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Proactive Steps to Optimize the Management of Polycythemia Vera and Myelofibrosis

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H&O What are the management goals for polycythemia vera?

RM The first goal is to control hematocrit levels and avoid erythrocytosis to decrease the likelihood of thrombosis or bleeding. We aim to control the white blood cell count to less than 10,000/µL and the platelet count to less than 400,000/µL. It is believed that both white blood cells and platelets can contribute to the risk of thrombosis and bleeding. Control of high blood counts should lead to a decrease in disease-associated symptoms, such as headaches, difficulties with concentration, visual disturbances, pruritis, night sweats, and fatigue. When splenomegaly is present, we seek to reverse it. The goals of management for polycythemia vera correspond to improvement in symptoms.

H&O Are symptoms always present?

RM Most patients have symptoms when they are diagnosed with polycythemia vera. In 25% to 50% of patients, symptoms are minimal. Most commonly, patients develop fatigue and other symptoms associated with high cell counts that impede blood flow, such as headaches, erythromelalgia, visual disturbances, migraines, and difficulty with concentration. Patients can also have pruritis, which is a common and difficult symptom, and night sweats. Less common symptoms arise from an enlarged spleen. Bone pain can also occur.

H&O Are thromboses readily apparent, and can measurement of hematocrit levels help detection?

RM Thrombosis is typically associated with localized discomfort and/or edema in the legs. A pulmonary embolism may cause chest pain or shortness of breath. More rarely, patients with polycythemia vera can experience abdominal pain from a blood clot in the liver or spleen. Although the hematocrit level is typically elevated in the setting of thrombosis, measurement of hematocrit is not a screening test for thrombosis. Unfortunately, there is no good screening test for thrombosis. Suspicion that a thrombosis has occurred is based on pain, swelling, and edema. Some patients may have elevations in the D-dimer level or show other laboratory abnormalities, but these are not helpful in predicting thrombosis.

H&O When is treatment initiated for polycythemia vera?

RM All patients with polycythemia vera receive some form of treatment that begins with control of the hematocrit level. At a minimum, all patients with polycythemia vera who have a hematocrit level higher than 45% undergo phlebotomy. Most patients with polycythemia vera receive baby aspirin (assuming they are not allergic). In polycythemia vera, frontline treatment refers to cytoreductive therapy given after phlebotomy and aspirin. Cytoreductive therapy to lower blood counts is initiated

in several settings: patients who are at increased risk based on age or prior thrombotic events, patients who have undergone 2 phlebotomies that were inadequate or intolerable, and patients with difficult symptoms that were not improved by phlebotomy or aspirin. For frontline cytoreductive therapy, hydroxyurea is considered the standard of care, along with pegylated interferons. Most international guidelines with recommendations based on current clinical trials list pegylated interferons as a frontline option, particularly for younger patients or women of child-bearing potential. Ruxolitinib (Jakafi, Incyte) is the second-line approach.

The symptoms are usually treated as part of the disease. For example, reduction of splenomegaly can be achieved with the typical treatments: hydroxyurea, interferon, or ruxolitinib. An exception would be patients with an active thrombosis. These patients require additional treatment for anticoagulation with an agent such as warfarin or low-molecular-weight heparin, which would not be part of the regimen for patients without a thrombosis.

H&O What symptoms indicate that frontline cytoreductive treatment was not effective?

RM The failure of frontline cytoreductive therapy can be attributed to resistance or intolerance. Resistance to hydroxyurea typically manifests as inadequate control of the blood count, residual symptoms, or residual splenomegaly. Patients who are intolerant to therapy show an improvement in blood cell counts, but also develop adverse events including leg ulcers, hair loss, fevers, gastrointestinal side effects, or excess cytopenia. In some cases, the treatment regimen required to lower the platelet count into the normal range can cause anemia or leukopenia.

H&O What are the subsequent treatment options for polycythemia vera?

RM Ruxolitinib is the only treatment approved by the US Food and Drug Administration (FDA) for the second-line setting in polycythemia vera. Ruxolitinib inhibits Janus kinase 1 (JAK1) and Janus kinase 2 (JAK2). The native JAK2 protein is overly active because of these mutations in patients with polycythemia vera. In randomized phase 3 studies, such as 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) and the RESPONSE-2 trial (Ruxolitinib for the Treatment of Inadequately Controlled Polycythaemia Vera Without Splenomegaly), ruxolitinib was superior to best available therapy for control of hematocrit, symptoms, and splenomegaly. Ruxolitinib was effective and led to durable responses for most patients. In the RESPONSE-2 trial of patients without splenomegaly, hematocrit control was seen in 62% of patients treated with ruxolitinib vs 19% of patients in the control arm. In the RESPONSE trial of patients with splenomegaly, hematocrit control was achieved in 60% vs 20%, respectively.

H&O Can treatment strategies be optimized for each patient?

RM The treatment goals are standard: resolution of symptoms, control of the blood count, hematocrit of less than 45% without phlebotomies, white count less than 10,000/µL, platelet count less than 400,000/µL, and control of splenomegaly. Ideally, the dose is optimized to achieve the best response with the least amount of toxicity. The goal of therapy is for the disease to become as invisible to the patient as possible.

H&O What percentage of patients will progress to myelofibrosis, and what signs indicate progression?

