Essential thrombocythemia, polycythemia vera, and myelofibrosis with myeloid metaplasia constitute the “classic” bcr/abl-negative myeloproliferative disorders (MPDs). Each of these MPDs represents a stem cell–derived clonal myeloproliferation with the respective features of thrombocytosis, erythrocytosis, and bone marrow fibrosis. Unlike with cases of chronic myeloid leukemia, in which the bcr/abl mutation is invariably detected, current diagnosis of essential thrombocythemia, polycythemia vera, and myelofibrosis with myeloid metaplasia is based on a consensus-driven set of clinical and laboratory criteria that have undergone substantial modification in recent times. The recent discovery of a recurrent activating Janus tyrosine kinase (JAK2) mutation (JAK2 V617F) in all 3 classic MPDs offers another opportunity for refining current diagnoses and disease classifications. In this article, we outline contemporary diagnostic algorithms for each of these disorders and provide an evidence-based approach to management.


AHSCt = allogeneic hematopoietic stem cell transplantation; AWfS = acquired von Willebrand syndrome; BM = bone marrow; CML = chronic myeloid leukemia; EMM = extramedullary hematopoiesis; ET = essential thrombocythemia; Hct = hematocrit; JAK = Janus kinase; MDS = myelodysplastic syndrome; MMM = myelofibrosis with myeloid metaplasia; MPD = myeloproliferative disorders; PV = polycythemia vera; RT = reactive thrombocytosis; sEPO = serum erythropoietin; vW = von Willebrand

**ESSENTIAL THROMBOCYTHEMIA**

**DIAGNOSIS**

A working diagnosis of ET is considered in the presence of persistent nonreactive thrombocytosis (above-normal platelet count) and after the diagnostic exclusion of another myeloid disorder that could mimic ET in its presentation. The latter include CML, PV, MDS, and MMM (including “cellular phase” MMM, discussed subsequently).19-21

The first step in approaching a patient with thrombocytosis is to consider the possibility of reactive thrombocytosis (RT) from various causes (Table 222-27). In such cases, patient history and physical examination are crucial and often are enough to suggest a diagnosis of RT. Additional help is readily available from routine laboratory tests including serum ferritin level (to consider the possibility of iron deficiency), peripheral blood smear (to look for Howell-Jolly bodies and other markers of hypoplaspenia), and C-reactive protein (to consider the possibility of occult inflammation or malignancy).28 The recent description of an acquired JAK2 mutation (JAK2 V617F) that occurs in 23% to 57% of patients with ET offers a molecular test that is potentially useful to distinguish ET from RT.11-17 Also, rare cases of genetically defined ET (eg, activating mutation of the c-mpl gene) have been described29 and must be kept in mind while evaluating a patient with either a lifelong history or a family history of thrombocytosis.30 In general, RT has not been shown to be associated with an increased risk of either bleeding or thrombosis and therefore does not require specific therapy.27,31

If neither the patient history nor the aforementioned laboratory tests suggest RT, a bone marrow (BM) examina-
tion is indicated both to reinforce the diagnosis of ET and to address the possibility of another chronic myeloid disorder (Figure 1).

Although a detailed analysis of megakaryocyte morphology may help distinguish CML (dwarf megakaryocytes and not too many clusters) from ET (giant megakaryocytes with cluster formation), cytogenetic studies and fluorescence in situ hybridization analysis for bcr/abl should accompany BM examination to rule out the possibility of CML.\textsuperscript{32} Also, we recommend mutation screening for JAK2\textsuperscript{V617F}, whose presence speaks against both CML and RT.\textsuperscript{13,17} Morphologic evaluation is key in distinguishing ET from both MDS and cellular phase MMM (discussed subsequently).\textsuperscript{33} Mild reticulin fibrosis (grades 1 or 2) is detected in approximately 14\% of patients with ET at diagnosis and does not portend an unusual outcome.\textsuperscript{34} Clonal cytogenetic lesions in ET are detected in less than 5\% of patients and are nonspecific.\textsuperscript{35}

**Prognosis and Treatment**

Essential thrombocythemia is associated with a near-normal life expectancy; therefore, treatment is never instituted to improve survival.\textsuperscript{36,37} Instead, specific treatment is sought either to alleviate microvascular disturbances (eg, headache, light-headedness, acral paresthesia, erythromelalgia, and atypical chest pain) or to prevent thrombohemorrhagic complications. Treatment to prevent vascular events is dictated by the presence or absence of defined risk factors for thrombosis\textsuperscript{30} (Table 3).

