

NCCN Guidelines® Insights

Myeloproliferative Neoplasms, Version 2.2018

Featured Updates to the NCCN Guidelines

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Abstract

Myeloproliferative neoplasms (MPNs) are a group of heterogeneous disorders of the hematopoietic system that include myelofibrosis (MF), polycythemia vera (PV), and essential thrombocythemia (ET). PV and ET are characterized by significant thrombohemorrhagic complications and a high risk of transformation to MF and acute myeloid leukemia. The diagnosis and management of PV and ET has evolved since the identification of mutations implicated in their pathogenesis. These NCCN Guideline Insights discuss the recommendations outlined in the NCCN Guidelines for the risk stratification, treatment, and special considerations for the management of PV and ET.

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*Provided content development and/or authorship assistance.

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Myeloproliferative Neoplasms, Version 2.2018

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Release date: October 10, 2017; Expiration date: October 10, 2018

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Myeloproliferative Neoplasms
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Myeloproliferative Neoplasms

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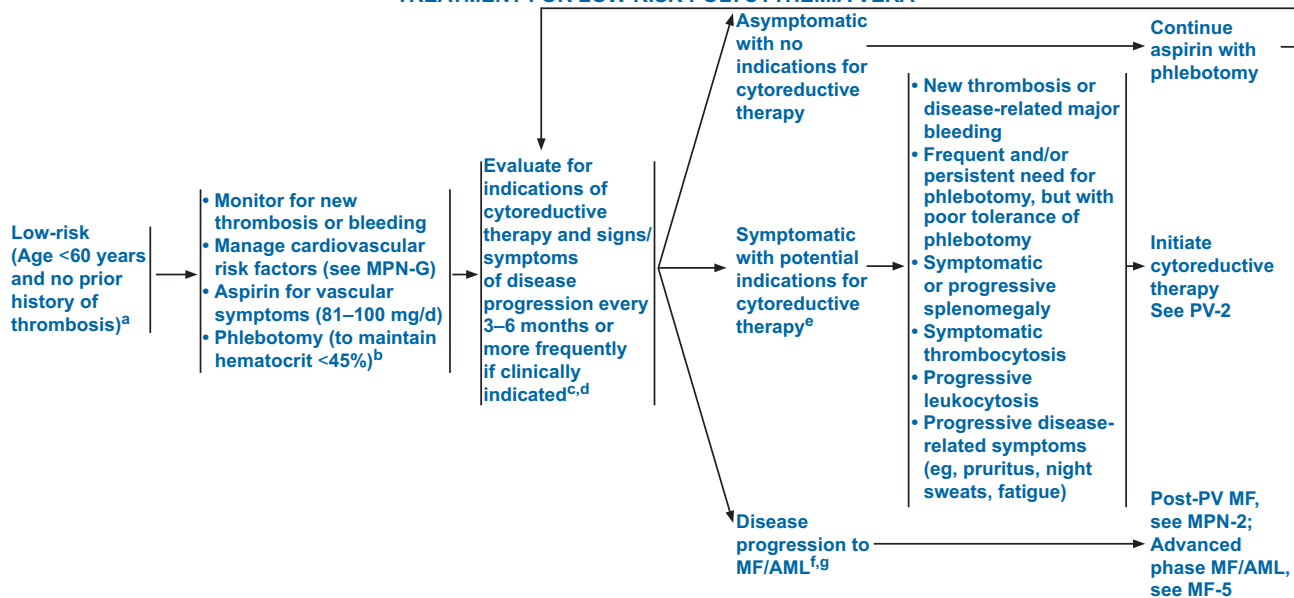
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Myeloproliferative Neoplasms, Version 2.2018

TREATMENT FOR LOW-RISK POLYCYTHEMIA VERA



^aCytoreductive therapy is not recommended as initial treatment.

^bHematocrit <45% is based on the data from CYTOPV Study (Marchioli R et al. *N Engl J Med* 2013;368(1):22-33). There may be situations in which a lower hematocrit cutoff may be appropriate and it should be individualized, eg, 42% for female patients and/or progressive symptoms.

^cSee Assessment of Symptom Burden (MPN-C 3 of 3).

^dBone marrow aspirate and biopsy should be performed to rule out disease

progression to myelofibrosis prior to the initiation of cytoreductive therapy.

^eBarbui T, Barosi G, Birgegard G, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol* 2011;29:761-770.

^fDiagnostic criteria for Post-ET or Post-PV MF. See (MPN-E).

^gThe WHO classification defines acute leukemia as $\geq 20\%$ blasts in the marrow or blood. A diagnosis of AML may be made with less than 20% in patients with recurrent cytogenetic abnormalities [eg, t(15;17), t(8;21), t(16;16), inv(16)].

