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Treatment of Philadelphia Chromosome-negative Myeloproliferative Neoplasms in 2024: A Concise Review

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Introduction

In 1951, William Dameshek coined the term myeloproliferative disorders (MPDs) for diseases characterized by abnormal proliferation of one or more terminally differentiated myeloid cell lines in the peripheral blood.[1,2] In 2008, the World Health Organization (WHO) renamed these disorders as myeloproliferative neoplasms (MPNs) in recognition of their clonal nature. There are currently two classification system for MPNs: WHO and International Consensus Classification (ICC), 2022.[3,4] This review will focus on the Philadelphia chromosome-negative MPNs, which include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF).

Genomic changes in MPNs

MPNs result from the constitutive activation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling pathway. The JAK2 p.V617F mutation, first described in 2005, is detectable in >95% of patients with PV and 50-60% of patients with ET or PMF. In-frame insertions or deletions in exon 12 of the *JAK2* gene are found in the remaining patients with PV but not in those with ET.[5-7] Mutations in the thrombopoietin receptor gene *MPL* were identified in 2006 and are present in 3–5% of ET and 5–10% of PMF, but not in PV cases.[8] Mutations in the calreticulin (*CALR*) gene were identified in 2013 and are found in 20–25% of ET and 25–30% of PMF but not in PV.[9,10] The *CALR* gene encodes for the endoplasmic reticulum chaperone protein (*CALR*). Mutant *CALR* interacts with the MPL protein, which is trafficked to the cell surface thereby activating the JAK-STAT signalling pathway.[11] Mutations in the *CALR* gene consist of insertions or deletions in exon 9 resulting in a positively charged amino acid sequence in the C-terminus. The mutations can be type 1, characterised by a 52-bp deletion that eliminates all the negatively charged amino acids in the C-terminus, or type 2, characterised by 5-bp insertion that eliminates half the negatively charged amino acids from the C-terminus. Type 1 and type 2 mutations constitute 80% of the *CALR* mutations.

In addition to the above three driver mutations, other somatic myeloid mutations are also found in MPNs. Common somatic mutations involve genes regulating DNA methylation (*TET2, DNMT3A,* and *IDH1/IDH2*), histone modification (*ASXL1* and *EZH2*), RNA splicing (S*F3B1, U2AF1, ZRSR2,* and *SRSF2*), and the RAS pathway (*NRAS* and *KRAS*). These mutations are common in PMF and the blast phase of PV and ET. While these mutations do not cause MPN, they may modify the disease phenotype. Mutations in *ASXL1, EZH2, SRSF2, U2AF1,* and *IDH1/2* are denoted as resulting in the "high molecular risk" phenotype.[12]

Management of PV

PV is a clonal hematopoietic stem cell neoplasm characterized by panmyelosis, disease-related symptoms, increased risk for thrombosis, and risk of transformation to post-PV myelofibrosis (MF) or acute leukemia. Goals of treatment for PV include prevention of thrombosis, reducing symptom burden, and prevention of disease progression.

PV-related thrombosis is multifactorial and related to hyperviscosity, increased red cell mass, and increased thrombin generation by platelets.[13]

JAK2 positivity contributes to thrombosis risk in MPN[14], as does increased allele burden.[15] Once-daily aspirin (81 mg/day; acetylsalicylic acid [ASA]) is recommended for all patients with PV without contraindications.[16] In addition, phlebotomies are performed to achieve a target hematocrit level of <45%.[17,18]

Beyond phlebotomy and aspirin, cytoreductive treatment is indicated for individuals with high-risk disease.[19] Traditionally, patients who are over 60 years of age and/or have a history of thrombosis are considered to have high-risk disease, while those without these factors are considered low risk.[19] In certain scenarios cytoreductive therapy may be considered even in patients with low-risk disease (**Figure 1.**):

1. Frequent phlebotomies with suboptimal hematocrit control or poor tolerability
2. Symptoms of PV (microvascular, pruritis) not controlled with ASA or phlebotomies
3. Phlebotomies leading to symptomatic iron deficiency anemia
4. Extreme thrombocytosis leading to acquired von Willebrand syndrome

