Polycythemia vera:

Recognizing and treating the patient with high-risk disease

Kim-Hien Dao, DO, PhD, is in a prime position to comment on high-risk polycythemia vera (PV). As Oregon Health & Science University is the only academic medical center in Oregon, 80% of Dr Dao’s patients with PV are referrals who have presented with poor prognosis or have already failed standard therapy. Dr Dao’s years of experience at this tertiary center allow her to provide valuable advice to both the hematologist and the primary care physician about working together to recognize and manage patients with poorly controlled, high-risk PV.

High-risk polycythemia vera

PV is a classic Philadelphia chromosome-negative myeloproliferative neoplasm characterized by an overactive Janus-associated kinase (JAK)-signal transducer and activator of transcription pathway through mutations in JAK2 exons 12 or 14 (JAK2V617F). While some patients with PV may survive for decades, a subset of patients with high-risk disease with abnormal karyotype has a life expectancy of 5.8 years, consistent with that of myelofibrosis. Burdensome symptoms, predilection for thrombosis, and the capacity to transform into acute myelogenous leukemia or myelofibrosis contribute to this excess mortality.

Risk stratification in PV currently focuses on the likelihood of thrombosis. In the absence of formal guidelines, high risk has been traditionally defined by age >60 years and/or a history of thrombosis. However, uncontrolled PV confronts the clinician with a range of high-risk presentations, from increasing symptomatology to disease progression, in addition to acute thrombotic events. As a practical matter at our institution, we adopt the broader definition of high-risk PV to address the broader spectrum of complications of PV.

Regarding thrombosis, results of the Cytoreductive Therapy in Polycythemia Vera study demonstrated improved thrombotic outcomes with maintenance of a hematocrit (Hct) level <45%, and some clinicians, including those at our institution, propose an Hct target of 42% for women. Suboptimal response to therapy can manifest as an uncontrolled Hct level, thrombotic events, leukocytosis, thrombocytosis, symptoms, or increasing spleen size. These features point to higher-risk features of PV. These indicators of inadequately controlled, high-risk disease are not confined to any one phase of treatment and may occur at any time during the course of the disease, ultimately reducing survival.

Classic cardiovascular risk factors are also worrisome, and the clinician should ensure that these patients have a well-controlled Hct level and take measures to modify their cardiovascular risk profile. We would consider a patient with PV with diabetes or poorly controlled blood pressure to have higher risks for developing thrombotic events. If possible, newly diagnosed patients with PV or patients with uncontrolled Hct should delay elective surgeries until Hct control is achieved for a longer period (eg, >3 months), as some study findings have indicated a worse surgical outcome under conditions of poorly controlled Hct or newly diagnosed PV. The ultimate indicator of inadequately controlled, high-risk PV is a thrombotic event. Both younger and older patients may present with a stroke or a heart attack as their initial presenting symptom of PV or after a period of uncontrolled, high-risk PV.

Common challenges

Challenge #1: A common scenario in rural states is that patients may not have access to a hematologist. Their PV is managed by their primary care physician, who may not fully recognize that having an uncontrolled Hct level constitutes a high risk in PV. Even hematologists may be lulled into complacency and lose sight of the target Hct goal when patients do well for a while. These are both issues that we have had to address in our practice.

Challenge #2: The challenge we face most often is that Hct levels in these patients are not being managed to an appropriate Hct target when they are first diagnosed with PV. It is important to closely monitor treatment effectiveness of the phlebotomies and hydroxyurea (HU) dose, especially and frequently during the first 6 months of therapy. All too often we see patients placed on HU and not followed up for 3 to 6 months, at which time the Hct level remains at 50%. Our protocol includes initiating phlebotomy immediately to bring the Hct level below 45% for men and 42% for women. Phlebotomy may be required quite frequently initially, at times every other day. The complete blood count (CBC) should be checked at least every 4 weeks until a steady-state target Hct level is achieved. The CBC may then be checked less frequently.
Use of hydroxyurea

The use of HU is considered first-line therapy for high-risk patients in conjunction with phlebotomy and for standard-risk patients who have Hct inadequately controlled by phlebotomy alone; however, there are issues to keep in mind. First, young patients in their 20s to 40s may have 20 or 30 years of HU use in their future. Even in the absence of controlled, prospective trials demonstrating the leukemogenic potential of HU, this potential risk must be addressed, and alternatives should be considered. Pegylated interferon is an alternative for select younger and older patients, but this off-label use is not often covered by health insurance.

