

# ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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## Prevention and Management of Thrombosis in Myeloproliferative Neoplasms



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### H&O What are the various myeloproliferative neoplasms (MPNs)?

**MK** The conventional BCR-ABL–negative MPN categories are polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis, unclassified MPN (MPN-U), chronic neutrophilic leukemia, chronic eosinophilic leukemia, and mastocytosis. The 2016 revision of the World Health Organization (WHO) classification of myeloid neoplasms<sup>1</sup> includes the category *prefibrotic myelofibrosis*, and some of the cases previously diagnosed as essential thrombocythemia may fall into this category.

### H&O Which of the MPNs are associated with thrombosis?

**MK** The MPNs associated with thrombosis are PV, ET, myelofibrosis, and prefibrotic myelofibrosis. MPN-U is also linked to thrombosis, but researchers have not examined this relationship with the same systematic approach that has been used for the other groups, and data on the association between MPN-U and thrombosis are lacking.

### H&O How strong is the association between each of these conditions and thrombosis?

**MK** The overall risk for thrombosis is approximately 20% in patients with any of these 4 MPNs. About 10% to 30% of patients report thrombotic events before diagnosis, and the incidence of thrombosis after diagnosis remains high, at 10% to 20%.<sup>2</sup> Many patients with prior thrombosis have elevated blood cell counts at the time of thrombosis, a finding that suggests a delay in the diagnosis of the MPN.

Regarding the specific types of MPN, the risk for thrombosis in PV was 5.5% per patient-year in 2000 but was found to have decreased to 2.6% per patient-year by 2015. The risk for thrombosis is approximately 2% to 4% per patient-year in ET, 2.2% per patient-year in primary or secondary myelofibrosis, and 2.1% per patient-year in prefibrotic myelofibrosis.

### H&O How does thrombosis manifest in these patients?

**MK** Arterial thromboses are more prevalent than venous thromboses. Arterial thromboses can lead to transient ischemic attack (TIA), stroke, myocardial infarction, angina, or abnormalities of the peripheral circulation that result in ischemia and gangrene. Venous clots can manifest as deep vein thrombosis, pulmonary embolism, or uncommon syndromes that affect the splanchnic (abdominal) or cerebral venous system. Small-vessel pathology can manifest as migraine-type headache, lightheadedness, paresthesia, erythromelalgia, and atypical chest pain; these are often responsive to treatment with aspirin. When thrombosis recurs, the prior distribution of thrombosis (arterial vs venous) is usually affected, but this pattern is not exclusive. One-third of patients with prior venous thrombosis have recurrence in arteries, and vice versa.

### H&O What are the mechanisms by which MPNs lead to thrombosis?

**MK** A common finding among people with thrombosis related to MPN is the Janus kinase 2 gene (*JAK2*) V617F mutation. This mutation leads to physical and functional abnormalities in red blood cells, white blood

cells, platelets, and endothelial cells. The result is that the aggregability of cells to one another and to the endothelium is increased, leading to thrombosis. The risk for thrombosis is lower in patients who have myeloproliferative disease with the calreticulin gene (*CALR*) mutation than in those who have myeloproliferative disease with the *JAK2* V617F mutation.<sup>2</sup>

A further mechanism relates to rheologic factors. For example, the hematocrit level is high in PV, which leads to abnormalities in the viscosity and shear rate of blood.

### H&O Which patients are at highest risk for thrombosis?

**MK** A patient may be assigned to a thrombotic risk categories depending on patient- and disease-related variables.<sup>3</sup>

In ET, the European LeukemiaNet criteria or the International Prognostic Score for Thrombosis in Essential Thrombocythemia (IPSET-T) may be used. The variables considered in these systems include the patient's age, any previous history of thrombosis, the presence of a *JAK2* mutation, and other cardiovascular risk factors, such as hypertension. The risk for thrombosis in a young patient without previous thrombosis, without cardiovascular comorbidities, and not bearing the *JAK2* V617F allele is considered to be very low.

In PV, age and prior history of thrombosis are typically used for categorization. Patients who are young and have not had clots are at a low risk, whereas patients

Patients who experience a vascular event despite treatment with aspirin will need cytoreduction.

who are older than 60 years or have had prior thrombosis are considered to be at high risk.

