

Review Article

Emerging therapeutic options for myelofibrosis: a Canadian perspective

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Abstract: Myelofibrosis (MF) is a clonal stem cell disorder characterized by cytopenias, splenomegaly, marrow fibrosis, and systemic symptoms due to elevated inflammatory cytokines. MF is associated with decreased survival. The quality of life of patients with MF is similar to other advanced malignancies. Allogeneic hematopoietic cell transplantation is a curative treatment, but is applicable to a minority of patients with MF. None of the conventional therapies are known to alter the natural history of the disease. Significant progress has been made in the last few years in the understanding of disease biology of MF. Discovery of the JAK2V617F mutation paved the way for drug discovery in MF, and the first JAK1/2 inhibitor, ruxolitinib, has been approved by FDA and Health Canada. Several other JAK1/2 inhibitors are at various stages of clinical development. As a consequence, the therapeutic landscape of MF is changing from a disease where no effective therapies existed to one with several novel treatment options on the horizon. In this report, we assess the changing therapeutic options for MF, and critically analyze the position of novel treatments in the current armamentarium.

Keywords: Myelofibrosis, JAK1/2, ruxolitinib, splenomegaly, treatment options

Introduction

Primary myelofibrosis (PMF) is a clonal disease of hematopoietic stem cells. It is characterized by cytopenias, leukoerythroblastic blood picture, marrow fibrosis, and extramedullary hematopoiesis. A disease phenotype similar to PMF occurs in the natural history of polycythemia vera (PV) and essential thrombocythemia (ET), known as post-polycythemic myelofibrosis (PPV-MF) and post-ET myelofibrosis (PET-MF). In this report, PMF, PPV-MF, and PET-MF will be referred to as myelofibrosis (MF).

The estimated incidence of MF is 0.5-1.5 per 100,000 population [1, 2]. The median age at diagnosis is 69 years [3, 4], and < 15% are below age 50 years at the time of diagnosis [4]. The diagnosis of PMF is based on well-accepted World Health Organization (WHO) criteria [5], and the diagnoses of post-PV MF and post-ET

MF are based on International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria [6] (**Table 1**).

Clonal myeloproliferation in MF is accompanied by abnormal proinflammatory and proangiogenic cytokine expression, resulting in a secondary inflammatory stage. Splenomegaly is the major sign of MF, present in about 90% of patients. Also common is hepatomegaly, present in about 50% of patients [4]. Organomegaly is due to extramedullary hematopoiesis and may be accompanied by symptoms of early satiety, left upper quadrant pain and peripheral edema [7]. Constitutional symptoms, which include fatigue, pruritus, night sweats and fever, have been associated with elevated inflammatory cytokines [8]. MF-related constitutional symptoms and abdominal symptoms from splenomegaly have a profound impact on patient quality of life. The QOL of patients with MF

Table 1. Diagnostic criteria for primary myelofibrosis (PMF) and myelofibrosis secondary to polycythemia vera (PV-MF) or essential thrombocythemia (ET-MF).

Diagnostic criteria	
PMF ⁵	Major criteria (all required) Presence of megakaryocyte proliferation and atypia,* usually accompanied by either reticulin or collagen fibrosis, OR in the absence of significant reticulin fibrosis, megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (i.e. prefibrotic cellular-phase disease) Not meeting WHO criteria for polycythemia vera, <i>BCR-ABL1</i>-positive CML, MDS or other myeloid disorders Demonstration of <i>JAK2</i> V617F or other clonal marker (e.g. <i>MPLW515K/L</i>), OR in the absence of the above clonal markers, no evidence that bone marrow fibrosis is secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies Minor criteria (min. 2 required) Leukoerythroblastosis Increase in serum lactate dehydrogenase level Anemia Palpable splenomegaly
Post PV-MF ⁶	Required criteria Documentation of a previous diagnosis of PV as defined by WHO criteria Bone marrow fibrosis grade 2-3 (on 0-3 scale) or grade 3-4 (on 0-4 scale) Additional criteria (two are required) Anemia or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis A leukoerythroblastic peripheral blood picture Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly Development of ≥ 1 of three constitutional symptoms: $>10\%$ weight loss in 6 months, night sweats, unexplained fever ($>37.5^{\circ}\text{C}$)
Post ET-MF ⁶	Required criteria Documentation of a previous diagnosis of ET as defined by WHO criteria Bone marrow fibrosis grade 2-3 (on 0-3 scale) or grade 3-4 (on 0-4 scale) Additional criteria (two are required) Anemia and a $\geq 2\text{mg/mL}$ decrease from baseline hemoglobin level A leukoerythroblastic peripheral blood picture Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly Increased LDH (above reference level) Development of ≥ 1 of three constitutional symptoms: $>10\%$ weight loss in 6 months, night sweats, unexplained fever ($>37.5^{\circ}\text{C}$)

CML=chronic myeloid leukemia; MDS=myelodysplastic syndrome; LDH= lactate dehydrogenase

is similar to those with advanced solid tumors and other hematologic malignancies [9, 10].

In addition, MF can lead sometimes to debilitating complications such as chronic thromboembolic pulmonary hypertension and portal hypertension, which may manifest at any time during the disease course [11, 12]. In a large series of 1,054 consecutive cases, the most common cause of death was transformation to acute

myeloid leukemia (AML; 31% of deaths) (**Figure 1**) [4]. Other causes of death included PMF progression (18%), thrombosis and cardiovascular complications (13%), infection (11%) or bleeding out of the setting of acute transformation (5%), and portal hypertension (4%).