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PV-1

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

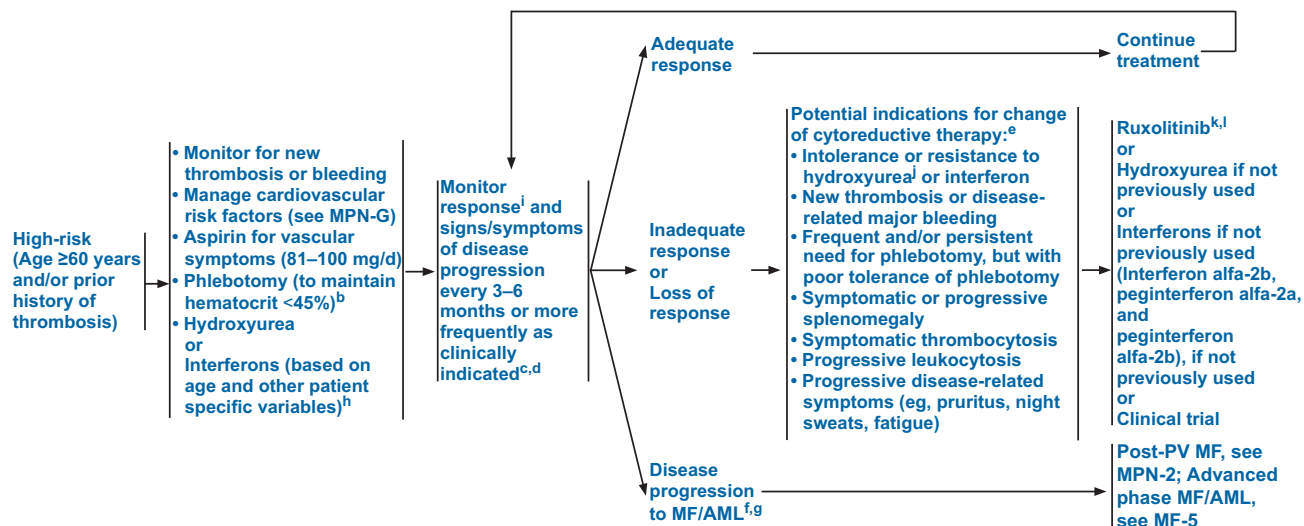
Overview

Myelofibrosis (MF), polycythemia vera (PV), and essential thrombocythemia (ET) are collectively known as Philadelphia chromosome–negative myeloproliferative neoplasms (MPNs). In the United States, incidence rates are highest for PV and ET.^{1,2} The diagnosis and management of patients with MPN has evolved since the identification of “driver” mutations (*JAK2*, *CALR*, and *MPL* mutations), and the development of targeted therapies has resulted in significant improvements in disease-related symptoms and quality of life.^{3,4} However, certain aspects of clinical management regarding the diagnosis, assessment of symptom burden, and selection of appropriate symptom-directed therapies continue to present challenges for hematologists and oncologists.⁵

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for MPNs provide recommendations for the diagnostic workup, risk stratification, treatment, and supportive care strategies for disease management in adults. These NCCN Guide-

Myeloproliferative Neoplasms, Version 2.2018

TREATMENT FOR HIGH-RISK POLYCYTHEMIA VERA



^bHematocrit $< 45\%$ is based on the data from CYTO-PV Study (Marchioli R et al. N Engl J Med. 2013;368(1):22-33). There may be situations in which a lower hematocrit cutoff may be appropriate and it should be individualized, e.g. 42% for female patients and/or progressive symptoms.

^cSee Assessment of Symptom Burden (MPN-C 3 of 3).

^dBone marrow aspirate and biopsy should be performed to rule out disease progression to myelofibrosis prior to the initiation of cytoreductive therapy.

^eBarbui T, Barosi G, Birgegard G, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. J Clin Oncol 2011;29:761-770.

^fDiagnostic criteria for Post-ET or Post-PV MF. See (MPN-E).

^gThe WHO classification defines acute leukemia as $\geq 20\%$ blasts in the marrow or blood. A diagnosis of AML may be made with less than 20% in patients with recurrent cytogenetic abnormalities [eg,

t(15;17), t(8;21), t(16;16), inv(16)].

^hInterferon alfa-2b, peginterferon alfa-2a, or peginterferon alfa-2b could be considered for younger patients or in pregnant patients in need of cytoreductive therapy or in those in need of cytoreductive therapy that defer hydroxyurea.

ⁱSee 2013 IWG-MRT and ELN Response Criteria for (PV-A). These response criteria were developed mainly for use in clinical trials. Clinical benefit may not reach the threshold of the IWG-MRT Response Criteria. Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician.

^jDefinition of intolerance/resistance to hydroxyurea (MPN-H).

^kSee Special Considerations for the Use of Ruxolitinib (MPN-F).

^lRuxolitinib is FDA approved for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea.

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PV-2

lines Insights discuss the recommendations outlined in the NCCN Guidelines for the risk stratification, treatment, and special considerations for the management of PV and ET.

Risk Stratification

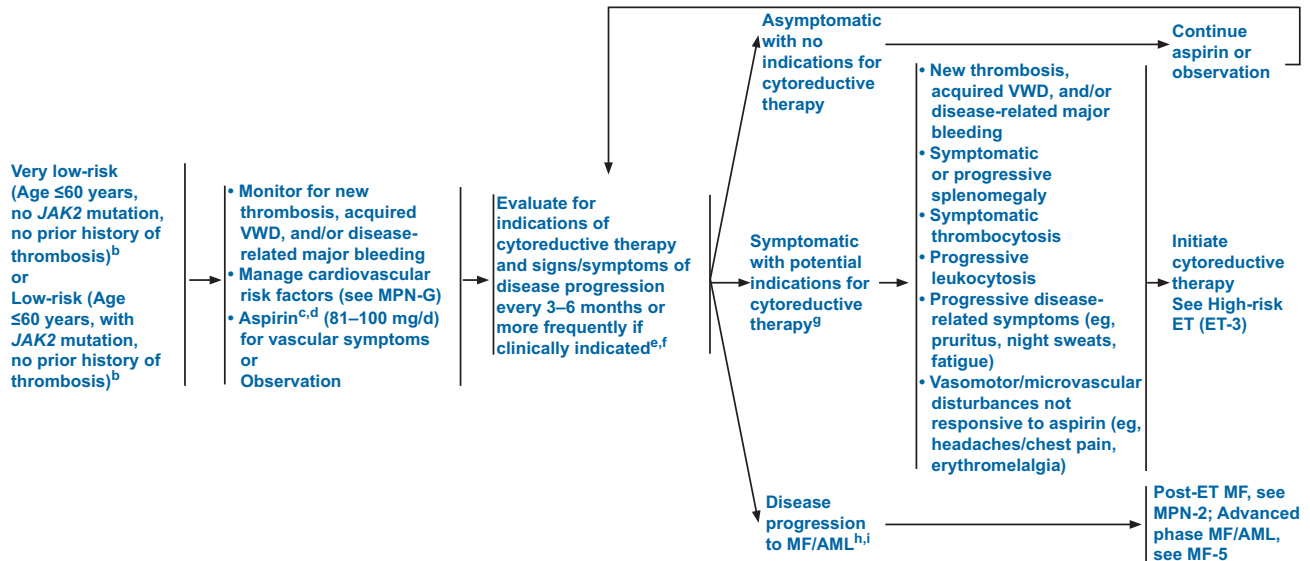
Retrospective studies have shown that leukocytosis at diagnosis is associated with a higher risk of thrombosis and major hemorrhage in patients with PV and ET.^{6–10} Data from some studies suggest that the prognostic significance of leukocytosis for the risk of recurrent thrombosis may be significant only in patients aged < 60 years,^{11,12} and other studies have reported that leukocytosis at diagnosis is not associated with the risk of subsequent thrombosis.¹³ Thrombocytosis (platelet count $> 1,000 \times 10^9/L$) has been associated with an immediate risk of major hemorrhage but not with the risk of thrombosis in patients with ET.¹⁰ In fact, some studies have reported that elevated platelet counts at diagnosis ($> 1,000 \times$

$10^9/L$) is associated with a significantly lower rate of thrombosis, and this association was significant even in patients with *JAK2*-mutated ET.^{8,9} The potential benefit of initiation of cytoreductive therapy based on elevated blood counts (leukocytosis or thrombocytosis) at diagnosis has not been evaluated in prospective studies.

