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Historical Views, Conventional Approaches, and Evolving Management Strategies for Myeloproliferative Neoplasms

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Abstract

The classical Philadelphia chromosome–negative myeloproliferative neoplasms (MPN), which include essential thrombocythemia, polycythemia vera, and myelofibrosis (MF), are in a new era of molecular diagnosis, ushered in by the identification of the *JAK2*[V617F] and c*MPL* mutations in 2005 and 2006, respectively, and the *CALR* mutations in 2013. Coupled with increased knowledge of disease pathogenesis and refined diagnostic criteria and prognostic scoring systems, a more nuanced appreciation has emerged of the burden of MPN in the United States, including the prevalence, symptom burden, and impact on quality of life. Biological advances in MPN have translated into the rapid development of novel therapeutics, culminating in the approval of the first

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treatment for MF, the JAK1/JAK2 inhibitor ruxolitinib. However, certain practical aspects of care, such as those regarding diagnosis, prevention of vascular events, choice of cytoreductive agent, and planning for therapies, present challenges for hematologists/oncologists, and are discussed in this article.

The classical Philadelphia chromosome–negative myeloproliferative neoplasms (MPN), which include essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF), were initially described in the medical literature in 1879, 1892, and 1934,[1] respectively, and in 1951, Dameshek[2] speculated on a "myelostimulatory factor" common to these conditions that he classified as "myeloproliferative disorders" (MPD). Then, nearly 55 years after Dameshek's treatise, the $JAK2^{V617F}$ mutation was discovered, representing a watershed moment that renewed research interests in MPN.[3]

Prevalence of MPN in the United States is now better understood, partly based on a recent analysis of 2 large health plans, which showed the prevalence (per 100,000) of ET as 38 to 57; PV as 44 to 57; and MF as 4 to 6.[4] These data showed the numbers of persons with ET, PV, and MF living in the United States in 2010 to be approximately 134,000, 148,000, and 13,000, respectively. The burden experienced by patients in the United States with MPN has also been better described. An analysis of the SEER-Medicare linked database showed that survival was shortest for patients with MF, but those with ET and PV also had inferior survival rates to matched controls.[5] In addition, more clarity now exists regarding the impact of the MPN symptom burden, attributed partly to cytokine excess, splenomegaly, hyperviscosity (PV), thrombotic complications, and cytopenias (MF). In some patients with MF, the impairment in quality of life is as or more severe than that observed in patients with metastatic cancer or acute myeloid leukemia.[6–8] Subsequently, validated tools, such as the MPN Symptom Assessment Form (MPN-SAF), have been created to assess the prevalence and impact of such MPN symptoms.[9] The ability to assess prognosis is also becoming increasingly sophisticated, especially in MF with expected incorporation of molecular genetic and cytogenetic abnormalities; current tools are used at diagnosis (International Prognostic Scoring System [IPSS])[10] or during follow-up (Dynamic IPSS [DIPSS], DIPSS plus; Table 1).[11,12]

As important, the recognition of JAK-STAT dysregulation has led to the identification of novel therapeutics, culminating in the first approval of a drug for patients with MF, the JAK inhibitor ruxolitinib. This article discusses the rapidly evolving understanding of disease pathogenesis, with an emphasis on driving mutations, and reviews practical aspects in the care of patients with MPN, focusing on diagnostic considerations, thrombosis prevention, supportive care, and therapeutic strategies.

Impact of Molecular Genetic Abnormalities

The discovery of $JAK2^{V617F}$, and subsequently $MPL^{W515L/K}$, in 5% to 10% of patients with ET or MF clarified the central theme of JAK-STAT dysregulation to MPN pathogenesis.[13,14] The $JAK2^{V617F}$ mutation is present in 95% of patients with PV ($JAK2$ exon 12 mutations are seen in 2%–3%,[15] and LNK mutations are infrequently identified in JAK2-negative erythrocytosis[16]) and in 50% to 60% of patients with ET or MF.[17] More recently, mutations