Accordingly, high-risk disease is defined by the presence of either age of 60 years or older or a history of thrombosis.\textsuperscript{38-41} In the absence of these 2 adverse features, patients are assigned to either a low-risk or an indeterminate-risk disease category on the basis of an unsubstantiated concern that extreme thrombocytosis (platelets, ≥1500 × 10\(^9\)/L) as well as the presence of cardiovascular risk factors may be detrimental in terms of thrombohemorrhagic complications (Table 3).\textsuperscript{39,40,42,43}

**Treatment of Microvascular Symptoms.** Microvascular symptoms often are controlled adequately by low-dose aspirin (40-100 mg/d).\textsuperscript{44} However, the possibility of acquired von Willebrand syndrome (AvWS) must be considered before initiation of aspirin therapy.\textsuperscript{45} Essential thrombocythemia–associated AvWS occurs usually in the presence of a platelet count greater than 1000 × 10\(^9\)/L, and the mechanism is believed to involve increased catabolism of large-molecular-weight von Willebrand (vW) proteins secondary to abnormal platelet–vW protein interaction.\textsuperscript{46} Symptomatic patients receive cytoreductive therapy, which reduces the platelet count to less than 1000 × 10\(^9\)/L, usually correcting both clinical and laboratory abnormalities.\textsuperscript{45} In asymptomatic patients, prophylactic cytoreduction is advisable only in the presence of a clinically relevant reduction in vW protein function (ristocetin cofactor activity <30\%). Furthermore, we are comfortable using aspirin therapy in the presence of ET-associated AvWS as long as the ristocetin cofactor activity remains above 50\%.\textsuperscript{45}

**Treatment of Low-Risk ET.** Thrombotic events in low-risk patients with ET are too infrequent to justify the long-term use of potentially harmful cytoreductive agents\textsuperscript{40,43,47-50} (Table 4\textsuperscript{51-79}). In such patients, the use of low-dose aspirin is encouraged on the basis of the recently demonstrated

---

**TABLE 1. Semimolecular Classification of Chronic Myeloid Disorders**

<table>
<thead>
<tr>
<th>I. Myelodysplastic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>II. Myeloproliferative disorders</td>
</tr>
<tr>
<td>Classic</td>
</tr>
<tr>
<td>Molecularly defined</td>
</tr>
<tr>
<td>1. Chronic myeloid leukemia (bcr/abl+</td>
</tr>
<tr>
<td>II. Clinically assigned (bcr/abl+ and frequently associated with JAK2V617F mutation)</td>
</tr>
<tr>
<td>1. Essential thrombocythemia</td>
</tr>
<tr>
<td>2. Polycythemia vera</td>
</tr>
<tr>
<td>3. Myelofibrosis with myeloid metaplasia</td>
</tr>
<tr>
<td>Atypical</td>
</tr>
<tr>
<td>Molecularly defined</td>
</tr>
<tr>
<td>1. PDGFR-A–arranged eosinophilic/mast cell disorders (eg, FIP1LI-PDGFR)</td>
</tr>
<tr>
<td>2. PDGFRB–arranged eosinophilic disorders (eg, TEL/ETV6-PDGFRB)</td>
</tr>
<tr>
<td>3. Systemic mastocytosis associated with c-kit mutation (eg, c-kitpathW)</td>
</tr>
<tr>
<td>4. 8p11 myeloproliferative syndrome (eg, ZNF198/FIM/RAMP-FGFR)</td>
</tr>
</tbody>
</table>

*JAK2 = Janus kinase 2; PDGFR = platelet-derived growth factor receptor.

