Optimizing the Management of Patients With Myelofibrosis

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Myelofibrosis (MF) is a rare myeloproliferative neoplasm of the bone marrow associated with shortened survival. The disease is characterized by splenomegaly, cytopenias, and multiple disease-related symptoms that reduce quality of life. The clinical management of MF can be challenging because of its heterogeneous presentation and disease course. Therefore, knowledge of the underlying pathology and clinical manifestations of MF is needed. Ruxolitinib, a Janus kinase (JAK) 1 and 2 inhibitor, is the first therapy to be approved by the U.S. Food and Drug Administration for intermediate- or high-risk MF. Ruxolitinib therapy offers advantages over the previous palliative treatments and has shown durable reductions in splenomegaly and disease symptoms as well as improvements in quality of life. Two-year follow-up of the phase III trials also has shown that ruxolitinib treatment was associated with a survival advantage relative to control groups. Dose-dependent thrombocytopenia and anemia are expected but manageable adverse effects caused by the targeted JAK inhibition of ruxolitinib. This review provides an overview of MF and assessment of the primary clinical disease manifestations, with a focus on ruxolitinib from the oncology nurse perspective.
Clinical Hallmarks of Myelofibrosis

Progressive failure of the bone marrow, characterized by reticulin/collagen fibrosis, underlies the clinical hallmarks of MF (Gregory et al., 2011). As the bone marrow becomes compromised, extramedullary hematopoiesis occurs as a compensatory response, primarily affecting the spleen, but the liver, lymph nodes, serosal surfaces, and epidural spaces may be involved (Abdel-Wahab & Levine, 2009; Barbui et al., 2011; Gregory et al., 2011). Despite this compensatory effort, anemia and, less often, thrombocytopenia develop as the disease progresses (Barbui et al., 2011). In addition, the overproduction of inflammatory cytokines occurs in part because of dysregulated JAK/STAT signaling and contributes to the constellation of MF symptoms (Ostojic, Vrhovac, & Verstovsek, 2012).

Moderate to severe anemia (hemoglobin less than 10 g/dl) and marked leukocytosis (greater than 25 x 10^9/L) are associated with more advanced disease and are independent risk factors for shortened survival in patients with MF (Cervantes et al., 2009; Gangat et al., 2011). Based on the experience of 1,000 patients at the Mayo Clinic, 54% of patients with MF had hemoglobin levels less than 10 g/dl, 38% were red blood cell transfusion dependent, 16% had marked leukocytosis, and 26% had platelet counts less than 100 x 10^9/L (Tefferi et al., 2012). Anemia can add to the symptom profile in patients with MF, with the potential for fatigue, dyspnea, palpitations, tachycardia, and weakness. These symptoms may exacerbate other comorbidities, such as heart failure and chronic obstructive lung disease, in this primarily older adult population. Thrombocytopenia, including platelet dysfunction, increases the risk of bruising and bleeding, and may complicate treatment in patients requiring aspirin therapy or anticoagulants (Barbui et al., 2011).

Splenomegaly, affecting 76% of patients with PMF in a large survey, is a major sign of MF and may substantially contribute to morbidity and reduced QOL (Mesa, 2009; Mesa et al., 2009). The enlarged spleen (and liver in some patients) can produce (the most common being JAK2 V617F) or regulatory molecules, is central to the pathobiology of MF (Vainchenker, Delhommeau, Constantinescu, & Bernard, 2011). This discovery led to the development of the oral JAKI/JAK2 inhibitor ruxolitinib, which currently is the only U.S. Food and Drug Administration-approved therapy indicated for intermediate- or high-risk PMF, post-PV MF, or post-ET MF. In phase III clinical trials, ruxolitinib treatment provided durable reductions in spleen volume and symptom burden, improved QOL, and provided evidence for a survival benefit over placebo or best available therapy (BAT) (Cervantes et al., 2012; Verstovsek et al., 2012; Verstovsek et al., 2013a).

The oncology nurse has an important role in patient assessment, symptom management, and patient education, but treatment of rare diseases can be challenging because of limited clinical experience. This review provides an overview of MF and the assessment of its primary disease manifestations. Treatment options are discussed, with a focus on ruxolitinib. Key strategies for educating patients and caregivers also are discussed, with the goal of optimizing treatment outcomes.