in exon 9 of the calreticulin (*CALR*) gene were identified in substantial proportions of patients with ET and MF who lacked *JAK2*[V617F] or c*MPL* mutations.[18,19] In contrast to the initial observations in patients with only ET or MF, *CALR* mutations were recently described in 2 patients with PV without *JAK2*[V617F] mutations.[20] Approximately 10% of patients with ET and MF lack *JAK2*, *CALR*, or *MPL* mutations, and have been referred to as being "triple-negative." *JAK2* and c*MPL* mutations were incorporated into the 2008 WHO criteria for ET, PV, and MF, and *CALR* mutations are similarly expected to be included diagnostic criteria in the next WHO classification. The high prevalence of these clonal markers and others permits reclassification of these diseases as neoplasms in lieu of prior nosology, MPD (Figure 1).

These "driving" mutations also impact prognosis, especially in MF. In a study of 617 patients with MF, the median overall survival was longest in patients with *CALR* mutations (17.7 years), intermediate-length in patients with MF with *JAK2* and *MPL* mutations (9.2 and 9.1 years, respectively), and shortest in patients considered "triple-negative" (3.2 years).[21] The cumulative incidence of leukemic transformation was also lowest in patients with *CALR* mutations (9.4%) compared with those with *JAK2* mutations (19.4%), *MPL* mutations (16.9%), or triple-negative status (34.4%).

Another study reported the longest median survival (16 years) and lowest rate of blast transformation (6.5%) in patients with *CALR*-mutated MF, especially when compared with patients with *JAK2* mutations considered triple-negative.[22] More specifically, the prognostic impact of *CALR* mutations may depend on the type of mutation, because improved outcomes seemed to be restricted to those with type 1 mutations (52 base pair deletions) compared with those with type 2 mutations (5 base pair insertions).[23] Other genetic lesions, outside the JAK-STAT pathway, have been identified in patients with MPN, particularly in those with MF, including *ASXL1*, *TET2*, *IDH1/IDH2*, *EZH2*, *TP53*, and *SRSF2* genes; *ASXL1*, *IDH*, *EZH2*, and *SRSF2* mutations have been associated with leukemic evolution and reduced survival time.[24]

Diagnostic Challenges

The MPN molecular markers lack specificity; therefore, consideration of clinical, laboratory, and histologic features is required to define the MPN subtype. Major and minor criteria for diagnosis of the MPN subtype were published previously.[25] Reactive thrombocytosis and secondary erythrocytosis are more common than ET or PV; MPN markers distinguish primary from secondary causes of abnormal blood counts. Because the *JAK2*[V617F] mutation is frequently identified in patients with hepatic (Budd-Chiari syndrome) or portal vein thrombosis, molecular testing should be considered even in the absence of overt MPN features.[26]

In his 1951 treatise, Dameshek[2] alluded to mimicry inherent to the MPNs; coupled with the potential for phenotypic evolution, distinction of the specific MPN subtype is sometimes difficult.[27] Distinguishing ET from prefibrotic MF can be challenging but is important, given that the natural history differs; although both can present with an isolated thrombocytosis, overt MF and leukemic transformation occur more frequently in the latter.[28] Anemia,

leukocytosis, and splenomegaly usually favor prefibrotic MF over ET, complementing recognition of such bone marrow features as hypercellularity, granulocytic predominance, and megakaryocyte atypia that also favor prefibrotic MF.[29] However, not all consider these morphologic criteria for distinction between ET and prefibrotic MF to be reliable or reproducible.[30] It is also important to recognize early or masked PV, which generally encompasses patients with PV features but without an absolute erythrocytosis (hemoglobin level >16.5 g/dL in women or >18.5 g/dL in men), and to distinguish it from $JAK2^{V617F}$-positive ET.[31] Although PV Study Group criteria relied on red cell mass testing, because of the limited availability of this test, the ideal surrogate for an increased red cell mass is under question, and the hematocrit level rather than the hemoglobin level is being proposed as such a marker.[32] In fact, hematocrit level (>48% in women or >52% men) is used by the British Committee for Standards in Haematology (BCSH), and a recent study suggested that these criteria were more adept at defining overt and masked PV compared with WHO criteria using hemoglobin level.[33] Recent studies suggest that nuclear red cell mass testing, although of limited availability, and bone marrow biopsy may be useful in patients with PV features without absolute erythrocytosis, especially when trying to distinguish $JAK2^{V617F}$-positive ET from PV.[34–36] It has been suggested that these MPNs do not exist along a spectrum but are distinct entities, and defining the MPN subtype has therapeutic and prognostic implications.[22] Recently, to aid in this distinction, experts have proposed lowering the hemoglobin threshold for men and women, and including bone marrow histology as a major criterion for PV diagnosis.[37]