Cytoreductive therapy

Over the years, hydroxyurea (HU) has been the standard cytoreductive agent in PV. HU is usually started at a dose of 500 mg once or twice daily, and titrated based on response. Another option, interferon alfa (IFNα), has long been shown to have cytoreductive and disease-modifying potential. However, its toxicity and need for frequent parenteral administration has been a deterrent to its usage. This has changed with the availability of pegylated forms of IFNα. The only formulation currently available in Canada is peginterferon alfa-2a (Pegasys). Another formulation is ropeginterferon alfa-2b (rIFN), which is a monopegylated form of IFNα. This formulation is characterised by an extended elimination half-life, resulting in less frequent dosing, better tolerability, and improved compliance.[20] This formulation is FDA-approved.

Phase 3 trials have established the role of IFNα in high-risk PV. The MPD-RC-112 trial, in which randomized patients with high-risk ET/PV received Pegasys or HU[21], and the PROUD-PV and CONTINUATION PV studies randomized patients with high-risk PV to receive rIFN or HU.[22,34] IFNα was non-inferior to HU in terms of complete hematological response (CHR) at 12 months in both these trials.[21-23] In the CONTINUATION-PV study, CHR was higher for the rIFN group in long-term follow-up.[23] JAK2 allele burden decreased consistently over time with both IFNα drugs, which was associated with improved event-free survival (EFS).[24] The starting dose for Pegasys is 45 mcg subcutaneously weekly. Doses are titrated with 45 mcg monthly increments to a maximum of 180 mcg.[21] rIFN is administered subcutaneously every 2 weeks at a starting dose of 100 or 50 mcg (for HU-exposed patients). Dosing increments of 50 mcg are made every 2 weeks up to a maximum of 500 mcg.[22,25]

Treatment of patients with HU-intolerant, resistant disease

A significant number of patients are intolerant to HU due to hematologic or non-hematologic toxicity or their disease is resistant to this therapy due to a lack of effective cytoreduction. HU intolerance or resistance has been defined by the European LeukemiaNet (ELN; **Table 1**)[26,27]:

1. Need for phlebotomy to maintain hematocrit levels <45% after 3 months of at least 2 g/day of hydroxyurea **OR**
2. Uncontrolled myeloproliferation (i.e. platelet count >400 × 10^9/L and white blood cell count >10 × 10^9/L) after 3 months of at least 2 g/day of hydroxyurea **OR**
3. Failure to reduce massive splenomegaly by more than 50% as measured by palpation or failure to completely relieve symptoms related to splenomegaly, after 3 months of at least 2 g/day of hydroxyurea **OR**
4. Absolute neutrophil count <1.0 × 10^9/L, or platelet count <100 × 10^9/L, or hemoglobin <100 g/L at the lowest dose of hydroxyurea required to achieve complete or partial clinical hematological response **OR**
5. Presence of leg ulcers or other hydroxyurea-related non-hematological toxicities like mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever at any dose of hydroxyurea

Table 1. Definition of clinical resistance and intolerance to hydroxyurea in polycythemia vera and myelofibrosis; *adapted from Barosi, G, et al., 2007 and Barosi, G, et al., 2010.*