### Clinical Hallmarks of Myelofibrosis

**Bone pain**
- **PMF (%):** 51
- **Post-PV MF (%):** 46
- **Post-ET MF (%):** 44
- **All Patients (%):** 47

**Fatigue**
- **PMF (%):** 85
- **Post-PV MF (%):** 81
- **Post-ET MF (%):** 85
- **All Patients (%):** 84

**Fever**
- **PMF (%):** 19
- **Post-PV MF (%):** 17
- **Post-ET MF (%):** 18
- **All Patients (%):** 18

**Night sweats**
- **PMF (%):** 55
- **Post-PV MF (%):** 58
- **Post-ET MF (%):** 53
- **All Patients (%):** 56

**Pruritus**
- **PMF (%):** 39
- **Post-PV MF (%):** 69
- **Post-ET MF (%):** 39
- **All Patients (%):** 50

**Symptomatic splenomegaly**
- **PMF (%):** 76
- **Post-PV MF (%):** 49
- **Post-ET MF (%):** 41
- **All Patients (%):** 54

**Weight loss (> 10%)**
- **PMF (%):** 30
- **Post-PV MF (%):** 15
- **Post-ET MF (%):** 16
- **All Patients (%):** 20

### TABLE 1. Most Common Disease-Related Symptoms in Patients With MF

<table>
<thead>
<tr>
<th>Symptom*</th>
<th>PMF (%)</th>
<th>Post-PV MF (%)</th>
<th>Post-ET MF (%)</th>
<th>All Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain</td>
<td>51</td>
<td>46</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>Fatigue</td>
<td>85</td>
<td>81</td>
<td>85</td>
<td>84</td>
</tr>
<tr>
<td>Fever</td>
<td>19</td>
<td>17</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Night sweats</td>
<td>55</td>
<td>58</td>
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<td>56</td>
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<td>Pruritus</td>
<td>39</td>
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<td>39</td>
<td>50</td>
</tr>
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<td>Symptomatic splenomegaly</td>
<td>76</td>
<td>49</td>
<td>41</td>
<td>54</td>
</tr>
<tr>
<td>Weight loss (&gt; 10%)</td>
<td>30</td>
<td>15</td>
<td>16</td>
<td>20</td>
</tr>
</tbody>
</table>

* Self-reported

ET—essential thrombocythemia; MF—myelofibrosis; PMF—primary MF; PV—polycythemia vera


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At each visit, ask patients about the appearance of or changes in:

**Splenomegaly**
- Daily or work activities impacted
- Length of time can comfortably lie down or sit
- Clothing size or style
- Belt notches used
- Quantity of food consumed at meals
- Types of food consumed at meals
- Level of abdominal pain
- Bowel and/or bladder habits

**Cytopenias**
- Dyspnea, tachycardia
- Fatigue
- Signs of bleeding risk (bleeding gums, bruises that increase in size, dark tarry stools, hematuria)
- Symptoms of neurologic hemorrhage (sudden onset headaches, loss of vision, vomiting, change in gait or balance)

**Pain**
- Frequency of pain
- Intensity of pain
- Pain at new or different sites
- Pain when starting or switching medication
- Bowel habits affected by pain medication

**Disease-Related Symptoms**
- Use of heavy emollients for itching
- Use of antihistamines for itching
- Energy or activity level
- Weight loss or gain
- Hypoglycemic episodes
- Sleep disturbance

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**FIGURE 1. Patient Assessment Checklist: Screening Aid for Emergent or Worsening Myelofibrosis Features**
a variety of symptoms, such as generalized abdominal pain, left upper quadrant pain, early satiety, changes in bowel habits, and frequent urination. Painful splenic infarcts, portal hypertension (causing ascites and variceal bleeding), and decreased mobility can occur (Barbui et al., 2011). The resulting pain from the organomegaly can be severe and may require pain medications, including opioids.

In addition to symptoms from splenomegaly and cytopenias, patients with MF can experience constitutional symptoms, largely from increased levels of cytokines. Those symptoms (e.g., fever, night sweats, weight loss) indicate poor prognosis (Cervantes et al., 2009; Mesa et al., 2007). Other troublesome symptoms often experienced by patients with MF include fatigue, pruritus, musculoskeletal pain, and cachexia (Abdel-Wahab & Levine, 2009; Barbui et al., 2011), with 20% losing more than 10% of their body weight (Mesa et al., 2009) (see Table 1).

Assessments in Patients With Myelofibrosis

The oncology nurse has an important role in establishing medical history, including previous diagnoses of PV or ET, which are associated with risk of thrombotic and hemorrhagic events. Because these events are among the most common causes of death in patients with MF (Cervantes et al., 2009; Gangat et al., 2011; Passamonti et al., 2010), patients should be asked about current signs and symptoms, previous and current drug therapy, and history of vascular events.

