Myeloproliferative Neoplasms

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Introduction

Myeloproliferative neoplasms (MPNs) comprise a group of stem cell disorders with defective regulation of myeloid cell proliferation. This results in an overproduction of mature erythrocytes, granulocytes, and megakaryocytes. MPNs were originally labeled as myeloproliferative disorders by Dr. William Dameshek in 1951.[1] The World Health Organization (WHO) in 2008 revised the nomenclature to emphasize that these conditions are, in fact, malignant entities arising from unrestrained clonal synthesis, albeit the clones are not dysplastic in nature.[2] "Typical" MPNs consist of chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF).[2] Initially grouped together based on similar clinical and bone marrow histologic findings, the 2008 WHO guidelines have now classified MPNs based on shared molecular and genetic abnormalities.[2] CML results from an acquired translocation known as the BCR-ABL or the Philadelphia chromosome; this hybrid oncogene is a constitutively active tyrosine kinase.[3] CML will be discussed separately. This review article focuses on BCR-ABL-negative MPNs.

BCR-ABL-negative MPNs are conditions associated with acquired mutations of tyrosine kinase.[4] Janus kinase (JAK2) V617F mutation is present in greater than 95% of PV and approximately 55% and 65% of ET and PMF, respectively.[5] JAK2 is a cytoplasmic tyrosine kinase signal transducer activated by erythropoietin (EPO) and other hematopoietic stimulating factors. Ubiquitous tyrosine kinase domains, JH1 and JH2, play a crucial role in regulation. Normal activation of JAK2 involves cytokine-dependent phosphorylation of JH1 and JH2; the negative regulatory effect of JH2 on JH1 is essential for normal signaling. A point mutation at Exon 14 substitutes phenylalanine for valine at Domain 617 (V617F) and results in a loss of inhibition, uncontrolled signal transduction, and cytokine hypersensitivity of affected cells.[6-11] Additional

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genetic mutations have been implicated in MPN, including the myeloproliferative leukemia (MPL) gene[12] and JAK2 Exon 12 mutations.[13] It should be noted that these genetic abnormalities do not necessarily initiate the primary event in the transformation of normal stem cell differentiation into MPNs.[5] This process appears much more complex than simply detecting the presence of affected markers. Currently, numerous other genetic mutations are being studied and will no doubt contribute to the growing importance of genetic analysis in the diagnosis and treatment of MPNs.

Staging and Workup

MPNs do not follow cancer staging. Instead, they are categorized into high vs low risk based on age and concomitant risk factors. Screening for the presence of associated molecular markers is essential to the diagnosis.[14] Patients presenting with hepatomegaly or splenomegaly, along with either a single cell line hyperproliferation or any combination of cytopenia or cytosis on a complete blood count (CBC), should be evaluated.

Epidemiology

Most patients are in their fifth to seventh decade of life. Incidence for BCR-ABL-negative MPNs ranges from 0.2 to 1.9 cases per 100,000 persons per year. MPNs are rare; the cumulative age-adjusted incidence rate in 2001-2003 is 2.1 per 100,000 persons per year.[15]

Polycythemia Vera

Epidemiology

The median age at diagnosis is 60-65 years.[16] Overall incidence is approximately 1.9 per 100,000 person-years.[17] Incidence increases with age, and age- and sex-adjusted rates show slight preference for men with the highest incidence in men aged 70-79 years.[17]

Clinical Presentation

Many patients are asymptomatic or present with nonspecific constitutional complaints. Often, patients are discovered via incidental CBC showing abnormal cell counts. Pruritus is a common symptom that can occur in 40%-50% of affected patients.[18] It can be spontaneous or follow exposure to extreme temperature fluctuations, such as after taking a hot shower.[19] Mast cell degranulation with release of histamine, prostaglandins, and other cellular components is thought to be the mechanism of action.[19] Erythromelalgia, defined as acral paresthesias in patients with platelet counts $>400 \times 10^9$/L, and intact peripheral pulses are rare, but

