ADVANCES IN LLM

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

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Refining the Management of Polycythemia Vera

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H&O What are the clinical characteristics of polycythemia vera?

RM Patients with polycythemia vera classically present with erythrocytosis, and they can also have thrombocytosis and/or leukocytosis. A subset of patients present with a thrombotic event, either thrombosis or bleeding. Symptoms reflect high blood counts, and can include transient ischemic attacks, complex headaches, migraines, and erythromelalgia. Patients can also experience itching, night sweats, and, in rare cases, bone pain. Splenomegaly may also occur.

H&O When is treatment initiated, and what are the first-line options?

RM All patients who are diagnosed with polycythemia vera receive some form of treatment. Management begins with control of the hematocrit level to below 45%. Patients usually receive low-dose aspirin at 100 mg/day or less (unless they are allergic to aspirin). For a subset of patients, frontline treatment consists of cytoreductive therapy with hydroxyurea. These patients have a history of thrombotic events or a higher risk for these events, are older than 60 years, have difficult-to-control symptoms, do not tolerate phlebotomy, or have strong cardiovascular symptoms. Patients who do not receive cytoreductive therapy as first-line treatment tend to be younger and asymptomatic, and they do not have a history of vascular events or significant cardiovascular risk.

H&O What are the goals of treatment?

RM There are short-term and long-term goals. Therapy with phlebotomy and aspirin is meant to decrease the risk of thrombosis and bleeding. In low-risk patients, thrombocytosis is not treated unless the platelet level exceeds 1000×10^9/L. The goals of cytoreductive therapy are to lower blood counts (both erythrocytes and platelets), improve symptoms, and decrease splenomegaly. It is hoped that achievement of these goals will decrease the impact of the disease and improve the patient's quality of life.

H&O What is the ideal hematocrit level needed to prevent thrombosis?

RM Strong evidence shows that hematocrit levels should be 45% or less. Some patients may benefit from a lower level; individualization is helpful. Historically, the hematocrit level was maintained at less than 42% in some women. Some patients may have fewer symptoms when the hematocrit level is less than 45%. Patients with recurrent thrombotic events might benefit from a stricter cutoff.

The key is to ensure that hematocrit levels do not exceed 45%. When a phlebotomy is needed after every blood count, then the blood counts are too infrequent, and not enough is being done to control the disease.

H&O What are the levels of white blood cells that lead to thrombosis and/or require treatment?

RM Leukocytosis can be associated with an increased risk for thrombosis. It would be inaccurate to say that a

Table. Symptoms in the MPN10 Questionnaire

- Fatigue
- Early satiety
- Abdominal discomfort
- Inactivity
- Concentration problems
- Night sweats
- Itching
- Bone pain
- Fever
- Weight loss

certain level automatically leads to thrombosis, but the higher the white blood cell count, the higher the risk of thrombotic events. Various studies have identified different cutoffs—from 11,000 cells/µL to 15,000 cells/µL—as relevant to that risk. The European LeukemiaNet guidelines recommend that patients initiating treatment with cytoreductive therapy should have normal white blood cell levels, in order to decrease the risk of thrombosis.

A rising leukocyte count, particularly above 20,000 cells/µL, can indicate progression toward myelofibrosis. The National Comprehensive Cancer Network (NCCN) guidelines recognize that progressive leukocytosis can be a sign of inadequately controlled disease or of progression toward myelofibrosis. If a patient is on cytoreductive therapy yet continues to have persistent leukocytosis, he or she may not be responding adequately to the cytoreductive agent selected.

H&O What are the clinical characteristics in uncontrolled polycythemia vera?

RM There are several phenotypes in uncontrolled polycythemia vera that can overlap. Uncontrolled disease is indicated by an inadequate response to therapy, progression toward myelofibrosis, and inadequate control of symptoms or thrombosis with cytoreductive therapy. A goal of treatment is to prevent thrombosis and bleeding; if they occur, then the disease is not adequately controlled. Symptoms are another indication, as is progressive splenomegaly. Inadequate control is also indicated by high blood counts—such as a platelet count higher than 400,000 cells/µL and a white cell count higher than 11,000 cells/µL—and by a persistent need for phlebotomies (eg, more than 6 phlebotomies per year after the initial procedure).

