maintain hematocrit below 45%. A prospective randomized study by Marchioli and colleagues proved that the maintenance of hematocrit below 45% decreased the risk of blood clots and cardiovascular events. All patients are also given baby aspirin, which has been shown to help with blood circulation.

It is important to control all of the blood cell counts, spleen size, and symptoms to improve the patient's quality of life and further decrease the risk of blood clotting. There is growing evidence that an increased white cell count may be a risk factor for blood clots.

The next management step depends on the patient's risk of a blood clot. The standard approach is to use only 2 factors to define high risk: age older than 60 years and history of a blood clot. Patients at high risk require cytoreductive therapy, which will decrease the count of red blood cells and likely those of white blood cells and platelets. The 2 standard options in the frontline setting

are hydroxyurea chemotherapy in an oral, daily pill, and injection of the biologic agent interferon. In the United States, the traditional approach is to use hydroxyurea first. In other parts of the world, such as Denmark and France, interferon is more popular. Hydroxyurea and interferon are used to eliminate the need for phlebotomy and decrease the blood cell count to further reduce the risk of blood clotting.

Quality of life is also paramount. Patients may live with a normal blood cell count, but still have a poor quality of life. It is not just about the numbers; it is about the whole person.

H&O Approximately how many patients treated with hydroxyurea have an inadequate response or develop unacceptable side effects?

SV Until approximately 10 years ago, there were so few treatment options that this question was irrelevant. There was not much more to do beyond controlling the red cell count with hydroxyurea and interferon. There was no appreciation of the importance of controlling other cell counts, spleen size, or symptoms.

The approach to management changed as we learned more about the biology of the disease, and with the subsequent development of JAK inhibitor therapy. The first advance was to recognize that the goals of therapy should address the 5 factors mentioned earlier: reducing counts of red cells, white cells, and platelets; decreasing an enlarged spleen; and improving symptoms. The question then became how many patients achieved a good response to those frontline therapies, hydroxyurea in particular. A study by Alvarez-Larrán and colleagues from Spain showed that 20% to 25% of patients do not do well on hydroxyurea. Approximately 12% of patients are resistant to hydroxyurea, meaning they lack a satisfactory response. Approximately 12% to 13% are intolerant, meaning they experience adverse events. In these patients, interferon can be used, if it had not already been used before hydroxyurea. (Interferon should not be used again if it was unsuccessful the first time.)

There is now a new therapy, approved in December 2014 in the United States and in March 2015 in the European Union. Ruxolitinib (Jakafi, Incyte Corporation) is a JAK inhibitor approved for patients with polycythemia vera who are intolerant or refractory to hydroxyurea.

H&O What is the mechanism of action of ruxolitinib?

SV In 2005, the *JAK V617F* mutation was discovered in patients with myeloproliferative neoplasms. As I mentioned, 95% of patients with polycythemia vera have this

mutation. There are several other mutations in myeloproliferative neoplasms with the same effect as the *JAK2* mutation. Within the intracellular signaling pathway of bone marrow cells, the *JAK2* mutations (along with others) activate the JAK-STAT pathway, which is intimately involved with the proliferation of the bone marrow cells. The *JAK2* enzyme is a tyrosine kinase that binds to the receptors for erythropoietin and thrombopoietin in bone marrow cells. These are the growth factors that stimulate production of red blood cells and platelets, respectively. When these growth factors bind to their receptors in healthy people, they make blood cells. A *JAK2* mutation, most commonly the *JAK2 V617F*, but also the *JAK2* exon 12 mutation and others, leads to hyperactivation of the JAK-STAT pathway and increased production of blood cells. With this discovery, the goal became to develop therapies that would inhibit the JAK-STAT pathway.

Ruxolitinib is one such therapy, and others are in development. Ruxolitinib aims to inhibit the hyperactive JAK-STAT pathway. It does not suppress or eliminate the mutated *JAK2* protein that is present in the cells, but it inhibits the effect of the protein. Inhibition of the hyperactive JAK-STAT pathway inhibits cell growth. The consequence is a reduction in red cells, white cells, and platelets; a decrease in the size of the spleen; and improvement in quality of life. Ruxolitinib was better than best-available therapy in the RESPONSE trial (Study of Efficacy and Safety in Polycythemia Vera Subjects Who Are Resistant to or Intolerant of Hydroxyurea: JAK Inhibitor INC424 [INCB018424] Tablets Versus Best Available Care), which evaluated second-line therapy in patients with polycythemia vera who were resistant to or intolerant of hydroxyurea.

H&O What was the design of the RESPONSE trial and the preliminary results?

SV RESPONSE was a phase 3, open-label, international, randomized study. All of the patients in RESPONSE had an enlarged spleen, as well as a need for phlebotomy. Patients were randomly assigned to receive ruxolitinib, taken orally twice daily, or the best-available therapy as selected by their doctor. The primary endpoint was the proportion of patients who achieved control of hematocrit (below 45%) and a reduction of 35% or more in spleen volume from baseline to week 32. The primary analysis was performed after approximately 52 weeks. It showed that ruxolitinib was much better than best-available therapy, particularly in the control of hematocrit. Ruxolitinib reduced hematocrit to below 45% in 60% of patients vs 20% for best-available therapy. A reduction of spleen volume greater than 35% occurred in 38% of patients in the ruxolitinib arm vs 1% in the best-available therapy arm.