considered pathognomonic if present.[20] Headache, dizziness, blurred vision, transient neurologic symptoms, and gastroduodenal lesions are other common symptoms.[16] The greatest impact on morbidity and mortality is due to the thrombotic and hemorrhagic complications. Major arterial or venous thrombosis of the hepatic (Budd–Chiari syndrome), splanchnic, or portal veins can occur.[21-23] Paradoxically, mucocutaneous bleeding diathesis can manifest secondary to dysfunctional platelets, or acquired von Willebrand Syndrome (aVWS) in patients with platelet counts $>1000 \times 10^9$/L.[24] Splenomegaly, plethora, and hepatomegaly and its associated complications may be present on physical examination. Systemic and pulmonary hypertension can also be seen. A hypercatabolic state can be present in the form of dramatic, unintentional weight loss. Tri-lineage myeloproliferation with marked erythrocytosis on a CBC and low or inappropriately normal EPO levels characterize PV.[25] Peripheral blood smear helps to distinguish the presence or absence of dysplasia. Histologic evaluation via a bone marrow biopsy is not necessary for diagnosis, however, if obtained, shows erythroid and megakaryocytic hyperplasia with clusters of abnormal megakaryotes.[26]

Differential Diagnosis

Absolute polycythemia is due to an increase in the total red cell mass. This can occur secondary to fluid overload or liver dysfunction. Conversely, relative polycythemia can occur with volume depletion. These cases are not reflective of absolute increase in cell counts; rather, they represent volume status and occur transiently with resolution once patients become euvolemic. Further workup or evaluation of absolute or relative polycythemia is therefore unnecessary. Autosomal-dominant primary familial PV and congenital erythrocytosis also have been documented in literature. These patients usually have a strong family history and present with low-serum EPO levels.[27] Chronic tissue hypoxemia, impaired tissue oxygenation, endogenous production, or exogenous EPO administration can all cause secondary PV.[28] These conditions are not associated with an absolute increase in cell counts. It is important to recognize that secondary causes of PV can occur as a normal physiological response to acclimate to a new environment (ie, high altitude).[29]

Diagnosis

Patients are diagnosed with PV if they present with both major criteria and 1 minor criterion or the first major criterion and 2 minor criteria, as listed in Table 1.[26]

TABLE 1. 2008 WHO Diagnostic Criteria for PV

Major Criteria	Minor Criteria
Men with hemoglobin >18.5 g/dLWomen with hemoglobin >16.5 g/dL Other evidence of increased red cell volume[a]	Bone marrow biopsy showing hypercellularity for age with tri-lineage myeloproliferation
PCR analysis positive for JAK2V617F, JAK2 Exon 12, or other similar mutations	Serum erythropoietin level below the normal reference range
	Endogenous erythroid colony formation in vitro

[a] (1) Hemoglobin (Hb) or hematocrit (Hct) >99th percentile of reference range for age, sex, or altitude of residence (2) red cell mass >25% above mean normal predicted in men with Hb 17 g/dL or women with Hb 15 g/dL, if with concomitant sustained increase of >2 g/dL from baseline not associated with treatment of iron deficiency anemia.
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TABLE 2. Treatment of PV based on risk stratification

Risk Stratification	Treatment
Low risk	Low-dose aspirin + phlebotomy
Low risk with extreme thrombocytosis	Low-dose aspirin if Ristocetin cofactor activity[a] is <30% + phlebotomy
High risk	Low-dose aspirin + Phlebotomy + hydroxyurea

[a]RCA evaluates the ability of von Willebrand factor to bind to platelets and stimulate primary hemostasis. Ristocetin is an antibiotic that augments von Willebrand factor binding to platelets, through a conformational change of platelet receptor glycoprotein Ib. Ristocetin Cofactor Activity <30% (normal range 50-160) confirms low levels of Von Willebrand factors. Adapted with permission from Tefferi and Vainchenker,[5]

Treatment

The current recommendation for treatment is phlebotomy targeting a hematocrit (Hct) of <45 and <42 in men and women, respectively, as listed in Table 2. All patients should receive low-dose aspirin, as listed in Table 3.[30] Interferon-α or bulsulfan, another alkylating agent, is recommended in high-risk patients <65 years of age who cannot tolerate hydroxyurea or are refractory to standard therapy, as listed in Table 3.[5]

The current practice of targeting Hct <45% for men and <42% for women is based on earlier studies evaluating the cerebral blood flow (CBF) in patients with PV. Phlebotomy mediated a decrease in the Hct from a mean of 0.536 to 0.455, increased CBF by 73%, and decreased blood viscosity by 30%.[31]