Vascular Risk Assessment

Clinical management of ET and PV is largely based on thrombosis prevention, given its morbidity and mortality.[38–40] In ET, the annual rate of thrombosis nears 1.9%.[38] Thrombosis rates in contemporary patients with PV are estimated to be 2.6% to 2.7% per year. This is lower than the rate of 4.4% reported previously.[39,41,42] Prevention is primarily based on predicting vascular risk, which is evolving in ET and now includes the impact of not only advanced age and thrombosis history but also cardiovascular risk factors and presence of the $JAK2^{V617F}$ mutation.[38] In PV, the most reproducible risk factors for thrombosis include age older than 60 years and prior thrombosis. The rate of thrombotic events in patients with MF may be comparable to that of those with ET, nearing 1.75% per year, especially in patients older than 60 years with a $JAK2^{V617F}$ mutation. Sex may be an additional risk factor for thrombosis, because presentation with abdominal venous thrombosis (AVT) is typically a feature seen in younger women with PV.[43] Leukocytosis and an increased $JAK2$ allelic burden are also emerging risk factors for thrombosis.[44] Patients with $CALR$ mutations were recently shown to have a lower risk of thrombosis[18,19,45,46] compared with those with $JAK2^{V617F}$ mutations. The pathophysiology of MPN-associated thrombosis is additionally influenced by platelet, leukocyte, and endothelial activation, and activated protein C resistance, inflammation, and circulating microparticles.[44] The hope is that surrogate markers that capture these derangements will be validated and incorporated into thrombosis risk assessment.

Cytoreductive Therapy

Goals of cytoreductive therapy include prevention of thrombosis, control of myeloproliferation, and relief of MPN symptoms.[47] In the United States, hydroxyurea emerged as the most widely used cytoreductive agent, based on lower observed thrombosis rates compared with phlebotomized historical controls and lower observed rates of leukemia or solid malignancies compared with chlorambucil or radioactive phosphorous.[48] Efficacy in PV is typically extrapolated from randomized controlled trials in patients with ET. In patients with ET at high risk, hydroxyurea was more effective in preventing thrombosis than placebo.[49] Compared with anagrelide, hydroxyurea was more effective in preventing arterial thrombosis and associated with lower rates of bleeding and myelofibrosis.[50] Interestingly, mutational status may influence response, because patients with $JAK2^{V617F}$ mutations appeared preferentially sensitive to hydroxyurea over anagrelide.[51] Use of anagrelide waned after this study, but it was more effective than hydroxyurea in preventing venous thrombosis, because the rate was nearly one-fourth that of hydroxyurea (odds ratio, 0.27; P=.006.).[50] More recently, a comparison between anagrelide and hydroxyurea in a noninferiority study showed similar rates of major and minor bleeding, thrombosis, and discontinuation in those with WHO-classified ET compared with the PT-1 study, which may have included patients with ET and prefibrotic MF.[50,52]

The association between cytoreductives (especially hydroxyurea) and leukemic transformation is controversial. Among 326 patients with ET treated with cytoreduction, 17 developed leukemia. Of these, 14 were treated with hydroxyurea; a high proportion had 17p deletions.[53] Associations with genetic alterations of 17p (including p53), hydroxyurea exposure, and evolution to MPN blast phase have also been reported in patients with PV.[54] A long-term follow-up from the French Polycythemia Study Group reported higher-than-expected rates of evolution to acute myeloid leukemia in patients treated with hydroxyurea: 6.6%, 16.5%, and 24.2% at 10, 15, and 20 years, respectively.[55] Other studies have argued against any association with leukemia and hydroxyurea[40,56] in ET or PV,[42] or have shown associations when only chemotherapies were used sequentially.[57]

