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Myelofibrosis

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Cancer Care Alberta

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http://www.ahs.ca/guru

Background

Myelofibrosis (MF) is a clonal myeloproliferative stem cell disorder characterized by reactive bone marrow fibrosis, extramedullary hematopoiesis, and abnormal cytokine expression leading to systemic symptoms. The purpose of this guideline is to provide a practical approach to diagnosis, investigation and management of myelofibrosis.

Primary myelofibrosis (PMF) is a "BCR-ABL1 negative MPN" categorized alongside polycythemia vera (PV) and essential thrombocytosis (ET) according to current 2016 World Health Organization (WHO) classification (**Table 1**)[1,2]. Myelofibrosis may arise *de novo* as primary myelofibrosis (PMF) or develop secondary to either PV or ET, post-PV and post-ET MF, respectively. Clinical manifestations of MF are heterogeneous including: cytopenias, hepatosplenomegaly, constitutional symptoms (night sweats, fevers, and weight loss), chronic fatigue and bone pain. Disease complications include: symptomatic portal hypertension, pulmonary hypertension, non-hepatosplenic extramedullary hematopoesis, bleeding and/or thrombosis and leukemic transformation[3]. Currently, the only curative treatment option is allogeneic stem cell transplant (alloSCT) which is an option in only a selection of patients. As a result, treatment options are to alleviate patient symptoms with novel therapy modalities being investigated.

Epidemiology

The estimated incidence of myelofibrosis (MF) is 0.1-1.0 per 100,000 worldwide. Reported prevalence ranges 0.5 to 2.7 per 100,000 in Europe to 4 to 6 per 100,000 in the United States[4]. The median age of MF diagnosis is 69 years with < 15% of patients under 50 years old at the time of diagnosis[5]. The causes of MF are largely unknown.

Signs and Symptoms

Patients with myelofibrosis (MF) can have significant debilitating symptoms and poor quality of life. Symptoms are caused by chronically elevated aberrant cytokine production, myeloproliferation, ineffective erythropoiesis and extramedullary hematopoiesis[6-8]. Symptoms of chronic cytokine production include night sweats, muscle and bone pain, pruritus, fever and cachexia. Myeloproliferation leads to progressive cytopenias and results in associated symptoms. Consequently, anemia causes fatigue, weakness, and/or dyspnea; thrombocytopenia results in bruising and bleeding; leukopenia leads to increased susceptibility to infections. Extramedullary hematopoiesis (EMH) leads to hepatosplenomegaly. Splenomegaly causes early satiety and abdominal discomfort and leads to portal hypertension with risks of variceal bleeds and progressive liver dysfunction causing further coagulopathies. Non-hepatosplenic EMH may lead to paraspinal masses with risks of cord compression and pulmonary hypertension[3].

Guideline Questions

1. What diagnostic and baseline investigations are recommended for adult patients with suspected or confirmed MF?
2. What are the recommended treatment options for MF?

Search Strategy

This guideline was generated using systematic literature searches of PubMed and MEDLINE databases, ASCO abstracts and proceedings, and ASH abstracts and proceedings. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials and clinical trials. The guidelines were also adapted from the Canadian MPN Group recommendations.

Target Population

Patients who are ≥18 years of age who are suspected of, or diagnosed with myelofibrosis.

Summary of Recommendations

1. The diagnosis of Myelofibrosis (MF) requires a bone marrow biopsy.
2. *JAK2V617F* mutation testing should be performed routinely in patients with MF.
3. If patients do not carry the *JAK2V617F* mutation, additional screening for driver mutations: *CALR* and *MPL* is required. Patients with no driver mutation are considered to be high risk “triple negative”. Additional high-risk mutations can be attained via Next generation Sequencing (NGS). MF patients <75 years of age will have NGS testing performed.
4. If significant eosinophilia is present: screen for *PDGFRA* (FISH), *PDGFRB* and *FGFR1* (conventional karyotype) rearrangements.
5. Prognostic scores should be calculated and documented which includes the IPSS used at time of diagnosis and the DIPSS and/or DIPSS-plus used during the remainder time of disease. If molecular information is available use MIPSS-70.
6. In low risk MF, watchful observation and symptom control is suggested.
7. For isolated anemia consider use of erythropoietin stimulation agents if epo level <125 u/l or if epo levels are elevated Danazol, IMIDS and/or steroids can be used in select patient populations.
8. In Intermediate or High-risk MF, treat symptomatic disease using JAK inhibitor first line therapy. Ruxolitinib and Fedratinib are both available for use with different side effect profiles and dosing. Drug dose modifications are based on the degree of thrombocytopenia. Thiamine levels are required and supplementation to normal levels is necessary in order to use Fedratinib. Current data supports fedratinib’s use post ruxolitinib failure.
9. Second line agents suggested are to use an alternative JAK inhibitor, or Hydroxyurea, Interferon-alpha, IMIDs +/- steroids and clinical trials.
10. Allogeneic stem cell transplant (alloSCT) is the only curative treatment in MF. Fit patients with DIPSS Intermediate -2 or higher risk disease are eligible for consideration of allogeneic stem cell transplant. Patients who are transplant eligible should have NGS testing in order to assist with

prognostication and alloSCT need (see below). Patients with estimated life survival <5 yrs. should be referred for alloSCT.

11. Other factors for early alloSCT consideration include: ineligibility for JAK inhibitor treatment or lack of response to *JAK* inhibitor therapy, pretreatment transfusion dependence, *ASXL*-1 or *EZH2* mutated MF, and "Triple negative" MF. Newer prognostic models such as the MIPSS-70 and MIPSS-70 Plus suggest "high" and "very high" risk patients should undergo alloSCT.
12. Patients with transfusion dependency (given > 20 U PRBCs) or with higher liver iron content based on MRI studies with anticipated longer life survival, such as those going to alloSCT, should receive iron chelation.
13. Splenectomy and splenic radiation are offered in very select palliative cases particularly in the setting of refractory splenomegaly and/or thrombocytopenia.
14. Thromboembolic events should be managed according to accepted management guidelines. Thromboprophylaxis should be used after surgery and in other high-risk situations.

Discussion

Diagnosis

Approximately 30% of patients with myelofibrosis (MF) are asymptomatic at time of diagnosis[9]. Diagnosis of PMF is based on revised 2016 WHO criteria (**Table 1**)[1,2]. Recently the 2016 WHO criteria also distinguish pre-fibrotic MF from overt PMF (**Table 1**). Post-PV MF and post-ET MF is based on International Working Group for MPN Research and Treatment (IWG-MRT) criteria (**Table 2**)[10]. MF must be distinguished from other closely related myeloid neoplasms including PV, ET, CML, and CMML.

Table 1: WHO Diagnostic Criteria for Pre-fibrotic MF and PMF[1,2].

WHO 2016 Criteria: PRE-Fibrotic PMF ALL 3 Major + 1 Minor	**WHO 2016 Criteria: OVERT PMF ALL 3 Major + 1 Minor**
Major Criteria: 1) MK proliferation and atypia WITHOUT reticulin fibrosis >1 with increased BM cellularity, gran proliferation, and decreased erythropoiesis 2) Not meeting WHO criteria: PV, CML, MDS or other myeloid neoplasm 3) *JAK2, CALR, MPL* or in absence another clonal marker or absence of reactive fibrosis	Major Criteria: 1) MK proliferation and atypia WITH reticulin or collagen fibrosis grade 2 or 3 2) Not meeting WHO criteria: PV, CML, MDS or other myeloid neoplasm 3) *JAK2, CALR, MPL* or in absence another clonal marker or absence of reactive fibrosis
Minor Criteria: 1) Anemia 2) WBC ≥ 11 x 10^9/L 3) Palpable splenomegaly 4) Increased LDH	Minor Criteria: 1) Anemia 2) WBC ≥ 11 x 10^9/L 3) Palpable splenomegaly 4) Increased LDH 5) Leukoerythroblastosis

Table 2: IWG diagnostic criteria for secondary MF[10].