The Polycythemia Vera Study Group (PVSG) evaluated patients on phlebotomy vs cytoreductive therapy with chlorambucil or radioactive isotope of phosphorus (^{32}P) supplemented with phlebotomy.[32] Patients on

TABLE 3. Risk stratification for PV according to patient presentation

Risk Stratification	Patient Presentation
Low risk	<60 years of age with no history of thrombosis
Low risk with extreme thrombocytosis	<60 years of age, no history of thrombosis but with platelet count >1000 $\times$ 10^9/L
High risk	≥60 years of age, or with history of thrombosis

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chlorambucil or ^{32}P experienced a higher incidence of solid and hematologic malignancies compared to patients on phlebotomy alone; therefore, the authors decided against the use of cytoreductive therapy as standard PV treatment.[32] Incidentally, the phlebotomy-alone group was found to have a higher incidence of thrombosis. In an attempt to lower the risk of thrombosis in patients on phlebotomy alone, high-dose aspirin was added to the treatment regimen; however, patients experienced minimal benefits and increased risk of bleeding.[32] Based on these findings, high-dose aspirin was not recommended. The European collaboration study on low-dose aspirin in polycythemia finally evaluated low-dose aspirin prophylaxis in PV patients and revealed that it reduced the cumulative rate of nonfatal myocardial infarction, cerebrovascular accident (CVA), pulmonary embolism, major venous thrombosis, and death from cardiovascular (CV) causes [relative risk, 0.40; 95% CI, 0.18-0.91; $P = 0.03$] without significant risk of bleeding.[30] This study confirmed that low-dose aspirin prophylaxis is beneficial in patients without contraindications.[30]

Phase II of the PVSG study was the first to evaluate hydroxyurea therapy in PV. Hydroxyurea is a ribonucleotide reductase inhibitor that affects the G1/S phase of the cell cycle. This trial showed promising results when >50% patients on hydroxyurea monotherapy achieved good long-term control (decrease in platelet count, morbidity, mortality) 5 years after starting treatment. This study was recently updated with a median follow-up of 16.3 years; the cumulative incidence of acute myelogenous leukemia/myelodysplastic syndrome (AML/MDS) at 20 years was 24% with hydroxyurea vs 52% with pipobroman ($P = 0.004$).[33]

Antihistamines, cholestyramine, psoralens with long wave ultraviolet radiation, or serotonin selective reuptake inhibitors are concomitant treatment options that can be used for patients with refractory pruritus.[34-36]

Prognosis

Patients are generally asymptomatic for many years. Median survival in untreated patients is estimated to be between 6 and 18 months, with CVA and CV thrombotic events conferring the highest mortality risk.[32,37,38] PV is a chronic and incurable disease, and most patients develop post-PV myelofibrosis (MF) over time. Between 25% and 50% of patients with or without post-PV MF also go on to develop AML[33]; this is augmented in patients on long-term hydroxyurea or those on multiple cytoreductive regimens.

Pregnancy and Perioperative Management

Hydroxyurea and busulfan are considered pregnancy category D medications; therefore, in the rare pregnant patient with PV, interferon-α (IFN-α) is recommended.[39] Pregnant women should continue phlebotomy and aspirin therapy.[39] Low-molecular-weight heparin should be provided for those at risk of thrombosis throughout the pregnancy and up to several weeks postpartum. Pregnant patients physiologically develop dilutional anemia; therefore, phlebotomy hematocrit goals should be reduced to $<37\%$.[40] For perioperative management, hematocrit and platelet counts should be normalized for at least several weeks before surgery. As per general population guidelines, routine anticoagulation should be provided to avoid postoperative thrombotic complications.

Essential Thrombocythemia

Introduction

The mean age at diagnosis of ET is approximately 60 years of age; however, up to 20% of patients are diagnosed at <40 years of age.[41] The incidence rate is approximately 2.5 cases per 100,000 persons per year.[42] Female-to-male ratio is 1.8.[42] Up to 50% of patients are asymptomatic on presentation.[43-45] In symptomatic patients, headaches and visual complaints are common.[44] Erythromelalgia, paresthesias, seizures, bleeding diathesis when platelet counts $>1000 \times 10^9$/L, and arterial or venous thrombosis can also be present.[44] Compared to PV, pruritus, hypercatabolic conditions, and constitutional symptoms are less commonly observed. In young women, recurrent first-trimester pregnancy loss can occur.[45] Roughly 25% of patients have palpable mild to moderate splenomegaly; however, hepatomegaly is rare.[45] Isolated thrombocytosis of 450×10^9/L or greater is usually seen with or without associated erythrocytosis or leukocytosis.[46] Histologic evaluation is necessary for diagnosis, and bone marrow biopsy typically reveals clusters of large, hyperlobulated, and mature

