LEUKEMIA & LYMPHOMA SOCIETY®

HEALTHCARE PROFESSIONALS

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Facts About
Myeloproliferative Neoplasms (MPNs)

Introduction

Myeloproliferative neoplasms (MPNs) are a group of related blood cancers characterized by clonal proliferation of hematopoietic stem cells in the bone marrow. The 3 classical MPNs, including polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (MF), are associated with mutations in specific genes that result in overproduction of one or more blood cell types. Treatment of MPNs is focused on alleviating symptoms, improving quality of life, and reducing risk of disease progression. This Fact Sheet provides a practical overview of MPN incidence and survival trends, classification, risk factors, clinical features, diagnosis and workup, treatment, and management of treatment-related side effects. This fact sheet also provides details on long-term and late effects of therapy, as well as an overview of survivorship needs in the years and decades following initial diagnosis and treatment. By using this fact sheet and related resources from LLS, healthcare professionals will be better prepared to support patients with MPNs as they navigate the journey through diagnosis, treatment, and survivorship care.

Highlights

- Classical MPNs include polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF). Myelofibrosis can develop with no preceding history of an MPN (primary MF), but can also arise from PV or ET (secondary MF).
- Chronic myeloid leukemia (CML) can also be classified as an MPN. Other less common MPNs include hypereosinophilic syndrome and systemic mastocytosis.
- PV, ET, and MF are characterized by abnormal proliferation of one or more blood cell types.
- Acquired mutations in the *JAK2, MPL*, and *CALR* genes are frequently implicated in the development of these MPNs. Other genetic mutations may be present, some of which are linked to poorer prognosis.
- Patients with MPNs may experience a variety of symptoms, including headache, fatigue, itching, bruising, and bleeding.
- Shared features of MPNs include constitutional symptoms, organ enlargement, and risk of disease transformation.
- MPNs can be diagnosed at any age but are most common in adults 50-60 years of age or older.
- Overall survival varies from a median of 4.4 years for primary MF to 18 years for ET.
- An MPN diagnosis is obtained through clinical history and evaluation, laboratory tests, bone marrow biopsy, and genetic evaluation.
- Risk stratification is useful to help predict disease progression and inform treatment decisions. Several scoring systems are available, include some that incorporate molecular and cytogenetic data.
- In MF, the only curative treatment is allogeneic hematopoietic stem cell transplantation (alloHSCT), an option for patients with MF. However, the introduction of JAK inhibitors (ruxolitinib, fedratinib, pacritinib, and momelotinib) has improved the care of MF, providing new options to improve symptoms and enhance quality of life.
- The treatment of PV and ET is focused on cytoreductive therapy (i.e., treatment to control blood cell counts), antiplatelet therapy (low-dose aspirin), and management of cardiovascular risk factors.
- New therapeutic approaches are under study in clinical trials, including several promising agents being evaluated as a stand-alone therapy or in combination with a JAK inhibitor (ruxolitinib).
- MPN treatments have characteristic side effect profiles, including specific adverse reactions that may require monitoring and management.
- Patients with MPNs may experience long-term and late effects that compromise quality of life or lead to adverse health outcomes.
- As patients with MPNs may live months or years after diagnosis, survivorship care is an important component of the overall care plan.

MPN Overview

The term myeloproliferative neoplasm (MPN) is used to describe a group of related blood cancers with varied features and variable prognoses. A key feature of MPNs is clonal proliferation of hematopoietic stem cells in the bone marrow, resulting in overproduction of mature blood cells.[1] Patients with MPNs may have elevated quantities of platelets, red blood cells (RBCs), or white blood cells (WBCs), either in isolation or in combination (e.g., elevated platelets and RBCs).[1] MPNs are rare, with approximately 20,000 persons diagnosed each year in the United States.[2] Although they can occur at any age, MPNs are most often seen among individuals in their 50s, 60s, or later decades of life.[2]

Defining MPNs

Classical MPNs include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (MF). These three diseases have shared features that help define them as MPNs. Each disorder is characterized by abnormal proliferation of one or more blood cell types;[1] this underlying feature is usually associated with acquired mutations in specific genes, most notably *JAK2*, *MPL*, and *CALR*, all of which are involved in signaling pathways that mediate blood cell production. These mutations are considered to be drivers of the disease, and constitute an important component of MPN diagnostic criteria.[3] The prevalence of these mutations varies by MPN subtype, with *JAK2* mutations (usually the *JAK2*V617F mutation) occurring in the majority of ETs and nearly all PVs; by contrast, *MPL* and *CALR* mutations are present in a substantial number of ET and MF cases, but almost never in PV.[1]

Although presentations vary, the three classical MPNs have several symptoms in common, including headache, fatigue, pruritus (itching), bruising, and bleeding.[4] Other important shared feature of these MPNs include organomegaly (organ enlargement) and risk of disease transformation. Each of these MPNs may progress to more severe forms of disease, including acute leukemia.[5] The risk of MPNs varies by age and sex, with PV being most common in men over 60 years of age. By contrast, ET most commonly seen in women over 50 years of age, while MF is most often seen in men and women over 60.[5] Patients with MPNs can live for years following a diagnosis, though survival varies by subtype. Based on a Mayo Clinic report including more than 3,000 patients, median overall survival was just 4.4 years for primary MF, as compared to 15 years for PV and 18 years for ET.[6]

What follows is a brief description of all 3 classical MPNs, followed by **Table 1**, which highlights the predominant features of each disorder.