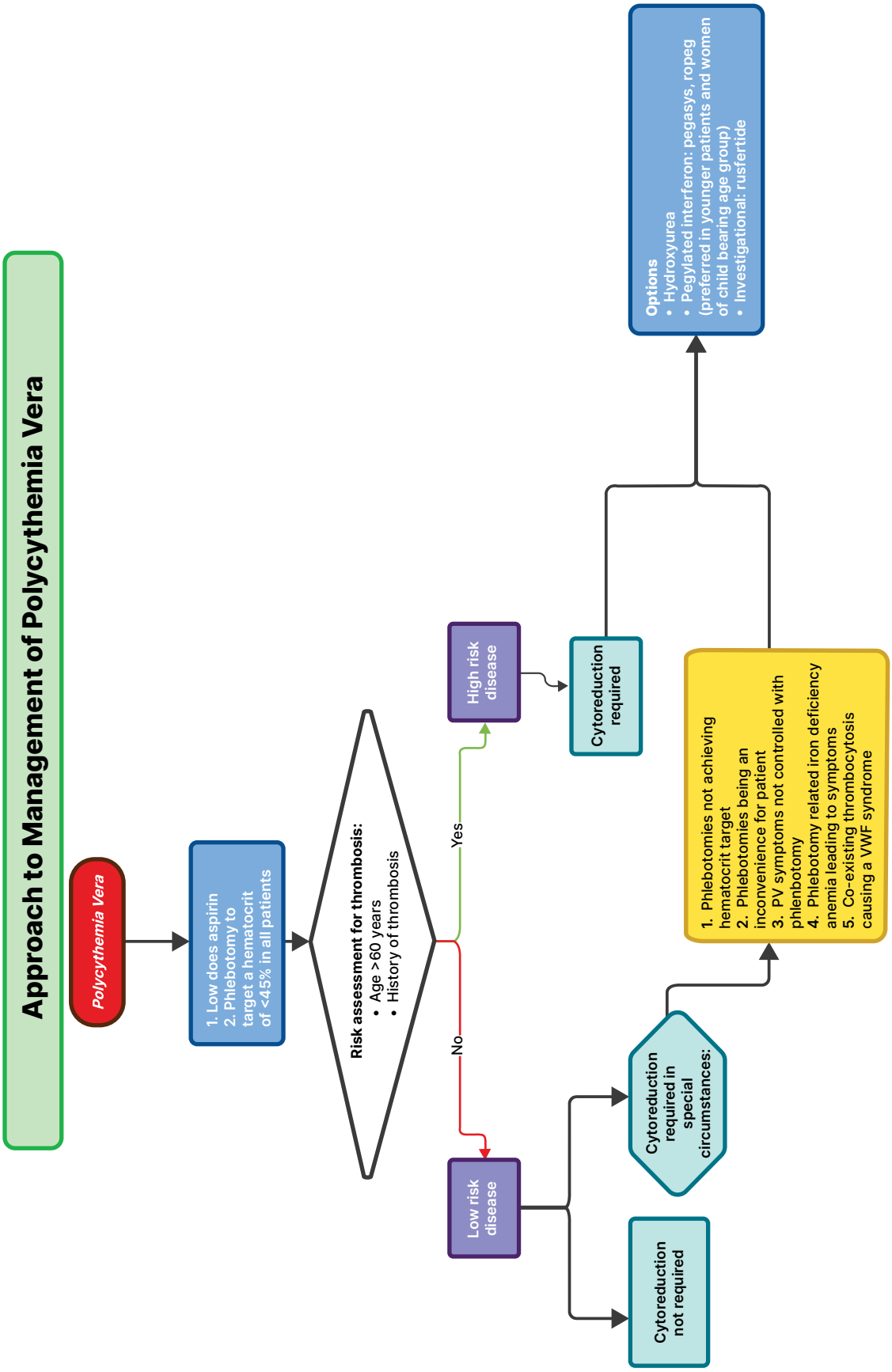

Figure 1. Approach to management of polycythemia vera; *adapted from Tefferi and Barbui, 2008.*[19]

In the MPD-RC-111 trial, a single-arm Phase 2 study, patients with HU-resistant or -intolerant disease were treated with Pegasys, which resulted in a 12-month overall response rate (ORR) of 60% and spleen normalisation in 32.7% of cases.[28] Ruxolitinib, an oral JAK inhibitor, was also assessed in this population in three randomized trials: the RESPONSE trial (with splenomegaly)[29], the RESPONSE-2 trial (without splenomegaly)[30], and the MAJIC-PV study (Phase 2). The comparator arm in these trials was the best available therapy (BAT). All three trials showed that ruxolitinib was better at achieving hematocrit control and spleen volume reduction compared to BAT. The MAJIC-PV trial also showed better EFS with ruxolitnib.[31] However, IFNα-based therapy constituted only 11.6%, 13%, and 15% of BATs.[29-31] Thus, whether ruxolitinib or pegIFNα is the best agent for those with HU-resistant/intolerant disease remains unknown. Future trials must focus on the appropriate sequencing of these agents for this group of patients.

