Diagnosis and Management of Myelofibrosis: Practical Strategies for the Healthcare Team

Proceedings from a Multidisciplinary Roundtable
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Proceedings from a Multidisciplinary Roundtable
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This publication further provides benefit design decision makers the integrated industry information they require to devise formularies and benefit designs that stand up to today’s special healthcare delivery and business needs.

This supplement has been supported by funding from Incyte.
Myelofibrosis (MF) is a serious and progressive bone marrow stem cell clonal malignancy that disrupts the body’s normal blood-cell production. It is characterized by extensive scarring of the bone marrow and is associated with debilitating constitutional symptoms, anemia, and progressive hepatomegaly/splenomegaly with advancing disease. Effective management of MF is essential given the increased morbidity and mortality of this disease, its complexities with respect to diagnosis and treatment, and its overall impact on patients’ quality of life.

A multidisciplinary roundtable was held on May 30, 2013, to acquire insights and guidance from experts on the diagnosis and management of MF, including practical strategies, recent advances, and emerging science. The roundtable consisted of 9 experts from a number of relevant fields: hematology, oncology, managed care, specialty pharmacy, translational research, and oncology nursing/nurse navigation. This publication highlights the discussions and recommendations of the roundtable experts, with the overarching goal of improving outcomes by advancing the quality, delivery, and continuum of care for patients with MF.

Clinical Aspects of MF
Disease Classification/Incidence and Prevalence

According to the World Health Organization (WHO) classification scheme for myeloid neoplasms, MF is classified as one of the BCR-ABL-1–negative myeloproliferative neoplasms (MPNs), along with polycythemia vera (PV) and essential thrombocythemia (ET). With an estimated incidence of 1 in 100,000 people, MF is diagnosed in 3000 persons in the United States each year. The prevalence of MF is 4 to 6 per 100,000—considerably lower than that of PV (44.57 per 100,000) and ET (38.57 per 100,000). A disease phenotype similar to primary MF occurs in the natural history of PV and ET known as post-PV MF and post-ET MF. The lower prevalence of MF compared with its MPN “cousins” PV and ET relates to its worse overall life expectancy. Although patients with low-risk disease exhibit a median overall survival of more than 10 years from the time of diagnosis, the median survival associated with intermediate risk-2 to high-risk disease ranges from approximately 2 to 4 years, respectively.

Several common themes characterize the chronic MPNs: (1) clonal involvement of a multipotent hematopoietic progenitor cell (acquired mutations such as Janus kinase [JAK]2 V617F frequently found); (2) marrow hypercellularity with effective hematopoiesis (vs the ineffective hematopoiesis characteristic of myelodysplastic syndrome [MDS]); (3) extramedullary hematopoiesis (enlarged spleen or liver); (4) thrombotic and hemorrhagic diathesis; and (5) potential evolution to acute myelogenous leukemia (AML). AML arising from MF is particularly challenging to treat and is associated with poor outcomes.

Establishing the Diagnosis of MF
Diagnostic Criteria

The WHO diagnostic criteria for MF are shown in Table 1. A formal MF diagnosis is based on the presence of all 3 major criteria and at least 2 minor criteria. It is important to rule out other MPNs or other reactive causes of fibrosis within the bone marrow. Identifying chromosomal abnormalities or mutations (eg, JAK2 V617F or MPL W515K/L) can establish the presence of a neoplastic condition, but a combination of clinical, histopathologic, and molecular findings is required to establish the presence of a specific type of MPN such as MF.

MF can arise de novo (primary MF [PMF]), or from PV (post-PV MF) and ET (post-ET MF). The diagnostic criteria for these secondary forms of MF are shown in Table 2.

The clinical presentation of patients with PMF may include splenomegaly and hepatomegaly and their related symptoms (eg, early satiety and abdominal pain), as well as bleeding, ecchymoses, petechiae, hyperuricemia, and gout. In addition, these patients may experience constitutional symptoms, including weight loss, cachexia, fatigue, fever, night sweats, and pruritus. An international survey of 1179 patients showed that individuals with MPNs suffer from substantially more fatigue and in excess of what is expected for an age-matched control group. In addition, a recent study showed that
the prevalence of symptoms in patients with MF is variable; fatigue is present in nearly 100% of patients, whereas abdominal discomfort and early satiety are seen in approximately 70% of patients, night sweats in more than 60%, weight loss in nearly 50%, and fever in nearly 30%. This constellation of clinical signs and symptoms may aid in establishing the diagnosis of MF.

**Making a Definitive MF Diagnosis**

There are a number of nonhematologic and nonmalignant conditions that can cause some of the same or similar clinical and pathologic findings as those seen in MF. There are also other closely related myeloid cancers that can be confused with MF. Consequently, making a definitive diagnosis of MF is complex and challenging for clinicians.

**Importance of Using the WHO Criteria as a Diagnostic Guide**

The diagnosis of MF is based on clinical and laboratory features and histopathologic findings in the bone marrow. Therefore, good communication between the clinician and the pathologist is important for accurate diagnosis. In this regard, it is important to convey relevant medical history (eg, whether the patient has had a long-standing MPN) and clinicopathologic data, such as prior blood counts, therapies, and bone marrow biopsy results. Although the WHO criteria are not perfect, knowledge and use of them may help expedite an accurate diagnosis, exclude other conditions that may mimic MF, and provide the basis for an appropriate treatment plan.

