Advancing Care for Patients with Myeloproliferative Neoplasms

Landscape Analysis

Background

Myeloproliferative neoplasms, while rare, are a group of hematopoietic stem cell cancers that despite recent advancements in the realm of hematologic malignancies, continue to be a challenge for patients diagnosed with these cancers. Gene expression analysis and next-generation sequencing has led to the identification of unique biomarkers associated with myeloid neoplasms, significantly improving the diagnostic and prognostic criteria of these cancers. Yet, while progress has been made in understanding and classifying the disease, myeloproliferative neoplasms continue to be challenging to diagnose, can be rapidly progressive, and demand complex treatment and follow-up care.

For years, myeloproliferative disease was classified as a blood disorder. In 2008, the World Health Organization (WHO) reclassified the disease to clonal hematopoietic stem cell malignancies,[1] and in 2016, the WHO reclassified it again, identifying four classic types of myeloproliferative neoplasms: chronic myeloid leukemia (BCR-ABL1 positive); polycythemia vera (BCR-ABL1 negative); essential thrombocythemia (BCR-ABL1 negative); and primary myelofibrosis (BCR-ABL1 negative).[2] The upcoming fifth edition of the *WHO Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms* is expected to offer further refinement of diagnostic criteria and emphasis on therapeutically and/or prognostically actionable biomarkers, for greater differentiation of different disease subtypes.[3]

While these evolving reclassifications have impacted incidence and epidemiological studies, according to the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, it estimates that approximately 20,000 people in the United States are diagnosed with myeloproliferative neoplasms each year and about 295,000 people are living with the disease.[4]

Chronic myeloid leukemia accounts for 0.5% of all new cancer cases in the US, with an incidence rate of 1.4 – 2.4 new cases per 100,000 people annually. Polycythemia vera is estimated as 0.4 to 2.8 cases per 100,0000, essential thrombocythemia between 1 to 2.5 cases per 100,000, and primary myelofibrosis varies from 0.8 to 2.1 per 100,000 people per year.[2]

Treatment and Care Challenges

Beyond complications with classification, the treatment and care of patients with myeloproliferative neoplasms remains a challenge. This is primarily due to a lack of uniform treatment plans for each of the classical subgroups, which carry a significant symptom burden for patients, from the disease itself and/or resulting from pharmacological treatments.[5]

Patients may suffer debilitating symptoms, including fevers, night sweats, fatigue, sleep disturbances, weight loss, bone pain, pruritis (itchy skin), headaches, difficulty concentrating, anxiety, and depressive symptoms.[6] Even in patients who are classified as having a low symptom burden or a low-risk score, these symptoms can cause a significantly reduced quality of life.[7]

While patients with myeloproliferative neoplasms are considered to have a favorable life expectancy, with up to 60% of patients living up to 15 years after diagnosis,[8] about 84% of patients report reduced quality of life directly due to symptom burden. Many low-risk patients with myeloproliferative neoplasms are given a "watch-and-wait" treatment plan, receiving no drug therapy despite experiencing a moderate to high symptom burden.[7] Moreover, approximately 89% of patients report increased anxiety regarding the possibility of disease progression.[8,7] These findings highlight the need

for standardized and proactive symptom assessments at diagnosis and throughout treatment.

Another major challenge for providers caring for patients with myeloproliferative neoplasms is disease progression—such as the progression of polycythemia vera or essential thrombocythemia to myelofibrosis, or the progression of any classical subtype to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). Thus, meticulous care coordination and monitoring of symptoms is critical, and underscores the importance and impact that timeliness of treatment has upon favorable patient outcomes.[9]

Symptom assessment tools like the Myeloproliferative Neoplasm-Symptom Assessment Form and the more recent ten-point assessment tool MPN10, have proven to be valuable tools to help patients accurately track and describe symptoms (eg, the MPN10 uses a scale of 0-10, score 0 means absent/no such issue and score 10 means worst imaginable/as bad as it can be). These tools, which generate a Total Symptom Score (TSS), in turn helps providers assess and track symptom progression and severity over time, as well as guide care management decisions and treatment plans.

Current Care Coordination Gaps

Systematic reviews of patients with myeloproliferative neoplasms show dissonance between patient and physician perceptions of disease management and symptom burden, which in turn affect patient outcomes.[10] Current standard-of-care pharmacological treatments do not fully relieve symptom burden, with approximately 84% of patients with myeloproliferative neoplasms reporting reduced quality of life due to managing symptoms and adverse effects of their current pharmacological interventions.[8]