The primary endpoint was met by 21% of patients receiving ruxolitinib vs 1% of those receiving placebo. These results led to approval of ruxolitinib for these patients.

The study permitted crossover to ruxolitinib for patients in the best-available therapy arm who did not meet the primary endpoint or showed signs of disease progression at week 32. In July 2016, we published the long-term results at 80 weeks of follow-up. The responses were durable, particularly in terms of the red blood cell count. Spleen response appeared to improve over time, as did the secondary endpoints: control of white cells and platelets. It is well-known in the myelofibrosis field that an important benefit of the JAK inhibitors is control of symptoms. In the RESPONSE trial, 49% of patients in the ruxolitinib arm had at least a 50% reduction in reported symptoms, as measured by the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) symptom score.

H&O What results from the RESPONSE trial were presented at the 2016 EHA congress?

SV We presented data from some additional analyses at the 2016 European Hematology Association (EHA) congress. A very interesting finding was a reduction in the *JAK2 V617F* allele burden. This measurement essentially shows the percentage of cells in a blood sample that have the mutation, and whether the therapy acts only on malignant cells to reduce the clonal burden. At the EHA meeting, Dr Alessandro Vannucchi presented an interesting analysis showing that over time, there is a continuous decrease in the *JAK2* allele burden in patients treated with ruxolitinib. From baseline to a median 3 years of follow-up, the median percent decrease in the *JAK2* allele burden was approximately 40%. This decrease persisted as the therapy continued. The same trend was observed in patients who crossed over to ruxolitinib after receiving best-available therapy.

Approximately a third of patients experienced a decrease in the *JAK2* allele burden of at least 50%. There were even a few patients who had a complete molecular response, meaning the *JAK2* allele burden was eliminated.

Another important finding concerns the safety of ruxolitinib, in particular, the incidence of thromboembolic events. A statistical analysis of thromboembolic events was not possible because this was not part of the goals of the study, which were to assess efficacy. However, throughout the 80-week follow-up, there appeared to be a decrease in the number of thromboembolic events in the ruxolitinib arm compared with the best-available therapy arm. This decrease is likely attributable to the reduction in the blood cell count and other improvements seen with ruxolitinib.

H&O Were any other data on ruxolitinib presented at the EHA congress?

SV Dr Francesco Passamonti presented the first results from the RESPONSE 2 study (Ruxolitinib Efficacy and Safety in Patients With HU Resistant or Intolerant Polycythemia Vera vs Best Available Therapy) at an oral session of the 2016 EHA meeting. A critique of the RESPONSE study was that all patients had to have an enlarged spleen, which is not always present in polycythemia vera. The RESPONSE 2 study shared an identical design with the RESPONSE trial, except that a nonpalpable spleen was required for enrollment.

The results of RESPONSE 2 were very similar to those of RESPONSE. Control of hematocrit was reported in 68% of patients receiving ruxolitinib vs 20% of those receiving best-available therapy. In RESPONSE 2, many of the patients receiving ruxolitinib had improved control of the white blood cells, platelets, and symptoms. Complete symptom resolution was reported in 50% of the ruxolitinib arm vs 7.7% of the best-available therapy arm. The results from RESPONSE 2 prove that ruxolitinib is active in patients without an enlarged spleen. Ruxolitinib was associated with impressive control of blood cell counts and symptoms, as was also shown in patients with an enlarged spleen.

H&O What other interesting data on polycythemia vera were presented at the 2016 EHA meeting?

SV Dr Alberto Alvarez-Larrán presented a study on prevention of thrombosis in approximately 500 patients with polycythemia vera treated with hydroxyurea. As I mentioned previously, patients at high risk for thrombosis require cytoreductive therapy in addition to phlebotomy and aspirin. In most cases, the cytoreductive therapy is hydroxyurea. The aim of therapy with hydroxyurea is to control the blood cell count to normalize the hematocrit below 45%, which would further decrease the risk of blood clotting. It was not known whether hydroxyurea should be administered with the goal of completely eliminating the need for phlebotomy (ie, not allowing patients to have an elevated hematocrit that would require phlebotomy while on hydroxyurea). An important observation from the study by Dr Alvarez-Larrán is that when hydroxyurea is introduced as a cytoreductive therapy in high-risk polycythemia patients, the goal should be to eliminate the need for phlebotomy. The study showed that tight control of hematocrit (<45%) with a proper dose of hydroxyurea was mandatory to decrease the risk of thrombosis. A better outcome was seen among the patients for whom hydroxyurea eliminated the need for phlebotomy than in patients who still required phlebotomy.

Another interpretation of this study is that a continued need for phlebotomy indicates that a patient is not receiving optimal benefit from hydroxyurea. In these patients, it would then be prudent to adjust the dosing of hydroxyurea or consider alternative therapies.

H&O Are the roles of hydroxyurea and phlebotomy likely to change with the new data?

SV The new data improve the ability to comprehend the utility of existing therapies. The analysis of hydroxyurea efficacy has provided insight into issues such as the optimal use of this agent, the goals of therapy, which patients benefit the most or least, and when treatment should be altered or replaced. Similar analyses are being performed for interferon and ruxolitinib in the second-line setting to fully understand when to introduce therapy, when to change therapy, and how to fully assess the benefit-risk ratio between these 2 steps.

Disclosure

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Suggested Readings

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