---

**TABLE 2. Causes of Thrombocytosis**

<table>
<thead>
<tr>
<th>Primary thrombocytosis</th>
<th>Reactive thrombocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential thrombocythemia</td>
<td>Infection</td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td>Tissue damage</td>
</tr>
<tr>
<td>Myelofibrosis with myeloid metaplasia (overt)</td>
<td>Chronic inflammation</td>
</tr>
<tr>
<td>Myelofibrosis with myeloid metaplasia (cellular phase)</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>Rebound thrombocytosis</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>Renal disorders</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>Postpolpectomy</td>
<td>Blood loss</td>
</tr>
</tbody>
</table>
TABLE 3. Risk Stratification in Polycythemia Vera and Essential Thrombocythemia

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Age younger than 60 years, and no history of thrombosis, and platelet count &lt;1500 × 10^9/L, and absence of cardiovascular risk factors (smoking, hypertension, hyperlipidemia, diabetes mellitus)</td>
</tr>
<tr>
<td>Indeterminate risk</td>
<td>Neither low risk nor high risk</td>
</tr>
<tr>
<td>High risk</td>
<td>Age 60 years or older, or a history of thrombosis</td>
</tr>
</tbody>
</table>

FIGURE 1. Diagnostic algorithm for essential thrombocythemia (ET) that incorporates JAK2V617F mutation screening.

Antithrombotic value in PV. The low-risk patient who is pregnant should receive no cytoreductive agents; the use of aspirin is optional and may not influence the outcome of pregnancy.81

**Treatment of High-Risk ET.** The risk of thrombosis in high-risk disease is substantial enough to consider specific therapy. The antithrombotic value of cytoreductive therapy in high-risk ET has been addressed by 2 randomized treatment trials.48,82 In the first study, treatment with hydroxyurea was compared with observation alone, and the risk of thrombosis was significantly less in the treated group (3.6% vs 24% at a median follow-up of 27 months).48 In the second study, hydroxyurea was compared with anagrelide, both in combination with aspirin therapy.82 After a median follow-up of 39 months, the composite risk of both thrombosis and bleeding was once again affected favorably by hydroxyurea treatment (36 vs 55 events in the anagrelide arm).

What about leukemia risk associated with hydroxyurea therapy? First, the occurrence of clonal evolution in ET is extremely low, estimated at 2% for leukemic transformation and at 4% for fibrotic transformation at 15 years.37 Second, the risk of leukemia was not increased by hydroxyurea use in the setting of both large retrospectively37,83 and prospectively82 controlled studies. The safety of hydroxyurea, in terms of drug leukemogenicity, also has been shown by other smaller retrospective studies.84,85 Therefore, there is no hard evidence to implicate hydroxyurea use in ET as being leukemogenic, whereas new information suggests that both anagrelide and interferon alfa may increase the risk of transformation into MMM.82,86 In pa-
**MYELOPROLIFERATIVE DISORDERS**