Polycythemia Vera (PV)

Polycythemia vera is characterized by erythrocytosis (a high concentration of RBCs). However, the erythrocytosis is rarely isolated, but instead, is often accompanied by elevated WBC and platelet counts. Patients with PV may experience splenomegaly over time and are at increased risk of thrombosis. Their disease may progress to MF, and sometimes to a blast phase that is similar to acute myeloid leukemia (AML).[3] Of note, nearly all PVs harbor *JAK2* mutations, and as a consequence, *JAK2* wild-type PV is extremely rare (see Table).

Essential Thrombocythemia (ET)

Essential thrombocythemia is characterized by increased platelet counts. Patients with ET are at an increased risk of thrombosis/bleeding and progression to MF. The mutational profile of ET influences a patient's risk of thrombosis and disease progression. The highest risk of thrombosis is in ET that harbors *JAK2* mutations, which may progress to PV or myelofibrosis. By contrast ET with *CALR* mutations have a lower risk of thrombosis, but a higher risk of progression to MF. Finally, ET with no *JAK2*, *CALR*, or *MPL* mutations (called "triple-negative" ET) have an indolent (slow-progressing) disease course and fewer vascular events.[3]

Myelofibrosis (MF)

Myelofibrosis is marked by the proliferation of granulocytes and megakaryocytes and is accompanied by fibrosis (scarring) that can compromise bone marrow function. While some patients are asymptomatic at diagnosis, most experience symptoms as the disease progresses. Characteristic symptoms include fever, night sweats, weight loss, and debilitating bone pain. While clinical signs often include anemia and enlargement of the liver and spleen. Of note, MF can be primary (i.e., occurring as a stand-alone disease in a patient with no history of an MPN) or secondary to PV or ET (i.e., a result of disease progression in patients with those MPNs).

Primary MF can be further categorized as early, pre-fibrotic MF, or overt MF. In overt MF, the disease has advanced such that patients experience bone marrow fibrosis and enlarged organs resulting from the expansion of abnormal clonal cells.[7] Primary MF is associated with a higher symptom burden compared to the other MPNs, while prognosis risk of progression depends on the mutational profile, among other clinical features. Patients with MF harboring *CALR* mutations have a longer survival compared to MF harboring *JAK2* or *MPL* mutations. In contrast to triple-negative ET, which has an indolent disease course, triple-negative MF is an aggressive MPN with a high risk of leukemic transformation.[3]

Table 1. MPN Overview

MPN Type	Key Clinical/Laboratory Findings	Molecular Features
Polycythemia vera	• Erythrocytosis • Bone marrow hypercellularity	• *JAK2* (98%+)
Essential thrombocythemia	• Thrombocytosis • Normocellular bone marrow • Proliferation of enlarged megakaryocytes	• *JAK2* (60-65%) • *CALR* (20-25%) • *MPL* (4-5%)
Myelofibrosis	• Splenomegaly • Bone marrow fibrosis • Cytopenias	• *JAK2* (60-65%) • *CALR* (25-30%) • *MPL* (4-5%)

Source: Table courtesy of Douglas A. Tremblay, MD. Adapted based on Rumi E and Cazzola M. *Blood* (2017) 129 (6): 680–692.

Other Notable MPNs

Chronic myeloid leukemia (CML) is sometimes also classified as an MPN. In contrast to the classical MPNs, CML is associated with the Philadelphia chromosome and expression of *BCR/ABL* fusion gene.[1] Consequently, ET, PV, and MF are sometimes referred to as the BCR:ABL1-negative MPNs. The diagnosis, workup, and treatment of CML is substantially different than the classical MPNs.

More information about CML management and patient support is available through our website (www.LLS.org/leukemia/chronic-myeloid-leukemia).

The umbrella of MPNs also includes some less common diseases, including hypereosinophilic syndrome and systemic mastocytosis, and conditions that have overlapping features with myelodysplastic syndromes (MDS), such as chronic myelomonocytic leukemia (CMML).[1]

Diagnosis

In patients with suspected MPNs, a diagnosis can be confirmed through a combination of clinical history and evaluation, laboratory tests, bone marrow biopsy, and genetic evaluation. Confirming the diagnosis and identifying the disease subtype (i.e., PV, ET, or MF) helps to inform appropriate therapeutic decision-making. The diagnosis should be based on criteria as included in the 5th edition of the 2022 World Health Organization (WHO) classification of myeloid and histiocytic/dendritic neoplasms.[8] In addition, a new International Consensus Classification (ICC) has been introduced that provides updates on clinical presentation, morphological features, and disease-specific mutations.[9,10]