An underestimation of disease burden, symptom prevalence, and severity by physicians was found,[10] leading to concerns that symptom alleviation and/or prompt treatment of disease progression for patients with myeloproliferative neoplasms may be delayed or hindered. There was also a reported disconnect between the information that physicians believed they were providing patients, and the information that patients actually understood.[10] While an average of 73%of physicians reported classifying patients by prognostic risk categories, an average of just 34% of patients reported that their physician has classified them by a prognostic risk score.[10] Additionally, most physicians report that their standard practice includes classifying patients by prognostic risk, despite a lack of uniform prognostic risk scoring assessments. This gap highlights the need for standardized assessment methods for patients with myeloproliferative neoplasms.[5,10]

Further disconnects were found, as patients with myeloproliferative neoplasms often did not recognize their symptoms as related to their disease although symptoms were recognized by physicians to be disease-related.[5,10] In addition, most patients reported reduced quality of life due to disease-related symptoms, whereas an average of 40% of physicians agreed that patient quality of life was not significantly affected in the absence of severe splenomegaly.[10]

Patient and physician perceptions regarding treatment goals were also generally unaligned.[5,10] Patients reported their most important treatment goal was to slow or delay disease progression, whereas physicians identified symptom improvement and prevention of vascular or thrombotic events as important treatment goals.[10] Disharmony between patient and physician treatment goals can limit patient treatment compliance, resulting in reduced clinical and quality of life outcomes. An average of 30% of patients with myeloproliferative neoplasms did not believe their physician had a treatment plan, and an average of 35%of patients believed their physician was not providing updates on new treatments.[10] These results show a need for transparency and shared decision-making, along with the need for standardized treatment algorithms when it comes to management of myeloproliferative neoplasms. [5,10]

Considerations of Health Disparities

Health literacy and economic health disparities play key roles in the care received by patients with myeloproliferative neoplasms. There is an emphasis in health literacy on the ability to not just understand but to use health information, along with the ability to make

well-informed decisions.[11] As myeloproliferative neoplasms involve complex diagnosis and treatment information, health literacy is integral to understanding and managing symptom burden, shared decision-making, and proper disease management.

According to a 2016 online survey completed by 904 adults (aged 18-70) diagnosed with myelofibrosis, polycythemia vera, or essential thrombocythemia, significant employment disruptions were common. At least one employment change due to myeloproliferative neoplasms was reported by 65.5% of patients with myelofibrosis, 48% of patients with polycythemia vera, and 38.8% of patients with essential thrombocythemia, all of whom had been employed at diagnosis. The most reported initial employment status change was leaving a job among patients with myelofibrosis and polycythemia vera. Reduced working hours were also reported among patients with essential thrombocythemia, and on average, tended to occur soon after diagnosis among myelofibrosis respondents (1.4 years) compared to essential thrombocythemia respondents (1.9 years) and polycythemia vera respondents (2.9 years). Respondents also reported medical disability leave, early retirement, dropping to part-time, and switching to lower-paying jobs. Some currently employed respondents experienced absenteeism, presenteeism, work impairment, and activity impairment. Career opportunity and salary limitations were reported by 54.4% and 43.9% of patients with myeloproliferative neoplasms, respectively.[12]

Health equity occurs when health disparities are accounted for in healthcare.[11] It is important when caring for patients with myeloproliferative neoplasms to address the complexities that come with this diagnosis and treatment to ensure patients are informed and involved in their care.

Current Treatment Landscape

While challenges in treating myeloproliferative neoplasms arise from a lack of uniform treatment plans for each classical subgroup,[5] the National Comprehensive

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Polycythemia vera is currently classified as an incurable disease, with treatment goals focused on preventing disease progression and symptom alleviation. Recommended treatment for polycythemia vera depends on a patient's risk stratification:

Low-risk: Younger than 60 years of age with no prior history of thrombosis

High-risk: 60 years of age or older and/or a prior history of thrombosis.

Risk Level	Recommended Management and Treatment[13, a]
Both risk levels	• Manage cardiovascular risk factors • Aspirin (81-100 mg/day) • Phlebotomy (to maintain hematocrit <45%; • Monitor for new thrombosis or bleeding • Monitor signs/symptoms of disease progression every 3-6 months or more frequently if clinically appropriate (see myeloproliferative neoplasm symptom assessment form)
Low-risk[b]	• Evaluate for indications of cytoreductive therapy (potential indications are new thrombosis, disease-related major bleeding, frequent phlebotomy or intolerant of phlebotomy, splenomegaly, progressive thrombocytosis and/or leukocytosis, disease-related symptoms) • Ropeginterferon alfa-2b-njft (other recommended regimen) is an initial treatment option