TABLE 4. Examples of common conditions associated with thrombocytosis

Medications	Infection/Inflammation	Malignancy	Other Reactive
IL-1β	Tuberculosis	AML	Alcohol
ATRA	Severe trauma	CML	Post surgery
LMWH	Chronic infections	MPN	Splenectomy
Vincristine	Myocardial infarction	MDS	Iron deficiency
Epinephrine	Chronic kidney disease	Metastasis	Acute blood loss
Glucocorticoids	Rheumatologic conditions		Post transplantation
Thrombopoietin	Inflammatory bowel disease		Correction of B12 deficiency

IL-1 β, interleukin-1β; ATRA, all-transretinoic acid; LMWH, low molecular weight heparin; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; MPN, myeloproliferative neoplasms; MDS, myelodysplastic syndrome.

megakaryocytes accompanied by granulocytic proliferation with a left shift in approximately 50% of cases.[25] Like PV, there are no specific cytogenetic abnormalities associated with ET; however, 7% of patients have deletion (20q), deletion (13q), +8, +9, and chromosome 1, 5, and 7 abnormalities. JAK2 V617F and MPL may or may not be present.[25]

Differential Diagnosis

Platelets are acute phase reactants; therefore, thrombocytosis can be related to a number of conditions, such as with malignancy, glucocorticoids and iron deficiency (Table 4).[47-49] Reactive thrombocytosis is transient and should resolve with treatment of the primary etiology. It is important to keep in mind that extreme thrombocytosis with platelet counts $>1000 \times 10^9$/L has been documented in inflammatory conditions, infections, functional or surgical postsplenectomy, trauma, blood loss, and rebound states, indicating that absolute platelet counts alone cannot distinguish between an autologous clonal process and secondary causes.[50]

Diagnosis

Diagnosis of ET requires meeting all 4 major criteria, as listed in Table 5.[26] Evaluation of iron stores can be helpful in distinguishing between ET and PV, as ET patients will be iron replete.[51] It is important to note that ET has heterogeneous properties that overlap with PMF; in advanced cases, this can make diagnosis somewhat difficult. Clinical and laboratory evaluation is important to distinguish between the 2, and in the absence of extreme splenomegaly, anemia, teardrop anisopoikilocytosis, and leukoerythroblastosis, advanced ET, or "prefibrotic MF," can safely be diagnosed.[51]

TABLE 5. 2008 WHO Criteria for ET

Major criteria
Sustained platelet counts $\geq 450 \times 10^9$/L
Bone marrow biopsy with proliferation predominantly of megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes with or without associated left of neutrophil granulopoiesis or erythropoiesis
Not meeting WHO criteria for PV, PMF, CML, MDS, or any other myeloid neoplasm
Positive for JAK2 V617F or other associated oncogenes *OR* if negative for presence of known oncogenes, no evidence of reactive thrombocytosis

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TABLE 6. Risk stratification for ET according to patient presentation

Risk Stratification	Patient Presentation
Low risk	<60 years of age, no history of thrombosis, platelet count $>1500 \times 10^9$/L without history of bleeding or aVWS, no cardiovascular risk factors, such as smoking, hypercholesterolemia, or diabetes mellitus
Intermediate risk	Neither low- nor high-risk category
High risk	≥60 years of age, history of thrombosis

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Risk Stratification

Approximately 10% of patients experience a thrombotic event and roughly 4% suffer a hemorrhagic episode[52,53] (Table 6). As with the general population, past or current smoking, diabetes, and hypercholesterolemia further increase the risk of CVA/CV. Despite limited data, most experts advise against oral contraception, hormone therapy, or exposure to other instigating prothrombotic conditions. Smoking cessation is strongly encouraged.[54] As in PV, leukocytosis is associated with a greater risk of arterial thrombosis.[54] There is evidence that a high burden of JAK2 V617F mutation also confers increased risk of thrombosis.[55] In a recent international study of 891 patients, a platelet count $>1000 \times 10^9$ was associated with an increased risk for venous thrombosis.