Lack of association with leukemia, along with improved safety and efficacy, renewed interest in the use of pegylated interferon-alpha in PV and ET. Pegylated interferon-alpha has shown high rates of hematologic response (95% at 12 months) and $JAK2$ allele burden response (partial 48%, complete 24%) in newly diagnosed patients with PV.[58] However, adverse events were noted in 89% of patients, and the treatment discontinuation rate was 35% (24% because of toxicity). Complete hematologic and molecular responses have also been reported in patients with previously treated ET (77% and 17%, respectively) and PV (76% and 18%, respectively); those who did not experience a complete molecular response were more likely to have mutations outside the JAK-STAT pathway.[59] Interestingly, in this study, 29% of patients discontinued therapy but maintained a hematologic remission for a median of 28 months of observation. The MPD Research Consortium is currently conducting studies comparing pegylated interferon and hydroxyurea in high-risk patients with ET and PV, and its use as salvage therapy for patients with hydroxyurea resistance or intolerance or AVT (ClinicalTrial.gov identifiers: NCT01259856 and NCT01259817).

Antiplatelet Therapy, Anticoagulation, Phlebotomy, and Special Clinical Situations

Additional strategies to reduce the risk of thrombosis include the use of antiplatelet therapies. Use of aspirin in ET is typically extrapolated from a large PV study. In this study of 518 patients with PV, aspirin reduced the risk of a combined end point of nonfatal myocardial infarction (MI), stroke, or death from cardiovascular causes and the risk of a combined end point of nonfatal MI, stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes.[39] A meta-analysis suggested that low-dose aspirin was associated with only a nonsignificant reduction in the risk of fatal thrombosis and all-cause mortality compared with no treatment.[60] No data support the use of clopidogrel alone or in combination with aspirin. Intriguing in vitro evidence is available to support twice-daily aspirin,[61] but this approach has not been validated in a clinical trial.

Phlebotomy is a cornerstone of PV therapy, and the hematocrit target of 45% or less has been established by a randomized trial given the lower risk of cardiovascular events reported when compared with a hematocrit of 45% to 50%.[62] In particular, the cardiovascular event rate was 10.9% in the higher hematocrit arm (hazard ratio, 2.69; P=.01) compared with 4.4% in the lower hematocrit arm, favoring more aggressive control in all prespecified subgroups (gender, advanced age, thrombosis history, platelet and white blood cell cut points, and presence of splenomegaly). In patients with thrombosis, the duration of anticoagulation therapy is not well established, but it is often prescribed indefinitely in those with AVT.[47] No current data are available on the use of novel oral anticoagulants. Plateletpheresis is a consideration for patients with life-threatening thrombohemorrhagic complications. Strategies for managing MPN in the perioperative period may include normalizing the red blood cell mass for patients with PV and the use of cytoreductive therapy to address thrombocytosis. Because thrombocytosis can increase the hemorrhagic rather than thrombotic tendency,[63] this becomes an important concern to communicate to the surgeon; the use of venous thromboembolism prophylaxis after surgery must be individualized, because bleeding and thrombosis rates are increased in this period.[64] Finally, MPN can present in younger women, and clarifying the use of cytoreductive agents, aspirin, and deep vein thrombosis prophylaxis is important when managing pregnant patients with MPN. Similarly, some reports of pediatric, adolescent, and young adult MPN presentations[43,65,66] suggest that adult diagnostic and treatment algorithms are not always applicable or appropriate (ie, use of hydroxyurea).