**TABLE 4. Clinical Properties of Platelet-Lowering Agents***

<table>
<thead>
<tr>
<th>Drug/class/ mechanism of action</th>
<th>Pharmacology</th>
<th>Starting dosage</th>
<th>Onset of action</th>
<th>Frequent</th>
<th>Infrequent</th>
<th>Rare</th>
<th>Cost†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyurea**/ myelosuppressive/ antimetabolite</td>
<td>Half-life 5 h, renal excretion</td>
<td>500 mg orally, 2 times daily</td>
<td>≈3-5 d</td>
<td>Leukopenia, oral ulcers, anemia, hyperpigmentation, nail discoloration, xeroderma</td>
<td>Leg ulcers, alopecia, skin atrophy</td>
<td>Fever, cystitis, platelet oscillations</td>
<td>$1714/y for 500 mg, 3 times daily</td>
</tr>
<tr>
<td>Anagrelide**/ unknown/unknown</td>
<td>Half-life 1.5 h, renal excretion</td>
<td>0.5 mg orally, 3 times daily</td>
<td>≈6-10 d</td>
<td>Headache, palpititations, diarrhea, fluid retention, anemia</td>
<td>Arrhythmias</td>
<td>Cardiomyopathy</td>
<td>$8500/y for 0.5 mg, 4 times daily</td>
</tr>
<tr>
<td>Interferon alfa**/ myelosuppressive/ biologic agent</td>
<td>Kidney is main site of metabolism</td>
<td>5 million U SQ, 3 times per week</td>
<td>1-3 wk</td>
<td>Flu-like syndrome, fatigue, anorexia, weight loss, lack of ambition, alopecia</td>
<td>Confusion, depression, autoimmune thyroiditis, myalgia, arthritis</td>
<td>Pruritus, hyperlipidemia, transaminasemia</td>
<td>$10,500/y for 3 million U, 5 d/wk</td>
</tr>
<tr>
<td>Phosphorus 32**/ myelosuppressive/ radionuclide</td>
<td>Half-life ≈14 d</td>
<td>2.3 mCi/m² IV</td>
<td>4-8 wk</td>
<td>Transient mild cytopenia</td>
<td>Prolonged pancytopenia in elderly patients</td>
<td>Leukemogenic</td>
<td>About $1025 for 4 mCi</td>
</tr>
<tr>
<td>Pipobroman**/ myelosuppressive/ alkylating agent</td>
<td>Insufficient information</td>
<td>1 mg/kg per day orally</td>
<td>≈16 d</td>
<td>Nausea, abdominal pain, diarrhea</td>
<td>Leukopenia, thrombocytopenia, hemolysis</td>
<td>NA in the United States</td>
<td></td>
</tr>
</tbody>
</table>

*IV = intravenously; NA = not available; SQ = subcutaneously.
†Current cost to patient.

Patients with hydroxyurea intolerance,**77 interferon alfa is a reasonable alternative and is the drug of choice during pregnancy.**72,88 When both hydroxyurea and interferon alfa are not tolerated, other drugs including anagrelide and pipobroman can be considered (Table 4). Once cytoreductive therapy is initiated, the therapeutic goal in terms of platelet count, based on anecdotal evidence of optimal thrombosis control, is less than 400 ×10⁹/L.**66,89**

**Treatment of Indeterminate-Risk ET.** Regarding indeterminate-risk patients with ET, the use of low-dose aspirin is encouraged in the absence of clinically relevant AvW5S (ristocetin cofactor activity of <50%) that may occur in a minority of patients with extreme thrombocytosis.90 On the other hand, the use of platelet-lowering agents (ie, cytoreductive therapy) in indeterminate-risk patients with ET is controversial. In general, cytoreductive treatment is appropriate in patients with extreme thrombocytosis (platelet count >1500 ×10⁹/L) that is associated with a bleeding diathesis or with aspirin-resistant microvascular symptoms. The target platelet count in this instance is the level that results in symptom relief or correction of the bleeding diathesis and is not necessarily below 400 ×10⁹/L. Table 5 outlines the treatment algorithm that we currently recommend for ET.

**POLYCYTHEMIA VERA**

**DIAGNOSIS**

In general, a perceived increase in hematocrit (Het) level may (true polycythemia) or may not (apparent polycythemia) represent a real increase in erythrocyte production (Table 6).**61,120**

**TABLE 5. Treatment Algorithm for Essential Thrombocythemia**

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Age &lt;60 y</th>
<th>Age ≥60 y</th>
<th>Women of childbearing age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Low-dose aspirin*</td>
<td>Not applicable</td>
<td>Low-dose aspirin*</td>
</tr>
<tr>
<td>Indeterminate risk†</td>
<td>Low-dose aspirin*</td>
<td>Not applicable</td>
<td>Low-dose aspirin*</td>
</tr>
<tr>
<td>High risk</td>
<td>Hydroxyurea and low-dose aspirin</td>
<td>Hydroxyurea and low-dose aspirin</td>
<td>Interferon alfa and low-dose aspirin</td>
</tr>
</tbody>
</table>

*In the absence of a contraindication, including evidence for acquired von Willebrand syndrome, ie, ristocetin cofactor activity of less than 50%.
†The decision to use cytoreductive agents in indeterminate-risk patients should be made on an individual basis (see text for details).
Apparent polycythemia results from either a decrease in plasma volume (relative polycythemia) or one’s misperception of what constitutes the upper limit of normal values for Hct. Although the causes of acute plasma contraction are well known, the existence of chronic plasma contraction, as in Gaisböck syndrome (relative polycythemia associated with hypertension and nephropathy) and traction, as in Gaisböck syndrome (relative polycythemia), is debated. Regardless, the main purpose in evaluating polycythemia is to determine the presence or absence of PV because of the therapeutic implications.