RM Approximately 10% of patients with polycythemia vera will progress to myelofibrosis. The rate may be higher among younger patients, who will have a longer duration of disease. For them, the time to progression to myelofibrosis is typically 10 years or longer. The longer a patient has polycythemia vera, the greater the likelihood of progression.

There are several signs of progression. There may be a decrease in myeloproliferation, which can eliminate the elevation in red cell counts or even lead to anemia. Patients may no longer require cytoreduction to control their blood cell counts. The size of the spleen can become markedly enlarged, leading to changes in the symptom pattern. Patients can experience unintentional weight loss, fevers, and bone pain. Immature cells can circulate in the peripheral blood owing to a fibrosing process in the bone marrow.

H&O What are the treatment options for patients with myelofibrosis?

RM Upon diagnosis with myelofibrosis, patients are stratified by risk. Younger patients with high-risk disease who are good candidates for stem cell transplant will undergo this procedure.

Current US guidelines list ruxolitinib as the frontline medical therapy for patients with myelofibrosis.

Ruxolitinib is approved by the FDA for the treatment of intermediate- or high-risk myelofibrosis, including primary myelofibrosis, post–polycythemia vera myelofibrosis, and post–essential thrombocythemia myelofibrosis in adults. The use of ruxolitinib is based on randomized phase 3 data from the COMFORT (Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment) 1 and 2 trials. In a pooled analysis of these trials, the risk of death was reduced by 30% among patients randomly assigned to treatment with ruxolitinib compared with patients in the control arm.

Ruxolitinib is clearly the standard medical therapy for myelofibrosis. It can improve splenomegaly and symptoms in the short-term, and likely improves survival in the long-term.

Most patients will receive medical therapy with ruxolitinib. Observation may be appropriate for asymptomatic patients at low risk. Over time, however, we may find that it is beneficial to intervene in this group, with agents such as interferons, to avoid progression.

H&O Can treatment strategies be optimized for each patient?

RM Similar to polycythemia vera, the goal is to achieve the best treatment outcome with the minimal amount of toxicity. The dose is optimized for each patient, based on tolerability. We try to administer at least 10 mg twice daily, and ideally reach 15 mg or 20 mg twice daily. We identify a tolerable dose of ruxolitinib to decrease the burden of symptoms to the greatest degree possible, improve splenomegaly to resolve spleen-related symptoms, and reduce the palpable component by at least 50%. The dose-limiting toxicities of ruxolitinib are mild anemia or thrombocytopenia. An adequate dose of ruxolitinib is likely necessary for long-term administration to achieve an optimal response.

H&O Are there any other adverse events?

RM The most common adverse events associated with ruxolitinib include anemia and mild thrombocytopenia. The events can be managed through dose modification. Less commonly, there is an increased risk of herpes shingles virus; a small but real risk of nonmelanoma skin cancers; and, rarely, atypical infections, such as reactivation of tuberculosis or progression of viral hepatitis.

H&O Are there other treatment options in development?

RM Three other JAK2 inhibitors have completed phase 3 testing: pacritinib, fedratinib, and momelotinib. Several combination studies have also been conducted. However, for most patients outside the setting of a clinical trial, the options are either initial transplant or ruxolitinib followed by transplant, if appropriate, at the time of relapse or progression.

H&O Do you have any further recommendations for the management of these patients?

RM Since patients with myeloproliferative neoplasms, including myelofibrosis, will have to manage their disease for many years, issues concerning their overall health and quality of life are very important. There are many ways to improve their quality of life, including optimizing their medication. Patients should also follow a nutritious diet and engage in a physical activity regimen to improve fatigue and insomnia.

Disclosure

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Suggested Readings

Griesshammer M, Saydam G, Palandri F, et al. Ruxolitinib for the treatment of inadequately controlled polycythemia vera without splenomegaly: 80-week follow-up from the RESPONSE-2 trial. *Ann Hematol*. 2018;97(9):1591-1600.

Harrison CN, Schaap N, Vannucchi AM, et al. Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA-2): a single-arm, open-label, non-randomised, phase 2, multicentre study. *Lancet Haematol*. 2017;4(7):e317-e324.

Harrison CN, Vannucchi AM, Kiladjian JJ, et al. Long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs best available therapy for myelofibrosis. *Leukemia*. 2016;30(8):1701-1707.

Harrison CN, Vannucchi AM, Platzbecker U, et al. Momelotinib versus best available therapy in patients with myelofibrosis previously treated with ruxolitinib (SIMPLIFY 2): a randomised, open-label, phase 3 trial. *Lancet Haematol*. 2018;5(2):e73-e81.

Mascarenhas J, Hoffman R, Talpaz M, et al. Pacritinib vs best available therapy, including ruxolitinib, in patients with myelofibrosis: a randomized clinical trial. *JAMA Oncol*. 2018;4(5):652-659.

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, Gotlib J, Mesa RA, et al. Long-term survival in patients treated with ruxolitinib for myelofibrosis: COMFORT-I and -II pooled analyses. *J Hematol Oncol*. 2017;10(1):156.

Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med*. 2012;366(9):799-807.

Verstovsek S, Mesa RA, Gotlib J, et al; COMFORT-I investigators. Efficacy, safety, and survival with ruxolitinib in patients with myelofibrosis: results of a median 3-year follow-up of COMFORT-I. *Haematologica*. 2015;100(4):479-488.