The myeloproliferative neoplasms (MPNs) are a group of Philadelphia-negative (PH), or BCR-ABL-fusion gene-negative clonal stem cell disorders. These disorders include primary myelofibrosis (PMF), polycythemia vera (PV), essential thrombocythemia and myelofibrosis secondary to PV (PV-MF) and ET (ET-MF). The principal signs and symptoms of these disorders are cytopenias, splenomegaly, marrow fibrosis, and systemic symptoms due to elevated inflammatory cytokines. Patients with advanced MF can have decreased quality and quantity of life, similar to that of patients with other advanced malignancies. Some patients with MPNs transform to acute leukemia, which has an extremely poor prognosis.

Although allogeneic stem cell transplantation (ASCT) is curative, this treatment is applicable to only a minority of patients. Conventional therapies such as hydroxyurea, danazol, and thalidomide and prednisone do not alter the natural history of the disease. Dysregulation of the JAK-STAT pathway is a hallmark of pathogenesis of MF. The discovery of the gain-of-function point mutation JAK2V617F in patients with MPNs increased our understanding of the pathophysiology of PH-negative MPNs and led to the advent of new, specific therapeutic options. The first-in-class JAK1/2 inhibitor ruxolitinib was approved by Health Canada in 2012. With the wider availability of ruxolitinib and other novel therapeutic agents, the therapeutic landscape for MF is rapidly changing and is briefly reviewed here.

**Therapeutic options**

**Allogeneic stem cell transplantation (ASCT)**

Although ASCT is the only curative treatment for MF, the significant morbidity and mortality resulting from it makes this procedure applicable to only 5% to 10% of patients. Major toxicities include graft failure and graft-versus-host disease. ASCT may be appropriate, however, for younger patients with good performance status without prohibitive comorbidities who have an expected survival of less than five years, are transfusion-dependent or are at increased risk of transformation to secondary AML. Progression-free survival of 40% to 50% at three years can be expected with ASCT.

**Conventional treatment**

There is a wide array of conventional treatments available, aimed at palliating symptoms and improving quality of life. These revolve around reducing splenomegaly (the most common manifestation of MF), reversing anemia and resolving constitutional symptoms.

**Splenomegaly**

Hydroxyurea is the most frequently used drug for reducing spleen size and gives a 45% to 50% clinical improvement, but it can take up to three months to see a response. Splenectomy has been shown effective in reducing transfusion dependence, pain and constitutional symptoms, but carries with it thrombosis, bleeding and sepsis that can occur in 25% of patients. Mortality can reach 10%. For patients in whom splenectomy is not appropriate (due to age or comorbidities) or are unresponsive to medication, splenic irradiation can be used. This can result in a reduction in spleen size and abdominal discomfort that can last three to six months. Unfortunately, splenic irradiation is accompanied by a high rate of severe cytopenias and increased transfusion dependence.

**Anemia**

Anemia is a frequent symptom of MF and, along with transfusion dependence, is a poor prognostic factor in MF. Conventional treatments include epoietin alpha, androgens such as danazol, and immunomodulators such as thalidomide, used with or without prednisone. Epoietin alpha, alone or in combination with interferon-α-2b and with or without GM-CSF, showed response rates of up to 60%. Female patients and patients with milder anemia appear to respond better. However, this treatment can result in progression of splenomegaly. The best patients to use epoietin alpha in are those with anemia and low erythropoietin levels. Thalidomide and related compounds have shown response rates of up to 30%, which can be improved with the concomitant use of prednisone. However, a large proportion of patients discontinue therapy due to adverse events such as neurotoxicity and myelosuppression.

**Constitutional symptoms**

These symptoms include fatigue, weight loss, night sweats and pruritus and can have an impact on disease prognosis. However, conventional treatments are largely ineffective.

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**Table 1: Tips on the use of ruxolitinib in routine clinical practice**

<table>
<thead>
<tr>
<th>Tip</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Dosing should be individualized based on platelet count to maximize efficacy and minimize toxicities. In the COMFORT trials, the ruxolitinib doses were 15 mg BID for platelet counts of 100–200 x 10^9/L, and 20 mg BID for platelet counts &gt;200 x 10^9/L. Start at 5 mg BID for platelet counts of 50–100 x 10^9/L.</td>
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<tr>
<td>2.</td>
<td>Ruxolitinib should be tapered slowly if treatment needs to be discontinued.</td>
</tr>
<tr>
<td>3.</td>
<td>Educate patients about potential adverse drug effects while on treatment and during discontinuation.</td>
</tr>
<tr>
<td>4.</td>
<td>Advise patients to maintain an adequate supply of drug at all times, e.g., going on vacation, etc. MF-related symptoms can return rapidly if the drug is discontinued abruptly.</td>
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</tbody>
</table>

Adapted from Gupta V, Foltz L, Sirhan S, et al.
Novel therapeutic options

JAK1/2 inhibitors constitute a major advance in the management of MF. The first of these, ruxolitinib, was recently approved by Health Canada under the brand name Jakavi® (known as Jakafi™ in the United States). Other JAK inhibitors are at various stages of clinical development, so, for the immediate future, ruxolitinib will be the most widely available agent in this class.3

Approval of ruxolitinib was based on the COMFORT-I and –II trials versus placebo and best available treatment (BAT), respectively. In patients with intermediate-2 or high-risk PMF, PV-MF or ET-MF, there was no survival difference between ruxolitinib and BAT in COMFORT-II.3

Ruxolitinib was generally well tolerated. Anemia, thrombocytopenia and neutropenia were the most frequent grade 3/4 hematologic adverse events. Dosage is determined by platelet counts (Table 1). The place in therapy of ruxolitinib is shown in Algorithms 1 and 2.1

Summary

MF is a rare but burdensome disease. Conventional therapies have not proven to be adequate treatment although, in the properly selected patients, ASCT can be curative. The discovery of the role of Janus Kinase in MF has resulted in the development of JAK1/2 inhibitors, most notably ruxolitinib, which is available in Canada. The decision-making regarding therapeutic options for MF can be challenging and these patients should ideally be managed on a shared care basis between the primary physician and a physician with expertise in management of MPNs. To improve the care and research efforts for MPNs, a nationwide coordinated and collaborative effort has been initiated by the recently formed Canadian MPN Group.

References