Mucocutaneous problems with HU can become a serious problem or dose-limiting issue. In the presence of a preexisting wound or skin ulcer, whether it is from surgery, long-standing diabetes, or even if the patient is at risk for having skin ulcers due to an unrelated treatment, HU should be prescribed with caution or stopped altogether. HU is a cytostatic agent that has a common effect in all cells during DNA synthesis, which is most obvious in tissues with a high cell turnover (eg, skin mucosa, oral mucosa, and gastrointestinal mucosa). HU toxicity is largely dose related, and a high dose of HU could impede wound healing.

Approximately 10% of our patients with PV are not candidates for HU because of wounds, and this includes patients with diabetes and patients recovering from surgery or with other ulcerative skin issues. Otherwise, we continue to dose HU and increase the dose until a reasonable Hct control is achieved. Phlebotomy is utilized simultaneously to achieve Hct control; however, if the frequency escalates to every 4 weeks, this is a good indicator that HU is not effective enough. This is similar to the European LeukemiaNet guidelines for resistance to and intolerance of HU. Resistance to and intolerance of HU have been reported to identify patients with high-risk disease and may contribute to an increased risk of death. Personally, we are much more concerned about the effect of HU failure in terms of Hct control rather than it necessarily being a biomarker for worse disease. Significant depression or other mood disorders and a history or presence of an autoimmune disease are considered warnings and precautions to the use of pegylated interferons, as are central nervous system diseases such as Parkinsonism; peripheral neuropathy; thyroid dysfunction; and significant hematologic, hepatic, renal, or cardiac abnormalities. Our facility has also noted that elderly patients are less likely than younger patients to tolerate interferon.

Hydroxyurea Failure in an Elderly Man With Depression and an Unrelated Skin Problem

A 79-year-old man with JAK2V617F mutation–positive PV was followed for approximately 5 years without any major constitutional symptoms or past thrombotic events. He was maintained on HU 500 mg 3 times daily and with phlebotomy every 4 to 6 weeks to achieve a target Hct level of <45%. He then developed severe palmoplantar psoriasis, and his phlebotomy needs escalated to every 3 weeks. Therapy for the palmoplantar psoriasis led to severe ulcerations and poor wound healing while on HU. A significant depressive episode and his advanced age suggested caution with the use of interferons.

Hydroxyurea Failure in a Young Woman

A 36-year-old woman presented 8 years ago with ascites and liver enzyme abnormalities during elective preoperative work-up. She was diagnosed with Budd-Chiari syndrome (hepatic vein thrombosis). As a result of this complication, often associated with PV, she was tested for the JAK2V617F mutation, which came back positive. She was diagnosed with JAK2V617F-positive PV and started on HU. Gastrointestinal upset occurred upon escalation of the dose of HU. CBC revealed erythrocytosis, thrombocytosis, and leukocytosis. She has been maintained on HU while alternating between doses of 1,000 mg daily and 500 mg daily, with phlebotomy every 3 to 4 months. Her spleen has started to enlarge, and phlebotomy requirements have escalated to monthly. Despite these measures, her Hct level remains in the 46% to 48% range. CBC, complete blood count; Hct, hematocrit; HU, hydroxyurea; PV, polycythemia vera.

This high-risk patient was high functioning and had few symptoms, but the CBC taken every 4 to 6 weeks indicated a need for phlebotomy, which still failed to achieve the target Hct level of 42%. The patient did not want to take injections (eliminating interferon) and wanted more information before trying alternative therapy.
Symptoms and high risk

Excessive symptoms or escalating symptoms may biologically suggest higher-risk PV. These are concerning features, and we would definitely make the extra effort to control their Hct to target levels at our institution. We have seen the literature on abnormal karyotype and age-weighted stratification, but in this author’s opinion, the goal is to achieve a target Hct level below 45% in men and 42% in women; therefore, these new parameters in isolation would not change our disease management. These and other proposed prognostic factors are informing us of what we should be doing with all high-risk patients, which is that they should receive aspirin and have a tight control of their Hct level. New risk factors may be helpful in talking to the patient about prognosis, but in high-risk disease, the goals of therapy remain the same.

In my opinion, it is essential for the Hct level to be promptly reduced to a sex-appropriate target, with frequent follow-up until the target is reached. Besides age >60 years and prior thrombosis, other high-risk features exist, including poor Hct control, cardiovascular risk factors, leukocytosis, HU failure, excessive or escalating symptoms, enlarging spleen, and recurrent thromboses. In rural areas where the patient must be followed by a primary care physician, a hematologist can explicitly communicate the importance and seriousness of strict Hct control. There is no place for complacency with high-risk patients. Patients who have experienced HU failure need alternative therapies to reduce the risk for PV-associated complications.

This article reflects the personal perspective of Dr Kim-Hien Dao, who was compensated for her participation in this interview. Dr Dao has also served as a consultant for Incyte Corporation (Wilmington, DE).

References


