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SPECIAL ARTICLE

Philadelphia-Negative Classical Myeloproliferative Neoplasms: Critical Concepts and Management Recommendations From European LeukemiaNet

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ABSTRACT

We present a review of critical concepts and produce recommendations on the management of Philadelphia-negative classical myeloproliferative neoplasms, including monitoring, response definition, first- and second-line therapy, and therapy for special issues. Key questions were selected according the criterion of clinical relevance. Statements were produced using a Delphi process, and two consensus conferences involving a panel of 21 experts appointed by the European LeukemiaNet (ELN) were convened. Patients with polycythemia vera (PV) and essential thrombocythemia (ET) should be defined as high risk if age is greater than 60 years or there is a history of previous thrombosis. Risk stratification in primary myelofibrosis (PMF) should start with the International Prognostic Scoring System (IPSS) for newly diagnosed patients and dynamic IPSS for patients being seen during their disease course, with the addition of cytogenetics evaluation and transfusion status. High-risk patients with PV should be managed with phlebotomy, low-dose aspirin, and cytoreduction, with either hydroxyurea or interferon at any age. High-risk patients with ET should be managed with cytoreduction, using hydroxyurea at any age. Monitoring response in PV and ET should use the ELN clinicohematologic criteria. Corticosteroids, androgens, erythropoiesis-stimulating agents, and immunomodulators are recommended to treat anemia of PMF, whereas hydroxyurea is the first-line treatment of PMF-associated splenomegaly. Indications for splenectomy include symptomatic portal hypertension, drug-refractory painful splenomegaly, and frequent RBC transfusions. The risk of allogeneic stem-cell transplantation–related complications is justified in transplantation-eligible patients whose median survival time is expected to be less than 5 years.

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INTRODUCTION

The discovery that the protein tyrosine kinase JAK2 is mutated (V617F) in more than 90% of patients with polycythemia vera (PV) and approximately 60% of patients with essential thrombocythemia (ET) or primary myelofibrosis (PMF)[1] has modified our understanding of the clinical and biologic features of the Philadelphia (Ph) -negative classical myeloproliferative neoplasms (MPNs). It is now clear that patients with the mutation are biologically distinct from those without the mutation and that the mutation is associated with different disease phenotypes. These new concepts have modified our criteria for diagnosis, the strategies for monitoring, and the tools for assessing the response to treatments. The discovery of JAK2 activating mutations in Ph-negative classical MPNs also spurred the development of small-molecule inhibitors that specifically target *JAK2*.[2] However, this discovery has not yet translated into changes in the management of the three disorders. Thus, the therapy of Ph-negative classical MPNs remains a challenging enterprise requiring a high degree of professional experience. For these reasons, the European LeukemiaNet (ELN) decided to review recent data regarding therapy, standard monitoring procedures, and definitions of responses and to produce recommendations aimed at contributing to the optimization and standardization of management of the three Ph-negative classical MPNs.

THE CONSENSUS PROCESS

An expert panel (hereafter referred to as the Panel) of 21 experts was selected for their expertise in research and clinical practice of management of Ph-negative classical MPNs. During an initial meeting

Table 1. Diagnostic Criteria for Philadelphia-Negative Classical Myeloproliferative Neoplasms According to WHO (2008)

Myeloproliferative Neoplasm	Criteria
Polycythemia vera*	
Major criteria	Hemoglobin > 18.5 g/dL in men or 16.5 g/dL in women or other evidence of increased RBC volume; presence of *JAK2*V617F or other functionally similar mutation such as *JAK2* exon 12 mutation
Minor criteria	Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation; serum erythropoietin level below the reference range for normal; endogenous erythroid colony formation in vitro
Essential thrombocythemia†	Sustained platelet count ≥ 450 × 10^9/L; bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes; no significant increase or left shift of neutrophil granulopoiesis or erythropoiesis; not meeting WHO criteria for polycythemia vera, primary myelofibrosis, BCR-ABL1–positive chronic myelogenous leukemia, myelodysplastic syndrome, or other myeloid neoplasm; demonstration of *JAK2*V617F or other clonal marker, or in the absence of *JAK2*V617F, no evidence for reactive thrombocytosis
Primary myelofibrosis‡	
Major criteria	Presence of megakaryocyte proliferation and atypia, usually accompanied by either reticulin and/or collagen fibrosis, or in absence of significant reticulin fibrosis, a prefibrotic cellular-phase disease; not meeting WHO criteria for polycythemia vera, BCR-ABL1–positive chronic myelogenous leukemia, myelodysplastic syndrome, or other myeloid neoplasm; demonstration of *JAK2*V617F or other clonal marker (eg, *MPL*W515K/L), or in absence of clonal marker, no evidence of secondary bone marrow fibrosis
Minor criteria	Leukoerythroblastosis; increase in serum lactate dehydrogenase level; anemia; splenomegaly

*Diagnosis requires the presence of both major criteria and one minor criterion or the presence of the first major criterion together with two minor criteria.
†Diagnosis requires meeting all four criteria.
‡Diagnosis requires meeting all three major and two minor criteria.

held in New Orleans, Louisiana, in December 2009, the areas of major concern in the management of Ph-negative classical MPNs were selected by generating and rank ordering clinical key questions using the criterion of clinical relevance, through group discussion. Twenty-nine candidate key questions were generated, and after discussion, the 25 that ranked highest formed the set of questions of the present concepts and recommendations.