Post –PV MF:	Post-ET MF:
WHO criteria of previous PV BM Fibrosis grade 2-3 (0-3 scale) or 3-4 (0-4 scale) AND ≥ 2 minor criteria: • Leukoerythroblastosis • Increased splenomegaly (palpable ≥ 5 cm, or newly palpable) • Development of 1 or more constitutional symptoms • Sustained loss of requirement for phlebotomy in absence of cytoreduction and/or anemia	WHO criteria of previous ET BM Fibrosis grade 2-3 (0-3 scale) or 3-4 (0-4 scale) AND ≥ 2 minor criteria: • Leukoerythroblastosis • Increased splenomegaly (palpable ≥ 5 cm, or newly palpable) • Development of 1 or more constitutional symptoms • Anemia and drop if Hgb ≥ 20 g/L from baseline • Increased LDH

The *JAK2V617F* mutation is an important driver mutation responsible for the pathogenesis of myeloproliferative disorders and is present in 50-60% of patients with PMF or post-ET MF and in 95% of those with post-PV MF[11-13]. A *JAK2V617F* mutation screening should be performed routinely on all patients with suspected MF. Although higher *JAK2V617F* allele burdens are associated with higher transformation rates and higher allele burden correlates with poorer survival in MF, quantitative assays are not required in MF and do not change clinical management[14-17]. Other driver mutations such as thrombopoetin receptor gene (*MPL*) have been documented in 3-8% of PMF and post ET MF patients, whereas Calreticulin gene (*CALR*), is present in approximately 50% of PMF and post ET MF patients without either JAK or MPL mutations[18-20]. The presence of *JAK2V617F, CALR, MPL,* trisomy 9, or del13q supports the diagnosis of MF. CALR-mutated patients are less likely to be anemic and/or require transfusions and display less leukocytosis[3].

Physical examination: Clinical features of MF may include cachexia and physical signs of anemia and thrombocytopenia. Ninety percent of patients with myelofibrosis have an enlarged spleen and hepatomegaly is present in 50% of patients[9]. Assess for clinical signs of portal hypertension.

Laboratory investigations: Baseline investigations include: complete blood count with differential (CBCD), peripheral smear, LDH, uric acid, liver panel including liver function (INR, PTT, Bilirubin, Albumin), ferritin and iron studies. Leukoerythroblastosis is present in most cases and with the presence of immature cells from the myeloid and erythroblastic lineages, dacrocytes (tear drop cells) and peripheral myeloid blasts. Additional baseline tests to consider are vitamin B12 level (often elevated in MPNs) and erythropoietin level (when considering treatment of anemic patients). HLA typing is suggested in young patients (≤ 75 years) who may be eligible for alloSCT. Hepatitis B/C serology and HIV testing are suggested for those patients anticipated to receive immunosuppressive therapy. Consider Quantiferon testing in patients with risk factors.

Bone marrow evaluation: Evaluation of bone marrow histopathology is critical for correct diagnosis of MF. The bone marrow aspirate is often difficult resulting in a “dry tap”. The bone marrow biopsy of MF typically reveals megakaryocyte proliferation and atypia, usually with reticulin or collagen fibrosis[21]. A bone marrow (BM) biopsy report should include: age adjusted cellularity, presence of fibrosis (reticulin and collagen stains), evaluation of granulopoiesis with special reference to blast clusters, and characterization of erythropoiesis and megakaryocytes[22].
Overt bone marrow fibrosis might be absent in the setting of prefibrotic PMF. The possibility of prefibrotic primary myelofibrosis, as opposed to ET, should be considered in the presence of persistently increased serum LDH, anemia, leukoerythroblastosis, increased circulating CD34+ cell count, and splenomegaly. ET and prefibrotic PMF are clinically distinct with both overall and leukemia-free survival are significantly worse in prefibrotic PMF[23,24].

Cytogenetics: Approximately one-third of patients with primary MF present with cytogenetic abnormalities. The most frequent are del(20q), del(13q), trisomy 8 and 9, and abnormalities of chromosome 1 including duplication 1q. Other less frequent lesions include -7／del(7q), del(5q), del(12p), +21 and der(6)t(1;6)(q21;p21.3). A >80% 2-year mortality in PMF was predicted in the setting of monosomal karyotype, inv (3)/i(17q) abnormalities or with any 2 factors: circulating blast >9%, WBC >40 x 10^9/L, or unfavorable karyotype[25]. Unfavorable karyotypes are incorporated into dynamic prognostic survival models (**Table 3**) and also result in a higher risk of leukemic transformation[25-27].

Mutation testing: Testing for the *JAK2V617F* mutation should be performed early during the diagnostic workup of suspected MPNs. *JAK2V617F* negative patients should be screened for mutually exclusive driver mutations *CALR* and/or *MPL*. *CALR*-mutated patients are less anemic and red cell transfusion dependent with less tendency to present with leukocytosis. *CALR* mutations are associated with younger age, higher platelet counts, lower DIPSS-plus score[3]. In the absence of all 3 driver mutations (“triple negative”) disease, consideration of additional molecular mutations is suggested. *BCR-ABL1* rearrangement testing should be considered if atypical features are present on the bone marrow biopsy with triple negative disease. *PDGFRA* and *PDGFRB* rearrangements should be performed in the setting of eosinophilia given that the presence of these rearrangements is highly sensitive to imatinib therapy.

Triple negative patients, who lack, *JAK2, CALR,* and *MPL* mutations have a poor outcome[28,29]. With access to next generation sequencing (NGS) additional mutations can be obtained. It has been found that mutations including: *IDH, EZH2, SRSF2* and *ASXL1* result in inferior survival[3,30-33]. In a study of 570 patients, longest survival was found in *CALR +/ASXL-* patients (median 10.4 yrs) compared to shortest survival among those with *CALR-/ASXL+* status (2.3 years). *CALR+/ASXL+* or *CALR-ASXL-* were considered intermediate with median survival of 5.8 years. The favorable prognostic impact of *CALR* is limited to type1 or type-1 like variants[28,34].

Diagnosis: Recommendations

1. *JAK2V617F* mutational screening should be carried out routinely in patients with suspected MF. *JAK2V617F* allelic burden is not required currently for clinical management.
2. Alternative driver mutations: *CALR* and *MPL* should be tested if JAK2 negative. Depending on your local laboratory capabilities this may be required via Next Generation Sequencing (NGS). Talk to your local hematopathologist regarding proceeding to NGS testing.
3. *BCR-ABL1* rearrangement should be excluded in cases of atypical biopsy results or in "triple negative" disease.
4. *PDGFRA*, *PDGFRB and FGFR1* rearrangements should be excluded in setting of significant eosinophilia.
5. Additional molecular testing via NGS assessing for poor prognostic markers such as: ASXL1, EZH2, SRSF2, IDH1/2 can be attained via NGS in **selective cases** and should be considered **particularly in alloSCT eligible MF patients**.

Prognosis

The clinical course of myelofibrosis (MF) is highly heterogeneous, and the disease can last from months to decades depending on risk status[9]. As the disease evolves, patients become symptomatic from their resultant cytopenias and increasing hepatosplenomegaly with constitutional symptoms. Complications such as variceal bleeding can occur from resultant portal hypertension as well as having a higher risk of thrombosis. The 10-year survival of PMF patients is 81% lower than that of the general population[35]. Evolution of primary MF to acute myeloid leukemia (AML) occurs at a rate of 8% to 30%[36-38]. Other causes of death include: MF progression (18%), thrombosis and cardiovascular complications (13%), infection (11%) or bleeding (5%), and portal hypertension (4%)[9].