Treatment

In a randomized controlled trial by Cortelazzo et al. of hydroxyurea plus antiplatelet therapy vs antiplatelet monotherapy, the incidence of thrombotic events was 3.6% vs 24% in the 2 groups, respectively.[56] Current recommendations advise dual therapy with hydroxyurea plus low-dose aspirin in high-risk patients (Table 7). Anagrelide inhibits platelet

TABLE 7. Treatment of ET based on risk stratification

Risk Stratification	Treatment
Low risk	Low-dose aspirin
Intermediate risk	Low-dose aspirin if Ristocetin cofactor activity is <30%
High risk	Low-dose aspirin + hydroxyurea

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aggregation by blocking cyclic adenosine monophosphate.[57] It also inhibits platelet counts by blocking megakaryocyte proliferation and differentiation at lower doses than needed to inhibit platelet aggregation.[57] The UK Medical Research Council Primary Thrombocythemia 1 Study compared hydroxyurea plus aspirin to anagrelide plus aspirin in high-risk ET patients, and found that patients who received anagrelide plus aspirin had an increased risk of arterial thrombosis, serious hemorrhage, and transformation to MF.[57] The incidence of venous thromboembolism was higher in the hydroxyurea group. Overall, more patients on the anagrelide arm experienced arterial thrombosis, myocardial venous thrombosis, serious hemorrhage, or death from thrombotic or hemorrhagic causes. Based on that study, hydroxyurea is the preferred platelet-lowering agent. The use of aspirin in patients with ET is largely based on the positive results seen in patients with PV. In a more recent publication, aspirin was effective mainly in patients with JAK2 V617F mutation and in patients with cardiovascular risk factors.[55]

Prognosis

An analysis of 322 ET patients followed at the Mayo Clinic in Rochester, MN revealed a medial survival of approximately 18.9 years.[58] Decreased survival was associated with age >60 years, leukocytosis $\geq 15 \times 10^9$/L, tobacco use, and diabetes mellitus.[58] Transformation to other myeloid disorders and acute leukemia were relatively low in the first decade (1.4% and 9.1%, respectively) but increased by 8.1% and 28.3%, respectively, in the second decade and 24.0% and 58.5%, respectively, in the third decade.[58] Age >60 years at diagnosis and leukocytosis were also found to be independent risk factors for decreased survival. Patients with 0, 1, or both risk factors had median survival rates of 25.3, 16.9, and 10.3 years, respectively.[58]

Pregnancy and Perioperative Management

Approximately 25% to 50% of first-trimester fetal loss occurs in ET patients.[51] Intrauterine growth retardation, stillbirth, and preeclampsia

appear to be more frequent in patients who test positive for JAK2 V617F. Similar to PV patients, daily aspirin in low risk, and aspirin plus IFN-α in high risk, is advised in patients with a history of thrombosis or prior pregnancy complication.[51] Patients should continue treatment throughout the pregnancy until 6 weeks postpartum. Before surgery, antiplatelet therapy is held for 7-10 days and restarted as soon as possible, per the surgeon's recommendations. If patients are on cytoreductive therapy, it is advised to be continued for as long as possible with additional supportive measures as needed pre- and postoperatively (ie, packed red blood cell transfusions, etc). The goal platelet count is mid normal range before surgery. Postoperative thromboprophylaxis recommendations follow that of the general population.[51] Close monitoring of blood counts is strongly suggested immediately following surgical procedure until the patient is stable.

Primary Myelofibrosis

Introduction

Median age at diagnosis is approximately the mid-60s.[42] It is the least common of the typical BCR-ABL-negative MPNs, with an annual age- and sex-adjusted rate of 1.46 per 100,000 persons per year, and carries a poor prognosis.[42] Many patients deny any symptoms or present with nonspecific complaints, such as fatigue.[59] The majority of patients have moderate to severe splenomegaly because of extramedullary hematopoiesis, with associated complications such as early satiety, abdominal discomfort, and portal hypertension.[59] Constitutional symptoms, hypermetabolic state, and diarrhea may also be present. Hepatomegaly can also occur.[60] Rarely, extramedullary hematopoiesis can occur in the vertebral column, lung, pleura, retroperitoneum, eyes, kidneys, bladder, mesentery, and skin, causing symptoms such as lymphadenopathy and pulmonary hypertension, which is associated with decreased survival.[61] Anemia is the predominant laboratory feature with 36% of patients presenting with hemoglobin $<$10 g/dL. It occurs secondary to decreased erythropoiesis, hemolysis, and, as thrombocytopenia and splenomegaly progress, hemorrhage and gastrointestinal bleeding.[5] Leukocytosis or thrombocytopenia occurs in 10% and 16% of patients, respectively. Histologic evaluation is essential for diagnosis, and bone marrow biopsy typically reveals clusters of abnormal megakaryotes with hyperchromatic, irregularly folded, and bulky nuclei "dwarf megakaryocytes," disproportionately elevated number of hematopoietic progenitor cells staining positive for $CD34^+$ with or