Clinical history and evaluation can reveal typical symptoms such as (in the case of MF) headaches, night sweats, bone pain, pruritus, fatigue, unexplained weight loss, and enlarged spleen. The symptoms of PV are similar to MF, while patients with ET may present with fatigue, headaches, and increased hemorrhage risk.[11] Key laboratory evaluations include complete blood count (CBC) with differential, comprehensive metabolic panel with uric acid, lactate dehydrogenase, and liver function tests.[12]

Bone marrow biopsy, a requirement for nearly all patients, can provide insights into bone marrow composition and structure characteristic of ET, PV, or MF.[3] The biopsy can also reveal the extent of fibrosis in the bone marrow. Furthermore, bone marrow samples are used to detect MPN-associated genetic mutations. Molecular testing can reveal mutations in genes that help define the disease and subtype (i.e., *JAK2*, *MPL*, and *CALR*). In addition, mutations in other genes are often present, especially in advanced disease. Many are linked to poorer prognosis, including *EZH2*, *IDH1/2*, *SRSF2*, *U2AF1*, and *ASXL1*.[8] In addition, fluorescence in situ hybridization (FISH) or reverse transcriptase polymerase chain reaction (RT-PCR) for BCR::ABL1 can be used to exclude a diagnosis of CML.[12]

Risk Stratification

Risk stratification tools are available to help predict disease progression and inform treatment decisions, largely through the identification of patients with disease that is considered high risk.[7] In PV and ET, a number of risk stratification systems are available that focus on thrombotic risk, leukemia risk, and/or survival, including the International Prognostic score for ET (IPSET), and in PV, criteria based on an international study including 1545 patients published in 2013.[13]

In MF, there are multiple risk stratification models available. The Dynamic International Prognostic Scoring System (DIPSS), which can be applied at any point in the clinical course, yields a risk score based on age, constitutional symptoms, hemoglobin, WBC count, and circulating blasts to classify patients as low, intermediate-1, intermediate-2, or high risk.[3,14] Subsequently, researchers developed the Mutation-Enhanced International Prognostic Scoring System for patients 70 years of age or younger (MIPSS70) with primary MF. The MIPSS70 integrates molecular and cytogenetic data with clinical information to generate a risk score.[15]

Treatment Options

The only curative option for patients with MPNs is allogeneic hematopoietic stem cell transplant (alloHSCT), which is an option for MF, but not PV or ET. Multiple treatments approved in recent years help alleviate symptoms, improve quality of life, and potentially extend survival in some cases without the need for stem cell transplant.[5] Notable new treatments include the Janus kinase (JAK) inhibitors, the first of which was ruxolitinib, approved in 2011 for MF. Today, there are three additional JAK inhibitors approved in MF (fedratinib, pacritinib, and momelotinib), while in PV, approvals include ruxolitinib and ropeginterferon alfa-2b, a next-generation interferon.[5] Details of MF, PV, and ET treatment standards are described below.

Treatment of Myelofibrosis

For patients with intermediate-2 and high-risk patients, the recommended treatment is often alloHSCT, which as noted is the only currently available curative option. However, the risk of early transplant mortality is high, so patient selection and transplant timing are critical variables in treatment decision-making (e.g., advanced age is a major reason not to proceed with transplant).[7] Ultimately, the majority of symptomatic patients will need treatments that are not alloHSCT, though failure of those treatment options suggests a need to reevaluate transplant as an option, particularly if the patient is fit (e.g., a younger patient with few or no comorbidities).

In addition to transplant, the traditional therapeutic armamentarium for MF included agents such as erythropoietin, interferon-alfa, danazol, hydroxyurea, and the immunomodulatory drugs thalidomide and l enalidomide.[7] The treatment landscape changed following the approval of the JAK inhibitors, which is now the

preferred treatment approach for patients with constitutional symptoms or symptomatic splenomegaly.[12] Of note some of the indications are specific to cytopenias, including low platelet counts in the case of pacritinib and anemia in the case of momelotinib. The available JAK inhibitors and their indications are described in **Table 2**.

Table 2. JAK Inhibitors Indicated for Treatment of Myelofibrosis

JAK Inhibitor	Year Approved (FDA)	Target	Indication in MF	Notes
Ruxolitinib	2011	JAK1/JAK2	Intermediate or high-risk MF, including primary or secondary MF	Also approved for PV in adults with an inadequate response to, or intolerance of, hydroxyurea
Fedratinib	2019	JAK2	Intermediate-2 or high-risk primary or secondary MF	–
Pacritinib	2022	JAK2/IRAK1	Intermediate or high-risk primary or secondary MF and platelet count below 50 x 10^9/µL	Accelerated approval based on spleen volume reduction
Momelotinib	2023	JAK1/JAK2	Intermediate or high-risk MF (primary or secondary MF) in adults with anemia	–

Abbreviation: FDA = Food and Drug Administration.

Note: Secondary MF = MF post-ET or post-PV.