The risk scoring systems in myelofibrosis address the severity of disease, but they do not address vascular thrombosis. This is because morbidity and mortality in these patients result mainly from progressive bone marrow failure and transformation to leukemia rather than from a cardiovascular event.

An additional 2 risk-related factors that appear in multivariate analyses are white blood cell count and cardiovascular risk profile, including diabetes and

hypertension. These are not consistently included in the standard scoring systems for risk stratification but are often used in treatment algorithms.

### H&O Which thrombosis prophylaxis measures should be used in these patients, and when?

**MK** Patients with PV should undergo venesection to maintain a hematocrit of less than 45%.<sup>4</sup> Aspirin should be used for the primary prevention of thrombosis in patients with PV or ET, and therapy should be commenced upon diagnosis. The dose varies across studies, but 75 to 100 mg/day is commonly used. Aspirin should be avoided in patients who have a very high platelet count ( $>1500 \times 10^9/L$ ) because these patients have a greater propensity to bleed owing to functional defects of platelets resulting from acquired von Willebrand disease. The use of aspirin also is especially risky in elderly patients with high platelet counts, who may be at greater risk for mortality and morbidity from hemorrhage than from thrombosis. In these latter groups, a history of bleeding should prompt the initiation of cytoreductive treatment in place of aspirin. Low-risk patients with ET and mutant calreticulin (*CALR*) may not receive any benefit from aspirin and have been reported to have a higher rate of complications from bleeding. Warfarin should be considered in patients with a previous history of venous thrombosis, given that the likelihood of recurrent venous thromboembolism (VTE) in these patients is increased. Despite the increasing use of direct oral anticoagulants (DOACs) in common conditions such as atrial fibrillation and VTE, scant data exist on the use of these drugs in patients with MPNs.

Thromboprophylaxis usually is not recommended in myelofibrosis, as thrombocytopenia is a common manifestation of the disease and the overall risk for thrombosis is overtaken by leukemic transformation. Furthermore, use of the JAK inhibitor ruxolitinib (Jakafi, Incyte) in these patients also contributes to thrombocytopenia and increased bleeding, necessitating caution with the administration of aspirin or warfarin.

An important component of primary prevention is treatment to reduce blood cell counts to the desired therapeutic target in patients identified to be in a high-risk category. This includes venesection to keep the hematocrit below 45%<sup>4</sup> and cytoreductive treatment with hydroxycarbamide (also known as hydroxyurea) and potentially interferon alfa, ruxolitinib, and anagrelide. The role of venesection in patients who have PV with thrombocytosis is variable because increasing the intensity of venesection can result in higher platelet counts due to iron deficiency. In such patients, cytoreduction in conjunction with periodic venesection may be appropriate. Ideally, treatment

should ensure stable control of hematocrit (<45%), white blood cells and neutrophils in the normal range, and platelets <400 × 10<sup>9</sup>/L). In some patients with PV, venesection alone is not sufficient to achieve this goal.

Primary prevention also should address adequate control of cardiovascular risk factors.

### **H&O** What approaches are used for secondary prevention?

**MK** Patients who have a vascular event despite treatment with aspirin require cyto-reduction for management of their blood cell counts. For patients with recurrence of

There are special concerns related to pregnancy and the postpartum period.

an arterial event, aspirin administration may be increased from once a day to twice a day, or clopidogrel may be used instead of aspirin. Recurrence of a venous event may necessitate a higher target international normalized ratio (INR). Patients with both arterial and venous thromboses may require treatment with aspirin and warfarin, although the risk for bleeding is increased with this combination. Data on combined treatment in patients who have MPNs with recurrent thrombosis are lacking.

The hematologist should take another look at factors related to cardiovascular risk, including blood pressure, lipid levels, and lifestyle factors, in patients in whom subsequent events develop.

An additional consideration is to optimize cyto-reductive treatment with a broad-spectrum agent, such as hydroxycarbamide, rather than a narrow-spectrum strategy, such as anagrelide or venesection. Unlike the standard cytotoxic agent hydroxycarbamide, anagrelide does not affect the white blood cell count or hemoglobin level. It has also been reported to increase the rates of arterial thrombosis.<sup>5</sup> For these reasons, elderly patients or those at high risk for thrombosis who require good control of their hematocrit, white blood cell count, or platelet count should be managed with hydroxycarbamide or interferon rather than with anagrelide. Patients who have PV that is refractory to hydroxycarbamide, or who cannot tolerate it, should be offered other agents, including ruxolitinib. The role of this agent in patients with ET who have a poor response to hydroxycarbamide is under review.