There may be a tendency to suspect MF when marrow fibrosis is present, as bone marrow fibrosis can be seen in a number of conditions, including malignant and nonmalignant disorders (Table 3).

Clinicians should be encouraged to use the term *myelofibrosis* in the context of patients meeting the WHO criteria specific for this clonal malignancy. For other disorders such as MDS, it may be preferable to use descriptive terminology such as MDS with fibrosis.

Analysis of the peripheral blood or bone marrow may be helpful in excluding other myeloid neoplasms. For example, marrow cytogenetic analysis to detect the Philadelphia chromosome (or fluorescence in situ hybridization [FISH]/polymerase chain reaction testing of the blood for BCR-ABL1 transcripts) may be used to exclude chronic myelogenous leukemia; FISH for the CHIC2 deletion (to detect the cytogenetically occult FIP1L1-PDGFRA fusion on chromosome 4q12) or chromosomal analysis to infer the presence of reciprocal translocations involving platelet-derived growth factor receptor alpha or beta (PDGFRA/B) or fibroblast growth factor receptor 1 in myeloid neoplasms associated with eosinophilia. The presence of dysplasia and/or monocytoysis are features that can help distinguish between MDS and MDS/MPN overlap disorders (eg, chronic myelomonocytic leukemia [CMML]) and MF, although monocytoysis can also be observed in MF. Ring sideroblasts are found in hereditary and nonclonal acquired sideroblastic anemias and in a subset of MDS and MDS/MPN overlap disorders (refractory anemia with ring sideroblasts with or without thrombocytosis). However, ring sideroblasts can be observed in several myeloid neoplasms and cannot be used as a singular feature to distinguish among them. Morphologic and immunophenotypic analysis of the peripheral blood and marrow can be used for several purposes, but most notably as complementary approaches to quantify the percentage of myeloblasts in these tissue compartments. Reticulin staining of the bone marrow is essential for evaluating the stage of marrow fibrosis (according to the European grading system, eg, MF-0 to MF-3), and trichrome staining of the core biopsy can establish whether collagen deposition, a sign of advanced fibrosis, is present. Moreover, the degree of osteosclerosis can be assessed and quantified by experienced hematopathologists.

**Case Study 1: Distinguishing MF from Other Hematologic Disorders**

The following case study illustrates some of the layers of complexity involved in distinguishing MF from other hematologic disorders, particularly when encountering...
Mr S is a 44-year-old African American man who had previously been seen by a hematologist. He was initially diagnosed with MF and the plan was to initiate an immunomodulatory drug (IMiD). However, the patient sought a second opinion. He presented with severe anemia and constitutional symptoms, including fatigue and night sweats. At this stage, his symptoms were suggestive of a myeloproliferative versus a lymphoproliferative disorder.12

His physical examination was unremarkable, a complete blood count showed leukocytosis with neutrophilic predominance and anemia, and his mean corpuscular value and platelet counts were normal. There was no leukoerythroblastosis.

A bone marrow biopsy showed a low myeloid-erythroid ratio, mild megaloblastoid changes in erythroid cells, a hypercellular bone marrow with panhyperplasia, and a diffuse and dense increase in reticulin fibers. The pSTAT-5 immunostain was negative.

The initial conclusion was that Mr S had PMF: molecular testing of JAK2 V617F, JAK2 exon 12, and MPL were negative; and the metaphase cytogenetics were normal. The clinical course of this patient’s blood counts described increases and decreases, fluctuating without any specific therapy. Upon closer inspection, although this patient had symptoms suggestive of MF, he did not exhibit other features, such as leukoerythroblastic changes or splenomegaly. Delving deeper into the history of Mr S revealed that he had a family history of lupus. An antinuclear antibody test and a lupus panel were ordered, and the patient was subsequently diagnosed with systemic lupus erythematosus. He was placed on corticosteroid therapy, with complete resolution of his anemia and symptoms. Moreover, a repeat bone marrow biopsy showed disappearance of both the reticulin fibrosis and hypercellularity of the marrow.

Mr S’s case study underscores the importance of referring to the series of WHO criteria. Otherwise, a patient may be misdiagnosed with MF, resulting in unnecessary therapy and adverse events.

Distinguishing Early-Prefibrotic PMF from ET

The WHO diagnostic criteria recommend bone marrow morphology as an integral aspect in the diagnosis of PMF, as patients with early PMF, where minimal fibrosis may be present (referred to as prefibrotic PMF), may be difficult to distinguish from ET, particularly when thrombocytosis is the major hematologic presentation.

A blinded evaluation was conducted on the bone marrows of 1104 patients diagnosed with ET to determine whether they had true cases of ET or whether they actually had early-prefibrotic PMF. The final assessment showed that 81% of these patients had true ET; however, 16% had early-prefibrotic PMF. This finding is important because a morphologic diagnosis of prefibrotic PMF rather than ET can have prognostic consequences, as shown in Table 4.13

Although thrombosis rates between true ET and early-prefibrotic PMF over time are not significantly dif-
ferent, conversion to overt MF, evolution to acute leukemia, and the risk of mortality are statistically higher with a diagnosis of early-prefibrotic PMF, compared with ET. The prognostic significance of distinguishing between early-prefibrotic PMF and ET is a relatively new paradigm that has gained focus in recent years. It is important to identify the patients with prefibrotic/early PMF to correctly prognosticate outcomes for these patients and the appropriateness of therapeutic interventions.