Polycythemia Vera

Advanced age (ie, > 60 years) and history of thrombosis are the most consistent risk factors associated with risk of thrombosis.¹⁴ In a cohort of 1,638 patients with PV screened for inclusion in the ECLAP trial, age > 65 years and a previous history of thrombosis were the 2 most important prognostic factors associated with an increasing risk of cardiovascular events, resulting in the identification of 2 different risk groups: low-risk (age < 60 years and no prior history of thrombosis) and high-risk (age > 60 years and/or prior history of thrombosis).

Myeloproliferative Neoplasms, Version 2.2018

TREATMENT FOR VERY LOW-RISK AND LOW-RISK ESSENTIAL THROMBOCYTHEMIA^a

^aThe revised International Prognostic Score of Thrombosis for ET (IPSET-Thrombosis) is preferred for the risk stratification of ET (Haider M, Gangat N, Lasho T, et al. *Am J Hematol* 2016;91:390-394. Barbui T, Vannucchi AM, Buxhofer-Ausch V, et al. *Blood Cancer J* 2015;5:e369).

^bCytoreductive therapy is not recommended as initial treatment.

^cAspirin should be used with caution in patients with acquired VWD. Higher-dose aspirin may be appropriate in selected patients as clinically indicated. The risk and benefits of higher-dose aspirin must be weighed based on the presence of vasomotor symptoms versus the risk of bleeding.

^dReport from a recent retrospective analysis (Alvarez-Larran et al. *Haematologica* 2016;101(8):926-31) suggests that the use of low-dose aspirin may not be beneficial in patients with low-risk *CALR*-mutated ET. However, at the present time, there is not enough evidence to recommend withholding aspirin for this group of patients.

^eSee Assessment of Symptom Burden (MPN-C 3 of 3).

^fBone marrow aspirate and biopsy should be performed to rule out disease progression to myelofibrosis prior to the initiation of cytoreductive therapy.

^gBarbui T, Barosi G, Birgegard G, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol* 2011;29:761-770.

^hDiagnostic criteria for Post-ET or Post-PV MF. See (MPN-E).

ⁱThe WHO classification defines acute leukemia as ≥20% blasts in the marrow or blood. A diagnosis of AML may be made with less than 20% in patients with recurrent cytogenetic abnormalities [eg, t(15;17), t(8;21), t(16;16), inv(16)].

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ET-1

A prognostic model incorporating leukocytosis at the time of diagnosis in addition to age has also been developed to stratify patients into 3 risk groups with different survival outcomes.¹⁵ However, this model has not been validated in prospective clinical trials.

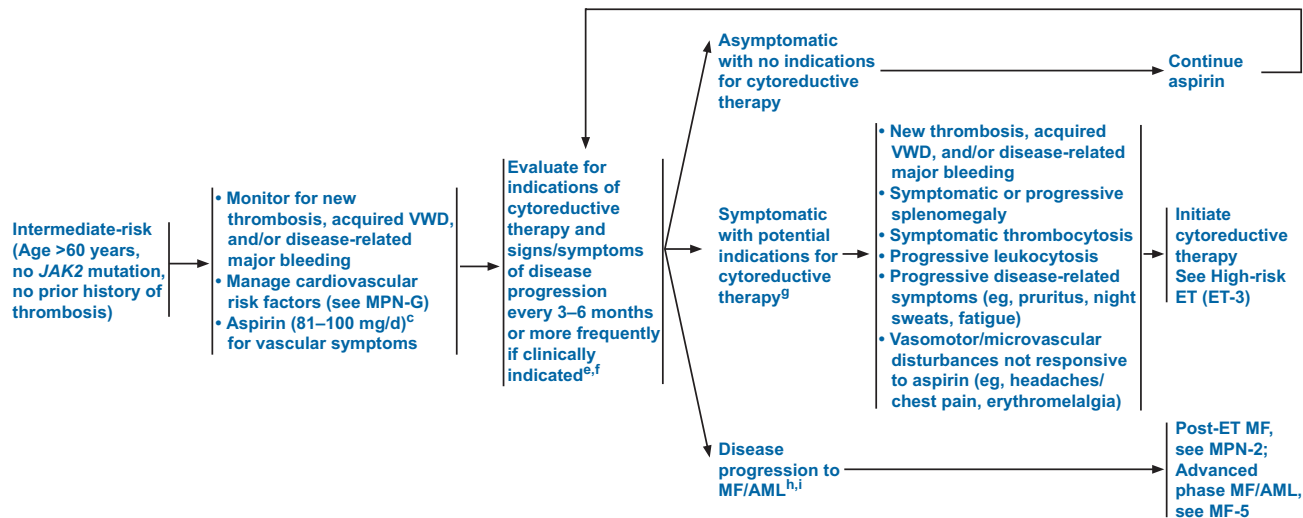
Essential Thrombocythemia

In an analysis of 867 patients with ET, age ≥60 years, leukocyte count ≥11 × 10⁹/L, and prior thrombosis were significantly associated with inferior survival.¹⁶ Based on these findings, the International Prognostic Score for ET (IPSET) was developed to stratify patients at time of diagnosis into 3 risk categories: low risk, intermediate risk, and high risk. In a subsequent analysis of 891 patients with ET, age >60 years, history of thrombosis, cardiovascular risk factors, and presence of *JAK2* V617F mutation retained their prognostic significance regarding thrombosis risk in multivariable analysis.¹⁷ Thus, a modified prognostic model (IPSET-Thrombosis), including cardiovascu-

lar risk factors and presence of *JAK2* V617F mutation status as additional risk factors, was developed to stratify patients into the same 3 groups with significantly different thrombosis-free survival: 87% after 15 years of follow-up for low-risk patients and 50% after 7-year follow-up for high-risk patients.¹⁷ In the intermediate-risk group, the thrombosis-free survival rate for the first 10 years was closer to that of the low-risk group and then progressively reached the high-risk survival rate in the subsequent 5 years.

Further analysis of IPSET-Thrombosis showed that among the low-risk patients, the risk of thrombosis was significantly lower in patients with *JAK2*-negative/unmutated ET in the absence of cardiovascular risk factors compared with those with *JAK2*-unmutated ET in the presence of those risk factors (0.44% vs 1.05%, respectively).¹⁸ The risk of thrombosis in the presence of *JAK2* mutation without cardiovascular risk factors and in the presence of both *JAK2* mutation and cardiovascular risk factors was 1.59% and 2.57%, respectively. These

Myeloproliferative Neoplasms, Version 2.2018

TREATMENT FOR INTERMEDIATE-RISK ESSENTIAL THROMBOCYTHEMIA^a

^aThe revised International Prognostic Score of Thrombosis for ET (IPSET-Thrombosis) is preferred for the risk stratification of ET (Haider M, Gangat N, Lasho T, et al. *Am J Hematol* 2016;91:390-394. Barbui T, Vannucchi AM, Buxhofer-Ausch V, et al. *Blood Cancer J* 2015;5:e369).