H&O What are the components of symptom assessment, and when would you consider a change in treatment?

RM The core symptom assessment is made through the MPN10, a 10-item questionnaire. The MPN10 has been highly validated in patients with myeloproliferative neoplasms and polycythemia vera, for both baseline and serial assessment. Symptoms include fatigue, early satiety, and abdominal discomfort (Table). Other important symptoms include progression toward myelofibrosis, toxicity from frontline therapy, recurrent thrombosis or bleeding (even with therapy), and inadequate control of splenomegaly. If the patient's disease is controlled, and he or she is doing well, has no blood clots or bleeding events, and is tolerating the medicine well, then there is no indication to change the cytoreductive therapy.

H&O What do the NCCN guidelines recommend?

RM The NCCN guidelines for polycythemia vera are the first set of US-based guidelines that aim to inform management and codify the evidence. A key component of the NCCN guidelines concerns the threshold for initiating cytoreductive therapy. As I mentioned, control of hematocrit levels is a goal for all patients, and treatment with aspirin is almost always initiated. Cytoreductive therapy is administered to most patients, with the exception of those who are young, asymptomatic, and without prior thrombotic events.

In their definition of an inadequate response to frontline therapy, the NCCN guidelines build on published reports and the European LeukemiaNet guidelines. Progressive disease can be indicated by worsening weight loss and increased splenomegaly. Progression to myelofibrosis can be indicated by a recurrent need for phlebotomy, leukocytosis, and unresponsive thrombocytosis. Inadequately controlled symptoms are not uncommon. All of these features can be a sign of inadequate response, and hence should prompt the consideration of second-line therapy.

H&O What are the options after cytoreductive therapy?

RM The US Food and Drug Administration has approved one treatment for second-line therapy: the Janus kinase 2 (JAK2) inhibitor ruxolitinib (Jakafi, Incyte). Nearly all patients with polycythemia vera have a *JAK2* mutation. Ruxolitinib was approved for polycythemia vera in 2014 based on data from the RESPONSE trial (Study of Efficacy and Safety in Polycythemia Vera Subjects Who Are Resistant to or Intolerant of Hydroxyurea: JAK Inhibitor INC424 Tablets Versus Best Available Care). This study compared ruxolitinib vs best available therapy in patients with an inadequate response to hydroxyurea, splenomegaly, and inadequately controlled disease. The primary

endpoint—the proportion of patients with both control of hematocrit levels and a reduction in spleen volume of at least 35% from baseline to week 32—was achieved in 21% of the ruxolitinib arm vs 1% of the control arm (P<.001). Ruxolitinib also improved symptom burden and decreased the need for phlebotomy as compared with the best available therapy.

> It is crucial to recognize polycythemia vera as a chronic disease.

The RESPONSE-2 study (Ruxolitinib Efficacy and Safety in Patients With HU Resistant or Intolerant Polycythemia Vera vs Best Available Therapy) enrolled a similar patient population, but without splenomegaly. Ruxolitinib was superior to best available therapy in controlling hematocrit symptoms and in achieving a complete hematologic response. There are now data through 5 years, which show durability, good safety, phlebotomy independence, and improvement in quality of life.

H&O Are there any other promising treatment options?

RM Phase 2 and phase 3 trials have evaluated the long-acting interferons ropeginterferon α-2b and pegylated interferon α-2a. The studies demonstrated benefit in both the first-line and second-line settings. Neither of these drugs is yet approved for polycythemia vera.

H&O Do you have any other insights into the management of polycythemia vera?

RM It is crucial to recognize polycythemia vera as a chronic disease. The goal of the management plan is to select a therapy that will adequately protect patients against thrombosis and bleeding, address any disease-related symptoms, and be well-tolerated.

There is some room for improvement in the management of these patients. In the United States, some clinicians are reluctant to initiate cytoreductive therapy, and therefore patients may start this treatment later than would be ideal. Clinicians may fail to strictly control the hematocrit level to less than 45% through the appropriate use of phlebotomy, thereby increasing the risk of thrombosis. There may also be a delay in identifying the failure of frontline therapy and the need to switch to second-line treatment.

Disclosure

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Suggested Readings

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