Prognostic risk scoring models

MF is a heterogeneous disease and the clinical

Therapeutic options in MF

course can vary from an indolent disease lasting for more than a decade to aggressive behaviour with an average life expectancy in the range of 2-4 years [2, 4, 13]. The behavior of MF can be predicted by the presence of various patient- and disease-related risk factors.

At diagnosis, risk can be stratified using the

International Prognostic Scoring System (IPSS), which scores five variables to predict survival [4, 14]. Based on the number of risk factors (0, 1, 2, and ≥ 3), IPSS stratifies patients as Low, Intermediate-1, Intermediate-2, and High risk; estimated median survival for these four groups is 135 months, 95 months, 48 months and 27 months, respectively (Table 2A, 2B) [4].

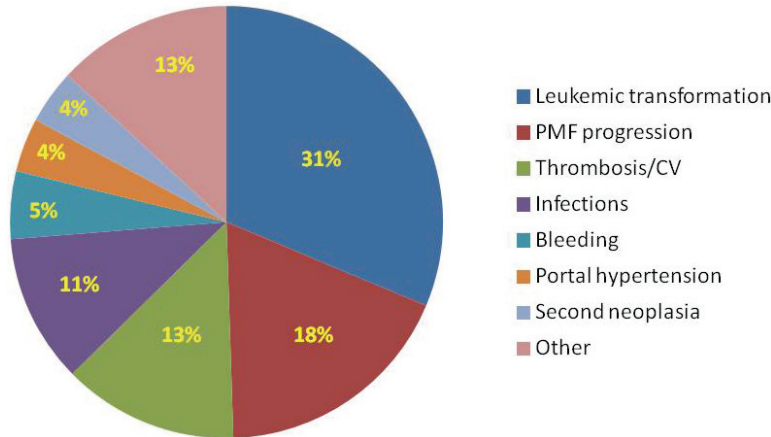


Figure 1. Known causes of death in a series of consecutive PMF cases at 7 centers. Adapted from Cervantes et al. [4].

The IWG-MRT group subsequently evaluated IPSS risk factors in a time-dependent fashion and described a dynamic IPSS (DIPSS) [13]. The same risk factors for IPSS were found to be of prognostic value in DIPSS (Table 2A). However, since mortality was almost two-fold higher with anemia than with other risk factors, anemia was given a score of 2. IPSS is usually recommended for use at the time of diagnosis and DIPSS at any time during disease management. Attempts have also been made by investigators from the Mayo clinic to refine the prognostic value of DIPSS by including three additional variables affecting

Table 2A. International Prognostic Scoring System (IPSS) and Dynamic IPSS (DIPSS) for survival in primary myelofibrosis.

Prognostic variable	IPSS	DIPSS
Age >65 years	√	√
Constitutional symptoms*	√	√
Hemoglobin < 100 g/L	√	√
Leukocyte count >25 x 10 ⁹ /L	√	√
Circulating blasts ≥1%	√	√
	1 point each	1 point each Hb=2 points

Table 2B. Scoring and median survival [4,13].

IPSS Score	Risk category	Median survival (months)
0	Low	135
1	Intermediate-1	95
2	Intermediate-2	48
>3	High	27
DIPSS Score	Risk category	Median survival (years)
0	Low	Not reached
1-2	Intermediate-1	14.2
3-4	Intermediate-2	4
5-6	High	1.5

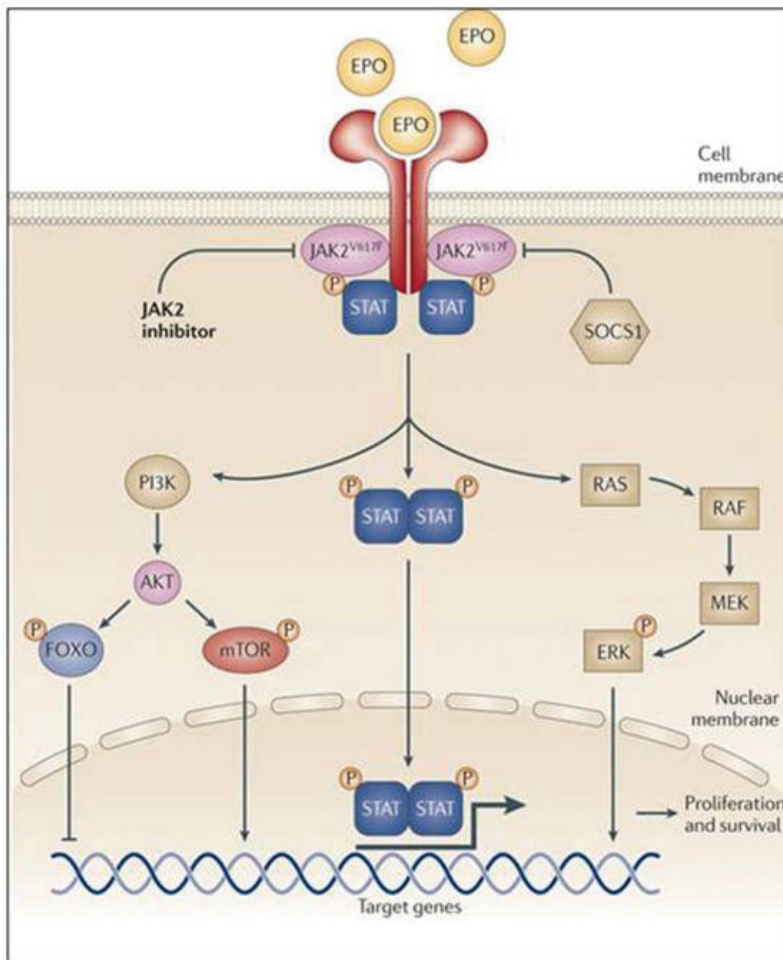


Figure 2. The Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway [29]. Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Drug Discovery 2004;3:555-64, copyright 2004.