Two panelists drafted statements that addressed the identified key questions, and the remaining panelists scored their agreement with those statements and provided suggestions for rephrasing. For exploiting this phase of the process, the Delphi questionnaire method was used.[3] Finally, the Panel convened once again for a consensus conference held in Barcelona, Spain, in June 2010. The nominal group technique was used by which participants were first asked to comment in round-robin fashion on their preliminary votes and then to propose a new vote.[4] For five of 25 statements produced, no consensus was achieved at first, and these statements were rediscussed. At the second vote, all of the statements were decided.

CRITICAL CONCEPTS

Diagnosis

Standard and uniform diagnostic criteria for Ph-negative classical MPNs are essential for clinical research, case reporting, and clinical practice. The 2008 WHO classification and diagnosis criteria meet these requirements (Table 1).[5] Some investigators remain loyal to red cell mass measurement as a diagnostic tool for PV,[6] whereas others are skeptical about the use of morphology in distinguishing ET from prefibrotic PMF.[7] The WHO classification system addresses both issues by allowing the diagnostic use of the red cell mass, when desired, and the incorporation of biologically relevant minor criteria to confirm histologic impression for prefibrotic PMF.

Patient Communication

Median survival in PV and ET approaches or exceeds 20 years,[8-11] and median survival in PMF is currently estimated at greater than 10 years.[12] This news should be underscored to patients as soon as diagnosis is established. At the same time, potentially life-threatening (eg, leukemic or fibrotic transformation, thrombohemorrhagic events) and non–life-threatening (eg, poor quality of life from constitutional symptoms, microvascular disturbances, pruritus, increased risk of miscarriage) disease complications and their likelihood of response to treatment should be disclosed. Therapeutic options must be discussed with the patient, along with comments regarding how both the disease and its treatment will affect the patient's quality of life.

Risk Classification

Because the current therapy in PV and ET is aimed at lowering the risk of thrombosis, the risk classification system in these disorders is shaped according to thrombosis risk. Several prospective and retrospective cohort studies in PV and ET have identified age older than 60 years and previous thrombosis as major predictors of vascular complications.[11,13-17] A clear association between platelet counts and major vascular events is lacking, but extreme thrombocytosis (ie, ≥ 1,500 × 10^9/L) can be associated with acquired von Willebrand disease and bleeding tendency.[18] Patients enrolled onto the Low-Dose Aspirin in Polycythemia Vera (ECLAP) study failed to show any correlation between hematocrit levels up to 50% and thrombosis.[19]

Risk stratification in PMF is addressed to death from any cause. The International Prognostic Scoring System (IPSS) uses variables obtained at time of diagnosis (Table 2),[20] and the same IPSS prognostic variables are used to stratify patients seen at any time during their disease course (dynamic IPSS).[21] Recent studies have demonstrated that transfusion need in the first year of diagnosis or the presence of cytogenetic abnormalities other than sole +9, 13q–, or 20q– identifies patients with median survival of less than 5 years.[22,23] In the aforementioned IPSS study,[20] the presence of *JAK2*V617F did not correlate with either survival or IPSS score. This lack of prognostic relevance in regard to presence or absence of *JAK2*V617F was also demonstrated in two recent large studies, which instead showed shortened overall survival in patients with PMF with lower as opposed to higher quartile *JAK2*V617F allele burden.[24,25]

Table 2. International Prognostic Scoring System Adverse Prognostic Factors for Primary Myelofibrosis

Adverse Prognostic Factors
Age > 65 years
Constitutional symptoms
Hemoglobin < 10 g/dL
WBC count > 25 × 10^9/L
Blood blasts ≥ 1%

NOTE. On the basis of the presence of zero (low risk), one (intermediate risk-1), two (intermediate risk-2), or ≥ three (high risk) of these variables, four risk groups are delineated.

Goal of Therapy

Goals of therapy in patients with PV and ET are to avoid first occurrence and/or recurrence of thrombotic and bleeding complications; to minimize the risk of acute leukemia and post-PV/ET myelofibrosis; and to control systemic symptoms, treat complications (thrombosis and hemorrhage), and manage risk situations (eg, pregnancy, surgery). The main goals of therapy in PMF are prolongation of survival and, if possible, also cure, which is currently only achieved by allogeneic stem-cell transplantation (alloSCT). If prolongation of survival or cure is not possible, symptom-orientated palliation and quality of life are the main goals.

