

ABOUT THE AUTHOR



Dawn Maze, MD, FRCPC, MSc

Dawn Maze, MD, FRCPC, MSc is a member of the Leukemia Program and the Elizabeth and Tony Comper MPN Program at the Princess Margaret Cancer Centre. Dr. Maze earned her medical degree and master's degree in clinical epidemiology from Memorial University. She completed postgraduate training in hematology at Queen's University, followed by a fellowship in blood and marrow transplantation and transfusion medicine research at The Ottawa Hospital.

Dr. Maze's current research interests include MPN management in the adolescent and young adult population, particularly around pregnancy. She is also interested in optimizing transfusion support for patients with hematologic malignancies and is Medical Director for the Malignant Hematology Day Unit. She is the primary investigator or co-investigator on numerous clinical trials of treatment and supportive care of patients with hematologic malignancies.

MYELOPROLIFERATIVE NEOPLASMS IN 2022: A CONCISE REVIEW

Introduction

The Philadelphia chromosome(Ph)-negative myeloproliferative neoplasms (MPN) are comprised of a heterogeneous group of disorders of myeloid hematopoietic stem cells that include polycythemia vera (PV), essential thrombocythemia (ET), and idiopathic myelofibrosis (MF). MPN are characterized by constitutional and other disease-related symptoms, an increased risk for thrombotic and hemorrhagic events, and a propensity to transform to acute myeloid leukemia (AML). Progress in our understanding of the molecular pathophysiology of MPN has led to improved prognostic tools, and increasingly personal risk-stratification. In PV, there has been renewed interest in interferon (IFN) for its potential to directly target the malignant clone and exert a disease-modifying effect. In MF, the introduction of Janus Kinase (JAK) inhibitors has significantly altered the therapeutic landscape over the past decade. Ongoing development in the area of JAK inhibitor therapy, as well as several novel pathways, holds promise for improved hematologic responses, lessening of overall burden of illness, increased quality of life, and application to a broader cohort of patients.

Molecular Pathogenesis

MPN result from constitutive activation of the JAK/STAT signalling pathway. In the majority of cases, a driver mutation in *JAK2*, *CALR* or *MPL* can be identified, and those without one of these mutations are classified as "triple negative". The first discovered, in 2005, was a point mutation in exon 14 of the *JAK2* gene which results in a valine to phenylalanine substitution at position 617 (V617F). This mutation results in constitutive activation of the JAK/STAT pathway independent of ligand activation of the erythropoietin (EPO), thrombopoietin (TPO) or granulocyte-colony stimulating factor (G-CSF) and as such, can drive the phenotype of either of the classical World Health Organization (WHO)-defined MPN. In comparison, the second type of driver mutation in *JAK2*, comprised of a variety of insertions and deletions in exon 12, activates primarily the EPO receptor. JAK2V617F is detected in 95% of PV cases and 50-60% of ET and MF.^{1,2} JAK2 exon 12 mutations can be identified in most of the remaining 5%.³

Calreticulin (CALR) is a chaperone protein that prevents exportation of misfolded proteins in the endoplasmic reticulum.⁴⁻⁵ Multiple mutations have been described, but 80% are either type 1, a 52-bp deletion, or type 2, a 5-bp insertion in exon 9. These frameshift mutations result in pathogenic binding of the CALR lectin-binding domain to thrombopoietin receptor (MPL, also known as TPOR), which activates JAK/STAT signalling. CALR mutations are identified in 20-25% of ET cases and 25-30% of MF cases.⁶⁻⁷ MPL is the receptor for TPO and gain of function mutations in tryptophan at position 515 (W515) in exon 10 of the *MPL* gene are identified in approximately 3-8% of ET and MF cases.⁸

In addition to driver mutations, the MPN phenotype and evolution over time is modulated by additional mutations such as those in genes involved in epigenetic regulation (e.g., *EZH2*, *ASXL1*), spliceosome machinery (e.g., *SRSF2*, *U2AF1*) and the RAS pathway (e.g., *NRAS*, *KRAS*). Mutations in *ASXL1*, *EZH2*, *SRSF2* and *IDH1/29*, denoted “high molecular risk (HMR)”, as well as those in *TP53*¹⁰, predict leukemic progression or shortened survival. In addition to these genetic drivers, there is growing evidence that proinflammatory processes play a role in MPN progression, from clonal hematopoiesis to chronic phase MPN to accelerated and blast phase disease.^{11,12}