survival: a need for red blood cell (RBC) transfusion, thrombocytopenia, and unfavorable karyotype [15]. This new scoring system, DIPSS plus, has not been validated in another independent database. RBC transfusion dependency has been shown to be an independent prognostic factor for poorer survival [16]. In addition, elevated levels of inflammatory cytokines also appear to have an adverse impact on survival [8].

After establishing the diagnosis, it is important to perform risk-stratification for each patient as this plays an important part in the treatment strategy. The risk score should be reviewed on a regular basis to determine whether any change in therapeutic strategy is needed.

Cytogenetics

Clonal karyotype anomalies are found in an estimated 33-45% of PMF cases and several studies have investigated the prognostic value of an abnormal karyotype [17-22]. Favorable karyotypes are normal karyotype, sole 13q-, sole 20q-, sole +9, sole chromosome 1 translocation/duplication, other sole abnormalities, and two abnormalities without an unfavorable type [22]. An unfavorable prognosis is associated with complex karyotypes (≥ 3 abnormalities), sole +8, sole -7/7q-, and two abnormalities including an unfavorable type [22]. Trisomy 8 and trisomy 9 are frequent aberrations in PMF, with each occurring in about 10% of chromosomally aberrant cases [23]. Unfavorable karyotypes are associated with thrombocytopenia, leukopenia, circulating blasts $\geq 1\%$, lower hemoglobin levels and a high-risk IPSS score [22]. Available data suggest that patients with unfavorable karyotypes are at high risk of leukemic transformation [22, 24].

Molecular pathogenesis of MF

Dysregulated Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling as a result of gain or loss of function mutations and/or high circulating levels of inflammatory cytokines plays a key role in pathogenesis of MF. The JAK/STAT signaling pathway is involved in normal hematopoiesis (JAK2), inflammation (JAK1), and immune functions (JAK3). Upon binding of the ligand to its receptor, JAK becomes activated through phosphorylation of key tyrosine residues and which results in activation of the STAT, the mitogen-activated protein (MAP) and the 3-kinase-AKT (PI3-AKT) pathways [25-29], which in turn lead to cellular proliferation (Figure 2). In 2005, a gain-of-function mutation in the JAK2 gene was discovered in a majority (about 95%) of

patients with PV, and in over 50% of patients with ET or PMF [30-33]. This mutation is a G to T nucleotide shift at position 1849 in exon 14 resulting in a valine to phenylalanine substitution at codon 617 of the JH2 auto-inhibitory domain of the protein [34]. The consequence of the *JAK2V617F* mutation is a loss of autoinhibitory control leading to a constitutively activated state of the JAK2 protein. Although, *JAK2V617F* is the most common mutation observed in MF patients, other gain-of-function mutations have been described. The second most frequent mutation (5-11%) occurs in the thrombopoietin receptor gene *MPL* (myeloproliferative leukemia virus oncogene), most commonly at codon 515 (W515L, W515K). Interestingly, rare cases have loss-of-function mutations in *LNK* or *CBL*, genes which potentially act as inhibitors of the JAK/STAT pathway.

Despite these recent discoveries implicating dysregulation of the JAK/STAT pathway as critical in the pathogenesis of MF, the above described mutations may not be the initial oncogenic event. The strongest evidence supporting a pre-*JAK2V617F* oncogenic state is the observation that close to one-half of *JAK2V617F*-positive patients who progress to secondary acute myeloid leukemia do not have the JAK2 mutation in their blast cells. Even though the precise molecular pathogenesis of myeloproliferative neoplasms (MPN) is still incomplete, the documented overactive JAK/STAT pathway is a potentially useful therapeutic target.

Therapeutic options for myelofibrosis

Allogeneic stem cell transplantation

Allogeneic hematopoietic cell transplantation (HCT) is the only curative treatment for patients with MF at present. Due to significant morbidity and mortality associated with HCT, divergent opinions have emerged about the application of HCT in MF. Significant regimen-related toxicities, graft failure and graft-versus-host disease are major barriers to the success of HCT in MF [35]. Use of reduced-intensity conditioning has helped to expand the applicability of HCT to older patients with MF. The trends from the Center for International Blood and Marrow Transplant Research (CIBMTR) indicate a slow increase in the number of patients undergoing HCT in recent times [35]. However, in overall disease management, the option of HCT is ap-

plicable only to a small proportion of MF patients.

A large proportion of patients are not in the transplant age group at the time of diagnosis. Among younger patients, suitable related or unrelated donors are found in about 40-50% of cases. In our experience, the option of transplant in MF patients is used in approximately 5-10% of patients diagnosed with MF in Canada [VG, Princess Margaret Hospital, unpublished data].

Data from the most recent studies suggest that progression-free survival in the range of 40-50% at three years can be expected with HCT. The evolving role of HCT in the management of MF has recently been reviewed [35]. There is a suggestion from recent studies that DIPSS score may also be predictive of success after transplant [36].