^cAspirin should be used with caution in patients with acquired VWD. Higher-dose aspirin may be appropriate in selected patients as clinically indicated. The risk and benefits of higher-dose aspirin must be weighed based on the presence of vasomotor symptoms versus the risk of bleeding.

^eSee Assessment of Symptom Burden (MPN-C 3 of 3).

^fBone marrow aspirate and biopsy should be performed to rule out disease progression to myelofibrosis prior to the initiation of cytoreductive therapy.

^gBarbui T, Barosi G, Birgegard G, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol* 2011;29:761-770.

^hDiagnostic criteria for Post-ET or Post-PV MF. See (MPN-E).

ⁱThe WHO classification defines acute leukemia as $\geq 20\%$ blasts in the marrow or blood. A diagnosis of AML may be made with less than 20% in patients with recurrent cytogenetic abnormalities [eg, t(15;17), t(8;21), t(16;16), inv(16)].

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ET-2

findings led to the development of the revised IPSET-Thrombosis that stratifies patients into 4 different risk groups: very low risk (age ≤ 60 years, no prior history of thrombosis, and no *JAK2* mutation), low risk (age ≤ 60 years, no prior history of thrombosis, and *JAK2* mutation), intermediate risk (age > 60 years, no prior history of thrombosis, and no *JAK2* mutation), and high risk (prior history of thrombosis and/or age > 60 years with *JAK2* mutation). The revised IPSET-Thrombosis has also been validated in an independent cohort of 585 patients.^{18,19} *CALR* mutation status, however, did not have a significant impact on the IPSET-Thrombosis prognostic score for predicting the risk of thrombosis.²⁰

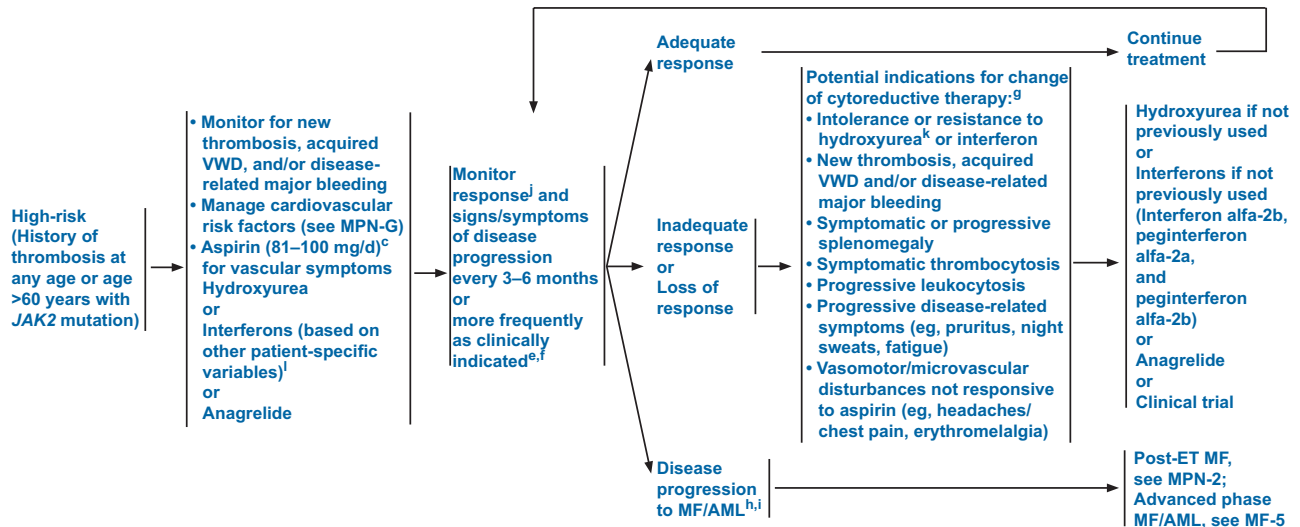
Treatment Options

Antiplatelet Therapy

The safety and efficacy of low-dose aspirin for the prevention of thrombotic complications in PV was established in a multicenter trial of patients with no

contraindication to aspirin therapy and no history of a thrombotic event (ECLAP study; 518 patients).²¹ Use of aspirin resulted in a significant reduction (60%) of combined risk of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes ($P=.03$), and the incidence of major bleeding was not significantly increased. The role of maintaining the hematocrit level of $< 45\%$ in patients receiving treatment was established in the CYTO-PV study.²² In this randomized study of 365 patients with PV treated with phlebotomy and/or hydroxyurea, the hematocrit target of $< 45\%$ resulted in a significantly lower rate of cardiovascular death and major thrombotic events (primary end point) than a hematocrit target of 45% to 50%.²² After a median follow-up of 31 months, death from cardiovascular causes or major thrombotic events was recorded in 2.7% of patients (5 of 182) with a hematocrit level of $< 45\%$ compared with 9.8% (18 of 183) of those with a hematocrit level of 45% to 50% ($P=.007$).

Myeloproliferative Neoplasms, Version 2.2018

TREATMENT FOR HIGH-RISK ESSENTIAL THROMBOCYTHEMIA^a

^aThe revised International Prognostic Score of Thrombosis for ET (IPSET-Thrombosis) is preferred for the risk stratification of ET (Haider M, Gangat N, Lasho T, et al. *Am J Hematol* 2016;91:390-394. Barbui T, Vannucchi AM, Buxhofer-Ausch V, et al. *Blood Cancer J* 2015;5:e369).

^cAspirin should be used with caution in patients with acquired VWD. Higher-dose aspirin may be appropriate in selected patients as clinically indicated. The risk and benefits of higher-dose aspirin must be weighed based on the presence of vasomotor symptoms versus the risk of bleeding.

^dSee Assessment of Symptom Burden (MPN-C 3 of 3).

^eBone marrow aspirate and biopsy should be performed to rule out disease progression to myelofibrosis prior to the initiation of cyto-reductive therapy.

^fBarbui T, Barosi G, Birgegard G, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol*

2011;29:761-770.

^hDiagnostic criteria for Post-ET or Post-PV MF See (MPN-E).