Novel approaches

IFNα in low-risk PV

The role of rIFN in low-risk PV was studied in the LOW PV study which was a Phase 2 randomized trial comparing rIFN with phlebotomy. The group receiving rIFN had better hematologic response,[32,33] (rIFN was dosed 100 mcg every 2 weeks with no escalation).

Hepcidin-mimetic (rusfertide) in PV

Hepcidin binds to ferroportin, blocking the export of intracellular iron to the blood leading to reduced serum iron levels and decreased erythropoiesis.[34] In the Phase 2 REVIVE trial involving patients with phlebotomy-dependent PV, rusfertide was associated with a significant decline in phlebotomies and better hematological response.[35] The ongoing Phase 3 VERIFY trial is evaluating its efficacy and safety in PV.[36]

In summary, patients with low-risk PV are managed with aspirin and phlebotomy to achieve hematocrit levels of <45%. Cytoreductive therapy is indicated in patients with high-risk PV. In certain scenarios in low-risk PV, cytoreductive therapy can be instituted. Both the National Comprehensive Cancer Network (NCCN) and ELN recommend either HU or pegIFNα/rIFN as first line cytoreductive therapies. pegIFNα or rIFN are favoured in younger patients (<60 years) and women of child-bearing age.[37] In the HU-resistant/intolerant population, both pegIFN and ruxolitinib can be used.

Management of ET

ET is characterised by predominantly thrombocytosis, occurrence of thrombosis, and microcirculatory symptoms, and occasionally disease transformation to fibrosis or leukemia.

Risk-stratified treatment

Similar to PV, treatment in ET is focused on thrombosis prevention. Traditional risk factors include age over 60 years and history of thrombosis.[38] More recently, the international prognostic score for ET (IPSET), has refined risk stratification in ET by incorporating *JAK2* mutation status. In its latest iteration the revised IPSET thrombosis score categorises patients into four risk groups (**Table 2**).[39,40]

Despite the lack of randomized evidence, low-dose aspirin is used for thrombosis prevention in ET. Recommendations are based on non-randomized studies[41,42] and by extrapolation from studies in PV.[16] In the absence of contraindications, low-dose aspirin is a reasonable choice in patients with low, intermediate, and high-risk disease and in those with very low-risk disease with microvascular symptoms. In a recent study of low-risk patients with mutated *CALR*, no benefit was observed for the use of low-dose aspirin, while it was associated with increased risk of bleeding.[41] In patients with extreme thrombocytosis (>1000 × 10^9/L), aspirin should be used with caution due to the risk of bleeding and acquired von Willebrand factor deficiency (**Figure 2**).

Cytoreductive therapy

The first line cytoreductive therapy of choice for ET is HU. Similar to PV, pegylated IFN can be used in ET. The MPD-RC-112 trial compared Pegasys with HU in high-risk ET. The percentage of patients with complete remissions (CR) at 12 months were 44% and 45% with Pegasys and HU, respectively.[21] Anagrelide, an oral imidazoquinoline, when compared with HU in the first line, resulted in higher rates of thrombosis (arterial and venous), hemorrhage, and transformation to myelofibrosis than HU.[43]

For the HU intolerant/resistant population, the MPD-RC-111 trial showed that Pegasys produces reasonable responses (ORR of 69% at 12 months).[28] On the other hand, in the

Risk	Attributes	Management
Very low	Age ≤60 years, *JAK2* wild type, no prior thrombosis	Observation Low-dose aspirin (in the presence of cardiovascular risk factors)
Low	Age ≤60 years, *JAK2* V617F mutated, no prior thrombosis	Low-dose aspirin
Intermediate	Age >60 years, *JAK2* V617F wild type, no prior thrombosis	Low-dose aspirin +/- cytoreductive therapy
High	Age >60 years and *JAK2* V617F mutated **OR** Prior thrombosis regardless of other factors	Low-dose aspirin + cytoreductive therapy

Table 2. Revised international prognostic score for ET; *adapted from Barbui et al., 2015.*[46]

MAJIC-ET trial, when ruxolitinib was compared to BAT in this population, the ORR, and rates of thrombosis, hemorrhage, and transformation were similar. The BAT used were IFNα, anagrelide, busulfan, and HU.[44]