RECOMMENDATIONS

Investigations Before Planning Therapy

Information regarding variables used in the patient's risk stratification should be collected (ie, age and thrombotic history for PV; age, thrombotic history, and platelet count for ET; and age, hemoglobin, blast count, WBC count, and constitutional symptoms for PMF). It is also important to consider general risk factors for thrombosis, including metabolic syndrome, diabetes mellitus, arterial hypertension, and hypercholesterolemia. The Panel agreed that obtaining additional information on transfusion status and cytogenetics is strongly recommended in PMF, and peripheral-blood $CD34^+$ count is a useful biomarker of disease aggression.

Management of PV

First-line therapy. Recommendations on treatment strategy for PV derive from historical Polycythemia Vera Study Group, European Organisation for Research and Treatment of Cancer, and French Polycythemia Study Group trials[26-30] and the more recent ECLAP study.[19] In the Polycythemia Vera Study Group trials, patients randomly assigned to the phlebotomy arm had a better median survival time than patients assigned to the chlorambucil or radiophosphorus arms because of the high frequency of acute leukemia in the latter two arms. However, overall long-term survival at 10 years showed no statistical significant difference between phosphorus-32 (^{32}P) and phlebotomy. In patients given hydroxyurea, the incidence of thrombosis was inferior to historical controls treated with phlebotomy. The European Organisation for Research and Treatment of Cancer trial compared ^{32}P with intermittent busulphan, and the overall survival was significantly better in the busulphan arm as a result of less vascular deaths. Patients with PV enrolled onto the ECLAP study were randomly assigned to receive aspirin 100 mg or placebo. After a follow-up of approximately 3 years, data analysis showed a significant reduction of events on aspirin. Major bleeding was not significantly increased by aspirin. Interferon alfa-2 (IFN-α-2) has been used in therapy of PV showing up to an 80% hematologic response rate.[31] Pegylated IFN-α has been demonstrated in phase II trials of patients with PV to have clinical efficacy as measured by normalization of myeloproliferation, lack of vascular events while on therapy, and a decrease in the *JAK2*V617F allele burden.[32]

All patients with PV should be managed with phlebotomy to maintain the hematocrit at less than 45% and low-dose aspirin. Cytoreduction is indicated in high-risk patients. Poor tolerance of phlebotomy or frequent phlebotomy requirement, symptomatic or progressive splenomegaly, severe disease-related symptoms, platelet counts greater than 1,500 × 10^9/L, and progressive leukocytosis are indications for cytoreductive therapy. Either hydroxyurea or IFN-α is first-line cytoreductive therapy at any age. Hydroxyurea should be used with caution in young patients (ie, age < 40 years). Busulphan may be considered in elderly patients (ie, age > 70 years). All patients should be managed aggressively for their generic cardiovascular risk factors and advised to stop smoking. The use of cytoreductive drugs in otherwise low-risk patients who have well-controlled cardiovascular risk factors is not indicated.

Monitoring response. Monitoring of response to conventional cytoreductive therapy of individual patients with PV should adopt the ELN criteria proposed for defining the clinicohematologic response[33] (Table 3). There is no strict indication to monitor molecular response routinely, including sequential assessment of the *JAK2*V617F allele burden, except if the therapeutic intervention may induce molecular responses (to date IFN-α), and no indication to monitor bone marrow response for clinical follow-up.

Table 3. European LeukemiaNet Definition of Clinicohematologic Response in Polycythemia Vera and Essential Thrombocythemia

Response Grade	Definition of Response in Polycythemia Vera	Definition of Response in Essential Thrombocythemia
Complete response	1. Hematocrit < 45% without phlebotomy, AND 2. Platelet count ≤ 400 × 10^9/L, AND 3. WBC count ≤ 10 × 10^9/L, AND 4. Normal spleen size on imaging, AND 5. No disease-related symptoms*	1. Platelet count ≤ 400 × 10^9/L, AND 2. No disease-related symptoms,* AND 3. Normal spleen size on imaging, AND 4. WBC count ≤ 10 × 10^9/L
Partial response	In patients who do not fulfill the criteria for complete response: 1. Hematocrit < 45% without phlebotomy, OR 2. Response in ≥ 3 of the other criteria	In patients who do not fulfill the criteria for complete response: platelet count ≤ 600 × 10^9/L or decrease of > 50% from baseline
No response	Any response that does not satisfy partial response	Any response that does not satisfy partial response

*Disease-related symptoms include microvascular disturbances, pruritus, and headache.