Goals of Therapy and Risk Stratification

The goals of treatment in MPN include symptom improvement, prevention of vascular events, control of abnormal blood counts, reduction in splenomegaly and delayed disease progression. Potential consequences of treatment must also be considered and may include side effects, impact on fertility, and the risk of second cancers. The MPN Landmark survey involving 813 patient respondents who had MPNs and 457 hematologist/oncologist respondents who treated patients with these conditions uncovered frequent discordance regarding treatment goals between patients and physicians.¹³ Indeed, the goals of treatment may vary depending on the MPN and its clinical and genetic features, as well as an individual’s life stage, values, and preferences. Hence, effective patient-physician communication is vital to treatment decision making.

An important component of therapeutic decision making is accurate risk stratification. Traditional stratification in PV and ET is based on age and history of thrombosis, with patients over the age of 60 years or with prior thrombosis considered

high risk, and those without either of these factors considered low risk.¹⁴ In ET, the newer International Prognostic Score of Thrombosis for ET (IPSET-thrombosis)¹⁵, which also incorporates the *JAK2V617F* mutation and conventional cardiovascular risk factors as risk factors for thrombosis, is the preferred scoring system.^{16,17} In MF, newer risk models incorporating both clinical and genetic information are recommended, particularly to inform decisions around allogeneic stem cell transplantation (SCT). In primary myelofibrosis (PMF), the Mutation-Enhanced International Prognostic Score System (MIPSS-70)¹⁸ or MIPSS-70+ Version 2.0¹⁹ are preferred if both molecular profile and karyotype are available, and the MYelofibrosis SECondary to PV and ET prognostic model (MYSEC-PM)²⁰ is a validated tool for post-ET or post-PV MF. The Dynamic International Prognostic Scoring System (DIPSS) continues to be the recommended scoring system in clinical practice if genetic information is unavailable.²¹

Treatment of PV and ET: The Old and the New

The mainstay of therapy for low-risk PV is low dose acetylsalicylic acid (ASA) and phlebotomy to maintain a hematocrit below 45%.²² However, in clinical practice, it can be challenging to maintain target hematocrit values with intermittent phlebotomies. Further, phlebotomies do not control progressive thrombocytosis or leukocytosis, and may result in symptomatic iron deficiency.²³ Hydroxyurea is commonly used in this setting for patients who are poorly tolerant or require frequent phlebotomies, however, new strategies are being explored. In the Low-PV study, in which 127 patients with low-risk PV were randomized to receive standard therapy with ASA (100 mg daily) and phlebotomy (300mL for each phlebotomy) with or without ropeginterferon alfa-2b (rIFN) administered subcutaneously every 2

weeks in a fixed dose of 100 µg, more patients treated with rIFN maintained a median hematocrit of 45% or lower without progressive disease during a 12-month period than those receiving standard therapy (84% vs. 60%, $p=0.0075$). There was no significant difference between grade 3 or higher adverse events, and serum ferritin concentrations progressively increased over time in the rIFN group.²⁴ Another promising approach to hematocrit control is with the hepcidin mimetic, rusfertide (PTG-300). In a phase 2 study, rusfertide was effective at limiting the number of phlebotomies and maintaining hematocrit below 45%, while the serum ferritin levels increased throughout the treatment period reflecting increase in iron stores.²⁵

In high-risk PV, either hydroxyurea or IFN are the currently recommended first-line cytoreductive therapies for patients of any age, however the initial choice is often strongly influenced by cost and drug availability.¹⁵ In Canada, IFN is most often considered in younger patients and in patients who are pregnant and require cytoreduction. In the PROUD-PV study, and its extension phase, CONTINUATION-PV, patients with high-risk PV were randomized to receive rIFN or hydroxyurea. While responses to rIFN occurred later, by 36 months hematologic responses without normalization of spleen size were seen in 71% of patients treated with rIFN vs. 51% of those treated with hydroxyurea ($p=0.012$).²⁶ At the 60-month follow-up, 56% of evaluable patients treated with rIFN had a decrease in their JAK2 allele burden to under 10%. Younger age and lower allele burden predicted a better molecular response, suggesting early treatment initiation may result in the greatest long-term benefit.²⁷