Because options for a cure are limited, control of symptoms and cytopenias to enhance QOL and maintain function underlie the treatment plan for most patients. Oncology nurses, along with the multidisciplinary care team, perform disease-specific assessments to monitor symptom severity over the course of the disease trajectory. These may include the use of specific symptom assessment tools, discussed later in this article, as well as information obtained from patients and caregivers. Assessment of the key clinical manifestations of MF is reviewed in this article, along with considerations for patient and caregiver interviews (see Figure 1).

Cytopenias

In patients presenting with cytopenias, potential reversible causes, such as vitamin B₁₂ deficiency, iron deficiency, and blood loss, should be ruled out. In those with MF-related cytopenias, regular monitoring of blood counts is required to assess for disease progression and the occurrence of cytopenias from drug therapy. The importance of regular monitoring should be discussed with patients and caregivers.

Patients with symptomatic anemia may require red blood cell transfusions. These patients should be counseled that fatigue...
TABLE 2. Palliative Therapies Used to Treat Myelofibrosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Use</th>
<th>Potential Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgens, danazol</td>
<td>Anemia</td>
<td>Effective in only roughly 20% of patients after three months of therapy</td>
</tr>
<tr>
<td>Erythropoiesis-stimulating agents</td>
<td>Anemia</td>
<td>Not durable</td>
</tr>
<tr>
<td>Busulfan, melphalan, cladribine</td>
<td>Splenomegaly</td>
<td>Cytopenias; leukemic transformation</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>Splenomegaly</td>
<td>Modest reduction in spleen size and transient effect; dose-limiting cytopenias</td>
</tr>
<tr>
<td>Interferon alpha</td>
<td>Splenomegaly, cytopenias</td>
<td>Poor tolerability</td>
</tr>
<tr>
<td>Thalidomide, lenalidomide</td>
<td>Splenomegaly, cytopenias</td>
<td>Neuropathy, myelosuppression, constipation, depression</td>
</tr>
</tbody>
</table>

Note. Based on information from Cervantes, 2011; Gregory et al., 2011; Mesa, 2009; Vannucchi, 2011.

may not resolve with transfusion therapy because its occurrence may be from other causes (Mesa, 2009). In patients who develop thrombocytopenia, education on signs and symptoms of bleeding is imperative for patients and caregivers, along with routine questioning about potential bleeding episodes, so that new onset thrombocytopenia can be caught early and monitored.

Splenomegaly

Spleen size should be assessed by palpation at each visit. In a normal patient, the spleen cannot be felt. However, in patients with MF, the spleen often extends below the left costal margin. In patients with more advanced disease, the spleen volume may be 10 times normal (Harrison et al., 2012), extending below the pelvic brim. Severity of splenomegaly from the patient’s perspective can be assessed by determining impact on normal daily activities, self-image, normal bladder and bowel habits, and dietary routines. Specifically, patients often substantially reduce meal size and also may reduce the nutritional value of foods they consume.

Disease-Related Symptoms

The multitude of symptoms that occur in patients with MF can substantially impair QOL and reduce daily functioning equivalent to that observed in recurrent or metastatic cancers (Mesa et al., 2013); therefore, the baseline symptom burden should be established. Patients may attribute more vague symptoms, such as fatigue and general decline in functioning, to advancing age, and may self-treat symptoms such as pruritus with frequent use of emollients or antihistamines, not recognizing these as symptoms of MF. Therefore, patients should be asked specific questions to identify disease-related symptoms, determine the timing of onset, and monitor severity over time.

Research indicates that the use of patient-reported symptom checklists improves documentation and management with corresponding improvements in health-related QOL (Williams et al., 2012). The Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) is a tool that includes the 10 most clinically important characteristics of myeloproliferative disorders, with the goal to assess symptom burden in clinical practice (Emanuel et al., 2012; Scherber et al., 2011) (see Figure 2). Currently, no standard symptom assessment form is in use across oncology centers; therefore, the oncology team may choose to develop specific questionnaires or evaluate the use of the MPN-SAF TSS. Regardless of the tool used, questions should be simple and phrased consistently from visit to visit to obtain an accurate picture of symptom burden. The information captured with these tools can be augmented with questions about the timing of symptom onset to determine if symptoms are related to treatment or disease to further guide treatment decisions.

Weight loss and cachexia are signs of disease progression and worse prognosis (Cervantes et al., 2009); therefore, body weight should be routinely monitored. Patients may benefit from an assessment of their nutritional intake and needs by a dietitian. Patients with diabetes receiving antihyperglycemic agents warrant particular concern, and communication with the patient’s primary care provider and/or endocrinologist will be needed.