Table 4. European LeukemiaNet Definition of Resistance/Intolerance to Hydroxyurea in Patients With Polycythemia Vera and Essential Thrombocythemia

Myeloproliferative Neoplasm	Definition of Resistance/Intolerance to Hydroxyurea
Polycythemia vera	1. Need for phlebotomy to keep hematocrit $< 45\%$ after 3 months of at least 2 g/d of hydroxyurea, OR 2. Uncontrolled myeloproliferation (ie, platelet count $> 400 \times 10^9$/L AND WBC count $> 10 \times 10^9$/L) after 3 months of at least 2 g/d of hydroxyurea, OR 3. Failure to reduce massive* splenomegaly by $> 50\%$ as measured by palpation OR failure to completely relieve symptoms related to splenomegaly after 3 months of at least 2 g/d of hydroxyurea, OR 4. Absolute neutrophil count $< 1.0 \times 10^9$/L OR platelet count $< 100 \times 10^9$/L OR hemoglobin < 10 g/dL at the lowest dose of hydroxyurea required to achieve a complete or partial clinicohematologic response,† OR 5. Presence of leg ulcers or other unacceptable hydroxyurea-related nonhematologic toxicities, such as mucocutaneous manifestations, GI symptoms, pneumonitis, or fever at any dose of hydroxyurea
Essential thrombocythemia	1. Platelet count $> 600 \times 10^9$/L after 3 months of at least 2 g/d of hydroxyurea (2.5 g/d in patients with a body weight > 80 kg), OR 2. Platelet count $> 400 \times 10^9$/L and WBC count $< 2.5 \times 10^9$/L at any dose of hydroxyurea, OR 3. Platelet count $> 400 \times 10^9$/L and hemoglobin < 10 g/dL at any dose of hydroxyurea, OR 4. Presence of leg ulcers or other unacceptable mucocutaneous manifestations at any dose of hydroxyurea, OR 5. Hydroxyurea-related fever

*Organ extending by > 10 cm from the costal margin.
†Complete response is defined as hematocrit less than 45% without phlebotomy, platelet count $\leq 400 \times 10^9$/L, WBC count $\leq 10 \times 10^9$/L, and no disease-related symptoms. Partial response is defined as hematocrit less than 45% without phlebotomy or response in three or more of the other criteria.

Therapy change and second-line therapy. The choice of second-line myelosuppressive drugs for PV should be carefully evaluated because some drugs administered after hydroxyurea may enhance the risk of acute leukemia.[34] IFN-α should be considered because this drug is reported to be nonleukemogenic.

Low-risk patients with PV who are ≥ 60 years old or develop major thrombotic or hemorrhagic complications require the introduction of cytoreductive therapy. In such patients, progressively increasing leukocyte and/or platelet count, enlarging spleen, uncontrolled disease-related symptoms, and poorly tolerated phlebotomy regimen may also justify the introduction of cytoreductive therapy. In high-risk patients, first-line therapy should be changed when intolerance has been demonstrated (Table 4).[35] Aspirin should be withdrawn in the event of major bleeding, most frequently GI, or in the rare cases of allergy or intolerance. Second-line therapy of PV is IFN-α in patients intolerant or resistant to hydroxyurea therapy. Conversely, hydroxyurea is the second-line therapy for patients who are intolerant or refractory to first-line therapy with IFN-α. Pipobroman, busulphan, and ^{32}P are second-line therapies reserved for patients with short life expectancy.

Management of ET

First-line therapy. Recommendations on treatment strategy for ET derive from two randomized controlled trials in high-risk patients[36,37] and a case-control study in low-risk patients.[38] In high-risk patients, Cortelazzo et al[36] showed that hydroxyurea lowers thrombotic complications compared with no treatment. In the Primary Thrombocythemia 1 Trial (PT-1),[37] hydroxyurea plus aspirin reduced a composite end point of arterial and venous thrombosis—major bleeding or death from thrombotic or hemorrhagic causes—compared with anagrelide plus aspirin. In untreated low-risk patients, the incidence of thrombosis was similar to that observed in a healthy control population.[14,38,39]

All patients with ET should be managed with low-dose aspirin if microvascular disturbances are present. Cytoreduction is indicated in high-risk patients. Hydroxyurea is the first-line cytoreductive therapy at any age; in young patients (< 40 years old), its use should be carefully considered. All patients should be managed aggressively for their cardiovascular risk factors and advised to stop smoking. The use of cytoreductive drugs in otherwise low-risk patients having well-controlled cardiovascular risk factors is not generally indicated. Platelet count greater than $1{,}500 \times 10^9$/L is a risk factor for bleeding, and at this level of thrombocytosis, a platelet-lowering treatment should be considered.

Monitoring response. Clinicohematologic, molecular, and histologic response criteria for ET have been identified by ELN experts for application in clinical trials.[33] The response of therapy should be evaluated by normalization of blood counts and disappearance of signs and symptoms of disease (Table 3). There is no indication to monitor bone marrow response for clinical follow-up. Bone marrow aspirate and trephine biopsy are useful in assessing hematologic transformation to myelofibrosis or acute leukemia. There is no strict indication to monitor molecular response routinely, including sequential assessment of the *JAK2*V617F allele burden.

Therapy change and second-line therapy. Patients with ET who receive more than one cytotoxic agent do have a significantly higher risk of developing acute myeloid leukemia/myelodysplastic syndromes.[40,41] For this reason, in patients resistant or intolerant to first-line therapy with hydroxyurea,[42] nonleukemogenic drugs such as anagrelide or IFN should be considered.