Following an accurate morphologic diagnosis, clues for considering the possibility of early-prefibrotic PMF are splenomegaly, anemia, leukocytosis, leukoerythroblastosis on blood film, and increased circulating CD34-positive cells.

Pathogenesis of MF and JAK-STAT Signaling

In 2005, the JAK2 V617F was identified as a highly recurrent activating mutation among MPNs. JAK2 belongs to a family of JAK tyrosine kinases, which includes JAK1, JAK2, JAK3, and TYK2. In the normal state, binding of ligands (eg, erythropoietin, thrombopoietin, granulocyte colony-stimulating factor) to their respective type I cytokine receptors results in phosphorylation of the intracytoplasmic portion of the receptor and binding of JAK2. This results in activation of downstream signaling circuits, including the PI3K/AKT antiapoptotic pathway and the RAS/MEK/ERK pathway, among others.

The frequency of the JAK2 mutation is approximately 50% to 60% of patients with PMF, and is found with less frequency in patients with CMML (approximately 5%-10%), atypical MPNs (approximately 5%), and AML (<5%).

In addition to JAK2, there are a number of other gene mutations or protein modifications that contribute to activation of JAK-STAT signaling in MPNs, including MPL, LNK (SH2B3), Cbl, suppressor of cytokine signaling (SOCS3), and others. The MPL W515K/L mutation is identified in 5% to 10% of patients with PMF and results in dysregulation of the JAK-STAT axis. LNK is a negative regulatory mediator for JAK2. Less than 5% of patients with PMF, PV, or ET carry mutations in LNK. Approximately 6% of patients with PMF carry the Cbl mutation. A decrease (or loss) of SOCS function or SOCS3 gene expression may lead to increased JAK-STAT signaling. It is not entirely known why patients with wild-type JAK2 respond to JAK2 inhibitors, but it likely relates to the fact that JAK-STAT pathway activation is almost universal in MF, and can be accounted for by some of the aforementioned mutations. Rather than calling these agents JAK2 inhibitors, the more appropriate term may be JAK2 regulators, based on other mechanisms that decrease the JAK-STAT signaling.

Diagnosing MPNs requires a combination of clinical, laboratory, and cytogenetic/molecular genetics testing. Based on the WHO diagnostic criteria, positive testing for the JAK2 V617F mutation is a major criterion for all 3 diseases. JAK2 V617F (or another mutation or
karyotypic abnormality) establishes the presence of a clonal myeloid disorder instead of a reactive condition. However, wild-type JAK2 does not rule out the presence of a myeloid neoplasm because 40% to 50% of patients with ET and PMF exhibit wild-type JAK2.

As of 2013, the mutation status of JAK2 or other genes has not yet been validated as a prognostic marker for PMF in the International Prognostic Scoring System (IPSS), Dynamic IPSS (DIPSS), or DIPSS-Plus systems. Consequently, treatment decisions about MF are generally not based on JAK2 mutation status.

**Risk Stratification in MF**

Understanding the natural history of MF, including the expected survival and risk of transformation to AML, is essential for decisions about which treatment to use, whether an intense and risky therapy (ie, allogeneic transplantation) is warranted, and how the therapeutic intervention can potentially modify the natural history or course of MF.

There are several scoring systems for MF. The Lille scoring system is based on hemoglobin and white blood cell (WBC) counts that assign the patient’s risk level into 3 categories—low, intermediate, and high.21 One of the limitations of the Lille scoring system is the difficulty discriminating between the patient who has intermediate- versus high-risk disease with respect to survival and other factors.

**IPSS**

In 2009, the International Working Group (IWG) published the IPSS, which uses 4 risk categories. The 5 risk factors used in the IPSS to develop risk categories include age >65 years, presence of constitutional symptoms, hemoglobin <10 g/dL, WBC count >25,000/mm³, and peripheral blood blasts ≥1%. Using these risk factors, 4 risk categories have been established: low (0 risk factor, with a median survival of 11.3 years), intermediate-1 (1 risk factor; median survival 7.9 years), intermediate-2 (2 risk factors; median survival 4 years), and high (≥3 risk factors; median survival 2.3 years). These tools help clinicians differentiate which patients are likely to do reasonably well with little or no intervention and which patients require a more intense treatment plan.4

**DIPSS**

The IWG subsequently validated the IPSS risk factors during the course of the disease and refined the scoring system to the DIPSS. In the DIPSS, anemia is more heavily weighted as a risk factor (double the value) because it was found that new-onset anemia had a higher impact on mortality. The DIPSS risk categories are based on points—2 points for anemia and 1 point each for the other 4 risk factors—and have their own assigned values (low indicates 0; intermediate-1, 1-2; intermediate-2, 3-4; high, 5-6).22,23

**DIPSS-Plus**

The DIPSS-Plus integrates the 5 risk factors from DIPSS and adds an additional 3 prognostic variables: platelet count <100 × 10⁹/L, unfavorable cytogenetics, and need for red blood cell (RBC) transfusion. The median overall survivals of DIPSS-Plus–generated risk groups range from “not reached” for the low-risk cohort to 1.3 years for the high-risk group (Table 5). In addition, median leukemia-free survival estimates are generated based on 2 variables: platelet count <100 × 10⁹/L and the presence of unfavorable cytogenetics.23

**Treatment of MF**

Treatment approaches for patients with MF take into consideration the interaction between patient-specific and disease/treatment-related factors. Patient-specific factors include age, performance status, comorbidities, and patient goals of care. Disease-related factors include the IPSS-DIPSS risk group, and the risk-benefit ratio of available therapies.