Thus, in patients with high-risk ET, the first line cytoreductive therapy of choice is HU. Pegylated IFN should be considered in younger patients and individuals of child-bearing age. Either of these agents (HU or IFNα) can be used in the second line if not previously used and anagrelide is an alternative option. Ruxolitinib has activity in ET and may be considered in certain circumstances. Results of the SURPASS-ET trial, comparing ruxolitinib with anagrelide in HU-intolerant/resistant ET are pending.[45]

Treatment of PMF and post-PV/ET MF

Primary myelofibrosis (PMF) is characterised by progressive cytopenia, marrow fibrosis, cytokine-driven inflammatory symptoms, and extramedullary hematopoiesis. A disease phenotype similar to PMF is observed in advanced phases of PV and ET and is defined as post-PV-MF and post-ET-MF, respectively. Aberration in the JAK/STAT signaling pathways is crucial to the pathogenesis of MF, which in 90% of patients is driven by mutually exclusive mutations in *JAK2, CALR,* or *MPL* genes.[47] Somatic mutations in the myeloid genes (mentioned under genomic changes) additionally influence MF biology.[48]

Risk stratification

Management of MF begins with risk stratification. Earlier risk models include the International Prognostic Scoring System (IPSS), Dynamic International Prognostic Scoring System (DIPSS), and DIPSS-plus.[49-51] Better genomic understanding has led to the incorporation of genetic mutations into the risk stratification. Mutations in *ASXL1, SRSF2, IDH1/2,* and *EZH2* confer poorer prognosis.[51] Mutational data has been integrated into the Mutation-enhanced (M) IPSS70, MIPSS70-plus, and MIPSS70+ version 2.0 risk stratification models.[53,54] Mutations in the *TP53* gene are not included in these risk systems. Seminal work by Grinfeld *et al.* showed that *TP53*-mutated MF has a high risk of leukemic transformation and very poor median overall survival (OS) of 2.4 years.[48] These risk models have been validated in primary myelofibrosis but not in secondary myelofibrosis. In clinical practice, these models are frequently used in secondary MF. The Myelofibrosis Secondary to PV and ET – Prognostic Model (MYSEC-PM) is a prognostic model developed specifically for secondary MF.[55]