Risk stratification: Various prognostic models have been developed in MF. These models have been validated in only the PMF population but for practical purposes can be used in the setting of secondary MF. The International Prognostic Scoring System (IPSS) estimates prognostic risk at the time of diagnosis of primary myelofibrosis. It was developed by the IWG-MRT and includes 5 variables: age older than 65 years, the presence of constitutional symptoms, hemoglobin level < 100 g/L, leukocyte count > 25 × 10^9/L, and 1% or more blasts in the peripheral blood[9]. An IPSS calculator is available online. See **Table 3** for IPSS score[9].

The Dynamic IPSS (DIPSS) is used for re-evaluating survival predictions during the course of the disease and includes additional risk factors not present at diagnosis, such as the acquisition of anemia in particular[26,39]. Subsequently the DIPSS Plus further refines DIPSS by incorporating three additional factors: platelet count <100 x 10^9/L, red cell transfusion status, and unfavorable karyotype (i.e. complex karyotype or sole or two abnormalities that include: +8, -7/7q-, i(17q), inv (3), -5/-5q-,

12p-, or 11q23 rearrangement with each variable being assigned one point[40] . A DIPSS[26,39] and DIPSS PLUS[40] calculator is available online. See **Table 3** for these scores.

Table 3: Prognostic scores for Myelofibrosis[9,26,39,40]:

IPSS (at diagnosis):	DIPSS:	DIPSS Plus**:
Risk factors (points):		
Age >65 yrs. (1)	Age >65 yrs. (1)	Age >65 yrs. (1)
Constitutional symptoms (1)	Constitutional symptoms (1)	Constitutional symptoms (1)
Hgb <100 g/L (1)	Hgb <100g/L (2)	Hgb <100g/L (1)
WBC >25 x 10^9/L (1)	WBC >25 x 10^9/L (1)	WBC >25 x 10^9/L (1)
Circulating blasts ≥ 1% (1)	Circulating blasts ≥ 1% (1)	Circulating blasts ≥ 1% (1)
		Platelet count <100 x 10^9/L (1)
		RBC transfusion dependent (1)
		Unfavorable karyotype* (1)
IPSS Survival:	DIPSS Survival:	DIPSS Plus Survival:
Low (0): 11.3 yrs.	Low (0): NR (> 20 yrs)	Low (0): 15 yrs.
Int-1 (1): 8 yrs.	Int (1-2): 14 yrs.	Int-1 (1): 6.5 yrs.
Int-1 (2) : 4 yrs.	Int-2 (3-4): 4 yrs.	Int-2 (2-3): 3 yrs.
High (≥3): 2.3 yrs.	High (≥5): 1.5 yrs.	(High (≥4): 1.3 yrs.

*Unfavorable karyotype: +8, -7/7q-, i(17q), inv(3), -5/5q-, 12p-, 11q23 rearrangement.

**For DIPSS-PLUS: Assign and incorporate DIPSS score (Low=0, Int-1 = 1, Int-2 =2; High =3) plus added variables (1 point each).

Risk assessment tools under investigation: Alternative approaches to MF prognostic risk has been based on specific gene mutations (i.e., *ASXL1*, *EZH2*, *SRSF2*, *IDH1*, *IDH2*, *CALR*, and *MPL*). Ongoing development of integrated systems for evaluating prognostic risk using molecular and cytogenetic markers in combination with clinical and hematologic findings have been proposed[41-43].

Mutation-enhanced International Prognostic Scoring System (MIPSS): The score was derived from a study of 986 PMF patients divided into learning (n=588) and validation (n=398) cohorts. In multivariable analysis, age >60 years, constitutional symptoms, hemoglobin <100g/L, platelets <200x10^9/L, Triple negative, *JAK2* or *MPL* mutation, *ASXL1* and *SRSF2* mutation were significant and these variables were subsequently assigned adverse points: 1.5, 0.5, 0.5, 1.0, 1.5, 0.5, 0.5 and 0.5, respectively. Based on this, four distinct risk groups were identified: low (score 0-0.5); intermediate-1 (score 1-1.5); intermediate-2 (score 2-3.5); and high (score 4 or greater). According to the MIPSS up to 67% of patients in the intermediate I category of the IPSS were upstaged to an intermediate II or high-risk MIPSS. The MIPSS also down staged 50% of IPSS high-risk patients. Median survival were 26.4 years, 9.7 years, 6.4 years, and 1.9 years for low, inter mediate-1, Intermediate-11, and high-risk disease, respectively[41].

A recent prognostic tool was developed for transplant eligible patients with PMF that integrates clinical and mutation data with cytogenetics (MIPSS70-plus) or without cytogenetics (MIPSS70). Risk

factors for OS included: hemoglobin <100 g/L, leukocytes >25 x 10^9/L, platelets <100 x 10^9/L, circulating blasts ≥ 2%, bone marrow fibrosis grade ≥ 2, constitutional symptoms and absence of CALR type -1 mutation, and presence of high molecular risk mutations (HMR) (*ASXL1, EZH2, SRSF2, IDH1/2)* and presence of 2 or more HMR specifically. Three risk categories were delineated for MIPSS70 (see **Table 4**) with 5-year OS: 95% in low risk (median OS 27.7 years), 70% for intermediate risk (7.1 years) and 29% in high risk 29% (median OS 2.3 years). The MIPSS70-plus model was divided into 4 categories with 5-year OS: 91% in low risk, 66% in intermediate risk, 42% in high risk, and 7% in very high risk. These models remained effective after inclusion of older patients[44]. Calculators are available: [Link]

Recently, a personalized MPN prediction model was developed which incorporates genomic and clinical data in order to provide a more personalized risk stratification and prognosis. A total of 2035 patients (63 genomic and clinical variables) were included in the analysis and outcomes correlated with an independent external cohort. The calculator can be found at: [Link] and may assist physicians in providing a more personalized treatment approach for MF

Table 4: MIPSS-70 prognostic model[41,44]

MIPSS-70 Model:	MIPSS-70 Plus Model:
Hemoglobin <100 g/L (1)	Hemoglobin <100 g/L (1)
WBC >25 x 10^9/L (2)	Circulating blasts ≥ 2% (1)
Platelets <100 g/L(2)	Constitutional symptoms (1)
Circulating blasts ≥ 2% (1)	Absence of CALR type 1 mutation (2)
Bone marrow fibrosis ≥ 2 (1)	Presence of HMR mutation* (1)
Constitutional symptoms (1)	Presence of ≥ HMR mutations* (2)
Absence of CALR type 1 mutation (1)	Unfavorable karyotype‡ (3)
Presence of HMR mutation* (1)	
Presence of ≥ HMR mutations* (2)	
MIPSS-70 Survival:	**MIPSS-70 Plus Survival:**
Low (0-1): 27.7 years	Low (0-2): 20.0 years
Intermediate (2-4): 7.1 years	Intermediate (3): 6.3 years
High (≥ 5): 2.3 years	High (4-6): 3.9 years
	Very high (≥7): 1.7 years

*HMR: High molecular risk mutations: *ASXL1, EZH2, SRSF2, IDH1/2.*

‡ Unfavorable karyotype: any abnormal karyotype other than normal karyotype or sole abnormalities of 20 q-, 13q-, +9, chromosome 1 translocation/duplication, -Y, or sex chromosomes other than –Y.

Genetics-based Prognostic Scoring System (GPSS): An alternative genetics-based prognostic scoring system (GPSS) complements the MIPSS. In addition to high-risk mutations and age, the GPSS includes high-risk karyotypes: 5q-, +8, inv(3), i(17q), -7/7q-, 11q or 12p abnormalities, autosomal trisomies (except +9), monosomal and complex non-monosomal karyotypes. High risk GPSS was also associated with higher blast transformation rate (HR 7.4, 95% CI 2.1-26.3)[43].

All of the above prognostic tools have been derived for primary myelofibrosis but often secondary myelofibrosis is categorized using the same tools. A post-PV and post-ET MF model has been developed: Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM) (**Table 5**), which was based on 685 patients with a median survival of 9.3 years. Secondary MF patients were divided into four risk categories based on: hemoglobin, circulating blasts, *CALR* status, platelet count and constitutional symptoms. Median survival according to risk group was: low (survival not reached), intermediate-1 (9.3 years), intermediate-2 (4.4 years), and high risk (2 years)[45]. A calculator is available for the MYSEC-PM:[Link]

Table 5: Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM)[45].