High-risk	• Initial Cytoreductive therapy options:
	  • Hydroxyurea (preferred)
	  • Peginterferon alfa-2a (preferred) (consider for younger patients or in pregnant patients in need of cytoreductive therapy or in those in need of cytoreductive therapy that defer hydroxyurea or ropeginterferon alfa-2b-njft)
	  • Ropeginterferon alfa-2b-njft (other recommended regimen)
	• Bone marrow aspirate and biopsy should be performed to rule out disease progression to myelofibrosis prior to the initiation of cytoreductive therapy
	• Monitor for response to cytoreductive therapy every 3-6 months or more frequently as clinically indicated (potential indications for change of cytoreductive therapy are intolerance or resistance to hydroxyurea or peginterferon alfa-2a, new thrombosis, disease-related major bleeding, frequent phlebotomy or intolerant of phlebotomy, splenomegaly, progressive thrombocytosis and/or leukocytosis, disease-related symptoms)
	• If change of cytoreductive therapy is indicated, these therapeutic regimens are recommended options:
	  • Clinical trial (preferred)
	  • Ruxolitinib (preferred): FDA approved in patients who have had an inadequate response to or are intolerant of hydroxyurea
	  • Other recommended regimens: Ropeginterferon alfa-2b-njft, hydroxyurea, or peginterferon alfa-2a (consider for younger patients or in pregnant patients in need of cytoreductive therapy or those in need of cytoreductive therapy that defer hydroxyurea or ropeginterferon alfa-2b-njft), if not previously used

a. This is a simplification of the Guideline recommendations. See www.NCCN.org for detailed recommendations including the order of the recommendations.
b. See the Guidelines for cytoreductive therapy options for symptomatic PV with potential indications for cytoreductive therapy and for subsequent recommendations.

Essential thrombocythemia is also classified as an incurable disease, with treatment goals focused on preventing further health complications and providing symptom relief. Treatment is based upon a patient's risks of thrombosis, measured by the International Prognostic Score of Thrombosis (IPSET-thrombosis), as follows:

Low-risk: 60 years of age or younger, with no JAK2 gene mutation and no prior history of thrombosis

Intermediate-risk: Older than 60 years of age, with no JAK2 gene mutation and no prior history of thrombosis

High-risk: 60 years of age or older and/or a prior history of thrombosis.

High-risk: Older than 60 years of age with a JAK2 gene mutation OR a history of thrombosis

Risk Level[a]	Recommended Management and Treatment[13, a]
All risk levels	• Manage cardiovascular risk factors • Monitor for new thrombosis, acquired von Willebrand disease (VWD), or disease-related major bleeding • Monitor signs/symptoms of disease progression every 3-6 months or more frequently if clinically appropriate (see myeloproliferative neoplasm symptom assessment form)

Very low-risk	• For patients with vasomotor/microvascular disturbances: Aspirin 81-100 mg/day (caution for patients with acquired VWD; higher dose aspirin may be appropriate in selected patients as clinically indicated; aspirin twice daily may be considered for patients with refractory symptoms) • Evaluate for indications for cytoreductive therapy (potential indications are new thrombosis, acquired VWD, and/or disease-related major bleeding; splenomegaly; progressive thrombocytosis and/or leukocytosis; disease-related symptoms; vasomotor/microvascular disturbances not responsive to aspirin)
Low-risk **Intermediate-risk**	• Aspirin 81-100 mg/day (caution for patients with acquired VWD; higher dose aspirin may be appropriate in selected patients as clinically indicated; aspirin twice daily may be considered for patients with refractory symptoms) • Evaluate for indications of cytoreductive therapy (potential indications are new thrombosis, acquired VWD, and/or disease-related major bleeding; splenomegaly; progressive thrombocytosis and/or leukocytosis; disease-related symptoms; vasomotor/microvascular disturbances not responsive to aspirin)

High-risk	• Bone marrow aspirate and biopsy should be performed to rule out disease progression to myelofibrosis prior to the initiation of cytoreductive therapy
	• Monitor for response to cytoreductive therapy every 3-6 months or more frequently as clinically indicated (potential indications for change of cytoreductive therapy are intolerance or resistance to hydroxyurea or peginterferon alfa-2a or anagrelide; new thrombosis, acquired VWD, and/or disease-related major bleeding; splenomegaly; thrombocytosis; leukocytosis; disease-related symptoms; vasomotor/microvascular disturbances not responsive to aspirin)
	• If change to cytoreductive therapy is indicated, these therapeutic regimens are recommended options:
	  • Clinical trial (preferred)
	  • Hydroxyurea (preferred), peginterferon alfa-2a (other recommended regimen) (consider for younger patients or in pregnant patients in need of cytoreductive therapy or in those in need of cytoreductive therapy who defer hydroxyurea), or anagrelide (other recommended regimen), if not previously used
	  • Ruxolitinib (useful in certain circumstances)
	  • Plateletpheresis for emergent situations (e.g., severe thrombocytosis-related neurologic complications) (useful in certain circumstances)

a. See the Guidelines for cytoreductive therapy options for very-low-risk, low-risk, or intermediate-risk ET with potential indications for cytoreductive therapy and for subsequent recommendations.
b. This is a simplification of the Guideline recommendations. See www.NCCN.org for detailed recommendations including the order of the recommendations.