JAK Inhibition in MF

Demonstration of universal JAK-STAT dysregulation in MPN[67] supports JAK inhibition as a useful therapeutic strategy, especially for patients with MF, regardless of mutational status. Ruxolitinib was the first JAK inhibitor to be approved for the treatment of MF, based on 2 randomized studies demonstrating a 35% or more reduction in spleen volume compared with placebo (COMFORT-I, 41.9% vs 0.7% at 24 weeks; P<.001) and best available therapy (COMFORT-II, 28.5% vs 0% at 48 weeks; P<.001).[68,69] Further, ruxolitinib resulted in clinically meaningful improvements in quality of life and the MF symptom burden.

Specifically, as assessed by a validated tool, a 50% or more improvement in baseline symptoms was seen in 45.9% of patients compared with 5.3% in the ruxolitinib versus placebo arm (*P*<.001).[68]

Grades 3 and 4 anemia and thrombocytopenia were reported in 45.2% and 12.9% of patients treated with ruxolitinib, respectively, in COMFORT-I,[68] and grade 3 or 4 anemia (34% and 8%, respectively) and thrombocytopenia (6% and 2%, respectively) were reported in COMFORT-II.[69] Nonhematologic adverse events included dizziness, headache, and easy bruising.[68]

The 2- and 3-year follow-up data from the COMFORT studies suggest durable responses.[70,71] Responses seem to be independent of *JAK2*^{V617F} status, because recently JAK inhibitor responses were reported in *CALR*-mutated MF.[72] Survival benefits have also been reported in patients treated with ruxolitinib compared with those treated with placebo or best available therapy and historical controls, including those from the DIPSS cohort.[70,71,73,74] With a longer follow-up duration, the magnitude of this survival benefit has decreased, perhaps because of a crossover effect. The survival benefit attributed to ruxolitinib may be due to improvements in physical function and performance from amelioration of splenomegaly and reduction in cytokine levels, rather than to a direct anticlonal effect or changes in bone marrow histopathology.

Data are emerging on the use of ruxolitinib before transplant, and a clinical trial from the MPD Research Consortium (ClinicalTrials.gov identifier: NCT01790295) will also address this issue. Other JAK inhibitors are being studied in phase III trials, including pacritinib (ClinicalTrials.gov identifiers: NCT02055781 and NCT01773187) and momelotinib (ClinicalTrials.gov identifiers: NCT01969838 and NCT02101268). Pacritinib appears to be nonmyelosuppressive,[75] and momelotinib[76] may improve the hemoglobin and/or red blood cell transfusion dependence. These findings require confirmation in phase III studies.

A New Role for JAK Inhibitor Therapy in PV

A prior study reported hydroxyurea resistance and intolerance in 11% and 13% of patients with PV, respectively, and the former was associated with a higher risk of death and disease transformation.[77] JAK inhibitors may have a role in this patient population. Phase II data for ruxolitinib given at 10 mg twice daily revealed a complete response in 59% of patients, with thrombocytopenia as the most common adverse event.[78] Subsequently, a phase III study compared ruxolitinib with best available therapy in patients with hydroxyurea-resistant/intolerant disease with splenomegaly and an ongoing phlebotomy requirement.[79] Significantly more patients in the ruxolitinib arm achieved the primary end point of phlebotomy independence and spleen volume reduction at week 32 (21% vs 1%; *P*<.0001). When evaluating each component individually, 38% and 60% in the ruxolitinib arm achieved spleen volume reduction and hematocrit control compared with 1% and 20% in the best available therapy arm, respectively. In addition, significant improvements in baseline PV symptoms (cytokine-mediated, hyperviscosity, and spleen-related) as assessed using the MPN-SAF were noted in patients treated with ruxolitinib versus best available therapy.

Although the study was not powered to detect any difference in thrombosis rates, this adverse effect was reported in 1 patient in the ruxolitinib arm and 6 patients in the best available therapy arm. Grade 3 or 4 anemia and thrombocytopenia occurred in 1.8% and 5.5% of ruxolitinib-treated patients, respectively. Diarrhea, muscle spasms, dizziness, and dyspnea were more commonly noted in the ruxolitinib arm.[79] Based on these results, the FDA approved ruxolitinib for use in patients with inadequate response or intolerance to hydroxyurea. The safety and efficacy of momelotinib will also be evaluated in patients with ET and PV (ClinicalTrials.gov identifier: NCT01998828).