TABLE 8. 2008 WHO criteria for PMF

Major criteria
Megakaryocyte proliferation and atypia accompanied by either reticulin or collagen fibrosis *OR* in the absence of significant reticulin fibrosis, megakaryocyte changes accompanied by increased marrow cellularity: granulocytic proliferation and decreased erythropoiesis (ie, prefibrotic cellular-phase disease)
Not meeting WHO criteria for PV, CML, MDS, or other myeloid disorders
Positive for JAK2 V617F or other associated mutations (ie, MPL W515K/L) *OR* in the absence of above mutations, no evidence of secondary marrow fibrosis
Minor criteria
Anemia
Splenomegaly
Leukoerythroblastosis
Increased serum LDH level

WHO, World Health Organization; PV, polycythemia vera; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; MPL, myeloproliferative leukemia.
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without significant reticulin and collagen fibrosis.[25] In advanced stages, a bone marrow biopsy of a completely fibrotic marrow will often yield a "dry tap." Like ET, JAK2 V617F and MPL mutations may or may not be present.[26]

Differential Diagnosis

MF secondary to CML, AML, ET, or MDS can be difficult to distinguish from that of PMF. Polymerase chain reaction assay can be used to identify BCR-ABL, which is diagnostic of CML.[25] AML presents with rapid disease development, pancytopenia, mild to no splenomegaly, and a high frequency of myeloblasts that contain Auer rods. As stated earlier, ET and PMF frequently have overlapping qualities; however, the presence of extreme splenomegaly, anemia, teardrop anisopoikilocytosis, and leukoerythroblastosis favors the diagnosis of PMF.[51] MDS can be distinguished from PMF by the presence of dysplastic cells seen on a peripheral smear.[62]

Diagnosis

Diagnosis requires all 3 major criteria and 2 minor criteria, as listed in Table 8.[26]

Risk Stratification

Based on the International Working Group for MF Research and Treatment developed by a Dynamic International Prognostic Scoring System, age >65 years, the presence of constitutional symptoms, Hb <10

TABLE 9. Risk stratification for PMF according to number of risk factors

Risk Stratification	Number of Risk Factors	Median Survival in Years
Low	0	15.4
Intermediate-1	1	6.5
Intermediate-2	2	2.9
High	>3	1.3

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g/dL, and white blood cell count $>25 \times 10 \times 10^9$/L plus circulating blast cells >1% were risk factors found to be independent predictors of decreased survival (Table 9).[60] Additionally, abnormal karyotype, Hb <10 g/dL, platelet count $<100 \times 10^9$/L, leukocyte count $>30 \times 10^9$/L, and older age are also associated with decreased survival.[5]

Treatment

Therapeutic regimens are largely aimed at relieving symptoms and preserving quality of life. In asymptomatic, low-risk patients with mild to no splenomegaly, a conservative management of "watchful waiting" is indicated.[63] Anemia and splenomegaly with its associated complications are the major adverse contributors to the patients' quality of life. Red blood cell transfusions, corticosteroids, androgens, erythropoiesis-stimulating agents, and immunomodulators, such as thalidomide, and lenalidomide are recommended for the treatment of anemia.[64] In addition, one of the JAK2 inhibitors CYT387 is showing promise in the therapy of anemia associated with MF, and further studies are currently ongoing with this agent.[65] As for splenomegaly, cytoreductive therapy with hydroxyurea, radiation, or splenectomy may be considered. Splenectomy is associated with a high-morbidity and high-mortality rate and should only be performed on a select group of patients. Allogeneic stem cell transplant is the only curative therapy; however, the procedure is considered high risk with an estimated 1-year post stem cell transplant mortality rate approaching 30%, and an estimated survival of 50% within the same length of time.[66] Clinical trials involving inhibitors of the JAK tyrosine kinase have shown promising results as an alternative medical therapy for splenomegaly. Verstovsek et al. conducted a Phase 1-2 trial on the efficacy of a selective JAK1 and -2 inhibitor ruxolitinib (INCB018424) on refractory, relapsed, and newly diagnosed post-PV/ET MF and PMF patients with at least intermediate-1 risk factor.[67] After a median duration of more than 14.7 months, 52% of the patients on continuous therapy had a