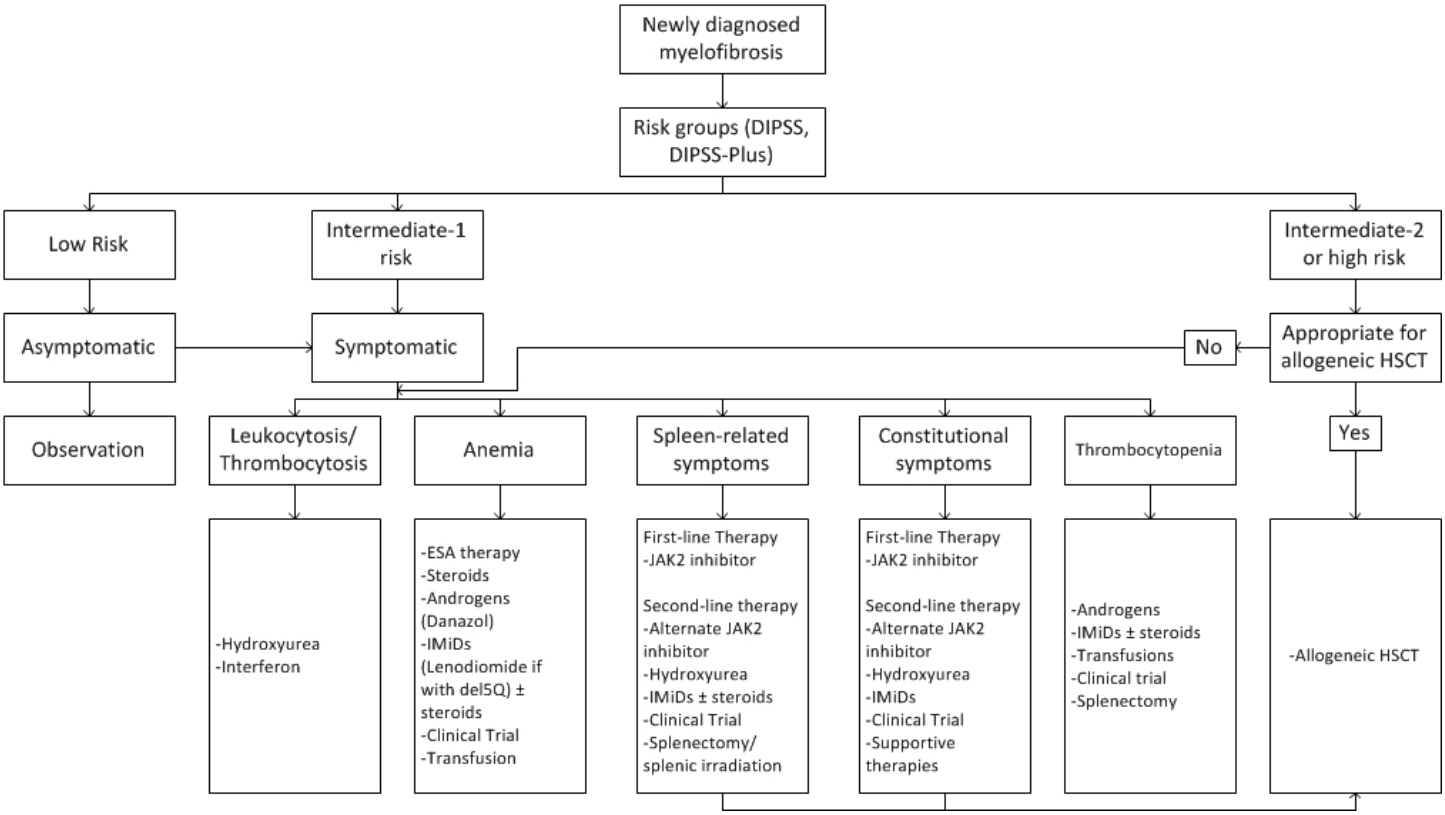
Secondary MF: MYSEC-PM (http://mysec-pm.eu/)
Risk factor (Points):
Hemoglobin <110 g/L (2)
Circulating blasts ≥ 3% (2)
CALR UNMUTATED (2)
Platelets <150 x 10^9/L (1)
Constitutional symptoms (1)
Age (~ 0.15 points per year of age)
Median Survival: Low risk (<11 points): NR Int-1 (11-13 points): 9.3 yrs Int-2 (14-15 points): 4.4 yrs High (≥ 16 points): 2 yrs

Prognosis: Recommendations

1. At time of initial diagnosis, MF prognosis should be based on IPSS.
2. During subsequent evaluation of MF patients, dynamic scores: DIPSS and/or DIPSS-Plus should be applied.
3. The IPSS, DIPSS, and DIPSS-Plus scores have not been formally evaluated for post-PV and post-ET MF, it is suggested they still can be used for prognostication however newer models such as: MYSEC-PM are dedicated for secondary MF.
4. Therapeutic decisions regarding alloSCT should be based on the DIPSS and/or DIPPS-Plus models given their validation at any time point and better prediction of median survival.
5. If molecular mutations are known, newer models such as MIPSS70 and MIPSS70-Plus (version 2.0) are available and may better predict fit patients who are best eligible for alloSCT.

Treatment

The only curative treatment option for MF patients is allogeneic stem cell transplant (alloSCT). However, due to the associated morbidity and mortality, alloSCT is usually limited to fit patients with high risk features. Current conventional therapies are used for symptom control and target the treatment of the two most prominent symptoms of MF: splenomegaly and anemia[37]. Initiation of treatment is suggested for symptomatic anemia (Hgb persistently <90 g/L) or transfusion dependence (Hgb <80 g/L) and/or for symptomatic splenomegaly or splenomegaly resulting in secondary comorbidities/complications.



DIPSS, Dynamic International Prognostic Scoring System; HSCT, Hematopoietic stem cell transplantation

Figure 1. Proposed treatment algorithm for primary myelofibrosis (Adapted from Harrison et al.[101])

Anemia: Prior to initiation of treatment, it is important to rule out secondary causes of anemia. Treatment of anemia is considered for a hemoglobin persistently below 100g/L and is suggested for symptomatic anemia or transfusion dependence. Therapeutic options include erythropoietic stimulating agents (ESAs), androgens and/or immunomodulators (IMiDS) either alone or in combination with low dose steroids[36,37].

Erythropoietin: Erythropoietin (EPO) is a reasonable treatment option for selected MF patients with anemia and low EPO levels (<125 mU/mL)[46-48]. Anemia responses are attained in 23-60% of patients with median duration of response of 12 months[46,47]. Starting doses of Eprex 20,000 - 40,000U SC weekly or 150 µg/weekly of Darbopoetin can be trialed and doses are doubled if no response within 4

weeks. If there is no response within 12 weeks, treatment should be discontinued[36]. Careful monitoring of spleen size is required as the use of EPO can result in progressive splenomegaly[37].

Androgens: Nandrolone, Fluxymesterone, methandrostenolone and oxymetholone have been found to improve anemia in 30-60% of patients. Favorable responses are associated with female gender, prior splenectomy, normal karyotype[36]. Danazol (Cyclomen), is a semisynthestic attenuated androgen associated with less toxicity with a response rate of 40%[49]. Prior to the initiation of treatment, men must be screened for prostate cancer and all patients must have hepatic enzymes and function assessed with baseline ultrasound to rule out presence of hepatic tumors. Initial dosing of Danazol is 600 mg daily and should be maintained ≥ 6 months given most responses can only begin at 3- 6 months of initiation. Once response is attained, consider dose reductions to maintain response, usually 200 mg/day is sufficient. Routine liver surveillance is required monthly and periodic hepatic ultrasounds are suggested with hepatic toxicity occurring in <20% of patients. Lastly, men require periodic prostate cancer screening and women should be counselled regarding hormonal side effects of treatment[36].