Most patients with ET likely benefit from ASA for prevention of vascular events. However, in a retrospective review of 433 patients with low-

risk ET, in patients with a CALR mutation, antiplatelet therapy did not affect the risk of thrombosis, but was associated with a higher incidence of bleeding (12.9 vs. 1.8 episodes per 1000 patient-years, $p=0.03$).²⁸ Patients with high-risk disease according to the IPSET-thrombosis should receive low dose ASA, while those with low- or intermediate-risk disease should receive ASA if they are 60 years of age or older, have the JAK2V617F mutation, or uncontrolled cardiovascular risk factors.¹⁵ Cyto-reduction is recommended for patients aged 60 years and older, those with a history of thrombosis and for a platelet count above $1500 \times 10^9/L$. Cyto-reduction is recommended for extreme thrombocytosis primarily to reduce the risk of acquired Von Willebrand syndrome and major hemorrhage, as the risk of thrombosis does not appear to be increased.²⁹ Hydroxyurea is generally favoured as first-line therapy in ET. Anagrelide and IFN are recommended as second line treatments, and the ongoing SURPASS ET study, comparing rIFN to

anagrelide in patients with resistance or intolerance to hydroxyurea, may help inform the optimal treatment in this setting (NCT04285086).

Treatment of MF: JAK Inhibitors and Beyond

Management of MF starts with risk assessment, as described below (**Figure 1**). In patients with lower risk disease, who have no or minimal disease-related symptoms, active surveillance is recommended. For patients with splenomegaly or MF-related symptoms, ruxolitinib may be beneficial; IFN or hydroxyurea may be indicated if cyto-reduction is required,^{17,30} and erythropoiesis-stimulating agents may be useful in patients with symptomatic anemia in whom the serum erythropoietin level is under 500 mU/mL.

In patients with higher risk disease, who are eligible for hematopoietic cell transplantation (HCT) and have an available donor, referral for consideration of upfront HCT is recommended.^{31,32} For patients with higher risk MF who are ineligible for

HCT, do not have a suitable donor, or prefer non-HCT therapy, ruxolitinib has been the mainstay of treatment for nearly a decade. Several studies have demonstrated that ruxolitinib may improve disease-related symptoms, splenomegaly and quality of life.^{33,34} Since ruxolitinib's approval, a number of other JAK inhibitors have been developed, most notably fedratinib, which was approved in Canada in September 2020. Momelotinib and pacritinib, which aim to improve the incidence of adverse events such as anemia and thrombocytopenia, respectively, are currently being evaluated in phase 3 trials.

In addition to novel JAK inhibitors, a number of investigational agents are being studied in combination with a JAK inhibitor. The bromodomain and extra-terminal domain inhibitor, pelabresib (CPI-0610), the BCL-2/BCL-XL inhibitor, navitoclax, and the phosphatidylinositol 3-kinase inhibitor, pascalisib, have all shown clinical benefit in phase 2 studies and are currently in phase 3 trials