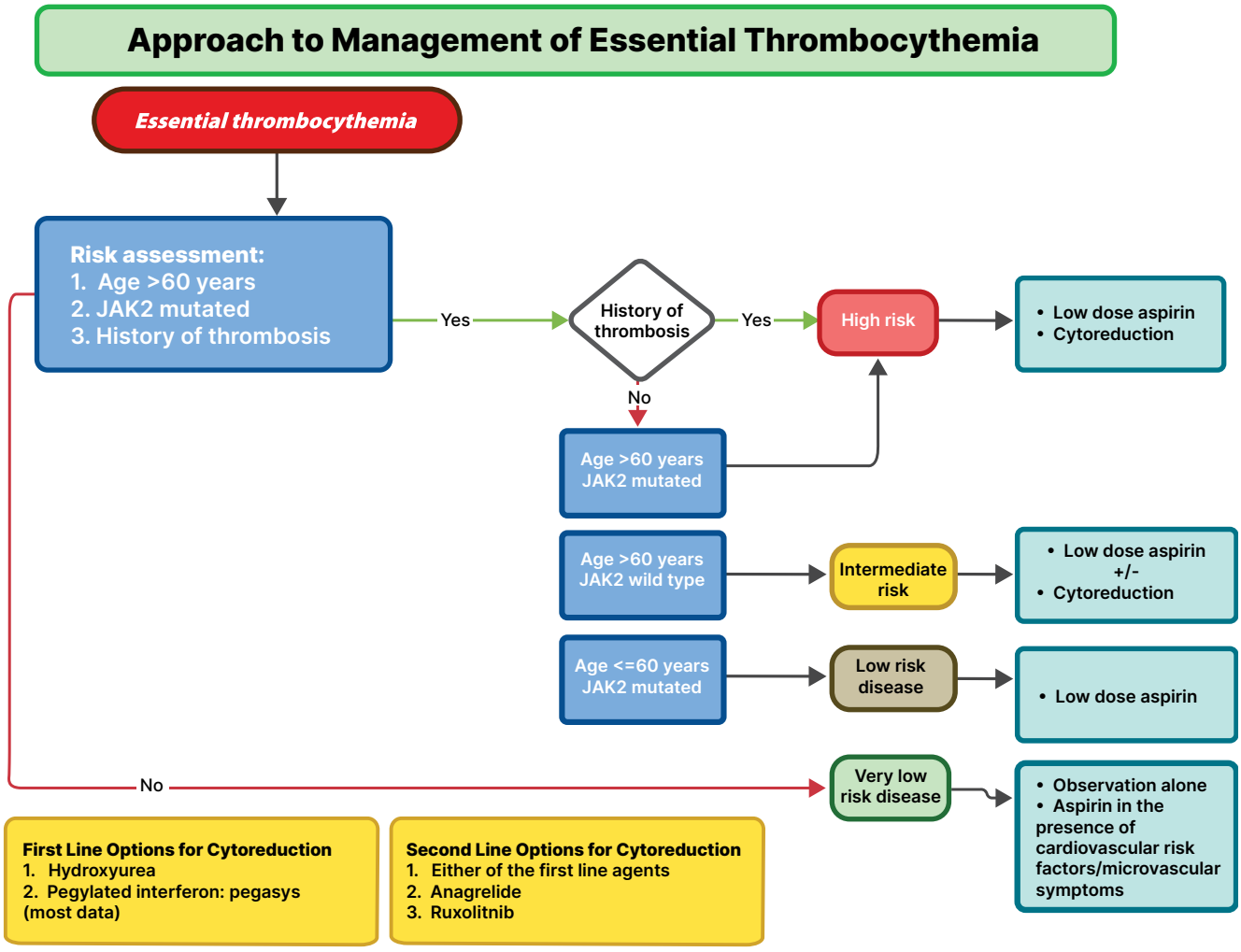

Figure 2. Approach to management of essential thrombocythemia; *adapted from Barbui et al., 2015.*[46]

Treatment of MF

Patients with DIPSS scores intermediate 2 or higher, MIPSS70 or MIPSS70-plus version 2.0 high risk, MYSEC-PM intermediate 2 or higher, and *TP53* mutations have a predicted median overall survival of <5 years and should be considered for allogeneic stem cell transplantation (**Figure 3**).[56] Peri-transplant management is directed at symptoms and splenomegaly and a bridging JAK inhibitor (JAKi) can be considered. Timing of the transplant in the JAKi era is controversial and is covered in other publications.[57-59] For patients who are ineligible for transplant, do not have a suitable donor, or prefer non-transplant therapy, JAKi have been the mainstay of therapy for symptomatic management. Patients who are not high risk per the above models can be monitored if asymptomatic, receive symptom-directed management, or refered to clinical trials as appropriate.

Choice of JAKi

There are currently four FDA-approved JAKi for myelofibrosis: ruxolitinib, fedratinib, pacritinib, and momelotinib, the first two of which are Health Canada approved. Ruxolitinib, a non-selective JAK1/JAK2 inhibitor, approved in the US in 2011 and in Canada in 2012, has the largest body of evidence. In the COMFORT-I and COMFORT-II trials comparing ruxolitinib to placebo and BAT, respectively, ruxolitinib resulted in a spleen volume reduction of 35% (SVR35) at 24 weeks (SVR35@24) in 41.9% and 32% of patients, respectively.[60,61] Anemia and thrombocytopenia are important side effects