Myelofibrosis is a myeloproliferative neoplasm that can occur in patients with or without a history of other subgroups. Myelofibrosis is classified as either primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis. Allogeneic hematopoietic cell transplantation (HCT) is the only potentially curative treatment option for patients with myelofibrosis.[13] Treatment is based upon risk stratification, and several prognostic risk models exist. Myelofibrosis secondary to polycythemia vera and essential thrombocythemia-Prognostic Model (MYSEC-PM) is used for post-polycythemia vera or post-essential thrombocythemia myelofibrosis. For primary myelofibrosis, Mutation-Enhanced IPSS for Patients with PMF Age ≤70 Years (MIPPS-70) or MIPSS-70+ Version 2.0 are preferred, though DIPSS or DIPSS-Plus may be alternatives when certain diagnostics are unavailable. These models consider factors such as age, various blood counts, symptoms, and genetic mutations. Lower versus higher risk is determined by the following cutoff scores:[13]

Lower-risk: MIPSS-70: ≤3, MIPSS-70+ Version 2.0: ≤3, DIPSS-Plus: ≤1, DIPSS: ≤2, MYSEC-PM: <14

Higher-risk: MIPSS-70: ≥4, MIPSS-70+ Version 2.0: ≥4, DIPSS-Plus: >1, DIPSS: >2, MYSEC PM: ≥14

Risk Level	Recommended Management and Treatment[13, a]
Lower-risk without symptoms	• Observation or Clinical trial • Monitor for signs and symptoms of disease progression every 3-6 months (see myeloproliferative neoplasm symptom assessment form) • Evaluation for allogeneic HCT recommended for patients with low platelet counts or complex cytogenetics; identification of higher risk mutations may be helpful for patients with primary myelofibrosis

Lower-risk with symptoms	• Supportive care and symptom management
	• Clinical trial
	• Initial Cytoreductive therapy options (all useful in certain circumstances)
	  • Ruxolitinib
	  • Peginterferon alfa-2a
	  • Hydroxyurea "if cytoreduction would be symptomatically beneficial"
	• Monitor response and sig Cytoreductive ns and symptoms of disease progression every 3-6 months (see myeloproliferative neoplasm symptom assessment form; bone marrow aspirate and biopsy at diagnosis and as clinically indicated)
	• If change of cytoreductive therapy is indicated (no or loss of response), recommend alternate options not used for initial treatment and continue to monitor disease progression
	• Evaluation for allogeneic HCT recommended for patients with low platelet counts or complex cytogenetics; identification of higher risk mutations may be helpful for patients with primary myelofibrosis

Higher-risk with platelets ≥50 x 109/L	• Evaluation for allogeneic HCT; identification of higher risk mutations may be helpful for patients with primary myelofibrosis • If patient is a transplant candidate: Allogeneic HCT

Higher-risk with platelets ≥50 x 109/L continued	• If patient is not a transplant candidate:
	  • Initial treatment options
	  • Ruxolitinib
	  • Fedratinib
	  • Clinical trial
	• Monitor response and signs/symptoms of disease progression every 3-6 months.
	• If no or loss of response, recommend clinical trial or alternate JAK inhibitor not previously used
	• If patient is not a transplant candidate, but only has symptomatic anemia:
	• Rule out and treat coexisting causes of anemia
	• Supportive care
	• If serum EPO <500 mU/mL: Erythropoiesis-stimulating agents or clinical trial are initial treatment options
	• If serum EPO≥500 mU/mL: Recommend as options clinical trial (preferred), or these drugs which may be "useful in certain circumstances": Danazol, Lenalidomide ± prednisoneb, Thalidomide ± prednisone[b], Luspatercept

Higher-risk with platelets <50 x 109/L	• Evaluation for allogeneic HCT; identification of higher risk mutations may be helpful for patients with primary myelofibrosis
	• If patient is a transplant candidate: Allogeneic HCT
	• If patient is not a transplant candidate, treatment options are:
	  • Consider clinical trial
	  • Pacritinib

a. This is a simplification of the Guideline recommendations. See www.NCCN.org for detailed recommendations including the order of the recommendations.
b. Start as a combination followed by tapering of prednisone over 3 months

Conclusion

Myeloproliferative neoplasms produce a heavy disease impact on patients. This is commonly attributed to worrisome disease advancements and a disruptive symptom burden. The absence of uniform treatment plans and risk diagnostic assessments can result in late diagnosis and rapid potential progression.[9] This also results in a lack of transparency between providers and patients, with many patients feeling excluded in their care. Additionally, there is a lack of awareness of available care guidelines, and a large need for standardized symptom alleviation and disease progression control plans for these patients. Further knowledge on the management of myeloproliferative neoplasms and their related symptoms is needed to provide optimal outcomes for these patients.

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