Key considerations related to goals of care include determining which relevant MF symptoms will become the focus of the patient’s treatment—spleen-related symptoms, constitutional symptoms, improvement of cytopenias, prolongation of survival, or a combination.

Conventional therapies for MF have been directed toward reduction of marked splenomegaly (eg, chemotherapeutics such as hydroxyurea, busulfan, and splenectomy or splenic irradiation), medicines for anemia (erythropoiesis-stimulating agents, androgens), and therapeutics that may elicit responses in both spleen reduction and anemia (eg, thalidomide or lenalidomide

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**Table 4** Disease Complication Risk: Early-Prefibrotic PMF versus ET

<table>
<thead>
<tr>
<th>Complication</th>
<th>Relative Risk for Early-Prefibrotic PMF Compared with ET</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis</td>
<td>1.1</td>
<td>.51ᵃ</td>
</tr>
<tr>
<td>Overt MF</td>
<td>2.0</td>
<td>.04ᵇ</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>5.2</td>
<td>.0012ᵇ</td>
</tr>
<tr>
<td>Death</td>
<td>2.1</td>
<td>.0002ᵇ</td>
</tr>
</tbody>
</table>

ᵃNot significant. ᵇSignificant.

ET indicates essential thrombocythemia; MF, myelofibrosis; PMF, primary myelofibrosis.

Treatments have generally not been useful for durable mitigation of debilitating MF-related constitutional symptoms such as fatigue, night sweats, or bone/muscle pain. Although improvement of splenomegaly and anemia can be attained in a low proportion of patients, these medications are generally considered palliative in nature, and whatever benefit they convey is typically short-lived. Transplantation is the only potential curative modality for patients with MF.

A New Era of Care for MF: JAK Inhibitors

The discovery of the activating JAK2 V617F mutation in 2005 accelerated the evaluation of targeted inhibitors of JAK2, leading to the first trial in patients with MF (eg, ruxolitinib, formerly INCB018424) in 2007. Following ruxolitinib’s lead, several additional JAK inhibitors have entered clinical trial testing, including fedratinib (SAR302503, formerly TG101348), pacritinib (SB1518), momelotinib (CYT387), and additional agents (Table 6). Consistent benefits of the JAK inhibitors are reduction of splenomegaly and MF-related constitutional symptoms.

Currently, ruxolitinib is the only JAK inhibitor approved by the US Food and Drug Administration for the treatment of MF (intermediate- or high-risk MF). Treatment indications for ruxolitinib include PMF, post-PV MF, and post-ET MF.24

**Ruxolitinib**

Ruxolitinib is a potent inhibitor of JAK1 and JAK2—enzymes that mediate the signaling of a number of cytokines and growth factors that are important for immune function and hematopoiesis. Ruxolitinib binds in the adenosine triphosphate binding pocket of both wild-type and V617F-mutated JAK2, and therefore is not specific to the mutant protein.25

The efficacy and safety of ruxolitinib were evaluated in a number of trials—COMFORT-I, which evaluated ruxolitinib versus placebo; COMFORT-II, which evaluated ruxolitinib versus the best available therapy (BAT); and other trials, including a phase 1/2 study in which the safety and efficacy of ruxolitinib were evaluated in 153 patients with JAK2 V617F-positive or JAK2 V617F-negative PMF, post-ET MF, or post-PV MF. In this study, at a starting dose of 15 mg twice daily (followed by individualized dose titration), 52% of the patients had a rapid objective response (≥50% reduction of splenomegaly) lasting for ≥12 months, and with grade 3/4 adverse events in <10% of patients. These clinical benefits were also associated with a marked and sustained reduction in the levels of circulating inflammatory cytokines commonly elevated in MF.26

In COMFORT-I, a double-blind, placebo-controlled phase 3 trial, patients with intermediate-2 or high-risk MF were randomly assigned to receive oral ruxolitinib 15 mg or 20 mg twice daily (based on a platelet count of 100-200 x 10^9/L or >200 x 10^9/L, respectively) versus placebo. Results for the primary end point (% of patients with a ≥35% reduction in spleen volume at 24 weeks) are shown in the Figure. At week 24, patients treated with ruxolitinib had a median 33% decrease in spleen volume compared with an 8.5% increase in patients given placebo (P <.0001).27

The secondary end points were changes in symptom burden, overall survival, and durability of response. At 24 weeks, 45.9% of patients in the ruxolitinib group had a ≥50% improvement in the total symptom score, compared with 5.3% in the placebo group (P <.001). Ruxolitinib showed an improvement in overall survival.