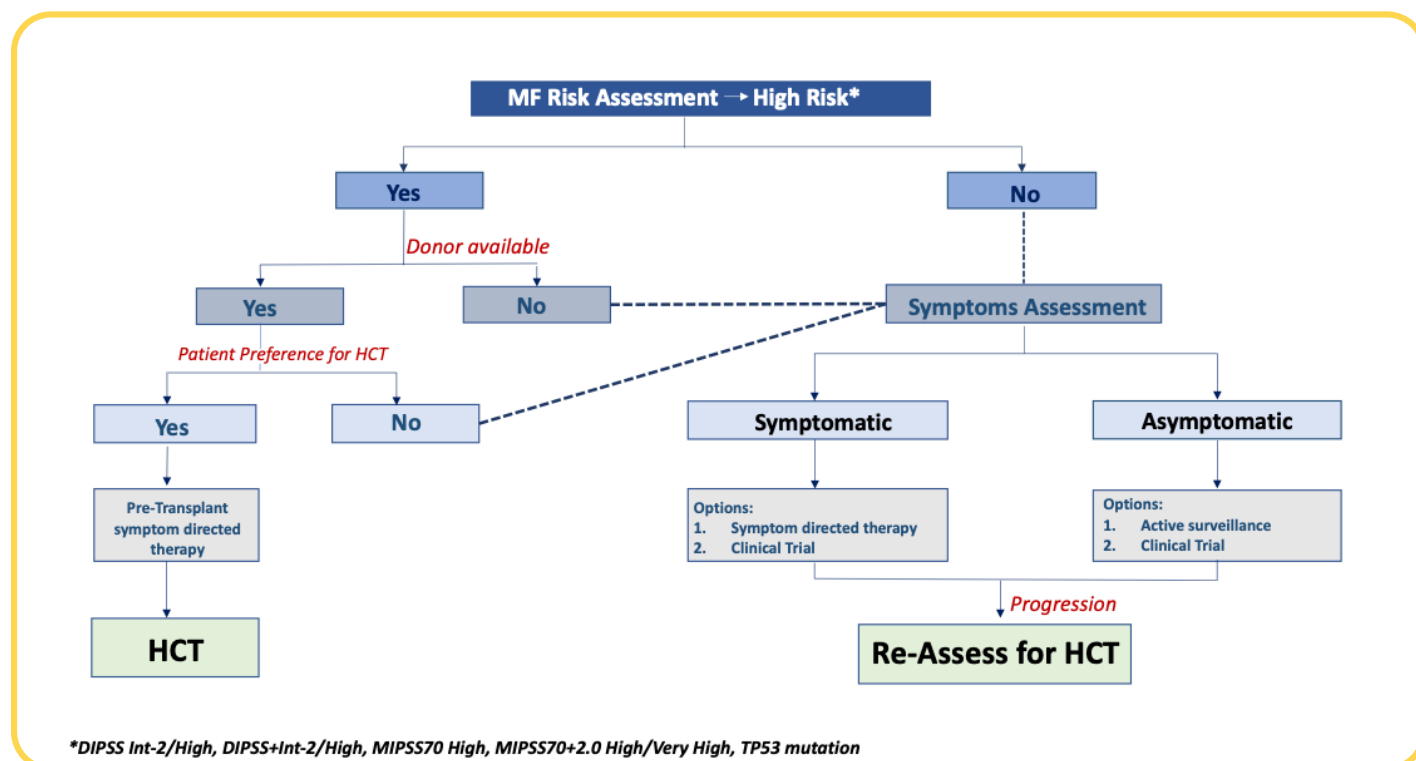


Figure 1. Management Algorithm for Transplant eligible MF Patients in chronic phase (used with permission from England J, Gupta V. Novel therapies vs hematopoietic cell transplantation in myelofibrosis: who, when, how? *Hematology Am Soc Hematol Educ Program* 2021; 2021(1): 453-462.)

(NCT04603495, NCT04472598, NCT04551066). Another agent of interest is luspaterecept, which has been demonstrated to improve hemoglobin and reduce transfusion requirements in patients with myelodysplastic syndrome.³⁵ Symptomatic anemia is an unmet clinical need in MF and in a phase 2 study, luspaterecept in combination with ruxolitinib resulted in 27% transfusion-independence for 12 consecutive weeks.³⁶ This drug is also in phase 3 testing for patients with MF and red cell transfusion dependence in combination with ruxolitinib (NCT04717414).

Conclusions and Future Directions

The past decade has seen major shifts in diagnosis, prognostication, and management of MPN. Driver mutations lead to constitutive activation of the JAK-STAT signalling pathway, and the clinical phenotype and disease evolution likely results from a complex interplay of host genomic background, inflammatory pressures, and acquisition of new mutations. There has been renewed interest in IFN for its disease-modifying potential and ongoing trials with long-term follow-up will help inform its place in the MPN therapeutic algorithm. Management of MF begins with risk assessment and a clear understanding of the patient's goals and preferences. For higher risk patients who are ineligible for, or chose not to undergo, HCT, there are several promising new agents and patients should be offered clinical trial participation whenever possible.

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