Low-risk untreated patients should start a cytoreductive treatment as soon as they move to the high-risk category as a result of increasing age, the occurrence of a major thrombotic or hemorrhagic event, or increasing platelet count greater than $1{,}500 \times 10^9$/L. In high-risk patients, treatment with hydroxyurea should be changed in case of intolerance (Table 4). In patients with disease resistant to hydroxyurea, changing therapy may be an option. Although less frequently than in PV, cytoreduction may also be required for progressive myeloproliferation (eg, increasing splenomegaly) or uncontrolled systemic symptoms. Aspirin should be withdrawn in case of major bleeding, most frequently GI, or in the rare cases of allergy or intolerance. Anagrelide is the recommended second-line therapy for ET. IFN is an experimental therapy and should be reserved for selected patients, such as young females or patients who have contraindications to anagrelide therapy. Pipobroman, busulphan, and ^{32}P are second-line therapies reserved for patients with short life expectancy.

Table 5. Clinical Issues in Patients With Primary Myelofibrosis

Issue
Shortened survival
Increased risk of leukemic transformation, which approaches 20% in the first 10 years of disease
Severe anemia often requiring frequent RBC transfusions and poor post-transfusion increments because of associated marked splenomegaly; some patients also have severe thrombocytopenia or neutropenia
Marked hepatosplenomegaly often accompanied by early satiety, severe abdominal discomfort, changes in bowel habits, painful splenic infarcts, portal hypertension leading to ascites and variceal bleeding, compromised mobility and movement, and cachexia
Nonhepatosplenic extramedullary hematopoiesis that might lead to cord compression, ascites, pulmonary hypertension, pleural effusion, lymphadenopathy, or skin tumors
Thrombohemorrhagic complications
Marked leukocytosis or thrombocytosis
Profound constitutional symptoms including fatigue, weight loss, cachexia, pruritus, night sweats, low-grade fever, and bone and joint pain
Recurrent gout

Management of PMF

Patients with PMF face a umber of clinical issues (Table 5). Clinical issues should be identified early and managed appropriately. Treatment is neither always indicated nor similar across the different aspects of the disease.

How to treat anemia. Drugs for the treatment of anemia in PMF include erythropoiesis-stimulating agents, corticosteroids, androgens, danazol, thalidomide, and lenalidomide.[43-46] Single-agent corticosteroid (0.5 to 1.0 mg/kg/d) or androgen therapy (eg, testosterone enanthate 400 to 600 mg weekly, oral fluoxymesterone 10 mg tid) or danazol at a dose of 600 mg/d has been used in PMF with response rates of 30% to 40%. Thalidomide at low doses (50 mg/d) and in combination with corticosteroids (prednisone 15 to 30 mg/d)[47,48] and lenalidomide in the presence of del(5)(q31)[47-51] show response rates of approximately 20%.

It is reasonable to initiate treatment for anemia in patients with a hemoglobin value less than 10 g/dL. Four agents have proved to be effective in the anemia of PMF; these are corticosteroids, androgens, erythropoiesis-stimulating agents, and immunomodulators. All of these agents have limitations, and there are no comparative trials. In the presence of del(5q), lenalidomide is preferred. There are no firm data to support the value of iron chelation therapy in PMF.

How to treat splenomegaly. The drug of choice for symptomatic splenomegaly is hydroxyurea, which is also used for controlling symptomatic thrombocytosis and/or leukocytosis.[52,53] Reduction of spleen volume with hydroxyurea reportedly occurs in approximately 40% of patients.[52] Hydroxyurea-refractory disease[35] is sometimes managed by the use of alternative myelosuppressive agents including intravenous cladribine (5 mg/m^2/d in a 2-hour infusion for 5 consecutive days to be repeated for four to six monthly cycles),[54] oral melphalan (2.5 mg three times a week),[55,56] and oral busulphan (2 to 6 mg/d with close monitoring of blood counts). In contrast, INF-α therapy is poorly tolerated and has limited efficacy in the treatment of PMF.[57-59]

Involved-field radiotherapy provides symptomatic relief of mechanical discomfort from hepatosplenomegaly. However, the response is transient (median duration, 3 to 6 months) and not useful to provide a consistent relief of this disturbance. When used, splenic irradiation is given in a total dose of 0.1 to 0.5 Gy in five to 10 fractions and is associated with a greater than 10% mortality rate from consequences of cytopenia.[60] Splenectomy is often considered for the treatment of drug-refractory symptomatic splenomegaly and is discussed further later.

Hydroxyurea is currently the first-line treatment of choice in PMF-associated splenomegaly. Splenic radiation is only of transient benefit, and splenectomy remains a viable treatment option for drug-refractory splenomegaly.