ⁱThe WHO classification defines acute leukemia as $\geq 20\%$ blasts in the marrow or blood. A diagnosis of AML may be made with less than 20% in patients with recurrent cytogenetic abnormalities [eg, t(15;17), t(8;21), t(16;16), inv(16)].

^jSee 2013 IWG-MRT and ELN Response Criteria for ET (ET-A).

^kDefinition of intolerance/resistance to hydroxyurea (MPN-H).

^lInterferon alfa-2b, peginterferon alfa-2a, or peginterferon alfa-2b could be considered for younger patients or in pregnant patients in need of cyto-reductive therapy or in those in need of cyto-reductive therapy that defer hydroxyurea.

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ET-3

Cyto-reductive Therapy

Hydroxyurea,²²⁻²⁴ interferon alfa,²⁵⁻²⁷ and peginterferon alfa²⁸⁻³⁰ have been shown to be effective for the prevention of thrombotic complications in patients with PV.

In a nonrandomized study of 51 patients with PV, the use of hydroxyurea along with phlebotomy as needed significantly reduced the risk of thrombosis compared with a historical control of patients treated with phlebotomy alone.²³ Long-term follow-up of this study (after a median follow-up of 8.6 years) showed that prolonged use of hydroxyurea was associated with leukemic transformations (5.9% vs 1.5% for phlebotomy).³¹ However, an analysis from the ECLAP study identified older age and the use of other alkylating agents (eg, P32, busulphan, pipobroman), but not hydroxyurea alone, as independent risk factors for leukemic transformation.³² In the randomized trial that compared hydroxyurea and pipobroman as first-line therapy in 285 patients with PV aged <65 years, at a median

follow-up of 15 years the cumulative incidence of leukemic transformation was significantly higher with pipobroman than with hydroxyurea (34.0% and 16.5%, respectively).²⁴

In a randomized, prospective, observational study that included 136 patients with *JAK2*-mutated PV, interferon alfa-2b resulted in greater molecular response (54.7% vs 19.4%; $P < .01$) and 5-year progression-free survival (PFS) rates (66.3% vs 46.7%; $P < .01$) than hydroxyurea.²⁷ A more recent phase II trial that included 43 patients with PV, peginterferon alfa-2a resulted in a complete hematologic response (CHR) rate of 76% and a complete molecular response (CMR) rate of 18% after a median follow-up of 42 months.³⁰ The presence of *TET2*, *ASXL1*, *EZH2*, *DNMT3A*, and *IDH1/2* mutations was associated with failure to achieve CMR.

Hydroxyurea,³³⁻³⁵ interferon alfa,^{25,27,36,37} and peginterferon alfa,^{28,30,38} and possibly anagrelide,^{34,35} have been shown to be effective for the prevention

Myeloproliferative Neoplasms, Version 2.2018

SPECIAL CONSIDERATIONS IN THE TREATMENT OF POLYCYTHEMIA VERA (PV) AND ESSENTIAL THROMBOCYTHEMIA (ET)

Management of Vascular Events**• Thrombosis**

- ▶ The use of clinically appropriate anticoagulant therapy (eg, low-molecular-weight heparin [LMWH], direct oral anticoagulant, warfarin) is recommended for patients with active thrombosis. The initial use of anticoagulant therapy for the prevention and treatment of thrombosis should be based on the current American College of Chest Physicians (ACCP) Guidelines.¹
- ▶ There are no data to guide the selection or appropriate duration of anticoagulation with or without antiplatelet therapy in patients with PV or ET. The duration of anticoagulant therapy is dependent on the severity of the thrombotic event (eg, abdominal vein thrombosis vs. deep vein thrombosis), degree of disease control, and assessment of likelihood of recurrence after cessation of anticoagulant therapy.
- ▶ Assess the need for cytoreductive therapy (if not done before) and initiate cytoreductive therapy (to maintain hematocrit <45% in patients with PV) if necessary. In the presence of inadequate response, consider intensification of therapy or switch to an alternate agent. The value of cytoreduction in reducing future vascular events has not been studied in a prospective, randomized, controlled trial.
- ▶ Plateletpheresis may be indicated in patients with ET presenting with acute life-threatening thrombosis or severe bleeding.

• Bleeding

- ▶ Rule out other potential causes and treat coexisting causes as necessary.
- ▶ Aspirin should be withheld until bleeding is under control. Consider the use of appropriate cytoreductive therapy to normalize platelet counts.
- ▶ Coagulation tests to evaluate for acquired VWD and/or other coagulopathies are recommended for patients undergoing high-risk surgical procedures and those with elevated platelet count and/or splenomegaly or unexplained bleeding (see MPN-1).
- ▶ In unanticipated gastrointestinal (GI) bleeding, particularly in the setting of splenomegaly, portal hypertension, and gastric varices, special consultation (for endoscopic evaluation) with a hepatologist or a GI specialist is recommended.

Surgery

- Multi-disciplinary management with surgical and perioperative medical teams (eg, review of bleeding and thrombosis history; medication list) is recommended.
- Emergency surgery should be performed as necessary with close postoperative surveillance for the symptoms of arterial or venous thrombosis and bleeding.
- Patients with PV and ET are at higher risk for bleeding despite optimal management. The thrombotic and bleeding risk of the surgical procedure (eg, orthopedic and cardiovascular surgery) should be strongly considered prior to elective surgery.
- Thrombosis and bleeding risk should be well controlled (normalization or near-normalization CBC without causing prohibitive cytopenias) prior to performing elective surgery (particularly for orthopedic surgeries or any surgical procedures associated with prolonged immobilization) with the use of appropriate anticoagulant prophylaxis and cytoreductive therapy. If surgery is associated with a high risk for venous thromboembolism (eg, cancer surgery, splenectomy, orthopedic and cardiovascular surgery), extended prophylaxis with LMWH should be considered. Prophylaxis with aspirin may be considered following vascular surgery.

See references on MPN-G 2 of 2

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MPN-G
1 OF 2

of venous thrombotic complications in patients with high-risk ET.

In a randomized study of 809 patients with high-risk ET, hydroxyurea plus low-dose aspirin was superior to anagrelide plus low-dose aspirin. After a median follow-up of 39 months, long-term control of platelet counts was equivalent in both groups and anagrelide plus aspirin was better in the prevention of venous thrombosis ($P=.006$).³⁴ However, the incidences of arterial thrombosis ($P=.004$), serious hemorrhage ($P=.008$), and transformation to MF ($P=.01$) were higher with anagrelide plus aspirin. In addition, the treatment discontinuation rate was also significantly higher with anagrelide plus aspirin. The diagnosis of ET in this trial was based on the Polycythemia Vera Study Group criteria. A more recent phase III randomized study showed that anagrelide was not inferior to hydroxyurea as first-line therapy for the prevention of thrombotic complications in patients with high-risk ET diagnosed according to the WHO criteria.³⁵ In this study, 259 patients

were randomized to either hydroxyurea ($n=122$) or anagrelide ($n=137$). After a total observation time of 730 patient-years, no significant difference was seen between anagrelide and hydroxyurea in the incidences of arterial or venous thrombotic events, severe bleeding, or rates of discontinuation.