References:
Ruxolitinib (Jakafi) Prescribing Information: https://www.jakafi.com/pdf/prescribing-information.pdf
Fedratinib (Inrebic) Prescribing Information: https://packageinserts.bms.com/pi/pi_inrebic.pdf
Pacritinib (Vonjo) Prescribing Information: https://www.vonjohcp.com/sites/default/files/2024-09/prescribing-information.pdf
Momelotinib (Ojjaara) Prescribing Information: https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Ojjaara/pdf/OJJAARA-PI-PIL.PDF

Treatment of Polycythemia Vera

The treatment of PV is often focused on addressing thrombosis risk that is characteristic of this MPN subtype. The cornerstones of PV treatment include cytoreductive therapy (i.e., treatment to control blood cell counts) and antiplatelet therapy (i.e., low-dose aspirin). The recommended therapeutic approach for low-risk PV includes regular large volume blood draws (phlebotomy) to eliminate excess RBCs and maintain the hematocrit below 45%, use of low-dose aspirin, and management of cardiovascular (CV) risk factors.[16] Additional options for cytoreductive therapy may be needed for low-risk PV with persistent symptoms despite phlebotomy or if phlebotomy is not tolerated.[16]

While the approach is the same in PV patients at high thrombotic risk (i.e., phlebotomy, aspirin, and CV risk factor management), additional cytoreductive therapies are recommended, including hydroxyurea and ropeginterferon alfa-2b, a novel interferon formulation approved by the US Food and Drug Administration in 2021.[16] Other potential options for cytoreductive therapy include peginterferon alfa-2b, as well as ruxolitinib, which is indicated for treatment of PV in patients who are intolerant of or resistant to hydroxyurea.[17]

The use of cytoreductive therapy should be an individualized decision based on toxicity profile and the goals of treatment and the anticipated toxicities.[18] Cytoreductive therapy is especially needed in patients who are symptomatic or at high risk for thrombosis.[19] Such treatment is not routinely recommended in younger patients, who are often considered low risk due to age and no history of thrombosis; however, some data suggest that in younger patients with PV, cytoreductive therapy is well tolerated, with acceptable toxicity levels and a potential therapeutic benefit.[20]

Treatment of Essential Thrombocythemia

While phlebotomy is not a therapeutic option for ET, management is otherwise similar to PV in that cytoreductive and antiplatelet therapies are utilized as appropriate. No treatment may be needed for young (<60 years), asymptomatic patients with acceptable platelet counts, though management decisions should be based on individualized assessment of factors such as CV risk and thrombosis history.[16,18] For patients at low to intermediate risk of thrombosis, the recommended management approach may include low-dose aspirin and management of CV risk factors.[16] Cytoreductive therapy is warranted in patients at

high risk, including those with a history of thrombosis and older patients with a *JAK2* mutation. Options for cytoreduction in ET include hydroxyurea, peginterferon alfa-2a, and the platelet-reducing agent anagrelide.[18]

Emerging Treatment Options/Clinical Trials

As new therapeutic approaches are under study, consideration of clinical trial enrollment is appropriate for all patients with MPNs at any point in the disease course.[12] The pace of treatment development is particularly brisk in MF, where a number of new agents are being evaluated alone or in combination with approved JAK inhibitor therapy (i.e., ruxolitinib).[7]

Among the treatments being paired with ruxolitinib is pelabresib, an oral small-molecule inhibitor bromodomain extra-terminal (BET) protein BRD4, which interacts with transcription factors that promote cancer cell growth and survival.[7] A randomized, phase 3 study of pelabresib plus ruxolitinib or placebo is ongoing (NCT04603495); in an updated report on the study, pelabresib plus ruxolitinib continued to improve spleen volume, symptoms, anemia, and bone marrow microenvironment, suggesting the potential for more profound and sustained responses compared with placebo plus ruxolitinib.[21]

Another promising combination is ruxolitinib plus selinexor, a selective nuclear export inhibitor that targets exportin-1 (XPO1). In an open label study, this combination was well tolerated and exhibited dose-dependent improvements in spleen volume reduction and symptom relief.[22] A randomized, placebo-controlled phase 3 trial of selinexor once weekly with ruxolitinib is currently underway (NCT04562389).

Another promising agent is navtemadlin (KRT-232), which inhibits murine double minute 2 (MDM2), a negative regulator of p53 that is overexpressed in certain MF cells. In a phase 2 study of patients with relapsed or refractory MF, navtemadlin demonstrated acceptable safety, clinical activity, and disease-modifying activity.[23] The randomized phase 3 BOREAS study is evaluating navtemadlin versus best available therapy for patients with MF who are relapsed or refractory to JAK inhibitor treatment (NCT03662126). In a recent report on BOREAS, navtemadlin monotherapy demonstrated clinically relevant efficacy with disease-modifying potential, prompting investigators to state that further studies are warranted (including the use of navtemadlin as add-on therapy in JAK inhibitor-naive patients with a suboptimal response to ruxolitinib).[24]