sustained response in splenomegaly defined as ≥50% reduction in the size of the spleen lasting 12 or more months.[67] Transfusion dependence, leukocytosis, leukemic transformation, and even constitutional symptoms, such as weight loss, fatigue, and night sweats, also improved.[67] Bone marrow fibrosis, cytopenia, and absolute $CD34^+$ counts remained stable.[67] Thrombocytopenia was found to be the dose-limiting side effect, and although few patients had other hematologic toxicities (ie; anemia), intolerance to therapy, or death, INCB018424 was tolerated relatively well by most patients. The authors noted that although patients with PMF have increasing dependence on extramedullary hematopoiesis, targeted therapy with INCB018424 did not result in significant hematologic toxicities, demonstrating the potential of targeted therapy as another treatment modality in patients with advanced disease.[67] In a recently completed Phase 3 trial, 309 patients were randomized to ruxolitinib vs best supportive care. Patients receiving ruxolitinib experienced a sustained improvement in symptoms and spleen size. With a median follow-up of 52 weeks, 13 and 24 patients on the ruxolitinib and placebo arms died, respectively. Several other JAK2 inhibitors are being evaluated and are preliminarily showing promising results.[65]

Prognosis

In general, PMF is associated with a poor prognosis. Age at diagnosis, number of circulating myeloid progenitor cells, progressive anemia secondary to a failing bone marrow, and transformation to AML are all independently associated with decreased survival.[53] Abnormal cytogenetics, constitutional symptoms, and leukocytosis also confer a poor prognosis.[53] Patients who are severely anemic with a platelet count $<100 \times 10^9$/L and a high number of circulating immature cells have a high risk of developing AML.[68] A hemoglobin <10 g/dL is the single worse prognostic indicator. Patients diagnosed at >55 years of age have an average lifespan of 3-5 years, whereas patients diagnosed at <55 years of age have a median survival of 8-10 years.[60]

Pregnancy and Perioperative Management

Patients of childbearing age with PMF are extremely rare. Limited data suggest the use of IFN-α in intermediate- to high-risk patients.[69] Fewer data exist for perioperative management. Guidelines before scheduled splenectomy have been discussed elsewhere in this issue under treatment for PMF.

Summary

BCR-ABL-negative MPNs are a heterogeneous collection of clonal neoplasms arising from unrestrained proliferation of any combination of erythrocytosis, leukocytosis, and thrombocytosis. In patients with PV and ET, CV and CVA thrombohemorrhagic events account for the greatest morbidity and mortality, and treatment is aimed at reducing the incidence of these episodes. Individuals less than 60 years of age with no prior history of thrombosis are considered low risk and advised to take prophylactic low-dose aspirin daily. High-risk patients, such as those older than 60 years of age with a prior history of thrombohemorrhagic event, are recommended to undergo phlebotomy as needed in addition to taking daily aspirin and hydroxyurea. Patients with PMF generally suffer from extreme fatigue and complications arising from moderate to severe splenomegaly. Diagnosis of PMF confers a poor prognosis and treatment is largely palliative in nature. Early satiety, abdominal discomfort, and portal hypertension are common symptoms secondary to an enlarged spleen. Hydroxyurea, and radiotherapy are widely practiced therapeutic regimens, and splenectomy is reserved for few select patients. SCT is the only curative known therapy at this time; however, as with splenectomy, it carries a high morbidity and mortality rate. With the discovery of JAK V617F mutation in the pathogenesis of MPNs, targeted therapy involving JAK2 tyrosine kinase inhibitors have shown encouraging outcomes in addition to providing additional medical treatment for splenomegaly. Ongoing clinical trials are underway to investigate the efficacy, safety, tolerability, and long-term outcomes on these novel therapeutic regimens.

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