Interferon alfa-2b has been shown to be effective for patients with *JAK2*-mutated and *CALR*-mutated ET.^{27,37} In a randomized, prospective, observational study that included 123 patients with ET, the 5-year PFS rate was 75.9% for those with *JAK2*-mutated ET compared with 47.6% for those without *JAK2* mutation ($P<.05$).²⁷ In another study of 31 patients, interferon alfa induced high rates of hematologic and molecular responses in *CALR*-mutated ET. However, the presence of additional mutations (*TET2*, *ASXL1*, *IDH2*, and *TP53*) was associated with poorer molecular response.³⁷ In a phase II trial that included 40 patients with ET, peginterferon alfa-2a induced a CHR rate of 77% and a CMR rate of 17% after a median follow-up of 42

Myeloproliferative Neoplasms, Version 2.2018

SPECIAL CONSIDERATIONS IN THE TREATMENT OF POLYCYTHEMIA VERA (PV) AND ESSENTIAL THROMBOCYTHEMIA (ET)

Surgery (continued)

- In patients with PV, hematocrit should be controlled for 3 months before elective surgery (normalization or near-normalization of CBC). Additional phlebotomy may also be necessary to maintain hematocrit <45% prior to performing elective surgery.
- Aspirin should be discontinued one week prior to surgical procedure and restarted 24 hours after surgery or when considered acceptable depending on the bleeding risk.
- Anticoagulant therapy should be withheld (based on the half-life/type of agent) prior to surgery and restarted after surgery when considered acceptable depending on the bleeding risk.
- Cytoreductive therapy could be continued throughout the perioperative period, unless there are unique contraindications expressed by the surgical team.

Pregnancy^{2,3}

- Pre-conception meeting and evaluation by high-risk obstetrician should be considered.
- Low-risk pregnancy: Low-dose aspirin (50–100 mg/d) is recommended throughout pregnancy (to maintain hematocrit <45% in patients with PV) and for six weeks postpartum. Aspirin could be stopped and LMWH could be considered about two weeks before labor is expected.
- High-risk pregnancy: ^{3,4} Consider the use of prophylactic LMWH (subcutaneously) with low-dose aspirin throughout pregnancy (to maintain hematocrit <45% in patients with PV) and for six weeks postpartum.
- Consider stopping low-dose aspirin 1 to 2 weeks prior to delivery. LMWH should be stopped 12 hours to 24 hours before labor is expected. In patients taking LMWH, consultation with high-risk obstetrician and obstetric anesthesiologist is recommended regarding the optimal timing of discontinuation in preparation for an epidural prior to delivery.
- In patients without prior bleeding or thrombotic complications, consider the use of LMWH instead of aspirin in the last two weeks of pregnancy (to maintain hematocrit <45% in patients with PV) and continued until six weeks post partum. The duration of LMWH post partum could be extended in high-risk pregnancy or in women who have undergone C-section.
- If cytoreductive therapy is needed, interferons (interferon alfa-2b, peginterferon alfa-2a, and peginterferon alfa-2b) should be considered. Patients on hydroxyurea prior to pregnancy should be switched to interferons.
- Hydroxyurea is excreted in breastmilk and should be avoided in women who are breast feeding.

¹Guyatt GH, Akl EA, Crowther M, et al. Executive summary: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141(2 Suppl):7S-47S. Updated articles are included in this website: http://journal.publications.chestnet.org/SS/Antithrombotic_Guideline.aspx. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest* 2016;149:315-352.

²Barbui T, Barosi G, Birgergard G, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol* 2011;29:761-770.

³Griesshammer M, Struve S, Barbui T. Management of Philadelphia negative

chronic myeloproliferative disorders in pregnancy. *Blood Rev* 2008;22:235-245.

⁴If any of the following factors are present then the pregnancy should be considered at high risk:

- Previous microcirculatory disturbances or presence of two or more hereditary thrombophilic factors.
- Severe complications in a previous pregnancy (≥ 3 first trimester losses or ≥ 1 second or third trimester pregnancy loss, birth weight <5th percentile for gestation, intrauterine death or stillbirth, stillbirth and pre-eclampsia necessitating preterm delivery <37 weeks, or development of any such complication in the index pregnancy).
- Age >35 years
- Platelet count >1000 x 10⁹/l.

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MPN-G
2 OF 2

months.³⁰ The presence of *TET2*, *ASXL1*, *EZH2*, *DNMT3A*, and *IDH1/2* mutations was associated with failure to achieve CMR.

Ongoing randomized clinical trials are evaluating hydroxyurea versus peginterferon alfa-2a or ropeginterferon alfa-2b as initial treatment for high-risk PV and ET.^{39,40}

Ruxolitinib

In a phase III randomized trial (RESPONSE), 222 phlebotomy-dependent patients with PV and splenomegaly with an inadequate response to or were intolerant of hydroxyurea were randomized to receive ruxolitinib (110 patients) or best available therapy (112 patients).⁴¹ The primary end point was hematocrit control without phlebotomy and at least a 35% reduction in spleen volume (as assessed by imaging) by 32 weeks. Patients randomized to best available therapy were eligible to crossover to ruxolitinib after 32 weeks if the primary end point was not met or if there were signs of disease progression.