Monitoring Therapy, Judging Net Effect, and Recognizing Disease Progression

An evaluation of the efficacy of MPN therapy involves assessment of subjective symptom relief and objective parameters through palpation of the spleen (or with ultrasound/CT if needed) and CBC count monitoring. Although molecular monitoring is paramount in assessing response in chronic myelogenous leukemia (CML), measurement of the $JAK2^{V617F}$ allelic burden is not currently recommended for widespread use in clinical practice. Routine, serial bone marrow biopsies are not typically indicated outside of clinical trials. Ruxolitinib has been shown to impair dendritic cell function,[80] which may explain both positive and negative consequences of an anti-inflammatory medication. Case reports exist of opportunistic infections such as progressive multifocal leukoencephalopathy,[81] retinal toxoplasmosis,[82] tuberculosis,[83,84] and cryptococcal pneumonia[85] in ruxolitinib-treated patients. Abrupt discontinuation of therapy also presents a potential for severe rebound symptoms.

Tyrosine kinase inhibitor therapy has had a remarkable impact on preventing disease transformation in CML, but currently progression is an expected consequence for *BCR-ABL*–negative MPN. In part, progression can be reflected by a change in the symptomology, because onset of constitutional symptoms and progression of splenomegaly heralds MF transformation in patients with ET or PV.[86] Criteria for this transformation also include development of anemia, leukoerythroblastosis, and bone marrow fibrosis. ET, PV, and MF can accelerate to an MPN blast phase, and consensus criteria for this transformation also exist.[86]

Supportive Care: Symptoms, Cytopenias, and Splenomegaly

Supportive needs include management of microvascular symptoms, such as migraines, atypical transient ischemic attack, visual disturbance, and erythromelalgia, which are often relieved by aspirin.[87] Fatigue is prevalent; treatment strategies for this symptom are challenging, but nonpharmacologic options have been attempted.[7] Pruritus can be debilitating, and treatments vary from antihistamines, paroxetine, interferon-alpha, and ultraviolet light therapy to JAK inhibitors.

Treatment for MF-associated anemia is an unmet need,[88] but conventional agents can be of modest benefit. Conventional strategies have included androgens, erythropoietin-stimulating agents, and immunomodulatory drugs such as thalidomide or lenalidomide. The presence of

transfusion-dependence, abnormal cytogenetics, increased erythropoietin levels, splenomegaly comorbidities (neuropathy), and other cytopenias can negatively impact tolerability or efficacy of these agents. Evidence of iron overload in patients with MF, particularly in those with hepatic or cardiac dysfunction, may have major implications for subsequent morbidity, but the use of parenteral or oral iron chelators in these settings needs prospective evaluation.[89] The role of thrombopoietic agents (romiplostim, eltrombopag) to treat thrombocytopenia requires further study, given their potential to increase marrow fibrosis.[90]

Among the myeloid neoplasms, massive splenomegaly is unique to MF, and for some patients, medical therapy is inadequate. Often, splenectomy or splenic radiation are proposed; however, given the associated morbidity and mortality[91] and the utility of JAK inhibitors in reducing marked symptomatic splenomegaly, providers must carefully select optimal candidates and suggest strategies to reduce perioperative complications, including use of prophylaxis or hydroxyurea to lessen risk of AVT and severe thrombocytosis.

Radiation therapy was shown to be useful for nonhepatosplenic extramedullary hematopoiesis (EMH).[92] In a retrospective study, low-dose radiation therapy was used for spinal EMH (median dose of 1 Gy; range, 1–10 Gy), pleural or pulmonary EMH (median dose of 1.25 Gy; range, 1.00–1.50 Gy), and abdominal or pelvic EMH (median dose of 2.02 Gy; range, 1.50–4.50 Gy).