HCT remains a valid option for patients in the transplant age group with adequate performance status and without any prohibitive comorbidities. The recommended indications for transplantation are expected survival less than five years, transfusion dependency, or an increased risk of leukemic transformation [35, 37].

Non-transplant treatment options: conventional options

The goals of treatment in MF are to palliate symptoms and improve quality of life. Primarily this involves reducing spleen size, alleviating anemia and treating constitutional symptoms.

Splenomegaly is the most common and most challenging manifestation of MF [38]. Symptoms related to splenomegaly include pain, early satiety, portal hypertension and, less commonly, infarction and cytopenias [14]. Options for treatment of splenomegaly include medications, splenectomy or splenic radiation.

Hydroxyurea is the most frequently used agent for the treatment of splenomegaly in Canada, and results in clinical improvement in about 45-50% of cases [39-41]. Responses can take 2-3 months; responses meeting IWG-MRT criteria for clinical improvement are seldom achieved. Busulfan and cladribine are other agents occasionally employed to manage splenomegaly al-

though less commonly due to concerns about serious adverse effects [38].

Splenectomy has been traditionally used to manage troublesome symptoms associated with splenomegaly. Some symptomatic MF patients benefit from this procedure, becoming transfusion-independent and having resolution of pain and improved constitutional symptoms [42], although the impact on survival appears to be minimal [42-44]. The main issue with splenectomy is perioperative morbidity (25%) and mortality (10%), which are substantial. Morbidity is mainly related to thrombotic complications, bleeding and sepsis [44]. In some patients, splenectomy is associated with compensatory hepatic enlargement.

Splenic irradiation has been used in selected patients for palliative purposes if splenomegaly is resistant to medication and a splenectomy is contraindicated due to advanced age or significant co-morbidities [45]. The doses used vary between 30-365 Gy in 5-10 fractions [45-47]. A temporary decrease in spleen size and resolution of abdominal discomfort are seen in some patients and can last 3-6 months [45, 47]. Severe cytopenias are seen in about 12-35%; an increase in transfusion requirement occurs in approximately 40% of cases [45].

Anemia (hemoglobin < 100 g/L) is seen in >50% of MF patients as result of splenic sequestration, hypoplasia of hematopoietic stem cells, or bleeding from gastrointestinal sources [24, 37, 48]. Anemia and transfusion dependency are predictors of poor prognosis in MF [16]. Conventional treatment options include androgens, erythropoietic stimulating agents (ESAs) or immunomodulators either alone or in combination with prednisone (**Table 3**) [37, 42].

The androgens oxymetholone and danazol are most widely employed in practice although only a few small studies have examined their use in MF [49-51] (**Table 3**). The largest study reported a response rate of 37% with danazol 600-800 mg/day tapered to the lowest dose after six months [51].

Several studies have reported on the use of epoietin alpha 100-200 U/kg administered three times/week either alone (**Table 3**) [52-54] or in combination with interferon- α -2b $\pm$ a short course of GM-CSF [55, 56]. Response rates

were comparable to those seen with androgens (about 53%; range 33-71%). The two largest studies employed a dose of 10,000 U three times/week [57, 58]; response rates were 45% and 60%, respectively. Response was greater in females and patients with less severe anemia. The response rate was 40% in the only published study of darbapoetin-alpha 150-300 mcg/week in MF [59]. A major concern of these agents is that they may result in progression of splenomegaly. Erythropoietin is a reasonable treatment option for selected MF patients with anemia and low erythropoietin levels; if erythropoietin is used, careful monitoring of spleen size is required. There are no consistent mechanisms of coverage of costs of these agents between various provincial funding agencies for patients with MF in Canada.

Immunomodulators include thalidomide and the next-generation immunomodulatory drugs (IMiDs) lenalidomide and pomalidomide (**Table 3**). A pooled analysis of five thalidomide studies (n=62) reported a response rate of 29%, but 66% of patients discontinued within six months due to poor tolerability [60]. Lower response rates and poorer tolerability were found in subsequent phase II studies [61-63]. Tolerability may be improved if low-dose thalidomide (50 mg/day) is administered with prednisone [64]. The addition of cyclophosphamide or etanercept does not improve efficacy [65]. The most troublesome toxicity with thalidomide is neuropathy, with grade 3 severity occurring in up to 6% of patients [65]. Thalidomide is available in Canada through a special access program. Poor tolerability and significant side effects are major concerns about wider use in MF.

The overall response for anemia with lenalidomide 5-10 mg/day given either as monotherapy or with a prednisone taper was 19-30% in phase II trials [66-68]. Myelosuppression was the main toxicity, with 88% of patients in the ECOG E4903 trial developing $\geq$ grade 3 hematologic toxicity [68]. A subsequent reassessment of phase II trials using IWG-MFT criteria reported higher efficacy with lenalidomide compared to thalidomide (34-38% vs. 16%) [69]. The combination of lenalidomide plus prednisone produced a more durable response (median 34 months) compared to lenalidomide alone (7 months) or thalidomide (13 months) [69]. Case reports have suggested that hematologic response may be more robust in

Therapeutic options in MF

Table 3. Summary of selected studies on use of conventional agents in the management of splenomegaly and anemia

