patients and women during pregnancy), and anagrelide (i.e., megakaryotoxic agent for treating refractory thrombocytosis).

The typical goal of therapy is maintenance of hematocrit values less than 45% in men and less than 42% in women. In a multicenter, prospective clinical trial, adult PV patients randomized to a therapeutic hematocrit target of less than 45% using hydroxyurea, phlebotomy, or both modalities had a significantly lower rate of cardiovascular death (2.7% vs. 9.8%) and major thrombosis than those with a hematocrit target between 45% and 50%.

Low-dose chemotherapeutic agents (e.g., chlorambucil, busulfan) may be used to treat leukocytosis and thrombocytosis not responding to hydroxyurea, but they are associated with increased toxicity and risk of secondary AML. As with all myeloproliferative disorders, initiation of cytoreductive therapy may precipitate hyperuricemia that results in secondary gout and uric acid stones, warranting treatment with allopurinol.

Low-dose aspirin and treatment of asymptomatic thrombocytosis decrease thromboembolic events in low- and high-risk PV patients and are especially important in older patients with significant cardiovascular risk factors. In younger patients, nonsteroidal anti-inflammatory drugs and antiplatelet agents should be used judiciously because of the risk of gastrointestinal hemorrhage.

With effective therapy, the long-term survival of PV patients is excellent. Clinical trials of novel agents targeting constitutively active JAK2 signaling pathways are being conducted (primarily in patients failing prior hydroxyurea therapy), and it remains to be seen whether this class of drugs will improve outcomes and/or quality of life for PV patients.

ESSENTIAL THROMBOCYTHEMIA

Definition and Epidemiology

ET (i.e., primary thrombocythemia) is a pluripotent stem cell disorder resulting in elevated levels of platelets and white blood cells. Platelet function and length of survival remain normal. ET is an uncommon disorder, with an increasing number of cases found among patients who are asymptomatic on routine laboratory testing. Although the median age at diagnosis is 60 to 65 years, 10% to 25% of patients are younger than 40 years.

Clinical Presentation

Up to two thirds of patients are symptomatic. Vasomotor symptoms include headache, dizziness, visual changes, and erythromelalgia (i.e., burning pain and erythema of feet and hands). Serious arterial thrombotic complications such as transient ischemic attacks, strokes, seizures, angina, and myocardial infarctions may occur. Patients may rarely have purpuric skin lesions or hematomas. The risk for gastrointestinal bleeding is less than 5%.

Diagnosis and Differential Diagnosis

Elevated platelet counts (i.e., thrombocytosis) can result from other causes (e.g., bacterial infections, sepsis, iron deficiency, autoimmune diseases, malignant diseases), which must be excluded before a diagnosis of ET is considered. The diagnosis requires a platelet count exceeding $450{,}000 \times 10^9$/L with a JAK2 V617F mutation or no evidence of reactive thrombocytosis. Bone marrow histology displays predominant proliferation involving the megakaryocytic lineage with increased mature megakaryocytes and little or no granulocytic or erythroid proliferation. Marrow immunohistochemical and cytogenetic studies are essential to exclude myelodysplasia, myelofibrosis, or the Philadelphia chromosome, which are diagnostic of CML (Table 46-4).

Although no genetic or biologic marker is 100% specific for ET, the JAK2 V617F mutation is found in more than one half of samples from patients with ET. Unlike other MPNs, bone marrow cells from patients with ET frequently do not show factor-independent colony growth, and the precise cause of this disease and its relation to JAK2 mutational status are under intense investigation.

Treatment and Prognosis

Patients with ET typically have long-term survival rates similar to those of age-matched control patients. Similar to PV, shortened overall survival is associated with increased age (>60 years), a history of thrombosis, and leukocytosis. The risk of leukemic transformation is extremely low (3% to 4%) compared with other MPNs. However, morbidity from recurrent hemorrhagic and thrombotic complications is high and cannot be reliably predicted from the platelet count or platelet function abnormalities.

Because treatment requires lifelong administration for disease control, assessment of risk factors and a history of clinical signs and symptoms dictate therapeutic choices. All patients benefit from aggressive management of cardiovascular risk factors (e.g., smoking, hypertension, obesity, hypercholesterolemia). Although low-dose enteric aspirin may be used in all patients to relieve neurologic symptoms and carries a minimal risk for bleeding, excessive thrombocytosis (platelet count $>1000 \times 10^9$/L) can be associated with excessive bleeding due to acquired von Willebrand syndrome. Although young and pregnant patients are often not treated until they become symptomatic, older patients (>60 years) and those with a history of thrombosis, long disease duration, or significant cardiovascular risk factors are likely to benefit from the addition of platelet-lowering agents.

Hydroxyurea, an oral cytotoxic, myelosuppressive agent, is the most common first-line agent, and it usually is well tolerated and has low long-term leukemogenic risks. Anagrelide, an oral antiplatelet agent that inhibits platelet aggregation and megakaryocyte maturation, is also used, primarily as a second-line agent

TABLE 46-4 WORLD HEALTH ORGANIZATION 2008 DIAGNOSTIC CRITERIA FOR ESSENTIAL THROMBOCYTHEMIA

Major criteria*

1. Platelet count $\geq 450 \times 10^9$/L
2. Megakaryocyte proliferation with large and mature morphology; no or little granulocytic or erythroid proliferation
3. Not meeting WHO criteria for CML, PV, PMF, MDS, or other myeloid neoplasm
4. Demonstration of JAK2 V617F mutation or other clonal marker or no evidence of reactive thrombocytosis

CML, Chronic myelogenous leukemia; MDS, myelodysplastic syndrome; PMF, primary myelofibrosis; PV, polycythemia vera; WHO, World Health Organization.

*Diagnosis of essential thrombocytopenia requires meeting all four major criteria.