How to treat constitutional symptoms. Current dogma implicates aberrant cytokine production to be causally related to PMF-associated constitutional symptoms and cachexia. Constitutional symptoms can be severe in patients with PMF and must be considered a key treatment indication. Constitutional symptoms often respond to treatment directed at splenomegaly.

How to treat nonhepatosplenic hematopoiesis. The thoracic vertebral column is the most frequent site of nonhepatosplenic extramedullary hematopoiesis (EMH) in PMF. Other sites include lymph nodes, lung, pleura, small bowel, peritoneum, urogenital tract, and heart. When symptomatic, such occurrences are effectively treated with low-dose radiation therapy (0.1 to 1 Gy in five to 10 fractions). Low-dose radiation therapy is currently the treatment of choice for PMF-associated nonhepatosplenic EMH.

Splenectomy. The perioperative mortality of splenectomy in PMF is between 5% and 10%, and postsplenectomy complications occur in approximately 50% of patients. Complications include surgical site bleeding, thrombosis, subphrenic abscess, accelerated hepatomegaly, extreme thrombocytosis, and leukocytosis with excess blasts. Consideration for splenectomy requires good performance status and absence of clinical or laboratory evidence of disseminated intravascular coagulation.[61,62]

Indications for splenectomy include symptomatic portal hypertension (eg, variceal bleeding, ascites), drug-refractory marked splenomegaly that is either painful or associated with severe cachexia, and established RBC transfusion-dependent anemia. In contrast, severe thrombocytopenia is a marker of impending leukemic transformation, and overall outcome might not be favorably affected by splenectomy. Cytoreduction and anticoagulants are recommended prophylactic measures before splenectomy. Platelet count should be kept below 400×10^9/L because of the potential for postoperative extreme thrombocytosis. An experienced surgical team is recommended.

AlloSCT. AlloSCT is currently the only treatment approach in myelofibrosis that is potentially curative, but it is complicated by relatively high treatment-related mortality and morbidity. The estimated 1-year treatment-related mortality associated with conventional-intensity conditioning alloSCT is approximately 30%, and overall survival is 50%; with reduced-intensity conditioning alloSCT, 5-year median survival is estimated at 45% with a similar incidence of treatment-related and relapse-related death rates.[63-66] By comparison, in a recent study of transplantation-eligible patients with PMF (high- or intermediate-risk patients, age $<$ 60 years) who did not undergo transplantation, the 1- and 3-year survival rates ranged from 71% to 95% and 55% to 77%, respectively.[67]

It is reasonable to justify the risk of alloSCT-related complications in otherwise transplantation-eligible patients whose median survival is expected to be less than 5 years. This would include IPSS

high-risk (median survival, approximately 27 months) or intermediate-2–risk (median survival, approximately 48 months) patients, as well as patients with either RBC transfusion need (median survival, approximately 20 months) or unfavorable cytogenetic abnormalities (median survival, approximately 40 months). Other additional adverse factors of outcome from alloSCT, including RBC transfusion load, presence of marked splenomegaly, use of a non–HLA-identical sibling donor, increased alloSCT-specific comorbidity index, advanced age, advanced stage of disease, and unrelated donor who is not fully HLA matched, must be considered. If alloSCT is a therapeutic option, a physician with extensive experience in allogeneic transplantation should be consulted.

Monitoring response. In the setting of alloSCT, monitoring *JAK2*V617F allele burden has been shown to be useful in predicting relapse.[68,69] In other scenarios, it is reasonable to use cytogenetic studies, *JAK2* or *MPL* mutant allele burden, spleen size, blood count, peripheral-blood leukoerythroblastosis, serum lactate dehydrogenase, circulating $CD34^+$ cells, and bone marrow morphology and fibrosis for assessing disease activity in PMF. The value of morphology or molecular studies in monitoring response to specific therapy must be evaluated in a prospective setting.

Treatment of Blast-Phase MPN

Blast-phase MPN is a terminal disease with short survival (median survival, $<$ 6 months) and limited therapeutic options.[70] Results of any treatment for blast-phase MPN are extremely poor. Experimental or palliative therapy should be considered. Selected candidates should be considered for aggressive induction chemotherapy followed by consolidation with alloSCT. In candidates for transplantation, complete remission may not be required to proceed to transplantation as long as the disease reverts to chronic phase.

Special Issues in MPNs

Children. MPNs are rare in children, and ET is the most frequent. By definition, children with ET are a low vascular risk population unless a major thrombotic or hemorrhagic event has already occurred. Thus, cytoreductive therapy is seldom indicated. Adverse effects of INF-α such as flu-like syndrome, neuropsychiatric symptoms, and autoimmune phenomena can be particularly dangerous for children. Long-term leukemogenicity of hydroxyurea may be a special concern for children, although none of the pediatric patients with MPN treated with this agent have undergone malignant transformation to date.