Immunomodulators: Immunomodulators (IMiDs) include: thalidomide (100 -200 mg/day), lenalidomide (5-10 mg daily) and pomalidomide. IMiDs in combination with low dose steroids is suggested as an alternative to isolated anemia and/or thrombocytopenia treatment in low/int risk MF. Hematologic toxicity is a major side effect and precludes the use of IMiDS and often requires dose reduction and use of concomitant low dose steroids: prednisone (0.5 mg/kg daily for 3 months with taper)[36,37]. Lenalidomide results in 22% anemia response and 10-42% improvement of splenomegaly. Typical dosing of Lenalidomide is 5-10 mg daily for 3 weeks on a 4-week cycle[50-52]. Pomalidomide is a less toxic IMID however, phase 3 studies failed to should a significant improvement in comparison to placebo[53]. Prednisone can be used as single therapy at dosing of 30 mg daily with dose tapering within a few weeks to 15 - 20mg daily[36].

Treatment: Recommendations

1. Erythropoietin therapy is suggested in low/intermediate risk patients with an erythropoietin level of <125u/L. Starting doses of Eprex 20,000U-40,000 SC weekly or Darbopoetin 150 µG/weekly can be trialed and doses are doubled if no response within 4 weeks. Treatment should be discontinued after 12-16 weeks (at maximal dose) if no response is attained.
2. Androgen therapy such as Danazol can be considered in patients ineligible or unresponsive to Epo agents. A starting dose of 600 mg daily is suggested and a minimal treatment period of 6 months. Responding patients should be continued on therapy and be titrated to a dose adequate to maintain response (usually 200mg daily). Male patients require prostate cancer screening and surveillance and liver toxicity should be carefully monitored on all patients.
3. IMiDs in combination with low dose steroids is suggested as an alternative to isolated anemia and/or thrombocytopenia treatment in low/int risk MF. Either thalidomide (100 -200 mg/day) or lenalidomide (5-10 mg daily) with low dose prednisone: 0.5 mg/kg daily for 3 months with taper can be used.
4. Androgens, IMiDS with or without steroids apply as treatment options for thrombocytopenia as well.
5. Int or High-risk MF patients with anemia should consider ruxolitinib therapy and erythropoetin agents can be used in combination in setting of severe anemia with or without transfusions.

Splenomegaly & Constitutional Symptoms

Medical treatment is suggested for patients with symptomatic splenomegaly. Sustained responses are difficult to obtain particularly in the setting of massive splenomegaly. The discovery of the Janus kinase *JAK2V617F* mutation triggered the development of targeted therapy for myelofibrosis (MF), resulting in approval of the JAK1/2 inhibitor, ruxolitinib (Jakavi®).

JAK Inhibitors:

Ruxolitinib: Ruxolitinib is an oral JAK1/JAK inhibitor that suppresses pro-inflammatory cytokines and growth factor receptors that use JAK1 and JAK2 for signaling and was first agent approved for treatment of MF[54]. Ruxolitinib is not selective for only JAK2 mutated disease and can be used in both JAK2 positive and JAK2 negative MF including secondary MF[55]. Regulatory approval in Canada was based on the results of two pivotal randomized phase III trials: Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment (COMFORT)-I and COMFORT II. Both trials included patients with Intermediate -2 or high-risk MF and compared ruxolitinib to placebo (COMFORT I) or to best available therapy (COMFORT II). In both COMFORT- I and -II, treatment with ruxolitinib led to significant

reduction in spleen size, with primary end point of > 35% reduction in spleen size, by imaging techniques (MRI), at 24 and 48 weeks, respectively. Patients had significant improvement in MF-related symptoms and quality of life. There was no significant difference in response among patients with or without the *JAK2 V617F* mutation or those with PMF compared to secondary MF[56,57].

The final 5 year updates on the COMFORT trials have been published. Long-term comparisons in both trials is limited by crossover design with patients transitioned to comparator arms at either 6 months (COMFORT 1) or 12 months (COMFORT II). The rates of best response improve over time and median duration of spleen response is 3 years[58,59]. Long term findings from the COMFORT II trial showed that 28% of patients achieved a >35% reduction in spleen size at week 48 compared to no patients on BAT (P <0.001). Median survival was not reached in the ruxolitinib arm compared to 4.1 years in BAT arm with 33% reduced risk (crossover corrected HR 0.44) of death among patients on ruxolitinib compared to BAT[59]. Pooled data from both COMFORT studies (n=528) found a 30% risk reduction in death among patients with ruxolitinib compared to control arms with median survival of 5.3 years versus 3.8 years, respectively. Based on subgroup analysis, OS was improved with ruxolitinib regardless of age, sex, IPSS risk, spleen size, primary or secondary MF, anemia or thrombocytopenia and JAK mutational status[58].

Overall, ruxolitinib is 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%). However, the platelet count and hemoglobin levels tend to stabilize and improve over time and do not affect response to ruxolitinib treatment[56]. Sudden withdrawal of ruxolitinib can lead to a shock-like syndrome due to re-emergence of suppressed cytokines therefore, tapering of the drug is strongly suggested and current recommendations are to taper by 5 mg weekly[60]. Lastly, occasional reactivation of tuberculosis and opportunistic infections have been reported and linked to chronic suppression of T lymphocytes[61-63]. Currently, no specific prophylaxis is provided for patients. Appropriate screening for TB is suggested in high risk populations.

The recommended starting dose of ruxolitinib is based on platelet count. For a platelet count >200 x 10^9/L, the recommended starting dose is 20 mg BID and for a platelet count 100-200 x 10^9/L, the recommended dose is 15 mg twice daily (BID). 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. Ruxolitinib can be used in moderate thrombocytopenia (50-100 x 10^9/L) and it is feasible to start at lower dose such as 5 mg BID and escalate accordingly without causing severe thrombocytopenia[64]. Dose reduction should be considered for patients receiving ruxolitinib 15 or 20 mg BID if the platelet count declines below 100 x 10^9/L. Complete blood and platelet counts must be performed before initiating therapy, every 2 to 4 weeks until doses are stabilized, and then as clinically indicated, typically on a 4-week basis. 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[37,65]. If no clinically meaningful response is achieved in 6 months, consider an alternative treatment. No specific criteria define ruxolitinib failure but if spleen response is less than 25% from baseline or constitutional symptoms persists it is suggested to consider alternative treatment[36].

Real-world data from the JAK Inhibitor Ruxolitinib Patients (JUMP) Phase IIIb trial illustrated an estimated 48-week OS of 94%, LFS 92% and PFS 90%. The study included 2233 patients from 26 countries with majority of patients from Europe. A majority of patients had >50% reduction in spleen length and another 25% had 20-50% spleen length reductions. Foltz et al reported a 39.1% discontinuation rate mainly related to adverse events (17.7%) followed by disease progression (8.6%). Anemia occurred in 58.7% with 34% having grade 3-4 severity. The majority of patients who received erythropoietin-stimulating agents with ruxolitinib had improvement or resolution of their anemia. Thrombocytopenia occurred 43.8% including 16.3% with grade 3 – 4[66,67].

In a subgroup analysis of 163 patients from the JUMP study with intermediate-1 risk MF (median treatment exposure, 14.4 months), 64% and 61% of evaluable patients had a ≥ 50% decrease in palpable spleen length at weeks 24 and 48, respectively. By 72 weeks, 21% of patients had complete resolution of splenomegaly. Thirty percent of patients had symptomatic improvement by 48 weeks based on Functional Assessment of Cancer Therapy-lymphoma (FACT-LYM) Scores[68,69].