Study	Design	Drug/Dose	N	Results
Hydroxyurea				
Martinez-Trillos 2010 ⁴⁰	Retrospective	500 mg/day	40	Clinical improvement in 16/40 (40%); median duration of response 13.2 months; worsening of anemia/pancytopenia in 18/40 (45%)
Androgens				
Cervantes 2005 ⁵¹	Retrospective	Danazol 600 mg/day	30	Response in 11/30 (37%); 4 stopped responding at 6-24 months
Erythropoietin				
Cervantes 2004 ⁵⁷	Prospective	10,000 U x 3/wk	20	Response in 9/20 (45%)
Tsiara 2007 ⁵⁸	Prospective	10,000 U x 3/wk	20	Response in 12/20 (60%)
Darbepoetin				
Cervantes 2006 ⁵⁹	Prospective	150-300 mcg/wk	20	Response in 8/20 (40%)
Thalidomide				
Barosi 2002 ⁶⁰	Pooled analysis	100 mg/day starting dose	62	Increase in Hb, reduced transfusion requirement in 29%
Thomas 2006 ⁶¹	Prospective phase II	200 mg/day, increased to max. 800 mg/day	44	Anemia improved in 7/35 (20%) with Hb <10.0 g/dL
Abgrall 2006 ⁶²	Prospective phase II	400 mg/day	52	No significant improvement in Hb levels or need for RBC transfusion
Marchetti 2004 ⁶³	Prospective phase II dose escalation	50 mg/day, increased to 400 mg/day	63	15 of 26 (56%) discontinued by month 4 Anemia improved in 22% Transfusions eliminated in 39% of transfusion-dependent subjects
Mesa 2003 ⁶⁴	Prospective phase II	50 mg/day; prednisone taper	21	51% discontinued at 6 months Anemia improved in 13/21 (62%) Improvement in 7/10 (70%) with transfusion-dependency
Thapaliya 2011 ⁶⁵	Pooled analysis	50 mg/day + prednisone taper ± cyclophosphamide 25 mg/day x 3 mo. or etanercept 25 mg twice/week	50	Anemia improved in 22%
Lenalidomide				
Tefferi 2006 ⁶⁶	Combined analysis of two prospective phase II trials	5-10 mg/day	68	Anemia improved in 22%
Quintas-Cardama 2009 ⁶⁷	Prospective phase II	5-10 mg/day + prednisone	40	Anemia improved in 30%
Mesa 2010 ⁶⁸	Prospective phase II	10 mg/day + prednisone taper	48	Anemia improved in 19%
Pomalidomide				
Tefferi 2009 ⁷¹	Prospective phase II	0.5 or 2 mg/day ± prednisone taper	84	Anemia improved in 24%
Begna 2011 ⁷²	Prospective phase II	0.5 mg/day	58	Anemia improved in 24%; response only in JAK2V617F-positive patients
Begna 2012 ⁷³	Combined analysis of two trials		94	Anemia response of 27% 53% in the absence of marked splenomegaly, presence of < 5% circulating blasts, or presence of JAK2V617F

JAK2V617F-positive *del(5q)*-associated MF [70]. However, the isolated *del5q*-cytogenetic abnormality is not common in MF.

Pomalidomide has been evaluated in two consecutive phase II studies [71, 72]. The response rate was 36% with pomalidomide 0.5 mg plus prednisone [71]. A second study reported a response only in *JAK2V617F*-positive patients [72]. A combined analysis of the two studies showed an overall anemia response of 27%. Response was greater (53%) in the absence of marked splenomegaly (≥ 10 cm), presence of $< 5\%$ circulating blasts, or in the presence of *JAK2V617F* [73]. The discontinuation rate was 68% and 89% at one and two years, respectively. Ongoing phase III randomized, placebo-controlled trials will further define the role of pomalidomide in MF.

Constitutional symptoms, including fatigue, loss of body weight, night sweats and pruritus, have prognostic significance but conventional treatments are only modestly effective. No conventional treatment has been shown to be very effective in ameliorating constitutional symptoms. Low-dose prednisone may provide some benefit but results are usually transient [14]. A small pilot study of etanercept reported an improvement in constitutional symptoms in 60%, and a 20% objective response [74]; however, the limited data do not support the use of etanercept in routine clinical practice.

Other therapies

A number of small studies have reported a reduction in cytopenias with recombinant interferon- α (rIFN α) in MF, although toxicities have limited the duration of treatment [75, 76]. Response rates were $< 10\%$ in two phase II trials of rIFN α and pegylated rIFN α , respectively [77, 78]. More recently, two retrospective series have reported a complete response and/or major response in about 30% of patients (EUMNET criteria) [79, 80]. A reduction in *JAK2V617F* allele burden was also seen in 53% of PPV-MF patients treated with IFN α -2a for one year [81]. Interferon remains an investigational agent for MF, and the use of interferon outside the clinical trial setting is not recommended.

Limitations of conventional agents

The lack of well-designed prospective studies

and limited treatment efficacy have been prohibitory factors in developing a consensus and defining the role of conventional agents in the management of MF. Moreover, the response criteria used in these studies are not uniform. None of these conventional agents has been shown to modify the natural history of the disease. Hydroxyurea, thalidomide, and low-dose prednisone are the most commonly used conventional treatment options in Canada. Splenectomy and splenic radiation are used in Canada in selected cases, although actual usage data are not available. The authors believe that among the various conventional agents, hydroxyurea may have some value in controlling some of the hyperproliferative symptoms associated with MF. There may be a select role for the use of IMiDs in alleviating anemia, and the anticipated results of randomized phase III trial of pomalidomide will further define the role of IMiDs in MF.