Finally, as anemia remains a major clinical dilemma in MF, new treatment approaches are needed. One agent being studied in this setting is luspatercept, the first-in-class erythroid maturation agent (EMA) that is FDA approved for treatment of anemia in patients with MDS and beta thalassemia. In a recently published phase 2 study, luspatercept improved anemia and transfusion burden in patients with MF. The benefit was observed across patient cohorts, but establishes transfusion dependent patients on a stable ruxolitinib treatment before and during the study.[25]

With these and other clinical trials underway, it is vitally important that all patients with MPNs be considered for relevant and appropriate clinical trials. This is especially true given the rarity of these disorders, which translates into difficulty recruiting enough patients to meet study enrollment targets, ultimately slowing drug approvals.[26] Of note, clinical trials are not only available to patients being managed at academic medical centers. Healthcare professionals in community practice can refer patients to trial sites or consider hosting a trial at their own institution.[26]

Side Effects of Treatment

Novel therapies, including JAK inhibitors and ropeginterferon alfa-2b, have advanced the treatment of MPNs but come with characteristic hematologic and non-hematologic side effect profiles including specific adverse reactions that may require monitoring and management **(see Table 3)**. Specific side effects tend to be associated with ruxolitinib (anemia and thrombocytopenia), pacritinib (diarrhea and nausea), fedratinib (gastrointestinal toxicity similar to pacritinib). Healthcare providers also should be aware of the complications of phlebotomy, which can include thrombocytosis, symptoms related to chronic iron deficiency, potential muscle weakness, and rarely, dysphagia.[16] Common side effects of hydroxyurea can include cytopenias, gastrointestinal issues, skin changes, and fatigue,[27] while low-dose aspirin may be contraindicated due to major bleeding or gastric intolerance.[16]

Table 3. Safety Profiles of Novel MPN Therapies

Medication	Common Adverse Reactions	Serious Adverse Reactions	Additional Notes
Ruxolitinib (Jakafi)	Anemia, thrombocytopenia, neutropenia, diarrhea, dizziness, headache	Infections, elevated cholesterol, rare secondary cancers	• Monitor blood counts and lipid parameters • Consider increased risk of specific clinical infections (e.g., herpes zoster) • Perform periodic skin examinations
Fedratinib (Inrebic)	Nausea, vomiting, diarrhea, anemia	Cardiac failure, anemia, cardiogenic shock, serious encephalopathy including Wernicke's (rare)	• Manage gastrointestinal toxicity, hepatic toxicity, and amylase/lipase elevation with dose modification • Monitor for major adverse cardiac events, secondary malignancies
Pacritinib (Vonjo)	Diarrhea, thrombocytopenia, nausea, anemia, peripheral edema	Anemia, thrombocytopenia, pneumonia, cardiac failure, pyrexia, squamous cell carcinoma of the skin	• Avoid use in patients with active bleeding, planned surgical procedures, prolonged QT interval • Monitor for signs of major adverse cardiac events, evaluate, and treat promptly • Delay treatment until resolution of active serious infections
Momelotinib (Ojjaara)	Thrombocytopenia, hemorrhage, bacterial infection, fatigue, dizziness, diarrhea, nausea, peripheral neuropathy	Infection, hemorrhage, acute kidney injury, pneumonia, pyrexia, thrombosis, syncope	• Monitor for infections, hepatotoxicity, cardiovascular symptoms, thrombosis, and secondary malignancies • Manage cytopenias with dose reduction
Ropeginterferon alfa-2b (Besremi)	Flu-like symptoms, arthralgia, fatigue, pruritus, nasopharyngitis, musculoskeletal pain	Neuropsychiatric effects (e.g., depression, suicidal ideation), autoimmune disorders, ischemic events, infections, hypersensitivity reactions	• Contraindicated in patients with severe psychiatric disorders, moderate to severe hepatic impairment, serious autoimmune disease

References:
Ruxolitinib (Jakafi) Prescribing Information: https://www.jakafi.com/pdf/prescribing-information.pdf
Lussana F, et al. *Am J Hematol*. 2018;93(3):339-347. doi:10.1002/ajh.24976
Fedratinib (Inrebic) Prescribing Information: https://packageinserts.bms.com/pi/pi_inrebic.pdf
Pacritinib (Vonjo) Prescribing Information: https://www.vonjohcp.com/sites/default/files/2024-09/prescribing-information.pdf
Momelotinib (Ojjaara) Prescribing Information: https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Ojjaara/pdf/OJJAARA-PI-PIL.PDF
Ropeginterferon alfa-2b (Besremi) Prescribing Information: https://us.pharmaessentia.com/downloads/Besremi_USPI_ENG.pdf

Long-term and Late effects

While treatments for MPNs ameliorate symptoms, improve patient outcomes, and improve quality of life, some are associated with significant long-term or late effects. Long-term effects are defined as those medical problems that may last for months or years, such as treatment-related fatigue. By contrast, late effects are medical problems that may occur years after treatment ends, such as heart disease or secondary cancers.[28]