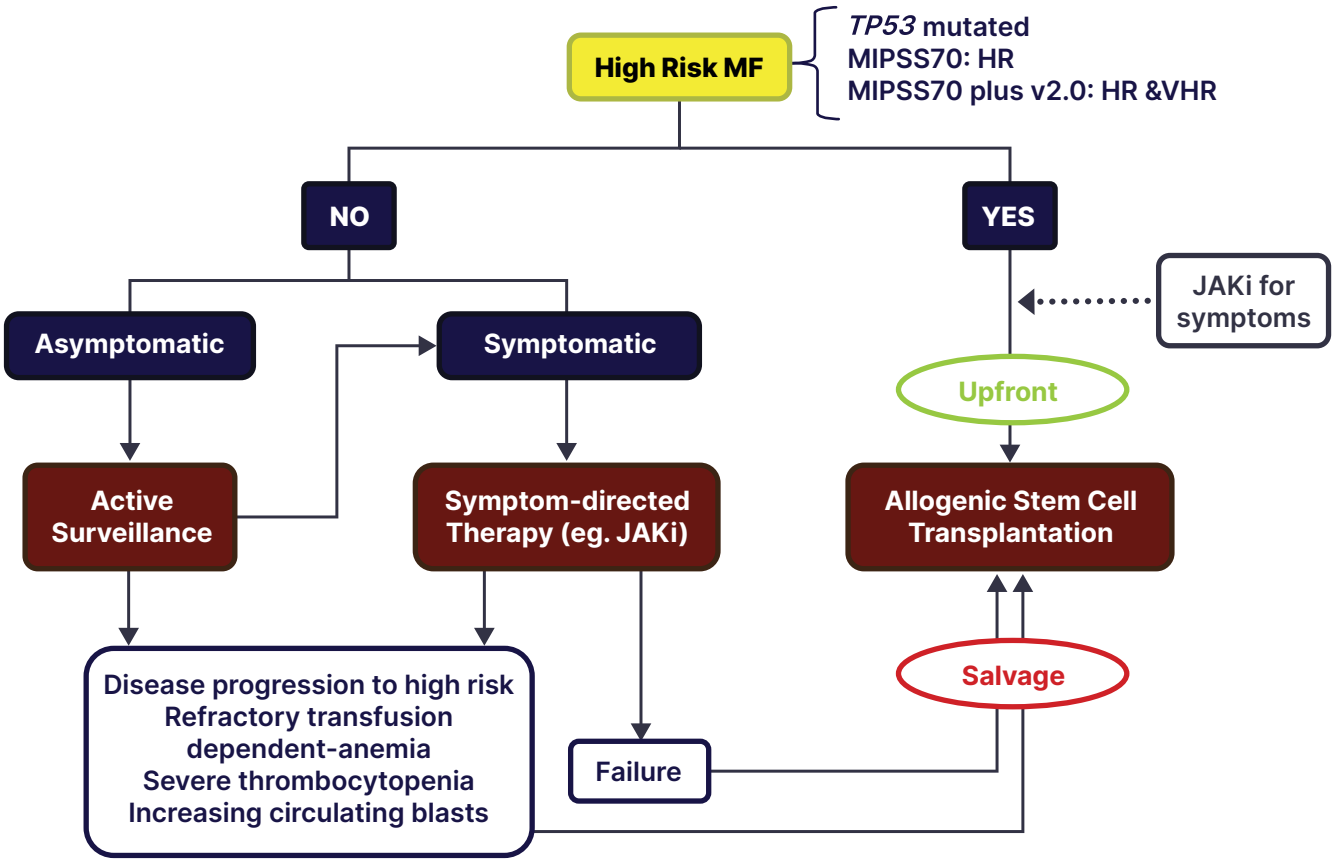

Figure 3. Management algorithm for transplant-eligible patients with MF in the chronic phase; *used with permission from Davidson and Gupta, 2021.*[58]

of ruxolitinib, which lead to dose reductions or treatment interruptions. At 3 years, 50% of patients had discontinued ruxolitinib, and this rate increased to 75% at 5 years.[62]

Fedratinib is a JAK2-FLT3-BRD4 inhibitor that has been studied in both ruxolitinib-naïve and -exposed patients in the JAKARTA and JAKARTA-2 trials. To be included in these trials, platelet levels had to be ≥50 × 10^9/L. Fedratinib resulted in a SVR35@24 of 36% and 55%, respectively, with good symptom burden reduction.[63-66] Even though fedratinib is effective in the first line setting, ruxolitinib is most often used in clinical practice. The Health Canada approval for fedratinib is for patients with MF with disease-related symptoms or splenomegaly, including those who have been previously exposed to ruxolitinib.[67]

Momelotinib is a JAK1/JAK2 inhibitor that has additional inhibitory effects against activin A receptor type 1 (ACVR1). ACVR1 is involved in SMAD2/3 signalling, which upregulates hepcidin production. Momelotinib has been found to have significant anemia benefits. In the SIMPLIFY-1 trial, momelotinib was found to be non-inferior to ruxolitinib in terms of the SVR35@24, but not for symptom score reduction.[68] In addition, this trial showed that red blood cell (RBC) transfusion independence and conversion to transfusion independence was better with momelotinib.[69] Momelotinib is an exciting option for the treatment of symptomatic MF with anemia. Approval in Canada is anticipated in the near future.