There is evidence to suggest that angiotensin-converting enzyme (ACE) inhibitors may be the drug of choice to treat hypertension in patients with PV; a review of data from patients in the CYTO-PV study (A Large-Scale Trial Testing the Intensity of Cyto-reductive Therapy to Prevent Cardiovascular Events in Patients With Polycythemia Vera) found a reduced need for cyto-reductive treatment in patients who received ACE inhibitors for hypertension.<sup>6</sup>

### **H&O** What special concerns exist for patients with splanchnic or abdominal vein thrombosis?

**MK** Approximately one-third of people with splanchnic vein thrombosis (SVT) have underlying myeloproliferative disease. This is even more common among patients with hepatic vein thrombosis or Budd-Chiari syndrome, in whom the rate of underlying myeloproliferative disease is approximately 50%.<sup>7</sup> SVT has a high morbidity and mortality rate and may necessitate the placement of stents in the abdominal veins; thrombolysis or occasionally orthotopic liver transplant may be required in some cases. These patients require prompt management of thrombosis with low-molecular-weight heparin; some also require antiplatelet agents and venesection/cyto-reduction to control their blood counts from early on. Long-term anticoagulation and control of blood cell counts are important, as is periodic review by a hepatologist for portal hypertension and stent patency. A bone marrow assessment should be undertaken, and myelofibrosis should be treated per standards. Patients with SVT who have the *JAK2* V617F mutation but have normal blood cell counts and normal marrow require anticoagulation and monitoring of their blood cell counts, but the role of cyto-reduction or JAK inhibitor treatment in this group is unclear.

### **H&O** What special concerns are there regarding the prevention of thrombosis in women with MPNs?

**MK** There are special concerns related to pregnancy and the postpartum period. One problem for women with MPNs who become pregnant is an increased risk for placental insufficiency. This may lead to preeclampsia, early pregnancy loss, low birth weight of the newborn, or postpartum hemorrhage. Another problem is a mild increase in the rate of overall thrombosis—especially venous thrombosis—in the antepartum and postpartum periods. A recent meta-analysis<sup>8</sup> calculated an absolute risk of 1.3% in the antepartum period and of 3% in the postpartum period, rates that are higher than those in women without MPN (pregnant women in the general population have a 0.1% risk for thrombosis in the

antepartum period and a 0.05% risk in the postpartum period). Although the confidence intervals are wide, the authors state that routine thromboprophylaxis is not required in pregnant women with MPNs unless additional risk factors are present, in which low-molecular-weight heparin should be given during pregnancy. Examples of risk factors are previous pregnancy loss and previous venous thrombosis. Unless these contraindications are present, pregnant women with MPNs should receive aspirin throughout the pregnancy.

### **H&O** What other advice do you have for physicians regarding the management of thrombosis in patients with MPNs?

**MK** Many general physicians fail to recognize the connection between MPNs and thrombosis. Patients who have SVT without obvious local pathology should have a *JAK2* mutation analysis. Isolated *JAK2* mutations occur in approximately 0.1% to 0.2% of the population, and a myeloproliferative phenotype can develop in individuals bearing this allele over a period of 4 or 5 years. In some cases, additional mutations of myeloid genes have been documented as second events. In the case of SVT—even in patients with a MPN phenotype on bone marrow assessment—the blood cell counts are usually lower than expected, in large part owing to splenomegaly. Patients with other forms of thrombosis, such as arterial thrombosis, DVT, PE, and cerebral venous thrombosis, should be investigated for an underlying MPN if they have abnormal blood cell counts as defined by the revised 2016 WHO criteria.

Risk stratification systems use age older than 60 years as an important variable that confers a high thrombotic risk. Most health care systems assess and treat individuals older than 60 years for cardiovascular risk factors. However, patients aged 40 to 60 years with MPNs may not be included in routine risk assessments. This should be highlighted to primary care physicians, and vascular comorbidities should be kept under review. An annual review of vascular risk status should be undertaken, and treatment should be escalated if required.

### **Disclosures**

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