Many of the clinical manifestations of MF result in debilitating pain, including abdominal pain from splenomegaly and resulting vascular complications (such as splenic infarcts) (Mesa, 2009), bone pain from remodeling caused by fibrosis (Abdel-Wahab & Levine, 2009), and joint pain from inflammation (Abdel-Wahab & Levine, 2009). Patients with MF who require medication for pain control will need to have routine evaluations for level of pain relief and side effects, such as worsening fatigue and constipation. Patient and caregiver education about pain management medications and side effects will help ensure optimal patient care.

![FIGURE 3. Change in Spleen Volume at Week 24 in Individual Patients Treated With Ruxolitinib and Placebo](image-url)

Therapeutic Interventions for Managing Myelofibrosis

Prior to the approval of ruxolitinib, only palliative therapies were available for treating MF. Hydroxyurea has been used as first-line treatment for symptomatic splenomegaly; however, its use is limited by modest efficacy and dose-related cytopenias. Therapies used to treat the clinical manifestations of MF and potential limitations are shown in Table 2. In patients who are refractory to medical therapy, splenic irradiation, performed serially at low doses to avoid life-threatening cytopenias, can provide transient pain relief (Barbui et al., 2011; Mesa, 2009). Patients with symptomatic portal hypertension refractory to medical therapy or red blood cell transfusion dependent anemia may be eligible for splenectomy, but the procedure is associated with a 5%–10% mortality rate and a 50% complication rate (Barbui et al., 2011).

Treatment with ruxolitinib, an oral JAK1/JAK2 inhibitor, has shown significant reductions in splenomegaly and other MF-related symptoms with manageable cytopenias in two phase III trials. In the COMFORT-I study, patients with intermediate- or high-risk MF (including PMF, post-PV MF, or post-ET MF) and palpable splenomegaly (5 cm or greater below the left costal margin) were randomized to ruxolitinib (n = 155; 15 mg twice daily for platelet counts greater than 200 x 10^9/L or BAT at the time of the trial) or placebo (n = 154) (Verstovsek et al., 2012) (see Figure 3). Mean reduction in spleen volume from baseline to week 24 was 32% in the ruxolitinib group and 8% in the placebo group (Verstovsek et al., 2012). The COMFORT-II study used similar major inclusion criteria; patients were randomized to ruxolitinib (n = 146; 15 mg twice daily for platelet counts at or below 200 x 10^9/L and 20 mg twice daily for platelet counts greater than 200 x 10^9/L or BAT at the time of the trial (n = 73) (Harrison et al., 2012). At week 48, palpable spleen length decreased by a mean of 56% from baseline in the ruxolitinib group compared with a mean increase of 4% in patients receiving BAT (Harrison et al., 2012). Patients without the JAK2 V617F mutation responded similarly to those with the mutation in both trials (Harrison et al., 2012; Verstovsek et al., 2012).

Improvements in disease-related symptoms were reported for patients receiving ruxolitinib in both COMFORT trials (Harrison et al., 2012; Verstovsek et al., 2012). In COMFORT-I, the ruxolitinib group had improvements in all symptoms assessed using the modified Myelofibrosis Symptom Assessment Form, version 2.0 (see Figure 4), and the Patient-Reported

![FIGURE 4. Changes in the Myelofibrosis Symptom Assessment Form, Version 2.0](image)

**Note.** Individual symptom scores at week 24 in patients treated with ruxolitinib and placebo. For all comparisons, p < 0.01.
Outcomes Measurement System Fatigue Scale compared with worsening in the placebo group (Verstovsek et al., 2012) (see Figure 5). Symptom improvements on the MFSAF were seen regardless of JAK2 V617F mutation status in the ruxolitinib group (Verstovsek et al., 2013b). These improvements were validated by favorable outcomes on the Patient Global Impression of Change in COMFORT-I (Verstovsek et al., 2012) (see Table 3). In COMFORT-II, patients treated with ruxolitinib had improvements in selected symptoms on the European Organisation for Research and Treatment of Cancer Quality of Life Core 30 questionnaire compared with worsening in patients receiving BAT (Harrison et al., 2012) (see Figure 6).

Data from both trials also have shown that patients treated with ruxolitinib had a mean weight gain versus the comparator (Harrison et al., 2012; Verstovsek et al., 2012), suggesting that ruxolitinib treatment helps reverse cachexia in these patients. In addition, continued follow-up of patients from both studies shows that ruxolitinib may be associated with improved survival over placebo and BAT (Cervantes et al., 2012; Verstovsek et al., 2013a).