Diagnostic criteria of MPNs in children are the same as in adults, but family screening is recommended to differentiate *JAK2*V617F-negative ET from rare familial disorders caused by mutations of *TPO* or *MPL* other than W515, particularly *MPL*S505N. In addition, in case of *JAK2*V617F-negative or exon 12–negative erythrocytosis with normal or reduced serum erythropoietin levels, a familial history should prompt search for rare mutations in erythropoietin receptor. Screening for inherited thrombophilia is recommended in patients with familial or personal history of thrombosis. Cytoreductive drugs should be used only as a last resort. There are insufficient data to recommend a specific agent, and the choice should be made on individual basis. Use of aspirin in children younger than 12 years of age should be considered with caution because of the risk of Reye's syndrome.

Hereditary predisposition. A recent large epidemiologic study found that the risk of any MPN is five- to seven-fold elevated among first-degree relatives of patients with MPN compared with control population, supporting the existence of susceptibility gene(s) predisposing to MPNs.[71] A strong association between the risk of developing a *JAK2*V617F-positive MPN and a germline haplotype (46/1 or GGCC; odds ratio, three- to four-fold), that includes the 3′ portion of the *JAK2* gene itself, has been recently described.[72-74] It has been calculated that this haplotype accounts for half the MPN risk attributable to inherited factors.

Heightened awareness of familial occurrence of MPNs should alert physicians to acquire as much relevant information as possible concerning relatives in any patient with novel, apparently sporadic MPN to exclude a previously unrecognized MPN kindred. There is no evidence of germline transmission of *JAK2*V617F mutation, and there is no indication to routinely genotype for *JAK2* mutations or *JAK2* 46/1 (GGCC) haplotype in relatives of individuals with MPNs in the absence of hematologic or clinical abnormalities.

Pregnancy. The presence of a Ph-negative classical MPN increases the risk of miscarriages and other complications of pregnancy, such as abruptio placentae, pre-eclampsia, and intrauterine growth retardation. Fetal loss in women with ET is approximately three to four times higher compared with the general population; risk factors include previous pregnancy complications and possibly the presence of *JAK2*V617F mutation. Venous thrombosis may occur, particularly in the postpartum period, and the risk is higher in patients with a history of vascular events.[75-77] Treatment options include no therapy, phlebotomy, aspirin, low molecular weight heparin, and IFN-α, but evidence for therapeutic recommendations is limited. Features consistent with high-risk MPN pregnancy and treatment recommendations are listed in Table 6.

Splanchnic vein thrombosis. Abdominal vein thrombosis, including extrahepatic portal vein occlusion, Budd-Chiari syndrome,

Table 6. Treatment Strategy for Philadelphia-Negative Classical Myeloproliferative Neoplasms in Pregnancy

Pregnancy Risk	Therapy
Low-risk pregnancy	Target hematocrit in polycythemia vera should be kept to $<$ 45% or midgestation-specific range, whichever is lower; low-dose aspirin; prophylactic dose low molecular weight heparin after delivery until 6 weeks postpartum
High-risk pregnancy*	As above, plus: 1. If previous major thrombosis or severe pregnancy complications: low molecular weight heparin throughout pregnancy (stop aspirin if bleeding complications) 2. If platelet count $>$ 1,500 $\times$ 10^9/L: consider interferon alfa 3. If previous major bleeding: avoid aspirin and consider interferon alfa to reduce thrombocytosis

*Features consistent with high-risk myeloproliferative neoplasm pregnancy include previous venous or arterial thrombosis (whether pregnant or not); previous hemorrhage attributed to myeloproliferative neoplasm (whether pregnant or not); previous pregnancy complication that may have been caused by myeloproliferative neoplasm, such as unexplained recurrent first-trimester loss (three unexplained first-trimester losses), intrauterine growth restriction (birth weight $<$ fifth percentile for gestation), intrauterine death or stillbirth (with no obvious other cause, evidence of placental dysfunction, and growth-restricted fetus), severe pre-eclampsia (necessitating preterm delivery $<$ 34 weeks), or development of any such complication in the index pregnancy; placental abruption; significant ante- or postpartum hemorrhage; and marked sustained increase in platelet count to greater than 1,500 $\times$ 10^9/L.

and mesenteric vein thrombosis, is frequently encountered in MPNs. Here, MPN may not be clinically obvious because concurrent hypersplenism, occult GI bleeding, or hemodilution can mask the blood count abnormalities. Diagnostic procedures include computed tomography scan, hepatic ultrasonography, angiography, and bone marrow biopsy. Of diagnostic help is the determination of *JAK2*V617F mutation, which is found in approximately 45% of patients with Budd-Chiari syndrome and 34% of patients with portal vein thromboses.[78] Intensive management including transjugular intrahepatic portosystemic shunt, angioplasty with or without stenting, surgical shunts, and liver transplantation should be considered in the most severe cases.