Traditionally, PV was diagnosed on the basis of criteria from the Polycythemia Vera Study Group, which required an elevated red blood cell mass. Presently, we seldom use either the Polycythemia Vera Study Group criteria or red blood cell mass but instead depend primarily on clinical presentation, serum erythropoietin (sEPO) level, and BM histology to make a working diagnosis of PV (Figure 2).

Initial work-up should include determination of the sEPO level. In PV, the sEPO level is usually low but can be normal; however, it is extremely unlikely to be elevated. Therefore, further work-up is considered only if the sEPO level is low or normal.

Low sEPO Level. A low sEPO level mandates a BM biopsy to look for morphologic evidence of PV as well as mutation screening for JAK2V617F (Figure 2). The characteristic histological features on BM biopsy include hypercellularity, atypical megakaryocytic hyperplasia and clustering, and decreased BM iron stores. Karyotypic abnormalities in PV are relatively infrequent (13%-18% in chemotherapy-naïve patients) and include trisomies of chromosomes 9 and 8 and deletions of the long arms of chromosomes 13 and 20. In contrast, an activating mutation of JAK2 tyrosine kinase (V617F) occurs in most patients with PV, but not in those with secondary erythrocytosis. Therefore, we recommend mutation screening for JAK2V617F, which if present strongly suggests PV as opposed to other causes of polycythemia.

Normal sEPO Level. The need to perform BM biopsy and JAK2 mutation screening, in the presence of a normal sEPO level, depends on the presence or absence of either clinical (pruritus, erythromelalgia, splenomegaly, arterial or venous thrombosis) or laboratory (thrombocytosis, leukocytosis, increased leukocyte alkaline phosphatase score, well-documented increase in Hct level from an individual’s baseline value) clues for PV. In such patients, ultrasonography to assess spleen size is reasonable. In the absence of the aforementioned PV-characteristic features, one should consider close observation with periodic monitoring of Hct and sEPO levels. We also consider it reasonable to use information from peripheral blood JAK2 mutation screening to pursue BM biopsy in equivocal cases.

In more than 90% of patients, a working diagnosis of PV can be made on the basis of the aforementioned clinical and BM histological findings, including mutation screening for JAK2V617F (Figure 2). In the remaining “equivocal” cases, one may need to resort to a specialized test. Four such tests have been publicized to be of use in distinguishing PV from other causes of polycythemia: BM immunohistochemistry for megakaryocyte thrombopoietin receptor (Mpl) expres-
**MYELOPROLIFERATIVE DISORDERS**

**FIGURE 2.** Diagnostic algorithm for polycythemia vera (PV).

* Clinical clues for PV include splenomegaly, thrombosis, aquagenic pruritus, and erythromelalgia. Laboratory clues for PV include thrombocytosis, leukocytosis, and increased leukocyte alkaline phosphatase score. Janus kinase 2 (JAK2) screening is to detect the V617F mutation that occurs in most patients with PV. BM = bone marrow; CBC = complete blood cell count.

† Alternatively, one can consider mutation screening for JAK2V617F to help decide necessity of BM examination.


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**PROGNOSIS AND TREATMENT**

Currently, identified risk factors and risk stratification in PV are similar to those in ET (Table 3). The cornerstone of treatment in PV is phlebotomy (target Hct level, <45% in men and 42% in women). To date, no other therapy has been shown to offer a survival advantage over treatment with phlebotomy alone. However, treatment with phlebotomy alone is associated with a substantial risk of thrombosis in high-risk patients for whom the concur-

rent use of myelosuppressive treatment is indicated. In the latter instance, the use of chlorambucil or radioactive phosphorus 32 is contraindicated because of an increased risk of acute leukemia, and hydroxyurea is the current drug of choice. Interferon alfa is the preferred drug in women of childbearing age. On the basis of results from a recent randomized treatment trial, low-dose aspirin is recommended for all patients with PV in the absence of contraindications. Table 7 provides a treatment algorithm for PV. Finally, PV-associated pruritus may be alleviated with...
TABLE 7. Treatment Algorithm for Polycythemia Vera