Ruxolitinib inhibits normal erythropoietin and thrombopoietin signaling that occurs via JAK2 (Quintas-Cardama, Kantarjian, Cortes, & Verstovsek, 2011), resulting in dose-dependent anemia and thrombocytopenia (Harrison et al., 2012; Verstovsek et al., 2012). In COMFORT-I, these cytopenias typically occurred within the first three months of ruxolitinib treatment and were managed by dose modifications and treatment interruptions or with red blood cell transfusions for anemia (Harrison et al., 2012; Verstovsek et al., 2012).

In COMFORT-I, mean hemoglobin levels decreased initially, but recovered to near baseline levels after the first 8–12 weeks (Verstovsek et al., 2012). Patients treated with ruxolitinib initially required more blood transfusions than those in the placebo group, but transfusion rates gradually returned to baseline values when assessed during a 36-week period (Verstovsek et al., 2012). Few patients discontinued because of treatment-related cytopenias: one patient for anemia and two for thrombocytopenia in both COMFORT studies (Harrison et al., 2012; Verstovsek et al., 2012).
symptoms (54% of patients) (Verstovsek, Gotlib, et al., 2013). However, patients who begin to feel better after starting ruxolitinib will need to be encouraged to continue treatment because it is a long-term therapy. Patients who interrupted ruxolitinib therapy in COMFORT-I reported their symptoms returning in about one week (Verstovsek et al., 2012). Nurses can reinforce the importance of treatment compliance by reminding patients of the benefits of continued therapy and the disadvantages of stopping, providing counseling on the proper use of multiple medications, and reassuring patients that their cytopenias and other adverse events are likely manageable.

TABLE 4. Adverse Events Observed in 10% or More of Patients Who Received Ruxolitinib

<table>
<thead>
<tr>
<th>Event</th>
<th>Ruxolitinib (N = 155)</th>
<th>Placebo (N = 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td><strong>Nonhematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>25.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>18.7</td>
<td>–</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>18.7</td>
<td>–</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>17.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>14.8</td>
<td>–</td>
</tr>
<tr>
<td>Headache</td>
<td>14.8</td>
<td>–</td>
</tr>
<tr>
<td>Constipation</td>
<td>12.9</td>
<td>–</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>12.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11.6</td>
<td>–</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10.3</td>
<td>2.6</td>
</tr>
<tr>
<td><strong>Hematologic abnormalities</strong></td>
<td>96.1</td>
<td>45.2</td>
</tr>
<tr>
<td>Anemia</td>
<td>69.7</td>
<td>12.9</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18.7</td>
<td>7.1</td>
</tr>
</tbody>
</table>

*Hematologic abnormalities are based on laboratory values. The data shown are for events of the worst grade during the study, regardless of whether this grade was a change from the baseline grade.


**Implications for Practice**

- Enhance assessment skills of symptoms of myelofibrosis, a rare hematologic cancer, by understanding the multiple clinical manifestations and the variable course it can take.
- Monitor symptom severity and response to therapy by the consistent use of disease-specific assessment tools.
- Detect the need for dose optimization of ruxolitinib, a Janus kinase 1 and 2 inhibitor, by monitoring routine blood counts for new onset thrombocytopenia or anemia, which are dose-related adverse effects that are most likely to occur within the first three months of therapy.

**Conclusion**

MF is a complex chronic disease with a heterogeneous clinical presentation. Typical manifestations such as splenomegaly, cytopenias, and disease-related symptoms vary in severity among patients, which presents a challenge in assessment and management for the oncology nurse.

Optimal management requires consistent use of assessment tools to monitor the multiple symptoms throughout the disease course and to assess therapeutic response and disease progression. Patient education is critical to this process, and oncology nurses are uniquely qualified to advocate for the patient, helping them overcome obstacles to treatment adherence.

Treatment for MF has progressed beyond the palliative chemotherapy options of just a few years ago, which only provided transient effects and required antiemetics, analgesics, and steroids to be tolerated. Unlike the temporary symptom-reducing effects of chemotherapy, ruxolitinib (although not curative) has been shown to provide durable reductions in spleen volume and disease-related symptoms and improvement in quality of life measures. The anticipated cytopenias associated with ruxolitinib therapy are manageable in most patients. Patient and caregiver education can help set realistic expectations for the occurrence of cytopenias, therefore limiting unwarranted discontinuation of therapy. Enhanced communication between healthcare providers and patients can help achieve maximum benefit from treatment.

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**References**