Novel therapeutic options

JAK1/2 inhibitor therapy

The availability of JAK1/2 inhibitor therapy is one of the most important developments in MF in recent years. The first-in-class JAK1/2 inhibitor, ruxolitinib (JAKAFI,TM JAKAVI[®]), has been approved by the FDA and Health Canada for patients with MF. Other JAK inhibitors are at various stages of clinical development. Ruxolitinib will be the most widely available JAK1/2 inhibitor for routine clinical use in patients with MF in the near future.

Ruxolitinib

Regulatory approval in the U.S. and Canada were obtained based on the results of two pivotal randomized phase III trials: Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment (COMFORT-I) in the U.S., Canada and Australia [82]; and COMFORT-II in Europe [83]. Both trials enrolled patients with primary, post-ET or post-PV myelofibrosis with INT-2 or High-risk disease as assessed by IPSS, and platelet count $> 100 \times 10^9/L$. In COMFORT-I, 309 patients were randomized 1:1 to ruxolitinib or placebo, whereas in COMFORT-II, 219 patients were randomized 2:1 to ruxolitinib or best available therapy (BAT).

In COMFORT-I, 41.9% of ruxolitinib patients had

Table 4. Tips on the use of ruxolitinib in routine clinical practice

1. 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 count 100-200 x 10⁹/L, and 20 mg BID for platelet count >200 x 10⁹/L. Start 5 mg BID for platelet count 50-100 x 10⁹/L.
2. Ruxolitinib should be tapered slowly if treatment needs to be discontinued.
3. Educate patients about potential adverse drug effects while on treatment and during discontinuation.
4. 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 drug is discontinued abruptly.

a ≥35% reduction in spleen size at 24 weeks versus 0.7% of placebo patients (p<0.001); 67.0% maintained this response for ≥48 weeks. There was a >50% improvement in symptom score at 24 weeks in 45.9% of ruxolitinib patients versus 5.3% of placebo patients (p<0.001). There was no significant difference in response among patients with or without the JAK2V617F gene mutation. The JAK2V617F allele burden was reduced by 21.5% at week 48. The survival analysis at 51 weeks' median follow-up demonstrated increased mortality in the placebo arm (15.6% vs. 8.4%; p=0.04).

In COMFORT-II, 28% of ruxolitinib patients achieved the primary endpoint of ≥35% reduction in spleen size by MRI at week 48 compared with 0% with BAT (p<0.001); 80% maintained the response at a median 12-month follow-up. There was no difference in overall survival or leukemia-free survival, and no change was observed in bone marrow pathology. There does not appear to be any difference in leukemic transformation in patients treated with ruxolitinib when compared with control arms in the two trials.

A post hoc analysis of data from both trials found that there was no difference in outcomes between the placebo arm of COMFORT-I trial and the BAT arm of COMFORT-II trial [84]. Moreover, neither placebo nor BAT groups showed any clinically meaningful improvements in symptoms or quality of life.

Overall, ruxolitinib was well tolerated, with the main toxicity being hematological. In COMFORT-I, Grade 3-4 hematological effects occurring more frequently with ruxolitinib included anemia (45.2% vs. 19.2%), thrombocytopenia (12.9% vs. 1.3%), and neutropenia (7.1% vs. 2.0%). On average, ruxolitinib-treated patients had a hemoglobin nadir of 15-20 g/L below baseline at 8-12 weeks, stabilizing at an average reduction of about 10 g/L at 24 weeks [83]. Similar improvements in symptom scores were seen in

ruxolitinib-treated patients with and without new grade 3-4 anemia. Thrombocytopenia led to dose modification in 41% of patients in COMFORT-II. Responses to ruxolitinib were not sustained following treatment discontinuation. Symptom scores returned to baseline within one week of discontinuation of ruxolitinib.

In clinical trials, a dose-adjustment strategy based on platelet count was used to minimize toxicity: the starting dose was 20 mg BID for platelet count >200 x 10⁹/L and 15 mg BID for platelet count 100-200 x 10⁹/L. A dose of 15 mg BID may also be considered in transfusion-independent patients, who may have difficulty tolerating a drop in hemoglobin of 20 g/L. In our personal experience, improvement of constitutional symptoms can be observed even at lower doses (5 mg BID). Dose reduction should be considered for patients receiving ruxolitinib 15 or 20 mg BID if the platelet count declines below 100. When treatment interruption is required, dose tapering is advised. Dose increases in increments of 5 mg BID can be considered on a monthly basis to a maximum dose of 25 mg BID in patients with inadequate response if no significant hematological toxicity occurs. Complete blood counts should be monitored at least every two weeks over the first two months until counts are stabilized.

Both COMFORT-I and COMFORT-II enrolled patients with platelet count >100 x 10⁹/L. Approximately 25-30% of MF patients in need of JAK inhibitor therapy may have a platelet count <100 x10⁹/L. Preliminary results of ongoing trials suggest that a starting dose of 5 mg BID followed by a dose escalation strategy is tolerable and efficacious for patients with platelet counts of 50-100 x 10⁹/L [85]. The use of ruxolitinib in practice is summarized in **Table 4**.

Other JAK1/2 inhibitors in development

There are several other JAK1/2 inhibitors at various stages of clinical development (**Table 5**).