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Age &lt;60 y</th>
<th>Age ≥60 y</th>
<th>Women of childbearing age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Phlebotomy and low-dose aspirin*</td>
<td>Not applicable</td>
<td>Phlebotomy and low-dose aspirin*</td>
</tr>
<tr>
<td>Indeterminate risk†</td>
<td>Phlebotomy and low-dose aspirin*</td>
<td>Not applicable</td>
<td>Phlebotomy and low-dose aspirin*</td>
</tr>
<tr>
<td>High risk</td>
<td>Phlebotomy + hydroxyurea and low-dose aspirin</td>
<td>Phlebotomy + hydroxyurea and low-dose aspirin</td>
<td>Phlebotomy + interferon alfa and low-dose aspirin</td>
</tr>
</tbody>
</table>

*In the absence of a contraindication, including evidence for acquired von Willebrand disease, ie, ristocetin cofactor activity of less than 50%.
†The decision to use cytoreductive agents in indeterminate-risk patients should be made on an individual basis (see text for details).
Adapted from Tefferi.93

use of a selective serotonin reuptake inhibitor (paroxetine, 20 mg/d).143

MYELOFIBROSIS WITH MYELOID METAPLASIA

DIAGNOSIS
Myelofibrosis with myeloid metaplasia is also known as idiopathic myelofibrosis. The disease presents either de novo (agnogenic myeloid metaplasia) or in the setting of either PV (post–polycythemic myeloid metaplasia) or ET (post–thrombocythemic myeloid metaplasia) at a rate of 10% to 20% after 15 to 20 years of follow-up.144,145

The first clue to the diagnosis of MMM is a myelophthisic peripheral smear (the presence of nucleated red blood cells, granulocyte precursors, and teardrop-shaped erythrocytes). However, it should be noted that a myelophthisic smear also may be associated with either another myeloid malignancy with BM fibrosis or a nonfibrotic BM infiltrating process including metastatic cancer, granulomatous infection, and lymphoma. Therefore, a careful morphologic evaluation of the BM is necessary before diagnosing MMM, and cytogenetic tests and fluorescence in situ hybridization for bcr/abl always should be performed to rule out fibrotic CML. Similarly, it is important to know that both MDS and other myeloid entities can be accompanied by BM fibrosis and that the input from an experienced clinical pathologist is essential to distinguish these disorders from MMM (Table 8).146-172 In such cases, the presence of JAK216176 supports a diagnosis of MMM as opposed to MDS or other atypical MPD.11-14

Typical MMM is characterized by the presence of dysplastic megakaryocytic hyperplasia, collagen and reticular fibrosis, osteosclerosis, and intrasinusoidal hematopoiesis. In cellular phase MMM, the degree of BM fibrosis may be minimal, but splenomegaly, myelophthisis, and an increased lactate dehydrogenase level are often present. Recurrent cytogenetic abnormalities are seen in approximately 50% of chemotherapy-naive patients with MMM,173 the most frequent of which are del(20)(q11;q13), del(13)(q12;q22), trisomy 8, trisomy 9, t(1;7), del(12)(p11;p13), monosomy or long-arm deletions involving chromosome 7, and trisomy 1q.173,174 However, individual lesions occur in only a minority of patients (10%-20%), and none are specific to MMM.