Currently no factors predict the efficacy of ruxolitinib. Patients with ≥3 non-driver mutations have a poor spleen response and inferior survival. Patients who discontinued ruxolitinib, had progressive thrombocytopenia, or clonal evolution predicted worse outcomes. Approximately 50% of patients discontinue ruxolitinib by 3 years with a median survival after discontinuation of 14 months[70].

Ruxolitinib failure: There is currently no consensus on the definition of Ruxolitinib failure. The Canadian MPN Group recently published practical recommendations for management of patients on ruxolitinib with suboptimal or loss of response and/or intolerance.[102]

Studies of second-line JAK inhibitor therapy in patients including fedratinib, momelotinib and pacratinib are briefly described below. Limited data exists for ruxolitinib usage second line. There are reports of the effectiveness of ruxolitinib rechallenge via a case series of 13 patients with MF who were retreated with ruxolitinib after loss of an initial response or inadequate response to a median initial ruxolitinib duration of 62 weeks. Among all 13 patients, ruxolitinib rechallenge was associated with a significant spleen size reduction in 9 patients and symptom improvement in 12 patients. Four patients received a second rechallenge and all 4 experienced some improvement in spleen length and constitutional symptoms.[103]

Fedratinib: In August 2019, the FDA has approved a second JAKi, fedratinib, for patients with intermediate-2 and high risk MF. In October 2020, Health Canada approved fedratinib for the treatment of splenomegaly and/or disease-related symptoms in adult patients with intermediate-2 or

high-risk primary MF, post-polycythemia vera (PV) MF, or post-essential thrombocythemia (ET) MF, including patients who have been previously exposed to ruxolitinib. Recommended dose of fedratinib is 400 mg taken orally once daily for patients with a baseline platelet count of ≥50 x 10^9/L

Approval was on the basis of two JAKARTA trials. The path to approval included a period of FDA clinical hold (2013-2017). Recent approval includes a “black box warning” regarding the risk of serious and fatal encephalopathy, particularly, Wernicke encephalopathy (WE), which, ultimately was determined not to be resulting from fedratinib, following investigations during the clinical hold.

Fedratinib is selective for JAK2 relative to other kinases which could be advantageous because JAK1, JAK3, and TYK2, the other members of the Janus family of kinases, are critical for proper immune function. Therefore, activity against JAK1, JAK3, or TYK2, promotes immune suppression which may pose increased risk of infections.[104]

The JAKARTA study was a phase 3 randomized MF study for intermediate 2 and high-risk disease including patients with platelets ≥50 x 10^9/L included 3 equal arms (400 mg daily, 500 mg daily, or placebo for 24 weeks with crossover from placebo after that time. The primary end point was reduction in spleen volume (SVR) by at least 35%, with confirmation 4 weeks later by diagnostic imaging. The secondary end point was 50% reduction in total symptom burden by the Myelofibrosis Symptom Assessment Form (MFSAF). Between 2011 and 2012, prior to hold, 289 patients were enrolled (96 at 400 mg of fedratinib, 97 at 500 mg of fedratinib, and 96 placebo). The SVR (all confirmed 4 weeks later) observed at week 24 was 36% in the 400mg group, 40% in the 500mg group versus 1% in the placebo group. The MFSAF symptom response (durable until week 24) was 36% for 400 mg, 34% for 500 mg, and 7% for placebo. Anemia was the most common hematological toxicity (~45%) with an initial nadir, as seen with ruxolitinib, but usually followed by improvement. GI toxicities (~50%) of nausea and diarrhea were the most common nonhematological side effects requiring supportive management.[105]

JAKARTA-2[72] was a single-arm, open-label, nonrandomized, phase 2, multicenter study conducted to evaluate the utility of fedratinib in intermediate-1, intermediate-2, or high-risk primary or secondary MF who had previously been treated with ruxolitinib, which was performed in parallel with the JAKARTA study and also included patients evaluated with platelet count of 50 x 10^9/L or higher. Patients received initial oral fedratinib doses of 400 mg once daily in repeated 28-day treatment cycles. The primary endpoint was SVR of ≥ 35% reduction from baseline spleen volume at the end of cycle 6 (EOC6), and a key secondary endpoint was symptom response rate of ≥ 50% reduction in total symptom score (TSS) on MFSAF. This study was also halted early due to the clinical hold placed by the FDA concerning Wernicke’s Encephalopathy (WE) and once resumed ruxolitinib failure was redefined. Patients initially were deemed resistant or intolerant to rollatini according to the individual investigator initially. Following removal of the clinical hold, a more stringent criteria for resistance/intolerance: relapse/refractory was defined for prior ruxolitinib therapy· In all, 97 patients were enrolled and treated in JAKARTA2 and comprised the intention-to-treat (ITT) population. For the entire intention-to-treat cohort, with a median age of 67 years, SVR of ≥35% after 6 cycles was met by 31% (95% confidence interval, 22, 41). Of the 79 patients (81% who met more stringent criteria for ruxolitinib resistance or intolerance) 30% (95% confidence interval, 21, 42) achieved at least 35%

SVR following 6 cycles of treatment with no significant difference in responses between either category. TSS reduction of ≥50% were observed in 27% of both the intention-to-treat group and stringent criteria groups. Most common grade 3-4 hematological adverse events were anemia (46%) and thrombocytopenia (24%). Non-hematological adverse events were mainly GI in ~50% in both JAKARTA studies.

Several ongoing trials. FREEDOM 1 and FREEDOM 2 (NCT03755518 and the second-line NCT03952039) are further evaluating the long term safety and efficacy of fedratinib. Both of these new studies include proactive management of GI symptoms, nutrition care, measurement of thiamine, and also thiamine replacement as indicated with the "black box warning." Thiamine (vitamin B1) is an essential micronutrient, which cannot be made in the body. Although thiamine deficiency is rare in MPNs[106,107] malnutrition is often seen among MF patients and the GI side effects experienced among the JAKARTA studies can predispose patients to nutritional deficiencies. Thiamine level assessments are required prior to initiating fedratinib, then periodically during treatment as per monograph (monthly x 3 then q3months while on treatment), and thereafter as clinically indicated. If thiamine deficiency is identified, thiamine must be replete prior to starting therapy. If encephalopathy is suspected, fedratinib should be discontinued immediately and parenteral thiamine should be initiated until neurologic symptoms resolve and thiamine levels normalize. (Fedratinib monograph [Link]). See Appendix B.

In the setting of current approval of both JAK inhibitors, Ruxolitinib and Fedratinib, there lacks data for direct head -to- head comparison of these drugs as first line treatment. Both JAKARTA[72,105] and COMFORT[58,59] studies do not guide clinicians concerning which drug should be used first line. National Comprehensive Cancer Network (NCCN) developed and published MPN guidelines for US-based MF[108] recently updated their guidelines [Link] including fedratinib as an option for initial therapy of intermediate-2 and high-risk MF for those with a platelet count ≥50 x 10^9/L. Practical issues for choosing first line JAKi might include their side effect profiles, thiamine requirements as well as dosing of therapy (once daily vs twice daily). Certainly, JAKARTA 2[72] provides data supporting fedratinib's effectiveness post ruxolitinib so it is reasonable to consider this as a second line option. Whether there is a benefit to the lack of JAK1 inhibition with fedratinib, or it has a wider kinome effects such as FLT3 and bromodomain targets remains uncertain. In terms of safely for transition from ruxolitinib to fedratinib, most patients can switch directly from one drug to another without "washing out" the first drug and ruxolitinib tapering is always advised. No tapering of fedratinib is required due to its long half-life (~41 hrs vs ~3 hrs for ruxolitinib).