Therapeutic options in MF

Table 5. Current status of JAK inhibitor therapy in myelofibrosis

JAK Inhibitor	Target	Current status	Non-hematological toxicities*	Hematological toxicities*	Clinical Benefit and comments
Ruxolitinib [82,83]	JAK1/2	IIIb, Approved by FDA in November 2011 based on two phase III trials, COMFORT-I and COMFORT-II	No significant difference from placebo	Compared with placebo (45% vs. 19%), thrombocytopenia (13% vs. 1%)	Reduction in splenomegaly seen in almost all patients, 29%-42% patients had $\geq 35\%$ reduction in Spleen volume, significant improvement in MF-associated symptoms, and improvement in self-reported QOL, marginal survival benefit in COMFORT-1, no survival benefit in COMFORT-II, equally effective in unmutated JAK2 pts.
SAR302503 (formerly TG101348) [87]	JAK2/FLT3	III	At MTD, Diarrhea 13%, Nausea 5%, hyperlipaemia 15%, increased ALT 8%	At MTD, anemia 54%, thrombocytopenia 28%, neutropenia 10%	At MTD, 45% pts has $\geq 50\%$ reduction in spleen size by 6 cycles, significant improvement in constitutional symptoms, Effective in reducing leucocytosis.
Lestaurtinib (formerly CEP-701) [93]	JAK2/FLT3	II	Diarrhea 9%	Anemia 14%, thrombocytopenia 23%	18% pts had $\geq 50\%$ reduction in spleen size, tested only in JAK2 mutation positive patients
CYT387 [86]	JAK1/2	II	-	Thrombo-cytopenia 16%	45% pts had $\geq 50\%$ reduction in spleen size, significant improvement in constitutional symptoms, 50% pts. had anemia response according to IWG criteria, grade I sensory peripheral neuropathy seen in about 25% patients
Pacritinib [88]	JAK2/FLT3	II	Diarrhea 6%	NR	32% had $\geq 35\%$ reduction in spleen volume, benefit on constitutional symptoms seen
LY2784544 [89]	JAK2	I	-	-	76% had $\geq 50\%$ reduction in spleen size, significant improvement in constitutional symptoms, increase in serum creatinine, uric acid, and K observed in some patients attributed to tumor lysis properties.
AZD1480	JAK1/2	I	-	-	-
BMS911543 [94]	JAK2	I	-	-	-
NS-018	JAK2/ SRC	I	-	-	-
INCB-39110	JAK1/2(pre-dominantly JAK1 inhibitor)	I	-	-	-

*Grade 3/4 toxicity in $\geq 5\%$; MTD, maximum tolerated dose.

Preliminary data from a phase I/II study of another JAK1/2 inhibitor, CYT387, demonstrated improvement in anemia, splenomegaly and constitutional symptoms; adverse events included first-dose hypotension, headache, and abnormal liver/pancreatic enzymes [86]. Also in development is the selective JAK2 inhibitor SAR302503 (formerly TG101348), which is currently being evaluated in a randomized placebo-controlled phase III trial of myelofibrosis. Phase I/II study results showed significant reductions in splenomegaly and improvements in symptom scores [87]. Adverse effects included anemia, thrombocytopenia, asymptomatic increases in amylase, nausea and diarrhea.

In a phase II trial of pacritinib (SB1518), 44% had decreases of $\geq 50\%$ in spleen size and 18% achieved clinical resolution of splenomegaly [88]. Adverse events included GI side effects, increased bilirubin, allergic reaction and nausea; one-third of patients required a dose reduction due to adverse effects. LY2784544 is a selective inhibitor of JAK2V617F/STAT5 signaling that is currently in phase I testing [89].

Apart from JAK1/2 inhibitors, several other novel agents are at various stages of clinical development. The most prominent are the third-generation IMiD pamolodimide (phase III); histone deacetylase (HDAC) inhibitors such as panobinostat and givonostat (phase II); mTOR inhibitors (phase I/II); inhibitor of hedgehog pathway (Saridegib, phase I); AB0024, a monoclonal antibody inhibiting LOXL2 (phase I); and a TGF- β signaling inhibitor (phase I).

Positioning of JAK1/2 inhibitor therapy in management of MF

Treatment of patients with myelofibrosis should be individualized based on DIPSS prognostic score and symptomatology [90] (**Figures 3A, 3B**). HCT should be considered for eligible patients with a DIPSS score of Int-2 or High-risk, or Int-1 risk patients who are transfusion-dependent or have a high risk of leukemic transformation. Management of non-HCT-eligible Int-2 or High-risk patients, and all Low- or Int-1-risk patients, is based on symptom assessment. Asymptomatic patients should be monitored regularly with assessments for symptoms and risk score. Ruxolitinib is the most effective commercially available medication for the management of constitutional symptoms

and symptomatic splenomegaly and is appropriate first-line therapy for patients with these symptoms. Patients with significant cytopenias (transfusion-dependent anemia or cytopenias) should ideally be enrolled in future clinical trials, if available. Use of hydroxyurea, ESA, danazol and splenectomy may be considered on a case-by-case basis if access to JAK1/2 inhibitor therapy is not available. Splenectomy will remain a useful option for select patients with MF, who are either resistant to or unable to tolerate JAK1/2 inhibitor therapy.