| Table 5 | Makeup of DIPSS-Plus Risk Groups for PMF and Survival in Risk Groups |
|--------|-------------------------|-------------------------|
| DIPSS Risk Category or Prognostic Factor | Value | DIPSS-Plus Risk Group (Value) | Median Survival, Years (Approximate) |
| Low | 0 | Low (0) | Not reached |
| Intermediate-1 | 1 | Intermediate-1 (1) | 5.3 |
| Intermediate-2 | 2 | Intermediate-2 (2-3) | 2.8 |
| High | 3 | High (4-6) | 1.3 |
| Thrombocytopenia (platelet count <100 x 10^9/L) | | 1 |
| Need for RBC transfusion | | 1 |
| Unfavorable karyotype | | 1 |

DIPSS indicates Dynamic International Prognostic Scoring System; PMF, primary myelofibrosis; RBC, red blood cell. Source: Reference 23.
At 24 weeks, there were 13 deaths in the ruxolitinib group versus 24 deaths in the placebo group (hazard ratio [HR] = 0.50; 95% confidence interval [CI], 0.25-0.98; P = .04). At the 2-year follow-up, 58% of patients in the ruxolitinib group had a ≥35% spleen volume reduction at any point during the study, and 64% of these patients maintained a ≥35% reduction for at least 2 years. At a median follow-up at 102 weeks, there were 27 deaths in the ruxolitinib group, compared with 41 in the placebo group (HR = 0.58 (95% CI, 0.36-0.95; P = .028), indicating a sustained difference in survival between the 2 arms. No differences in progression to leukemia were noted between the placebo and ruxolitinib arms.

The most common hematologic adverse events in the ruxolitinib group were anemia (96% of patients; 45% grade 3 or 4) and thrombocytopenia (70% of patients; 13% grade 3 or 4), which occurred in the early part of the treatment. Nonhematologic adverse events included fatigue (25%; 5% grade 3 or 4), diarrhea (23%; 2% grade 3 or 4), peripheral edema and ecchymoses (19%; 0% grade 3 or 4), and other constitutional symptoms in <20% of patients, with ≥1% grade 3 or 4 severity. These adverse events rarely led to discontinuation of the drug.

The COMFORT-II phase 3 study consisted of a 2:1 randomization of patients to ruxolitinib versus BAT with dosing of ruxolitinib based on baseline platelet count similar to the COMFORT-I study. A total of 28% of the patients in the ruxolitinib group had a ≥35% reduction in spleen volume at week 48 (primary end point) compared with 0% in the BAT group (P < .001).

The median duration of response with ruxolitinib was not reached; at a median follow-up of 12 months, 80% of patients were still responding to treatment. The ruxolitinib-treated group showed an improvement in overall quality-of-life measures and a reduction in MF-associated symptoms. In an update of the findings from COMFORT-II, with a median follow-up of 112 weeks, the increased reductions in splenomegaly seen with ruxolitinib compared with BAT were sustained at 2 years; importantly, patients randomized to ruxolitinib showed longer survival than those randomized to BAT (HR = 0.52; 95% CI, 0.27-1.00).

The most common adverse events (≥grade 3) in both study groups were anemia (ruxolitinib 40%, BAT 23%), lymphopenia (ruxolitinib 23%, BAT 32%), and thrombocytopenia (10% in both groups). However, there were no significant differences among the ruxolitinib and BAT groups in the mean monthly RBC transfusion rate. No new hematologic or nonhematologic events were observed with ruxolitinib over the 2-year interval, and the observed events were managed primarily with dose reduction, treatment interruption, or transfusion.

To date, minimal changes in JAK2 V617F allele burden have been reported with ruxolitinib or other JAK2 inhibitors, which are not felt to be clinically relevant. Improvement in bone marrow fibrosis has been reported in selected patients treated with JAK inhibitors, usually over long periods of time. However, moving forward, the use of blinded, central histopathologic analysis of bone marrow biopsies from patients treated with JAK inhibitors versus those randomized to placebo or BAT will be required to fully appreciate comparative effects on marrow fibrosis.

In a phase 2 study of patients with MF with low starting platelet counts (50-100 × 10^9/L), an alternative dosing strategy for ruxolitinib was assessed, with subsequent dose escalation. Patients were started on a dose of 5 mg ruxolitinib twice daily, and with adequate platelet count, doses could be increased by 5 mg once daily every 4 weeks to 10 mg twice daily. Further dose

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Table 6  JAK Inhibitors in Clinical Use/Clinical Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial Name</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib (Jakafi)</td>
<td>COMFORT-I</td>
<td>FDA approved in 2011</td>
</tr>
<tr>
<td></td>
<td>COMFORT-II</td>
<td></td>
</tr>
<tr>
<td>Fedratinib (SAR302503, formerly TG101348)</td>
<td>JAKARTA</td>
<td>Phase 3 accrued</td>
</tr>
<tr>
<td>Momelotinib (CYT387)</td>
<td>PERSIST-1</td>
<td>Phase 3 commencing 2013</td>
</tr>
<tr>
<td>Pacritinib (SB1518)</td>
<td>PERSIST-2</td>
<td>Phase 3 commencing 2013</td>
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<tr>
<td>CEP-701</td>
<td></td>
<td>Phase 2</td>
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<tr>
<td>LY2784544</td>
<td></td>
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<td>BMS-911543</td>
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<td>Phase 1</td>
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<tr>
<td>NS-018</td>
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<td>Phase 1</td>
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</table>

FDA indicates US Food and Drug Administration; JAK, Janus kinase.
increases required evidence of suboptimal efficacy. Of the 19 patients who completed 24 weeks of treatment, >70% attained a final dose of ≥10 mg ruxolitinib twice daily, and 33% of the patients achieved the primary clinical end point of a ≥35% reduction in spleen volume. Treatment with ruxolitinib was generally well tolerated; no patients had to discontinue treatment as a result of thrombocytopenia or bleeding events. No new safety signals were seen in patients with MF with low platelet counts.31

Designing Individualized Care Plans for Patients with MF: JAK Inhibition or HCT or Both?