Of note, patients with MPNs are at increased risk of developing secondary malignancies as compared to the general population, encompassing not only acute leukemias but also solid tumor malignancies. In one recent analysis, the risk of new cancers was increased by 1.5- to 3.0-fold, with notable increased risks of lymphomas, and cancers of the lung, kidney, thyroid gland, and skin.[29] The cause of the increased risk is thought to be multifactorial, encompassing both disease- and treatment related factors. In a nested case-control study, exposure to hydroxyurea, alkylating agents, and ruxolitinib increased risk of non-melanoma skin cancer, with odds ratios of 2.3 to 3.9; by contrast, no increased risk was observed for interferon-alfa, busulfan, or anagrelide.[30]

Cardiovascular risk factors, common in patients with MPNs, are associated with worse survival and thrombotic outcomes, underscoring the importance of addressing these risks as a part of MPN care to improve morbidity and mortality.[31] Recommended treatment can effectively reduce risks; for example, in PV, treatment with phlebotomy or hydroxyurea (or both) to achieve a target hematocrit of 45% or less is associated with a significantly lower rate of CV death and major thrombosis.[32]

Some MPN treatments are associated with clear long-term risks. Patients who undergo splenectomy (i.e., surgical removal of the spleen) to alleviate symptoms are at long-term risk of life-threatening infections, particularly with organisms such as pneumococci, *Haemophilus influenzae* and meningococci. Appropriate management of these patients includes immunization, antibiotic prophylaxis, and patient education to ensure the risks are well understood.[33]

As many MPN treatments may be given indefinitely, the implications of long-term therapy must be carefully considered, particularly in younger patients, who may have higher cumulative risks of adverse outcomes due to longer time on treatment.[34] For example, concerns over the potential associations between hydroxyurea and secondary malignancies may lead to consideration of alternative treatments such as interferons.[30]

Survivorship Care

As patients with MPNs can live for years or decades beyond the diagnosis, survivorship care is an important component of the overall care plan. Patients and caregivers may have difficulty adjusting to the "new normal" and may encounter significant physical and emotional challenges. To help patients and caregivers adjust, healthcare providers can help prepare a written survivorship care plan that incorporates a list of relevant healthcare providers, a summary of the diagnosis and workup, an overview of the treatments used, follow-up appointment schedules, lists of possible long-term and late effects, and health and wellness recommendations (e.g., nutrition and exercise).[35]

Survivorship care plans may be particularly important to younger MPN patients transitioning back into their daily lives and regular routines. Family planning is also an important concern for younger patients with MPNs. In these patients, it may be prudent to avoid specific medications. For example, hydroxyurea is not recommended during pregnancy or among patients trying to conceive due to animal studies suggesting a risk of fetal harm.[36] For more information on Survivorship Care, visit www.LLS.org/survivorship.

Resources for Patient/Caregiver Education and Support

From LLS

MPN Overview

www.LLS.org/myeloproliferative-neoplasms

Patient Education Booklet: Myeloproliferative Neoplasms

www.LLS.org/booklet/myeloproliferative-neoplasms

Inspirational Stories

Teri (living with polycythemia vera)

www.LLS.org/story/teri

Lauren (living with essential thrombocythemia)

www.LLS.org/node/180521

Ariana (living with essential thrombocythemia)

www.LLS.org/story/ariana-0

Facts: Updated Data on Blood Cancers

www.LLS.org/master/facts-updated-data-blood-cancers

Myeloproliferative Neoplasms (MPN) Research Funded by LLS

www.LLS.org/research/myeloproliferative-neoplasms-mpn-research-funded-lls

Patient Education Webcasts

Myelofibrosis: Charting the Course for Care

www.LLS.org/patient-education-webcasts/myelofibrosis-charting-course-care

Spotlight On Myeloproliferative Neoplasms (MPNs)

www.LLS.org/patient-education-webcasts/spotlight-myeloproliferative-neoplasms-mpns

From Others

MPN Research Foundation: Patient and Caregiver Resources

https://mpnresearchfoundation.org/patient-caregiver-resources/

Overview of Myeloproliferative Neoplasms: MSD Manual (Consumer Version)

https://www.msdmanuals.com/home/blood-disorders/myeloproliferative-disorders/overview-of-myeloproliferative-neoplasms

MPN Cancer Survivor Self-Care Tips

https://mpncancerconnection.org/2019/03/mpn-cancer-survivor-self-care-tips/

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We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has regions throughout the United States and Canada. To find the region nearest to you, visit our website at www.LLS.org/ChapterFind or contact

The Leukemia & Lymphoma Society

3 International Drive, Suite 200 Rye Brook, NY 10573
Phone Number: (800) 955-4572
(M-F, 9 a.m. to 9 p.m. ET)
Website: www.LLS.org

LLS offers free information and services for patients and families touched by blood cancers as well as for healthcare professionals. The resources listed below are available to you and your patients and are meant to be a compliment to the HCP team and an additional source of support.