After 32 weeks, hematocrit control was achieved in 60% of patients treated with ruxolitinib compared with 20% of those receiving best available therapy. A reduction in spleen volume ($\geq 35\%$), CHR, and at least a 50% reduction in symptom burden were achieved in 38%, 24%, and 49% of patients, respectively, in the ruxolitinib group and in 1%, 9%, and 5% of patients, respectively, in the best available therapy group. The incidences of grade 3/4 anemia and herpes zoster infection were higher among patients treated with ruxolitinib (occurring in 2% and 6%, respectively, vs 0% treated with best available therapy). The 80-week follow-up data confirmed the long-term efficacy of ruxolitinib, and the probability of maintaining complete hematologic remission for ≥ 80 weeks was 69%.⁴² Ruxolitinib was also associated with a lower rate of thromboembolic events (1.8% and 4.1%, respectively, for patients originally randomized to ruxolitinib and for those receiving ruxolitinib after crossover vs 8.2% for best available therapy).⁴²

Myeloproliferative Neoplasms, Version 2.2018

DEFINITION OF RESISTANCE/INTOLERANCE TO HYDROXYUREA¹

Myeloproliferative Neoplasm	Definition of Resistance/Intolerance to Hydroxyurea
Polycythemia vera	<ol style="list-style-type: none"> 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 x 10⁹/L AND WBC count >10 x 10⁹/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 x 10⁹/L OR platelet count <100 x 10⁹/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	<ol style="list-style-type: none"> 1. Platelet count >600 x 10⁹/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 x 10⁹/L and WBC count <2.5 x 10⁹/L at any dose of hydroxyurea, OR 3. Platelet count >400 x 10⁹/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
<p>*Organ extending by >10 cm from the costal margin. †Complete response is defined as hematocrit less than 45% without phlebotomy, platelet count ≤400 x 10⁹/L, WBC count ≤10 x 10⁹/L, and no disease-related symptoms. Partial response is defined as hematocrit less than 45% without phlebotomy or response in three or more of other criteria.</p>	

¹Barbui T, Barosi G, Birgegard G, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol* 2011;29(6):761-770.

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MPN-H

Treatment Recommendations Based on Risk Stratification

Treatment options should be individualized based on age and history of thrombosis for patients with PV.¹⁴ The revised IPSET-Thrombosis is preferred for risk stratification of patients with ET.^{18,19} Referral to specialized centers with expertise in the management of MPNs is strongly recommended for all patients diagnosed with PV or ET.

Polycythemia Vera

Low-Risk Disease: Aspirin (81–100 mg/d) and phlebotomy (to maintain a hematocrit level of <45%) are recommended for all patients with low-risk PV (see PV-1; page 1195).^{21,22} Cytoreductive therapy is not recommended as initial treatment. In the CYTO-PV study, the hematocrit target was the same in both men and women. No thrombotic event was observed in the 66 women with a hematocrit level of <45% compared with 9 events reported in the 72 women

with a hematocrit target of 45% to 50%.²² However, normal hematocrit levels vary in men (42%–54%) and women (38%–46%). Although the target hematocrit level of <45% may be adequate for most patients, there may be situations in which a lower hematocrit cutoff may be appropriate, and therefore it should be individualized (eg, 42% for women and/or for patients with progressive or residual vascular symptoms).

High-Risk Disease: In addition to aspirin and phlebotomy, cytoreductive therapy is also used to reduce the risk of thrombotic complications for patients with high-risk PV (see PV-2; page 1196). Cytoreductive therapy (hydroxyurea) with aspirin (81–100 mg/d) for vascular symptoms and phlebotomy (to maintain a hematocrit level of <45%) is recommended as initial treatment. Interferon alfa-2b, peginterferon alfa-2a, or peginterferon alfa-2b could be considered for younger patients, pregnant patients requiring cyto-

Myeloproliferative Neoplasms, Version 2.2018

ductive therapy, or patients requiring cytoreductive therapy who defer hydroxyurea.

Essential Thrombocythemia

Very Low-Risk, Low-Risk, or Intermediate-Risk Disease: The efficacy of low-dose aspirin for the prevention of thrombosis in patients with ET has not been evaluated in randomized clinical trials (see ET-1 and ET-2, pages 1197 and 1198, respectively). The results of a recent systematic review suggest that the risks and benefit of antiplatelet therapy in patients with ET remains highly uncertain.⁴³ The data supporting the use of aspirin in patients with ET are based on the extrapolation of results from the ECLAP study that evaluated the efficacy of aspirin in patients with PV.^{21,22} Results from one retrospective analysis suggest that aspirin may be effective for preventing thrombosis in patients with low-risk *JAK2*-mutated ET and in those with cardiovascular risk factors.⁴⁴ In a more recent retrospective analysis, the use of low-dose aspirin did not affect the risk of thrombosis but was associated with a higher incidence of bleeding in patients with *CALR*-mutated ET.⁴⁵ These findings must be confirmed in prospective clinical trials. Therefore, the panel felt that there is not enough evidence to recommend withholding aspirin for patients with *CALR*-mutated ET.

Observation is appropriate for patients with very low-risk or low-risk ET. Aspirin (81–100 mg/d) could be considered to reduce the risk of thrombotic complications for patients with very low-risk, low-risk, or intermediate-risk ET. Aspirin should be used with caution in patients with acquired von Willebrand disease (VWD) who have an increased risk of bleeding. In carefully selected patients, twice-daily aspirin at a 100 mg dose has been found to be superior to once-daily aspirin (100 mg), a finding that is yet to be confirmed in randomized controlled studies.⁴⁶ The risk and benefits of higher-dose aspirin must be weighed based on the presence of vasomotor symptoms and the risk of bleeding; it may be appropriate in carefully selected patients, as clinically indicated.

High-Risk Disease: Cytoreductive therapy (hydroxyurea or anagrelide) with aspirin (81–100 mg/d) is recommended as initial treatment. Interferon alfa-2b, peginterferon alfa-2a, or peginterferon alfa-2b could be considered for younger patients, pregnant

patients requiring cytoreductive therapy, or patients requiring cytoreductive therapy that defer hydroxyurea (see ET-3; page 1199).

Monitoring Response and Follow-Up Therapy

Monitoring for new thrombosis, acquired VWD, and/or disease-related major bleeding (in patients with ET) and management of cardiovascular risk factors are recommended for all patients. After initiation of low-dose aspirin (and phlebotomy for patients with PV), the guidelines recommend monitoring symptom status using the MPN Symptom Assessment Form Total Symptom Score (MPN-SAF TSS), evaluating for signs and symptoms of disease progression every 3 to 6 months, and assessing for potential indications for cytoreductive therapy. Bone marrow aspirate and biopsy should be performed as clinically indicated (if supported by increased symptoms and signs of progression).