Decision-making as to whether a patient should have a hematopoietic cell transplantation (HCT), or be placed on JAK inhibitor therapy, or both, is quite complex. In most cases, a patient must meet certain criteria to be eligible for HCT consideration (ie, be <70 years of age and have a reasonable performance status without any significant comorbidities or prohibitive comorbidities for the HCT). The criteria may vary from one institution to another.

Knowing the patient (age, functional status) and the patient’s goals (whether the patient is a transplant candidate or could become a transplant candidate through disease modification) is an essential aspect of determining a treatment plan. Once a patient is deemed eligible for transplant, the next step is to work closely with the patient to establish the patient’s therapeutic goals. Establishing these goals involves candid discussions with the patient and agreement whether the focus will be on curative treatment (meaning that transplant will factor into their care plan) or on symptom control (addressing quality-of-life issues).

For patients with intermediate-2 or high-risk MF who have symptomatic disease whose goal is symptom control, the commercially available JAK inhibitor therapy (ruxolitinib) or enrollment in a clinical trial is generally considered. For patients with symptoms of hypermyeloproliferation (high WBC count or high platelet count), treatment with hydroxyurea may still have a role. The rather rare patients with advanced MF without symptomatic disease are followed up at regular intervals for symptom and risk assessment.32

Asymptomatic patients who have a low risk of leukemic transformation are followed up every 3 to 4 months, and a risk score assessment is conducted at each visit. Patients who have symptoms related to splenomegaly or have constitutional symptoms are reasonable candidates for JAK inhibitor therapy or a clinical trial. Patients with a high risk of leukemic transformation (ie, patients with unfavorable cytogenetics or severe thrombocytopenia) or those who are transfusion-dependent should be assessed to determine whether they are eligible for transplant.

Selection of JAK Inhibitor Therapy or HCT for an Individual Patient

Treatment decisions, including whether to select JAK inhibitor therapy or HCT, are based on the individual needs of the patient with MF.

JAK inhibitor therapy is generally well tolerated, supported by robust data, and helps improve quality of life. However, there are some unknowns about JAK inhibitor therapy (eg, duration of response in a particular patient). Some patients who start on JAK inhibitor therapy may have to discontinue treatment as a result of intolerance, nonhematologic toxicity, cytopenias, and/or lack of response. Resistance to JAK inhibitor therapy, although not well defined, is a possibility. The impact of JAK-inhibitor–related cytopenias on survival or leukemic transformation is unknown.

Currently, HCT is the only therapy that provides a potential cure for MF. However, there are a number of barriers to successful outcomes with HCT, including the risk of early mortality, regimen-related toxicities, decreased quality of life, and potentially serious complications, including graft-versus-host disease and recurrent infection. Considerations for HCT include the patient’s age, performance status, and comorbid conditions. For patients who are not candidates for HCT, JAK inhibitor therapy would likely be selected. For patients with a high risk of leukemic transformation, HCT may be considered
in preference to JAK inhibitor therapy.\textsuperscript{32}

Identifying the appropriate donor for patients with MF who are HCT candidates is particularly challenging. According to a study of 103 patients with MF, the expected survival outcome associated with reduced-intensity conditioning transplant at 5 years for a human leukocyte antigen (HLA)-matched donor was 74%, whereas the outcome dropped to 38% for an HLA-mismatched donor.\textsuperscript{33} Given the poor outcomes of a partially matched or mismatched unrelated donor, this option may be reserved for patients who fail JAK inhibitor therapy.

Potential Role for Combining a JAK Inhibitor with HCT

There is a tremendous interest in combining JAK inhibitor therapy in the transplant protocol, because there is a theoretical rationale that this may help in improving the performance status of the patient prior to HCT, which may have a beneficial effect on transplant outcomes. Such an approach should only be carried out as part of clinical trials or at expert centers well experienced in the use of JAK inhibitor therapy. An international clinical trial conducted by the Myeloproliferative Disorders Research Consortium will study the safety and efficacy of this approach in a systematic fashion.

Emerging Therapies and Future Directions in MF

Emerging treatments for MF include IMiDs, histone deacetylase (HDAC) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, and other agents that target novel pathways in MF. There are a number of unmet needs in MF, including treatment of AML transformation, cytopenias (especially anemia and thrombocytopenia), bone marrow fibrosis, and managing patients who stop responding to JAK inhibitor therapy.