The Role and Timing of Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) represents the only potential cure and is typically restricted to highly selected patients with MF, given the risk-benefit ratio. In part, decision-making is based on risk-assessment; currently, the risk of transplant may be justified in patients with intermediate-2 or high risk disease, as assessed by IPSS or DIPSS/ DIPSS plus. In a retrospective series of 289 patients undergoing transplant between 1989 and 2002, transplant-related mortality (TRM) at day 100 was 22% and 42%, respectively, for those with matched sibling donor (MSD) and matched unrelated donor (MUD).[93] The overall survival rates at 5 years were 39% and 31% for MSD and MUD, respectively.

Outcomes were slightly improved in 162 patients undergoing reduced-intensity conditioning transplants from 1999 to 2009, with a 22% TRM at 1 year and 62% overall survival at 5 years.[94] A larger study of reduced-intensity conditioning transplants (N=233) reported a 5-year overall survival rate of 47% (56% for MSD, 48% with MUD).[95] A recent prospective study of 66 patients undergoing reduced-intensity conditioning reported on the strong influence of donor type, because overall survival and nonrelapse mortality rates were 75% and 22% in the MSD group, compared with 32% and 59% in the MUD group.[96] Splenectomy before HSCT is not recommended given the associated morbidity, mortality, and lack of clear benefit.[97] The role of JAK inhibitors before HSCT is still being defined in clinical trials. Interestingly, JAK inhibition after transplant may be useful for the treatment of acute graft versus host disease.[98]

Additional Novel Therapies

JAK inhibition may address symptoms and splenomegaly and has improved survival in MF; however, complete remission is not expected, resistance can develop because of heterodimer formation with other JAKs, and responses are rapidly lost with drug discontinuation.[99] JAK inhibitors may serve as a foundation to which novel therapies may be added, however. As with most hematologic malignancies, combination strategies may further impact the natural history of MF (Figure 1). Several novel companions to JAK inhibitors are being evaluated in clinical trials, particularly in transplant-ineligible patients.

In early MF, there is renewed interest in using interferon-alpha (ClinicalTrials.gov identifier: NCT01758588) based on smaller studies showing impressive response rates, including a minority of patients experiencing histologic improvements.[100] Although neither has an established role in early or low-risk MF, combining pegylated interferon and a JAK inhibitor represents a novel concept. In patients with anemia, adding a conventional agent to JAK inhibitors may offset myelosuppression. Danazol (ClinicalTrials.gov identifier: NCT01732445) has been added to ruxolitinib, and although combination therapy was well tolerated (no incremental toxicity with danazol), only 1 patient experienced clinical improvement.[101] The combination of immunomodulatory drugs such as lenalidomide (ClinicalTrials.gov identifier: NCT01375140) or pomalidomide (ClinicalTrials.gov identifier: NCT01644110) and JAK inhibitors has also been preliminarily reported, with poor tolerability of the former combination when used concurrently, and relative safety of the latter, noting a sample size of 6 patients.[102,103]

In accelerated MF or blast phase MPN, a novel approach involves the use of hypomethylating agents (decitabine or 5-azacytidine; ClinicalTrials.gov identifiers: NCT02076191 and NCT01787487, respectively) with a JAK inhibitor. Other unique and recently reported combinations include the addition of histone deacetylase inhibitors (ClinicalTrials.gov identifiers: NCT01693601 and NCT01433445), PI3K inhibitors (ClinicalTrials.gov identifier: NCT01730248), and hedgehog signaling inhibitors (ClinicalTrials.gov identifier: NCT01787552) to ruxolitinib; the combinations seem to be tolerable and have shown impressive (preliminary) splenomegaly responses.[104–106] JAK inhibitors paired with mTOR inhibitors, aurora kinase A inhibitors, and heat shock protein 90 inhibitors are also rational combinations.[107]