TABLE 8. Causes of Bone Marrow Fibrosis

<table>
<thead>
<tr>
<th>Myeloid disorders</th>
<th>Lymphoid disorders</th>
<th>Nonhematologic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelofibrosis with myeloid metaplasia146</td>
<td>Hairy cell leukemia157</td>
<td>Metastatic cancer154</td>
</tr>
<tr>
<td>Chronic myeloid leukemia147</td>
<td>Hodgkin lymphoma158</td>
<td>Autoimmune myelofibrosis162</td>
</tr>
<tr>
<td>Myelodysplastic syndrome148</td>
<td>Non-Hodgkin lymphoma159</td>
<td>Systemic lupus erythematosus163</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia149</td>
<td>Multiple myeloma160</td>
<td>Kala-azar (leishmaniasis)194</td>
</tr>
<tr>
<td>Chronic eosinophilic leukemia150</td>
<td></td>
<td>Tuberculosis195</td>
</tr>
<tr>
<td>Systemic mastocytosis151</td>
<td></td>
<td>Paget disease196</td>
</tr>
<tr>
<td>Acute megakaryocytic leukemia152</td>
<td></td>
<td>Human immunodeficiency virus infection187</td>
</tr>
<tr>
<td>Other acute myeloid leukemias153</td>
<td></td>
<td>Vitamin D–deficient rickets158</td>
</tr>
<tr>
<td>Acute lymphocytic leukemia154</td>
<td></td>
<td>Renal osteodystrophy159</td>
</tr>
<tr>
<td>Acute myeloblastic155</td>
<td></td>
<td>Hyperparathyroidism170</td>
</tr>
<tr>
<td>Malignant histiocytosis156</td>
<td></td>
<td>Gray platelet syndrome171</td>
</tr>
<tr>
<td></td>
<td>Hairy cell leukemia157</td>
<td>Familial infantile myelofibrosis172</td>
</tr>
</tbody>
</table>


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**Prognosis and Treatment**

Because of similarities in clinical manifestations and prognosis, post–polycythemic myeloid metaplasia and post–thrombocythemic myeloid metaplasia are managed similarly to agnogenic myeloid metaplasia. In general, drug therapy has not been shown to prolong survival in MMM and is used to palliate symptoms. Similarly, both splenectomy and involved field irradiation engender a defined palliative role in the treatment of MMM. Allogeneic hematopoietic stem cell transplantation (AHSCT) has been shown to be both feasible and effective but has substantial procedure-related mortality and morbidity. As a result, defined risk factors are used to select suitable patients for AHSCT (Table 9).

Five factors have been identified as being independently predictive of poor survival: hemoglobin less than 10 g/dL, hypercatabolic symptoms (drenching night sweats, profound weight loss, and fever), 1% or greater circulating blasts, extreme ranges of leukocyte count (>30 × 10^9/L or <4 × 10^9/L), and the presence of cytogenetic abnormalities other than 13q– and 20q–. In the absence of these adverse features, median survival exceeds 10 years. Median survival is shortened to 5 to 10 years in the presence of 1 adverse feature or to less than 5 years in the presence of 2 or more adverse features.

**Drug Therapy.** Androgen preparations (eg, oral fluoxymesterone, 10 mg twice daily), corticosteroids (eg, oral prednisone, 30 mg/d), and erythropoietin (eg, 40,000 U subcutaneously once per week) are used as first-line therapy for alleviation of anemia. An approximate 30% response rate with median remission duration of 1 year is expected from the use of 1 or more of these treatment modalities. Symptomatic splenomegaly is treated initially with hydroxyurea (eg, starting dosage of 500 mg, 2 or 3 times daily). Thalidomide is considered an effective drug in MMM. Studies of 10 or more patients have revealed a response rate of 20% to 62% in anemia, 25% to 80% in thrombocytopenia, and 7% to 30% in splenomegaly. These studies indicate that low-dose thalidomide (50 mg/d) was as effective as higher doses (200 mg/d or more) and that the addition of prednisone to the lower-dose schedule improves drug tolerance and may enhance the erythropoietic activity of the drug.

**Splenectomy.** Splenectomy is indicated in the presence of drug-refractory splenic pain and/or discomfort, high red blood cell transfusion requirements, and symptomatic portal hypertension. This procedure provides symptomatic relief for most patients and durable anemia response in 25% of patients. Splenectomy in MMM has an operative mortality of approximately 9%, and 25% of patients may experience postsplenectomy thrombocytosis and progressive hepatomegaly. In general, we recommend adequate control, with use of cytoreductive agents, of thrombocytosis before as well as after splenectomy. After splenectomy, there is increased risk of both intra-abdominal bleeding, which may require surgical reexploration, and thromboembolic events, which may require systemic anticoagulant therapy; patients must be monitored closely for these complications.