Additional JAK inhibitors have been tested in MF and reviewed in detail elsewhere with most having been discontinued due to toxicity or poor response in comparison to ruxolitinib[71]. Momelotinib (MMB) is a JAK1/JAK inhibitor, which in murine models of anemia in chronic disease, inhibited bone morphogenic protein receptor kinase activin A receptor type I (ACVR1)–mediated hepcidin expression, which resulted in erythropoiesis.[109] In a phase I/II study of momelotinib in

myelofibrosis (MF) the rates of spleen and anemia response, per International Working Group criteria, were 48% and 59%, respectively[110] SIMPLIFY-1[74] and SIMPLFY-2[75] phase III studies compared momelotinib(MMB) to ruxolitinib in MF without prior Jak inhibitor therapies and momelotinib vs BAT in MF with prior JAK inhibitor exposure, respectively. SIMPLIFY I (n=432) found MMB to be non-inferior to ruxolitinib with ≥35% spleen response of 26.5% vs. 29.0% (p=0.011) although it had a better anemia response at Week 24. Secondary endpoints of TSS reduction was seen in 28.4% and 42.2% of patients in MMB cohort and ruxolitinib cohort with no statistical difference (p = 0.98). The incidence of grade ≥3 AEs in MMB and ruxolitinib group were 35.5% and 43.5%, respectively. The most common hematological toxicities in both groups were thrombocytopenia and anemia, but the incidence of grade 3 or 4 anemia in ruxolitinib group was significantly higher than that in MMB (23.1% and 5.6%). A main side effect was neuropathy with 10% vs 5% peripheral neuropathy (grade <3) experienced in each arm. Overall, in JAKi-naïve MF patients, MMB treatment was noninferior to ruxolitinib for spleen response and TSS reduction but with evidence supporting MMB providing better anemia response. [74] SIMPLIFY-II (N=156)[75] compared the efficacy and safety of MMB with BAT (which included ruxolitinib, chemotherapy, steroids, hydroxyurea, no treatment, or other standard interventions) in the treatment of MF patients who had previously been treated with ruxolitinib. To note, is that most patients (89%) in BAT group chose ruxolitinib as comparator. In this study, momelotonib was not superior to BAT (mainly ruxolitinib) with a SVR of 6.6% vs. 5.8% at week 24 (p=0.9). In secondary endpoint analyses, more patients in the momelotinib arm were transfusion independent at week 24 than patients in the BAT arm (43% vs. 21%, P = 0.0012), and 40% of momelotinib-treated patients required no transfusions over the treatment phase, compared with 27% of patients in the BAT group (P = 0.10).[75]

Alternative JAK inhibitors have been studied for use in thrombocytopenia, such as Pacritinib, a JAK2/IRAK1 inhibitor. Pacritinib's selectivity results in minimal immune suppression. The phase III PERSIST-1 study enrolled patients with JAK inhibitor–naïve MF[111]. Phase 3 study (PERSIST-2)[76] (n=311) compared pacritinib 400 mg OD versus 200 mg BID to best available therapy (BAT), including ruxolitinib (n =44, 45% of BAT). Patients with intermediate-1, intermediate -2 and high risk DIPSS MF with platelets ≤ 100 x 10^9/L and palpable splenomegaly were included and randomized in 1:1:1 fashion and included patients with prior JAK inhibitor therapy. Co-primary endpoints were ≥ 35% SVR and ≥ 50% TSS reduction at week 24. Pacritinib (arms combined) was more effective than BAT for SVR 18% vs 3% p=0.001 with no significant difference in TSS reduction (~25%) (p=0.08). The most common BAT was ruxolitinib (44 patients [45%]); 19 patients (19%) received watchful-waiting only. Pacritinib (arms combined) was more effective than BAT for ≥35% SVR (18% vs. 3% P = .001) but had a nonsignificant greater rate of 50% or more reduction in TSS (25% vs14%]; P = .08). Pacritinib twice daily led to significant improvements in both end points over BAT (≥35% SVR: 16 patients [22%] vs 2 patients [3%]; P = .001; ≥50% reduction in TSS: 24 patients [32%] vs 10 patients [14%]; P = .01). Clinical improvement in hemoglobin and reduction in transfusion burden were greatest with pacritinib twice daily dosing. Adverse events (>10%) grade 3 or 4 were thrombocytopenia and anemia. Overall in patients with platelet counts < 50 x 10^9/L, there was no

evidence of increasing thrombocytopenia in the pacritinib or BAT arms during treatment. However, there were concerns of high-grade cardiac and hemorrhagic events in the PERSIST studies which led to clinical hold. The follow-up PAC203 trial[112] a dose-finding study of pacritinib in patients with ruxolitinib failure, evaluated the efficacy of the 200 mg BID dose compared to lower pacritinib doses (100 mg QD and 100 mg BID). This incorporated more stringent eligibility/exclusion criteria, monitoring, and further dose modifications were implemented to mitigate risk of cardiac and hemorrhagic events. Patients had strict ruxolitinib failure criteria (similar to JAKARTA-2.[72)] The endpoints were ≥35% SVR and ≥50% reduction in TSS at week 24. Of 161 patients, 73% were intolerant of and 76% had ruxolitinib resistance with a total of 50% meeting criteria for both. Severe thrombocytopenia (platelet count <50 x 10^9/L) was present in 44% of patients enrolled. SVR rates were highest with 200 mg twice per day (100 mg once per day, 0%; 100 mg twice per day, 1.8%; 200 mg twice per day, 9.3%). The TSS response rate was not statististically different between doses (100 mg once per day, 7.7%; 100 mg twice per day, 7.3%; 200 mg twice per day, 7.4%). Overall the greatest SVR and TSS reduction were seen at 200 mg twice per day compared with lower doses. Pacritinib 200 mg twice per day demonstrated clinical activity and an acceptable safety profile without an excess of hemorrhagic or cardiac events at 200 mg twice per day therefore this is recommended dose for a following phase three studies and use.[112] Several ongoing trials are investigating novel therapies that target different pathways used alone or in combination with ruxolitinib[77,78].

Cytoreductive therapies: Hydroxyurea has been longstanding treatment prior to the development of JAK inhibitors and can be initiated at a dose of 500-1000 mg oral daily. The overall response is 40% with median duration of 13.2 months. Hydroxyurea does provide symptom control for constitutional symptoms and is suggested to be used second line to ruxolitinib. Alternatively, it can be used first line for low risk MF patients who would not be eligible for ruxolitinib. Other drugs such as busulfan are rarely used and its use is limited to elderly patients with shortened life survival due to concerns of leukemic potential[36].

Interferon: Myelofibrosis can be very symptomatic resulting from elevated cytokines with a large inflammatory component that may benefit from immune modulation through interferon. Silver *et al*. performed a prospective single centre study on the use of recombinant interferon-α (rIFN-α) in “early” primary myelofibrosis in settings of grade 1 and 2 myelofibrosis with residual hematopoiesis. Seventeen patients received either rIFNα-2b 500,000 to 3 million units three times weekly or pegylated rIFN-α-2α 45 to 90μg weekly. Based on IWG prognostic and response criteria, 11 patients were low risk with 6 were intermediate-1 risk with complete remission (CR) and partial remission (PR) achieved in 2 and 7 patients, respectively. Overall, 58.8% patients derived clinical benefit with 23.5% achieving disease stability. The median time to any documented response was 1.0 years (0.4-7.4 years) with median duration of response of 2.0 years (0.1-14.0 years). Based on bone marrow follow-up in 15 patients, performed in a median of 3.2 years (0.9 -7.6 years) after therapy initiation, marrow morphology remained unchanged in 11 patients with 4 remissions achieved (2 CR and 2 PR). In the 4 with marrow improvement, sustained reduction in splenomegaly was also achieved. Quantitative