Treatment of splanchnic vein thrombosis includes low molecular weight heparin followed by long-life oral anticoagulation with international normalized ratio in the range 2.0 to 3.0. Joint management with liver team, follow-up of varices, and warning about pregnancy are recommended in this context. For patients with thrombocytosis, hydroxyurea should be used to restore counts to $\leq 400 \times 10^9$/L as soon as possible.

Pruritus. Intractable pruritus, typically aquagenic, can represent a disabling condition in some patients with MPN, particularly PV. The pathogenesis is unknown, although *JAK2*V617F-induced constitutive activation and agonist hypersensitivity in basophils of these patients have been recently demonstrated.[79]

Antihistamines, such as cyproheptadine 4 to 16 mg/d, may be of benefit. If unsuccessful, IFN-α 3.0×10^6 U subcutaneously three times a week or pegylated IFN 0.5 to 1.0 μg/kg/wk is reported to be effective in the majority of patients. Other treatment options include the selective serotonin uptake inhibitor paroxetine (20 mg/d) and photochemotherapy using psoralen and ultraviolet A light.

Pulmonary hypertension. Ph-negative classical MPNs associated with pulmonary hypertension (PH) are included in the group 5 category, corresponding to PH for which the etiology is unclear and/or multifactorial.[80] The following two major distinct clinical forms of PH have been described in patients with MPNs: chronic thromboembolic PH and precapillary PH mimicking pulmonary idiopathic arterial hypertension. Diagnosis of PH should be established as recommended by expert guidelines,[81] and a technetium-99m sulfur colloid scintigraphy should be specifically used for documenting precapillary PH as a result of diffuse occult pulmonary EMH. Pulmonary endarterectomy is the treatment of choice in patients with chronic thromboembolic PH. In PH that is inaccessible to surgery, medical therapy including diuretics, anticoagulants, and antihypertensive drugs such as sildenafil should be considered. In patients with high thrombotic risk, cytoreductive therapy with hydroxyurea is recommended. Case reports suggest that in patients with MPNs and PH with EMH, a treatment trial with whole-lung, low-dose, external-beam radiotherapy may be a useful palliation.[82]

The final examination in patients with PH associated with Ph-negative classical MPNs is right heart catheterization, which is useful to differentiate different types of PH. In the case of idiopathic PH of PMF, pulmonary bone marrow scan is recommended to document pulmonary EMH. Current treatment of choice is radiotherapy for patients in whom the technetium scan shows EMH involvement.

DISCUSSION

This document is mainly based on the experience and knowledge of experts in the field coordinated by the methods of group decision. The rationale of current therapy for Ph-negative classical MPNs is to prevent the risk of thrombosis or hemorrhage in PV and ET and to address the presenting major clinical issues in PMF. Invasive therapies, such as splenectomy and alloSCT in PMF, are used in the setting of failed drug therapy and for patients with advanced disease.

Many research issues are open in Ph-negative classical MPNs. The difficulties in dissecting the continuum of clinical phenotypes are reflected in the recently revised WHO classification,[5] which arranges hematologic, morphologic, and molecular parameters to separate the three clinical disorders. Although this classification has endorsed the concept of prefibrotic early stage of PMF to capture the stepwise evolution of the diseases, the boundary between so-called true ET and prefibrotic PMF is uncertain, being currently based on morphologic features, the reproducibility of which has been questioned.[7] The definition of this issue can have conceptual, clinical, and prognostic relevance.

Researchers in the field agree that new prognostic parameters could help in planning early treatment for patients with Ph-negative classical MPNs who now remain untreated. Leukocytosis and *JAK2*V617F allele burden have been hypothesized to represent disease-associated surrogate markers of increased thrombotic risk in ET and PV[83-87] and merit validation in controlled trials.

Several investigational drugs are currently being evaluated in symptomatic patients with Ph-negative classical MPNs. In a recent phase II randomized study, oral pomalidomide (a second-generation thalidomide analog) alone or with a tapering dose of prednisone resulted in anemia response rates of up to 36%. At the effective dose level of 0.5 mg/d, the drug did not cause either neuropathy or severe myelosuppression.[88] Its role in the treatment of anemia should be tested in a controlled manner. Verstovsek et al[89] reported the results of a phase I/II trial first using an oral JAK1/JAK2 inhibitor, INCB018424, in patients with PMF. The majority of the 153 patients with advanced disease who received INCB018424 experienced an improvement in constitutional symptoms, pruritus, and overall performance status. The enlarged spleen at least halved in 50% of the patients at the optimal drug dose, producing durable improvement in abdominal discomfort, pain, and weight loss. Thus, results of this trial point to JAK1/JAK2 inhibition as a novel therapeutic avenue for producing unforeseen clinical benefits in myelofibrosis. Two ongoing phase III studies, with either placebo (Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment [COMFORT] -1; NCT00952289) or best-available therapy control arms (COMFORT-2; NCT00934544), will hopefully raise our enthusiasm. Furthermore, the drug could have considerable efficacy in advanced PV or ET refractory to hydroxyurea, according to a preliminary report of a phase II trial (NCT00726232).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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