The fourth JAKi is pacritinib, which was studied in the PERSIST-1 and PERSIST-2 trials that included patients with platelet counts <50×10^9/L (both JAKi-naïve and JAKi-exposed). Pacritinib achieved SVR35@24 of 23.1% and symptom control in 25% of patients.[70]

Combination therapy

A number of novel agents have been combined with JAKi therapy in clinical trials. In the MANIFEST-2 trial, patients with treatment-naïve symptomatic MF with an enlarged spleen (DIPSS intermediate-1 or higher) were randomized to receive ruxolitinib + pelabresib (BET inhibitor) or ruxolitinib + placebo.[71] In the TRANSFORM-1 trial, the combination of ruxolitinib + navitoclax (BCL-2 inhibitor) was compared with ruxolitinib + placebo.[72] Both combinations resulted in a doubling of the SVR35@24 in comparison to ruxolitinib + placebo. However, neither combinations significantly reduced the symptom burden in comparison to ruxolitinib + placebo. Therefore, the place of these combinations for treatment remains unclear and longer follow-up studies are awaited. These two trials also highlight the need for better endpoints to evaluate therapies in MF. In addition, the combination of ruxolitinib + pelabresib showed improvement of bone marrow fibrosis.[73] This could be evidence of disease modification with the BET inhibitor. Other therapies with disease-modifying potential are required.

Agents addressing anemia

Transfusion dependence is a major symptom in MF. Transfusion dependence is associated with poorer overall survival in patients with MF.[74,75] Apart from momelotinib and pacritinib, which positively affect anemia due to *ACVR1* inhibition, there are other adjunctive therapies that have been used in patients with MF and anemia. RBC transfusion is the most commonly used strategy in clinical practice. Erythropoietin (EPO)-stimulating agents can be used in patients with EPO levels <500 U/L with an expected response ranging from 40–60%.[76-78] Androgens (danazol), steroids, immunomodulatory agents (lenalidomide, thalidomide), and splenectomy are other strategies that have been used.[79] Recently, the Phase 2 open label ACE-536-MF-001 trial tested luspatercept in patients with MF. Luspatercept resulted in improvement of the primary endpoint (anemia response) in transfusion-dependent (9.5%) and non-transfusion-dependent (13.6%) patients and in patients who were on ruxolitinib (26.3% and 14.3%, respectively).[80]

In summary, management of MF begins with risk stratification. Patients with high-risk disease should be offered a transplant. JAKi can be used in peri-transplant symptom management. In patients who are ineligible for transplant or decline transplant, management is symptom-directed using JAKi. Ruxolitinib is the JAKi with the most clinical experience. Newer JAKi, such as momelotinib and pacritinib, have a role in the setting of co-existing cytopenia. Trials are assessing agents that modify the disease biology and also address anemia.

Conclusions and future directions

The past decade has seen major shifts in the diagnosis, prognostication, and management of MPN. The focus of treatment for PV and ET is thrombosis prevention and monitoring for disease progression. New data support the use of IFNα therapy for cytoreduction, especially in PV, and also appears to result in sustained decline in JAK2 allele burden in a proportion of patients. Management of MF begins with risk assessment. Patients with high-risk disease should be considered for transplant. Symptom management of MF has seen the availability of several JAK inhibitors which may help address the co-existing cytopenia in MF. With the availability of many agents, sequencing of therapies will become increasingly important in the future. Several agents are focused on addressing anemia in MF, which continues to be an area of unmet need. Patients should be offered clinical trial participation whenever possible.

Disclaimer: At the time of publishing this review, there is a global shortage in the supply of Pegasys, which is expected to last until the second half of 2025.

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Financial Disclosures

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D.M.: None declared.

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