Summary

MF is a rare chronic hematological malignancy. It is important that patients be referred for a consultation to a center with expertise in the management of MPN. Given the long natural history of this disease, a shared-care model (where the community physician and the MF specialist jointly manage the patient with MF) may serve the unmet needs of these patients in an optimal way. Risk stratification is vital for choosing an optimal treatment strategy, and should be done at the time of diagnosis and reviewed periodically during follow-up to identify a change in risk profile. The goals of therapy for each patient need to be defined up front, taking into consideration factors such as age, symptom burden, predicted risk of mortality and leukemic transformation, availability of donors and personal risk tolerance. Therapy should be individualized and should include a spectrum of choices ranging from watchful waiting to drug therapy or HCT.

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Declaration of conflicts of interest

VG: clinical trial research funding from Incyte, Novartis, Celgene, YM Biosciences, and Sanofi-Aventis; served on advisory board of Incyte, Novartis, YM Biosciences, and Sanofi-Aventis; consulting fees from Novartis, Incyte, YM Biosciences, and Sanofi-Aventis. LF: clinical trial research funding from Incyte, Novartis, Sanofi-Aventis; served on advisory board of Novartis; consulting fees from Novartis, Sanofi-Aventis.

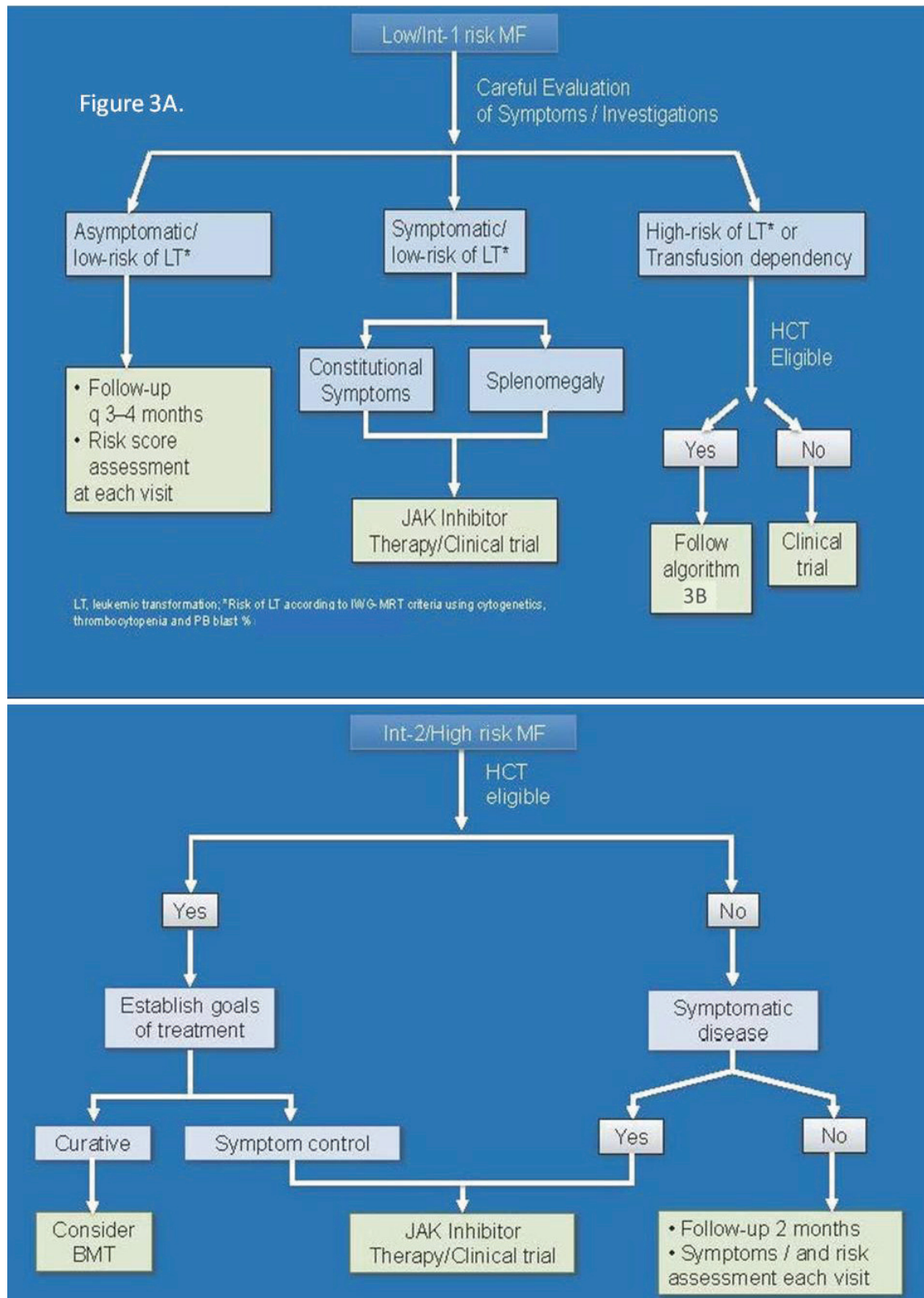


Figure 3. Management of patients with: (A) Low/Int-1 myelofibrosis; and (B) Int-2/High-risk myelofibrosis [35]. Used with permission.

SS: clinical trial research funding from Novartis, YM Biosciences, and Sanofi-Aventis; served on advisory board of Novartis, Celgene; consulting fees from Novartis, and Sanofi-Aventis. LB: clinical trial research from Sanofi-Aventis; research funding from Novartis; served on advisory board of Novartis. ART: clinical trial research funding from Novartis and Celgene; served on advisory board for Novartis.

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