PRM-151, a recombinant form of pentraxin-2 and novel antifibrotic agent, was tolerable alone or with ruxolitinib, and despite a lower overall response rate, trended toward improvement in anemia and thrombocytopenia and bone marrow fibrosis grade (ClinicalTrials.gov identifier: NCT01981850).[108] Finally, the telomerase inhibitor imetelstat (ClinicalTrials.gov identifier: NCT01731951) was myelosuppressive, leading to grade 4 neutropenia (18%) and thrombocytopenia (21%). However, treatment resulted in 4 complete responses and 3 partial responses, justifying further study in an expanded clinical trial.[109]

Conclusions

The discovery of $JAK2^{V617F}$ has ushered in a new era for the MPN field, characterized by identification of recurring molecular aberrations such $JAK2^{V617F}$ and *CALR* mutations. This era has raised awareness of the impact of the MPN symptom burden, and prognostic tools have become increasingly sophisticated. The discovery of JAK-STAT dysregulation has been rapidly translated into novel therapeutic strategies for MF, with the JAK inhibitor ruxolitinib receiving approval and several additional agents in this drug class currently in advanced stages of clinical development. Specific targeting of *CALR*-mutant MF is also an intriguing concept. Although improvement in symptoms and splenomegaly is clearly important, novel strategies will hopefully result in anticlonal activity, improved bone marrow histopathology, and ultimately, complete remissions. The rapid pace and abundance of these developments are both overwhelming and encouraging for hematologists/oncologists and patients. The hope is that this MPN era will see significant alterations in natural history and improved clinical outcomes, as has occurred with Dameshek's other "MPD," CML.

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From Disorder to Neoplasm: "MPD to MPN"

MPN	Molecular Genetic Abnormality
Polycythemia vera	$JAK2^{V617F}$, JAK2 exon 12
Essential thrombocytosis	$JAK2^{V617F}$, CALR, cMPL
Myelofibrosis	$JAK2^{V617F}$, CALR, cMPL
Chronic myeloid leukemia	BCR-ABL
Chronic neutrophilic leukemia	CSF3R and SETBP1 mutations
Chronic eosinophilic leukemia, NOS	??
Systemic mastocytosis	KIT^{D816V}
MPN, unclassifiable	??
Myeloid (and lymphoid) neoplasms with eosinophilia	PDGFRA, PDGFRB, FGFR1

Figure 1.

Molecular genetic abnormalities in the myeloproliferative neoplasms.

Abbreviations: MPD, myeloproliferative disorders; MPN, myeloproliferative neoplasms;

NOS, not otherwise specified.

Table 1

Prognosis in Primary Myelofibrosis

	LILLE[10]	IPSS[10]	DIPSS[11]	DIPSS Plus[12,a]
Anemia	X	X	XX	
Leukocytes	X	X	X	
Blasts		X	X	
Constitutional symptoms		X	X	
Age >65 y		X	X	
Karyotype (−8,−7,−5, i17q,12p−, inv3, 11q23, or complex)				X
PLT <100 × 10^9/L				X
Transfusion dependence				X
	Low (0 points)[a] 185 mo; Int-1 (1 point)[a] 78 mo	Int-2 (2–3 points)[a] 35 mo	High (4 points)[a] 16 mo	

X, included variables; XX, anemia weighted with 2 points in DIPSS.

IPSS at diagnosis: Low = 0 points, Int-1 = 1 point; Int-2 = 2 points; High risk 3 points.

DIPSS during disease course: Low = 0 points; Int-1 = 1–2 points; Int-2 = 3–4 points; High = 5–6 points.

Abbreviations: DIPSS, Dynamic International Prognostic Scoring System; Int, intermediate; IPSS, International Prognostic Scoring System; PLT, platelet count.

[a] DIPSS plus during disease course: Incorporate DIPSS score (Low = 0; Int-1 = 1; Int-2 = 2; High = 3) plus added variables, including karyotype (1 point), thrombocytopenia (1 point), and transfusion dependence (1 point). For example, a patient with advanced age (1 point), anemia (2 points), and constitutional symptoms (1 point) would have DIPSS Int-2–risk disease; if transfusion-dependence and deletion of chromosome 8 are considered with DIPSS plus, this patient would have 2 points for the DIPSS score and 2 points (plus variables), for a DIPSS plus score of 4 (high risk).