Pomalidomide

Pomalidomide, a next-generation IMiD, successfully completed phase 1/2 trials. Early studies showed an improvement in anemia and transfusion needs.\textsuperscript{34,35} Minimal spleen improvement was observed in these studies. Adverse events were generally comparable to early-generation IMiDs, except there was less severe peripheral neuropathy with pomalidomide.\textsuperscript{35} Despite this early promise, a phase 3 randomized clinical study with pomalidomide in patients with MF who had severe anemia with RBC transfusion dependence did not meet its primary end point.\textsuperscript{36}

HDAC Inhibitors

Panobinostat (LBH589), a pan-HDAC inhibitor, underwent a phase 1 study in MF. Reductions in spleenomegaly were observed in the 3 dosing cohorts (20 mg, 37.5%; 25 mg, 38.8%; and 30 mg, 18.4%, respectively). An improvement in anemia was seen in 2 of 5 patients treated with panobinostat. After the sixth treatment cycle, 3 of 5 evaluable patients achieved clinical improvement with 100% reduction in palpable splenomegaly from baseline. Of the 3 patients treated with panobinostat who achieved clinical improvement, 1 patient had a near-complete remission (after 15 treatment cycles) and 1 patient had resolution of bone marrow fibrosis (after both 16 and 24 treatment cycles). The most common adverse events associated with panobinostat were myelosuppression, elevated creatinine level, and elevated bilirubin.\textsuperscript{37}

Givinostat, a class I and II HDAC inhibitor, is in phase 2 trials in patients with JAK V617F mutant MPNs (N = 29). The efficacy and safety of givinostat in MF, PV, and ET were studied in a phase 2 multicenter, open-label, nonrandomized study. Patients received a starting dose of givinostat 50 mg twice daily for 24 weeks, which could be escalated to 3 times daily if tolerated. Responses included 2 patients with clinical improvement, 5 with stable disease, 3 with major response, and a reduction of splenomegaly in 38%. There was a trend toward reduction of the JAK V617F allele burden in the study. The most common adverse events (≥10%) associated with givinostat were diarrhea, nausea, anemia, thrombocytopenia, and QT-prolongation.\textsuperscript{38}

Pracinostat was evaluated in a phase 2 prospective study in patients with MF (N = 22). Patients received pracinostat 60 mg every other day for 3 weeks per month. A clinical benefit was observed in 8 (36%) patients, with a reduction in splenomegaly in 6 (27%) patients. The most common adverse events associated with pracinostat were fatigue (91%), neutropenia (13%), and thrombocytopenia (21%).\textsuperscript{39}

Other Agents

Everolimus, an mTOR inhibitor, was evaluated in a phase 1/2 proof-of-concept trial in patients with intermediate- or high-risk MF (N = 39). Based on responses evaluated in 30 patients (phase 2), spleen size was reduced by >50% in 20% of patients, and by >30% in 44% of patients. Systemic symptoms completely resolved in 69% of patients. There were improvements in leukocytosis, anemia, and thrombocytosis in 15% to 25% of patients. The most common side effect was stomatitis.\textsuperscript{40}

Simtuzumab (GS-6624), a lysyl oxidase–like-2 inhibitor (phase 2); GS-1008, a transforming growth factor–inhibitor (phase 1); LDE225, a smoothened inhibitor (with ruxolitinib, phase 1b/phase 2); soratcept, an SMAD inhibitor (phase 2); and imetelstat sodium, a
telomerase template antagonist (pilot trial) are other novel therapies on the horizon for the treatment of patients with MF. Single-agent therapies targeting various pathways may hold promise. Moreover, the role of combination therapies is also being explored.

Community Hematologist Perspective: Referrals to Academic Centers

Key considerations for referrals to an academic center include the patient’s risk category, symptom burden, disease complications, complex diagnosis, and whether the patient is a candidate for clinical trial enrollment. Some community clinicians make it a point to have their patients with MF seen at least once at an academic center that offers expertise and clinical trial participation.

Identifying MF academic centers of excellence or shared care models that would serve as a resource for partnership with community clinicians seems to be a useful approach given the rarity of MF. Potential barriers to such a partnership for community clinicians may include difficulty deciding on which center to send their patients and a concern about losing their patients to other physicians or practices. Concerns about losing a patient to an academic center may be unfounded. In most cases, the academic institution will provide hematopathologic expertise, and guide the patient and referring physician. When patients are referred to an academic center, the frequency of patient visits and laboratory studies can be part of the shared decision-making between the community and academic-setting physician.

Given that many elderly patients with MF have comorbid conditions such as heart disease and vascular issues, and may warrant more frequent monitoring, these patients might be better served by remaining with community physicians located closer to their homes. Conversely, some patients may initiate a self-referral to an academic center for a second opinion and expect to continue treatment at such a facility.

Time is a key consideration for some patients with MF, because some patients may transition from intermediate- to high-risk disease very quickly, and this quick progression to the high-risk phase may limit therapeutic options. Thus, earlier referral and involvement of academic centers may expand the patient’s therapeutic options. Access to academic institutions also encourages increased clinical trial participation for appropriate patients.

Counseling and Monitoring Patients with MF

Role of the Oncology Nurse Navigator

Oncology nurse navigators have an increasingly important role as crucial members of the multidisciplinary healthcare team. The Academy of Oncology Nurse Navigators defines a nurse navigator as a “clinically trained individual responsible for the identification and removal of barriers to timely and appropriate cancer treatment.” Nurse navigators are charged with the proactive, personalized guidance of patients throughout the cancer journey from diagnosis through survivorship.