Consult with an Information Specialist. Information Specialists are highly trained social workers and nurses who assist through treatment, financial, and social challenges. They offer up-to-date disease and treatment information. Language services are available. For more information, please:

- Call: (800) 955-4572 (M-F, 9 a.m. to 9 p.m. ET)
- Visit: www.LLS.org/IRC
- Email or Live chat: www.LLS.org/InformationSpecialists

Clinical Trials Support Center (CTSC). Work one-on-one with an LLS clinical trial nurse navigator who will personally assist throughout the entire clinical trial process. A nurse navigator will help identify potential clinical trials and overcome the barriers to enrollment (navigators help HCPs and patients). For more information about this free service, please:

- Call an Information Specialist: (800) 955-4572 to be referred to the CTSC
- Visit: www.LLS.org/CTSC
- Complete a referral form for your patient at: www.LLS.org/CTSCreferral

Nutrition Consultations. Nutrition Education Services Center (NESC) provides one-on-one *free* nutrition education and consultations to patients and caregivers of all cancer types with registered dietitians who have expertise in oncology nutrition.

- Visit: www.LLSnutrition.org

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- Visit: www.LLS.org/booklets

LLS Disease Information for Patients and Caregivers: Myeloproliferative Neoplasms (MPNs)

- www.LLS.org/MPN

Información en Español. (LLS information in Spanish) Para mayor información por favor:

- Visite: www.LLS.org/espanol

LLS Community. LLS Community is an online social network and registry for patients, caregivers, and healthcare professionals. It is a place to ask questions, get informed, share your experience, and connect with others. To join:

- Visit: www.LLS.org/community

LLS Regions. LLS offers community support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), in-person support groups, and other great resources. For more information about these programs or to contact your region, please:

- Call: (800) 955-4572
- Visit: www.LLS.org/ChapterFind

Patti Robinson Kaufmann First Connection® Program. A free peer-to-peer support program that connects patients and their loved ones to a trained peer volunteer who has gone through a similar experience.

- www.LLS.org/FirstConnection

Resources for Healthcare Professionals: Webinars, Podcasts, In-person Education Programs, Videos, and Fact Sheets:

- www.LLS.org/CE (free accreditation)
- www.LLS.org/HCPpodcast
- www.LLS.org/HCPvideos
- www.LLS.org/HCPbooklets

Resources for your Patients:

- www.LLS.org/programs
- www.LLS.org/EducationVideos
- www.LLS.org/podcast

Additional Resources

The National Cancer Institute (NCI)

www.cancer.gov
(800) 422-6237

The National Cancer Institute, part of the National Institutes of Health, is a national resource center for information and education about all forms of cancer. The NCI also provides a clinical trial search feature, the PDQ® Cancer Clinical Trials Registry, at www.cancer.gov/clinicaltrials, where healthcare professionals and patients can look for clinical trials.

