Over time, the disease may progress from a chronic phase to an accelerated phase, with acute leukemic transformation in 8% to 20% of patients. Treatment of PMF-related AML is usually ineffective. Other causes of nonleukemic death include heart failure, infection, intracranial hemorrhage, and pulmonary embolism.

Medical therapy for PMF is predicated on the risk category of patients. Low-risk, asymptomatic patients may be treated expectantly. All patients with symptomatic anemia benefit from palliative transfusions and administration of recombinant EPO, androgens (e.g., danazol), or low-dose thalidomide to maintain red blood cell levels. Symptoms caused by excess thrombocytosis and leukocytosis or progressive extramedullary hematopoiesis may be managed with hydroxyurea as a first-line agent or interferon-α in younger or pregnant patients. Symptomatic splenomegaly is best managed with hydroxyurea because open splenectomy is associated with significant operative morbidity and mortality and splenic irradiation is poorly tolerated except as a palliative approach. Young patients with intermediate- to high-risk PMF and possible HLA-matched donors should be considered for potentially curative allogeneic stem cell transplantation (SCT) at academic medical centers.

Although not all patients with PMF have the JAK2 V617F mutation, almost all have constitutive activation of the JAK1 and JAK2 signaling pathways, rendering them potentially responsive to treatment with novel JAK1/2 inhibitors. Ruxolitinib is an oral JAK inhibitor approved for the treatment of patients with intermediate- or high-risk myelofibrosis, including PMF, and myelofibrosis arising from prior PV or ET independent of JAK2 mutational status.

In two prospective, randomized, phase III clinical trials, ruxolitinib therapy for myelofibrosis patients was compared with placebo (COMFORT-I trial) and with best available therapy (COMFORT-II trial). Patients receiving ruxolitinib had significantly greater spleen volume reduction and symptom improvement (e.g., abdominal pain, early satiety, night sweats, muscle pain), which correlated with overall improvement in quality of life. Updates from both trials have demonstrated significantly prolonged overall survival and improvements in bone marrow fibrosis in the ruxolitinib-treated patients compared with control arms.

Many other JAK2 inhibitors are in active clinical development as single agents and in combination with ruxolitinib. Preliminary results of these trials suggest that even more effective therapies for PMF are on the horizon.

CHRONIC MYELOGENOUS LEUKEMIA

Definition, Epidemiology, and Pathology

CML is the most common MPN, accounting for 15% to 20% of all leukemias and occurring in 1 of 100,000 people. The median age at diagnosis is 53 years, but patients of any age may be affected. CML is characterized by a predominant increase in the granulocytic cell line associated with concurrent erythroid and platelet hyperplasia. It is unique among the MPNs in its natural history, including an inevitable transformation to acute leukemia.

CML was the first malignant hematologic disease shown to be associated with a specific chromosomal abnormality. More than 95% of patients with CML have a clonal expansion of a stem cell that has acquired the Philadelphia chromosome, which is a balanced translocation between chromosomes 9 and 22 that is designated t(9;22)(q34;q11). The translocation juxtapositions the *ABL* gene from chromosome 9 (region q34) to the *BCR* gene on chromosome 22 (region q11) and generates the oncogenic *BCR/ABL* fusion gene. The gene product, the BCR/ABL protein, is a deregulated, constitutively active cytoplasmic tyrosine kinase that induces a leukemic phenotype in hematopoietic stem cells. Expression of the BCR/ABL fusion protein activates multiple downstream signal transduction pathways that permits proliferation independent of cytokine and stromal regulation and renders cells resistant to chemotherapy and normal programmed cell death (i.e., apoptosis).

Diagnosis and Differential Diagnosis

Laboratory tests for CML patients typically demonstrate a markedly elevated white blood cell count (median, 170×10^9/L), with low leukocyte alkaline phosphatase levels, high uric acid and lactate dehydrogenase levels, and thrombocytosis. Review of the peripheral smear in chronic phase CML demonstrates a full complement of myeloid cells in all stages of granulocytic development, including immature myeloblasts (usually <5%), myelocytes, metamyelocytes, basophils, eosinophils, bands, and neutrophils. In contrast, the peripheral blood smear in reactive granulocytic hyperplastic states (i.e., leukemoid reaction) caused by acute infection or sepsis consists predominantly of mature neutrophils and bands with few myelocytes, basophils, or eosinophils.

The bone marrow in CML is densely hypercellular, with an overwhelming predominance of myeloid cells at all developmental stages and reticulin fibrosis (see E-Fig. 46-2). The differential diagnosis of CML includes reactive leukocytosis (e.g., in active infection or sepsis with a profound neutrophilic response) and other MPNs (e.g., myelofibrosis).

Detection of the Philadelphia chromosome on standard cytogenetic studies and abnormal BCR/ABL transcripts using reverse transcriptase–polymerase chain reaction (RT-PCR) or fluorescent in situ hybridization (FISH) analysis is required for the diagnosis of CML. Assessment of the *BCR/ABL* fusion gene by the same methods is used to monitor disease and response to therapy. Exquisitely sensitive and quantitative RT-PCR procedures allow detection of up to a single BCR/ABL-positive cell in 10^5 to 10^6 peripheral cells and permit measurement of disease status in peripheral blood and marrow samples.

A subset of patients with CML lacking a detectable Philadelphia chromosome was found to possess detectable BCR/ABL fusion products by RT-PCR, indicating a subchromosomal translocation resulting in the same pathologic gene product. Responses to treatment regimens for CML are defined as hematologic (i.e. restoration of normal peripheral blood cell counts), cytogenetic (i.e., loss of the Philadelphia chromosome determined by normal karyotypic or FISH analysis), and molecular (i.e., a three log or greater reduction of detectable BCR/ABL transcripts below a standard baseline by RT-PCR) remissions.