By “navigating” patients through the system, nurse navigators help patients address the most common barriers encountered, including ancillary service referrals and knowing what resources are available and how to use them. Acting as a central point of contact for the patient with cancer, nurse navigators coordinate the patient’s care with surgical, medical, and radiation oncologists, as well as with social workers. They provide patient education, community support, and financial and insurance assistance. In addition, they orchestrate nutrition assessment and education, genetic risk assessment, and resources for medications, transportation, and community agencies. They also help patients with scheduling and finding support groups, counseling services, and mind/body/spirit wellness.

The most important functions of the nurse navigator are to educate patients about the importance of medication adherence, side effects, and reportable signs and symptoms, and to provide ongoing communication, follow-up, and monitoring.

Case Study 2: Guiding a Newly Diagnosed Patient with MF

This case study highlights questions and concerns that arise when a patient finds out she has MF and approaches to guiding the patient through the care journey.

Mrs M is a 65-year-old widow who lives alone. She is newly diagnosed with MF. She is afraid and confused and has financial issues. After her initial hematology consult, Mrs M has numerous questions: What is this disease again? What is the medication? Where will I get the medication? What are the side effects? How will I pay for it? How will I be monitored? What does the lab work entail?

Mrs M is referred to a nurse navigator. Initial steps for the nurse navigator include establishing a relationship with the patient either in person or via telephone conversation. In some cases, a translator may be needed. The nurse navigator subsequently assesses the treatment plan by communicating with the physician and reviewing hospital records and staying current on Mrs M’s care plan and expected outcome. He or she subsequently continues to help Mrs M understand how the healthcare system operates and guides her through key processes along her continuum of care.

Improving the Patient’s Quality of Life

Fatigue, the most commonly reported symptom in
patients with MPNs, has a substantial impact on the patient's quality of life and productivity. Other factors that impact quality of life include medication-related toxicities, financial and emotional stress associated with the disease, the day-to-day challenges of medical care, and other comorbidities.

Steps for improving the patient’s productivity include symptom management (medications, transfusions), lifestyle changes, education, and support from family, friends, and the healthcare team. It is also essential to connect the patient with MF with survivorship and support groups to help them through the ups and downs of living with, through, and beyond their disease. Some practices and institutions offer monthly support programs. The MPN Research Foundation is a valuable resource for patients, offering online chats, support groups, and in-person local support groups. Online access to the MPN Research Foundation support is available at www.mpnresearchfoundation.org/support-groups.

Given its symptom burden, MF has a substantial impact on a patient’s quality of life. Symptom measurement is a crucial tool for estimating survival as well as for evaluating the impact of therapies on a patient’s symptom burden. Effective tools for assessing symptoms in patients with MF provide helpful information about the impact of novel therapies on symptom control and improved quality of life.

The former lack of an effective tool to measure symptoms and patient-reported outcomes covering the full range of symptoms seen in patients with MF led to the development of the Myelofibrosis Symptom Assessment Form (MFSAF) and, subsequently, to the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF).

The MFSAF is a validated instrument that captures the most prevalent symptoms that patients with MF experience, including fatigue, splenomegaly, night sweats, itching, fever, bone pain, and weight loss, and includes a measure of quality of life. Another tool—the MPN-SAF—is a validated, 27-item single tool that assesses the prevalence and severity of 3 MPNs, including MF, PV, and ET, whereas the MFSAF is focused solely on MF.10

Value-Based Management of MF: Role of Specialty Pharmacy in Support of Patients with MF

Specialty pharmacies can play a key role in the support of patients diagnosed with MF. Because of the regular interaction with patients receiving drug treatment for MF, specialty pharmacies are positioned to address constitutional symptoms of the disease, potential side effects of medications, and other patient assessment and education on a monthly basis at a minimum. Specialty pharmacies can provide the following list of services in support of patients receiving drug treatment for MF:

- Assessment of disease symptoms and possible side effects of medications
- Prevention of drug–drug interactions
- Prior authorization support
- Financial assistance with out-of-pocket cost-sharing
- Patient education regarding disease and drug therapy
- Referral to patient assistance programs, if needed
- Quality-of-life assessments
- Direct-to-patient delivery of medications
- Medication adherence calls and management of prescription refills

Conclusions

Significant strides have been made in understanding and potentially altering the trajectory of MF. The diagnosis of MF is complex, given that some of its symptoms and features may overlap with other MPNs and hematologic disorders. Use of the WHO diagnostic criteria can help provide clinicians with a quicker path to accurate diagnosis and appropriate therapy. A clear diagnosis also requires conveying all relevant information about the patient to the hematopathologist.

Management of MF requires symptom assessment, risk assessment, and candid discussions with the patient about therapeutic goals. Treatment plan decisions involve considerations about the risks and benefits of a particular treatment plan, and patient-tailored factors, including the patient’s net symptom burden and quality of life.

JAK inhibitor therapy has been shown to be effective in reducing splenomegaly and MF-related symptoms. The decision whether to select JAK inhibitor therapy or HCT should be individualized, based on patient preferences and other patient-, disease-, and transplant-related factors. The use of JAK inhibitor therapy in the transplant setting may have a role in overcoming some of the current issues with transplantation in MF.

Currently, ruxolitinib is the only FDA-approved JAK inhibitor for the treatment of intermediate- or high-risk MF. A number of novel agents that target various pathways are currently being investigated.

Author Disclosure Statement

Dr Godlib has received research funding and honoraria from Gilead, Incyte, Novartis, and sanofi-aventis.

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July/August 2013 | www.AHDBonline.com | S141