References

1. Liesveld J. Overview of Myeloproliferative Neoplasms. Merck Manual – Professional Version. Reviewed and revised December 2023. https://www.merckmanuals.com/professional/hematology-and-oncology/myeloproliferative-disorders/overview-of-myeloproliferative-neoplasms.
2. Yale Medicine. Myeloproliferative Neoplasms: Overview. https://www.yalemedicine.org/conditions/myeloproliferative-neoplasms.
3. Rumi E, Cazzola M. Diagnosis, risk stratification, and response evaluation in classical myeloproliferative neoplasms. *Blood*. 2017;129(6):680-692.
4. Pemmaraju N. Myeloproliferative Neoplasms Defined: What Are ET, PV, and MF? June 24, 2021. https://powerfulpatients.org/2021/06/24/myeloproliferative-neoplasms-defined-what-are-et-pv-and-mf/.
5. MPN Research Foundation. An overview of MPNs. https://mpnresearchfoundation.org/understanding-mpns/.
6. Szuber N, Mudireddy M, Nicolosi M, et al. 3023 Mayo Clinic patients with myeloproliferative neoplasms: risk-stratified comparison of survival and outcomes data among disease subgroups. Mayo Clin Proc. 2019;94:599-610.
7. Swaminathan M, Jain A, Choi SD, Pemmaraju N. Janus kinase inhibitor monotherapy and combination therapies for myelofibrosis: what"s the current standard of care? *Expert Rev Hematol*. 2024;17(11):769-780.
8. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703-1719.
9. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. *Blood*. 2022;140(11):1200-1228.
10. Williams O. International Consensus Classification 2022 for myeloproliferative neoplasms. November 17, 2022. https://mpn-hub.com/medical-information/international-consensus-classification-2022-for-myeloproliferative-neoplasms.
11. Murfin K. Myeloproliferative neoplasms (MPNs): 7 questions, answered. May 21, 2021. https://www.mdanderson.org/cancerwise/myeloproliferative-neoplasms--mpns--types-diagnosis-treatment-research-7-questions--answered.h00-159460845.html.
12. National Comprehensive Cancer Network. NCCN Guidelines Version 2.2024. Myeloproliferative Neoplasms. August 8, 2024. .
13. Harrison CN, Garcia NC. Management of MPN beyond JAK2. *Hematology*. 2014;2014(1):348-354.
14. Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). *Blood*. 2010;115(9):1703-1708.
15. Guglielmelli P, Lasho TL, Rotunno G, et al. MIPSS70: Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients With Primary Myelofibrosis. *Journal of Clinical Oncology*. 2018;36(4):310-318.
16. National Cancer Institute. Myeloproliferative Neoplasms Treatment (PDQ®)–Health Professional Version. Updated September 27, 2024. https://www.cancer.gov/types/myeloproliferative/hp/myeloproliferative-neoplasms-treatment.
17. Ruxolitinib tablets, for oral use [Prescribing Information]. Wilmington, DE: Incyte Corporation. 2021.
18. Tremblay D. Cytoreduction for ET and PV: who, what, when, and how? *Hematology Am Soc Hematol Educ Program*. 2023;2023(1):660-666.
19. Tremblay D. Tremblay on the Use of Cytoreductive Therapy in PV and ET. January 8, 2024. https://www.targetedonc.com/view/tremblay-on-the-use-of-cytoreductive-therapy-in-pv-and-et.
20. Chamseddine RS, Savenkov O, Rana S, et al. Cytoreductive therapy in younger adults with polycythemia vera: a meta-analysis of safety and outcomes. *Blood Adv*. 2024;8(10):2520-2526.
21. Mascarenhas JO, Grosicki S, Chraniuk D, et al. Updated Results from the Phase 3 Manifest-2 Study of Pelabresib in Combination with Ruxolitinib for Janus Kinase Inhibitor-Naïve Patients with Myelofibrosis. *Blood*. 2024;144(Supplement 1):3178-3178.
22. Duan M, Ma L, Wu Q, et al. The Efficacy and Safety of Selinexor in Combination with Ruxolitinib in Ruxolitinib-Treated Myelofibrosis Patients: The Interim Analysis of a Prospective, Open-Label, Multicenter, Parallel-Cohort, Phase 2 Study. *Blood*. 2023;142(Supplement 1):4578-4578.
23. Al-Ali H, Delgado R, Lange A. First-in-class, Murine Double Minute 2 Inhibitor (MDM2i) for Myelofibrosis relapsed or refractory to Janus Associated Kinase Inhibitor Treatment. Paper presented at: European Hematology Association Annual Meeting 2020.
24. Mascarenhas JO, Popov VM, Mohan S, et al. Results from the Randomized, Multicenter, Global Phase 3 BOREAS Study: Navtemadlin Versus Best Available Therapy in JAK Inhibitor Relapsed/Refractory Myelofibrosis. *Blood*. 2024;144(Supplement 1):1000-1000.
25. Gerds AT, Harrison C, Kiladjian J-J, et al. Safety and efficacy of luspatercept for the treatment of anemia in patients with myelofibrosis. *Blood Advances*. 2024;8(17):4511-4522.
26. MPN Research Foundation. 30 facts about MPNs. https://mpnresearchfoundation.org/30-facts-about-mpns/.
27. MPN Alliance Australia. Hydroxycarbamide (hydroxyurea). https://www.mpnallianceaustralia.org.au/understanding-mpn/treatments/hydroxycarbamide-hydroxyurea/.
28. Leukemia & Lymphoma Society. Long-Term and Late Effects of Treatment in Adults: Facts. https://www.lls.org/sites/default/files/file_assets/longtermlateeffectsadults.pdf.
29. Brabrand M, Frederiksen H. Risks of Solid and Lymphoid Malignancies in Patients with Myeloproliferative Neoplasms: Clinical Implications. Cancers. 2020; 12(10):3061. https://doi.org/10.3390/cancers12103061.
30. Barbui T, Ghirardi A, Masciulli A, et al. Second cancer in Philadelphia negative myeloproliferative neoplasms (MPN-K). A nested case-control study. *Leukemia*. 2019;33(8):1996-2005.
31. How J, Leiva O, Marneth AE, et al. Cardiovascular Risk Factors Are Common in Myeloproliferative Neoplasms and Portend Worse Survival and Thrombotic Outcomes. *Blood*. 2023;142(Supplement 1):4568-4568.
32. Marchioli R, Finazzi G, Specchia G, et al. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med*. 2013;368(1):22-33.
33. Brigden ML. Detection, education and management of the asplenic or hyposplenic patient. *Am Fam Physician*. 2001;63(3):499-506, 508.
34. Joszt L. The Balance of Managing Younger Patients With MPNs for Long-Term Treatment. December 26, 2024. https://www.ajmc.com/view/the-balance-of-managing-younger-patients-with-mpns-for-long-term-treatment.
35. Leukemia & Lymphoma Society. Survivorship Workbook. https://www.lls.org/children-and-young-adults/young-adults/survivorship.
36. Hydroxyurea: Package Insert/Prescribing Info. Last updated November 5, 2024. https://www.drugs.com/pro/hydroxyurea.html.