**Radiation Therapy.** Involved field radiation therapy works best for nonhepatosplenic extramedullary hematopoeisis (EMH) but has limited value in controlling symptomatic enlargement of the spleen and liver. Therefore, we do not encourage radiation treatment for hepatosplenomegaly because of the associated risk of severe pancytopenia and the transient nature of the benefit in alleviating organomegaly. However, low-dose irradiation is effective for treatment of paraspinal/epidural EMH (1000 cGy in 5-10 fractions) and EMH resulting in pleural and peritoneal effusions (100-500 cGy in 5-10 fractions). Symptomatic pulmonary hypertension has been associated with MMM and is believed to arise from diffuse pulmonary EMH. Diagnosis is confirmed by technetium Tc 99m sulfur colloid scintigraphy, which shows diffuse pulmonary uptake, and treatment with single-fraction (100 cGy) whole-lung irradiation has been shown to be effective.

**Hematopoietic Stem Cell Transplantation.** Treatment with AHSCT, either myeloablative or reduced-intensity conditioning, is directed at eradicating the mutant MMM clone. The 3 largest studies regarding myeloablative AHSCT (both related and matched unrelated) consist of a
total of 147 patients. In general, engraftment was not a problem, with more than 80% of patients achieving safe neutrophil counts by day 30. However, transplant-related death and morbidity were not trivial, resulting in a 5-year survival of only 14% for patients older than 44 years in 1 study and a 2-year overall survival of 41% in another study. In the most favorable of the 3 studies, 20 of 56 patients had died within 3 years of undergoing transplantation, and the reported incidence of chronic graft-versus-host disease was 59% during a median follow-up period of only 2.8 years. In general, transplantation outcome in younger patients was encouraging in all 3 studies, with projected 5-year survival rates of more than 60%, and clinical as well as histological remissions were documented in the surviving patients.

At present, we do not recommend AHSCHT, either myeloablative or reduced-intensity conditioning, for the patient whose life expectancy is estimated to exceed 10 years (Table 9). Also, we are not too enthusiastic about patients older than 60 years undergoing transplantation and instead recommend that such patients, if in need of treatment, participate in an experimental drug treatment protocol. In contrast, it is reasonable to consider AHSCST in patients younger than 60 years in whom a survival of less than 5 years can be reliably predicted. It is currently unknown whether reduced-intensity conditioning would perform as well as myeloablative AHSCST in this instance. The same can be said regarding the use of related vs unrelated transplant donors. In young patients (<60 years) with intermediate-risk disease (Table 9), the decision regarding transplantation is made on an individual basis, and 1 option is to postpone transplantation until an individual patient develops features consistent with high-risk disease.

SUMMARY

The oncogenic mutations in bcr/abl-negative, classic MPD (ie, ET, PV, MMM) remain at large, and their discovery is key to the development of rational, targeted drug therapy. Fortunately, life expectancy is affected only marginally in ET, and the median survival of patients with PV approaches 20 years. Therefore, in these 2 diseases, current therapy is directed toward preventing thrombosis and not toward improving survival. Having either an age of 60 years or older or a history of thrombosis reliably identifies patients at risk of thrombosis for whom cytoreductive therapy with hydroxyurea is indicated, in addition to phlebotomy and aspirin therapy for patients with PV. We strongly recommend avoidance of other cytoreductive agents unless there is a contraindication to hydroxyurea use, including drug intolerance and pregnancy. In contrast to the situation in both ET and PV, both survival and quality of life are compromised considerably in MMM. Presently, drug therapy is strictly palliative and has not been shown to improve survival in MMM. Useful drugs in such cases include androgen preparations, prednisone, hydroxyurea, erythropoietin, thalidomide, and danazol. Similarly, both involved field radiation for nonhepatosplenic EMH and splenectomy have defined roles in palliative therapy. Finally, both myeloablative and reduced-risk conditioning AHSCST are being investigated for their roles in the treatment of MMM.

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