The development of new thrombosis or disease-related major bleeding, frequent or persistent need for phlebotomy, symptomatic or progressive splenomegaly, symptomatic thrombocytosis, progressive leukocytosis, or progressive disease-related symptoms are considered potential indications for cytoreductive therapy. In one recent retrospective study, the need for ≥ 3 phlebotomies per year was associated with a significantly higher rate of thrombosis in patients with PV treated with hydroxyurea (20.5% at 3 years vs 5.3% at 3 years for those receiving ≤ 2 phlebotomies per year; $P < .0001$).⁴⁷ However, these findings could not be confirmed by other investigators.^{48,49} The development of cytopenia (one of the European LeukemiaNet [ELN]-defined criteria for resistance or intolerance to hydroxyurea) at the lowest dose of hydroxyurea is an adverse prognostic factor associated with higher risk of death and transformation to AML.^{50,51} Patients with high-risk PV or ET treated with cytoreductive therapy as initial treatment should also be monitored for intolerance or resistance to hydroxyurea (see MPN-H; page 1202).⁵²

The International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and ELN have published treatment response criteria for PV and ET.⁵³ The NCCN Guidelines Panel acknowledges that these response criteria were developed mainly for use in clinical trials and that clinical benefit may not reach the threshold of the IWG-MRT and ELN response criteria. Response

Myeloproliferative Neoplasms, Version 2.2018

criteria are not defined for patients treated with low-dose aspirin. Available evidence from retrospective studies that have evaluated these response criteria in patients with PV and ET treated with cytoreductive therapy suggests that achievement of complete response as outlined in the response criteria did not correlate with a lower incidence of thrombosis or improvement in thrombosis-free survival.^{50,54–56} In selected patients with a severe thrombotic event, normalization of blood counts might be an essential goal of treatment. Although normalization of blood counts after initiation of treatment is usually performed in clinical practice, it is not associated with long-term clinical benefit and there are no evidence-based data to recommend a target WBC or platelet count for patients receiving cytoreductive therapy. Response assessment should be performed based on the improvement of disease-related symptoms at the discretion of the clinician, and target WBC or platelet counts should be individualized to prevent new thrombosis or bleeding in each patient depending on the presence of risk factors.

Continuation of prior treatment is recommended for both asymptomatic patients (low-risk PV and very low-risk, low-risk, or intermediate-risk-ET) with no potential indications for cytoreductive therapy and patients with high-risk PV or ET with adequate response to initial cytoreductive therapy. Initiation of cytoreductive therapy is recommended for symptomatic patients with potential indications for cytoreductive therapy.

Ruxolitinib is FDA-approved for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea. Switching to ruxolitinib (for patients with PV) or alternate cytoreductive therapy (not used before) is recommended for patients with intolerance or disease that is resistant to hydroxyurea or interferon. Busulfan has also been effective in the treatment of PV and ET that is refractory to hydroxyurea, resulting in a CHR rate of 83% and a partial molecular response rate of 33%.⁵⁷ However, it is also associated with a significant rate of transformation to AML, and the sequential use of busulfan and hydroxyurea has also been reported to significantly increase the risk of second malignancies.^{57,58} Therefore, the panel does not recommend the use of busulfan as a treatment option.

Special Considerations

Management of Thrombosis and Bleeding

No evidence-based data exist to guide the selection or appropriate duration of anticoagulation therapy with or without antiplatelet therapy in patients with PV or ET. It is essential to rule out other potential causes of bleeding and treat any coexisting causes as necessary. Specific recommendations for the management of thrombosis, bleeding, and the use of anticoagulant therapy in patients undergoing surgery are outlined (see MPN-G; pages 1200 and 1201).

Surgery

The thrombotic and bleeding risk should be strongly considered before elective surgery because patients with PV and ET are at higher risk for bleeding despite optimal management. In a retrospective analysis that evaluated postsurgical outcomes in patients with PV (n=105) and ET (n=150), although most patients (74.0%) were treated with cytoreductive therapy and phlebotomy before surgery and antithrombotic prophylaxis, a significant proportion of surgeries was complicated by vascular occlusion (7.7%) or major hemorrhage (7.3%). Arterial thrombotic events were more frequent in patients with ET (5.3% vs 1.5%; $P=.08$) and venous thrombotic events were more frequent in those with PV (7.7% vs 1.1%; $P=.002$).⁵⁹ Multidisciplinary management with careful review of bleeding and thrombosis history is recommended before surgery for all patients.

Pregnancy

Pregnancy is considered a high-risk clinical situation in patients with PV and ET.⁶⁰ The presence of JAK2 V617F mutation is as an adverse prognostic factor for pregnancy outcome, and pregnancy complications are associated with a higher risk of subsequent thrombotic events in patients with ET.^{61–64} Use of aspirin has been reported to be effective in reducing pregnancy complications, especially in patients with JAK2-mutated ET.^{65,66} Aggressive intervention for the control of hematocrit, the use of aspirin, and low-molecular-weight heparin were associated with a significantly better pregnancy outcome in patients with PV.⁶⁷ Results of a recent UK prospective cohort study (58 women with MPN; 47 with ET) suggest that maternal MPN is associated with higher incidences of maternal complications, preterm delivery, and small-for-gestational-age infants compared with

Myeloproliferative Neoplasms, Version 2.2018

the general population.⁶⁸ Preeclampsia was the most common antenatal complication reported in 9% of women, and 22% of neonates were below the 10th percentile for growth.

Evaluation by a high-risk obstetrician should be considered before conception, and consultation with a high-risk obstetrician and an obstetric anesthesiologist is recommended regarding the optimal timing for discontinuation of anticoagulant therapy in preparation for an epidural before delivery. Specific recommendations for the use of anticoagulant therapy during pregnancy are outlined on MPN-G, 2 of 2 (page 1201). Interferons (interferon alfa-2b, peginterferon alfa-2a, and peginterferon alfa-2b) should be considered if cytoreductive therapy is necessary.^{62,69,70} Hydroxyurea is excreted in breastmilk and should be avoided in women who are breastfeeding. Patients

on hydroxyurea before pregnancy should be switched to interferons.

Summary

PV and ET are characterized by significant thrombotic and hemorrhagic complications. The goal of treatment is to reduce the risk of developing thrombohemorrhagic complications. Use of cytoreductive therapy is based on the risk status determined by patient age, history of thrombosis, and *JAK2* V617F mutational status (in patients with ET). Regular monitoring of disease-related symptoms, assessment of need for cytoreductive therapy, and appropriate evaluation to rule out disease progression should be an integral part of management for patients with PV and ET.

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Posttest Questions

1. Which of the following are considered appropriate treatment options for the management of patients with high-risk PV?
 - a. Aspirin (81–100 mg/d) with phlebotomy for vascular symptoms
 - b. Hydroxyurea to reduce the risk of thrombotic complications
 - c. A and B
 - d. Cytoreductive therapy with anagrelide
2. True or False: The use of low-dose aspirin (81–100 mg/d)

for vascular symptoms is not recommended for patients with low-risk ET with *CALR* mutation.

3. Which of the following is FDA-approved for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea?
 - a. Ruxolitinib
 - b. Pacritinib
 - c. Busulfan
 - d. All of the above