JAK2 allele burden was assessed in 17 patients with 12 patients having mutated *JAK* status and 16 undergoing serial analysis whereby 14 had no molecular response and 2 had partial response. There was no correlation between molecular response and spleen response. Overall, rIFN-α was tolerated with 80 % of patients having some clinical benefit or stability in early phase PMF[79]. Overall, 13 small clinical studies have evaluated the use of interferon with PMF but unfortunately, are variable on disease definition and treatment response criteria. Overall response rates ranged from 0-79% with spleen reductions 0-26%. Three studies have included pegylated IFN-α2α or IFNα2b with overall response rates of 9-85% and spleen reductions of 0-76% with Silver *et al.* showing the most clinical benefit of 80% among patients, specifically among early PMF[79,80]. The largest study of 62 patients from French and Belgium centres retrospectively reviewed use of PEG-IFNα-2α therapy in myelofibrosis including 29 PMF, 19 PPV-MF, and 14 PET-MF of all risk categories. Treatment was initiated at median of 19.1 months from time of diagnosis with median age of 66 years at time of initiation of therapy. At mean follow up of 26 months, 64% of anemic patients achieved a complete response (time to achieve best response was 7.1 months) with 38.5% becoming transfusion independent. For patients in proliferative stages of their disease, complete resolution of leukocytosis and thrombocytosis occurred in 68.8% and 82.8% of patients, respectively. Eighty-two percent had resolution of constitutional symptoms and 46.5% had resolution of splenomegaly. Treatment was stopped in 45% patients after mean time of 11.7 months but was relatively well tolerated with majority of adverse events being grade 1-2 toxicities relating to cytopenias. Routine bone marrow assessments were not performed to assess morphological response. Spleen enlargement greater than 6 cm below costal margin was negatively associated with treatment response[81]. In a long-term follow up of these patients, at 58 months after PEG-IFN-α2α initiation and 69.6 months after MF diagnosis, 30 patients (48.4%) of patients were still alive and had treatment duration of 39 months. The median overall survival (OS) of the cohort was 7.4 years with leukemia free survival (LFS) not reached. Median OS was 30 months among patients treated with PEG-IFN-α2α for less than 2 years compared to 70 months if treated >2 years ($p<0.0001$). Overall survival was greater than expected based on reference cohorts according to DIPSS scores (6.9 years vs. 4 years Int-2 risk and 4.58 vs 1.5 years in high risk). The 5 –year actuarial survival rate was 69.4% among entire cohort, or 60% among Int-2 and high risk patients. Median mutant allele burden was studied in 31 *JAK2* patients. A greater than 50% decrease in *JAK2* allele burden was observed in 10/27 (37%) of patients, including 15% with >95% reduction however, no difference in OS or LFS was observed based on allele burden reduction. All seven patients that proceeded to alloSCT died within median time of 10 months associated with mainly graft versus host disease (GHVD) in 5/7 patients. Overall, PEG-IFN-α2α is a treatment option in MF and is currently being considered moreso, in low risk MF. Its impact on molecular allele burden does not clearly correlate with survival rates and also requires further understanding[82].

Splenectomy: Traditionally, splenectomy has been used to manage burdensome symptoms associated with splenomegaly, but the procedure involves substantial risk with 31% and 9% morbidity and mortality, respectively[83]. The main complications are bleeding, infections, and thrombosis

(primarily in the splanchnic veins)[84]. Subsequent extramedullary hematopoiesis resulting in massive hepatomegaly develops in 16- 24% of patients and can result in liver failure[85]. Splenectomy may be considered in immune related hemolysis unresponsive to steroids or in refractory transfusion-dependent anemia or those with refractory splenomegaly. Durable responses in transfusion-dependent anemia occur in 23% of patients[84].

Splenic irradiation: Splenic irradiation has been used in selected patients for palliative purposes when splenomegaly is resistant to medication and a splenectomy is contraindicated. The doses used range from 30-365 Gy in 5-10 fractions. The benefit is transient but the risk of severe and prolonged cytopenias occurs in 1/3 of patients and an increase in transfusion requirements occurs in 40% of cases[37,86].

Treatment: Recommendations

1. JAK inhibitors should be used as first line treatment for symptomatic splenomegaly or for patients with constitutional symptoms with Intermediate or high risk disease. Both ruxolitinib and fedratinib are approved as first line treatment options.
2. An alternative JAK inhibitor or hydroxyurea can be second line in patients intolerant or resistant to ruxolitinib. It is preferred that fedratinib be considered a second line treatment option post ruxolitinib failure.
3. Hydroxyurea can be considered first line for low risk/int-1 risk MF when patients are asymptomatic with thrombocytosis and/or leukocytosis requiring cytoreduction.
4. Splenic radiation is a palliative treatment for drug-refractory splenomegaly in patients with an adequate platelet count (>50 x 109/L) and can provide transient symptom improvement.
5. Splenectomy is reserved for drug-refractory splenomegaly and is not routinely performed. Appropriate vaccination is required pre-operatively.

Transplant

Allogeneic hematopoietic stem cell transplantation (alloSCT) remains the only curative approach, but carries a considerable risk of mortality and morbidity. Significant regimen-related toxicities, graft failure and graft-versus-host disease are major barriers to the success of alloSCT in MF. Recent studies suggest that the Dynamic International Prognostic Scoring System (DIPSS) score may predict success after transplant[87]. Patients with MF who are age ≤ 65 years, and have intermediate-2 or high-risk disease by DIPSS have superior survival with alloSCT compared with non-transplant approaches and are considered the best alloSCT candidates[36,88]. We currently recommend transplant eligible patients with DIPSS-plus int-2 or high risk disease be considered for transplant.

Additional prognostic factors may influence transplant recommendations. Triple-negative patients who lack any of the three driver mutations: *JAK2, CALR* or *MPL*, have an increased risk of leukemic transformation and shortened overall survival[28,29]. In addition, High-molecular risk (HMR) genes such

as *ASXL1, EZH2, IDH1/2* and *SRSF2* have been associate with inferior prognosis[33,34,89]. Speigel *et al* performed a 54-gene myeloid panel on 100 MF patients treated with either ruxolitinib (n=77) or momelitonib (n=23) and correlated mutational profiles with treatment outcomes. Patients with high risk DIPSS scores or pretreatment transfusion dependency had a shorter time to treatment failure (TTF). Those with a HMR profile (HR 2.06, p=-0.01), *ASXL1* (HR 1.86, p=0.03) or *EZH2* mutations (HR 2.94, p=0.009) had shorter TTF. Based on multivariate analysis, *ASXL1* and *EZH2* mutations remained negatively associated with shorter TTF and overall survival. Patients with ≥ 3 HMR mutations had shorter TTF (p=0.006) and shorter OS (p=0.0005)[90]. These findings identify MF patients who may likely benefit from earlier alloSCT given their anticipated poorer response to medical treatment and expected shorter survival. We therefore recommend that MF patients who are ineligible for JAK inhibitor treatment or lack of response to JAK inhibitor therapy, display pre-treatment transfusion dependence, have high risk DIPSS score, are "triple negative" or have the presence of *ASXL1* or *EZH2* be referred and considered early for alloSCT. In retrospective comparative analysis of patients treated with drugs or alloSCT, the latter was superior in DIPSS int-2 and high risk patients with expected median survival of 4.5 year and 2 years, respectively[88]. Recently, integrated clinical, genetic and molecular prognostic models with (MIPSS70-plus) or without (MIPSS-70) cytogenetics have been developed to better stratify transplant eligible patients who are ≤ 70 years old and are best suited for transplant[44]. Risk factors for OS included: hemoglobin <100 g/L, leukocytes >25 x 10^9/L, platelets <100 x 10^9/L, circulating blasts ≥ 2%, bone marrow fibrosis grade ≥ 2, constitutional symptoms and absence of CALR type -1 mutation, and presence of high molecular risk mutations (HMR) *(ASXL1, EZH2, SRSF2, IDH1/2)* and presence of 2 or more HMR specifically. Three risk categories were delineated for MIPSS70 (**see Table 4**) with a median OS of 2.3 years among high risk patients and a risk of death of 81% at 5 years without disease intervention, suggesting upfront use of alloSCT. Similarly, based on the MIPSS70-plus model with four categories (**Table 4**), the 5-year OS among patients with high risk and very high risk was 42% and 7%, respectively with median OS of 3.9 years and 1.7 years, respectively[44]. In both cases, alloSCT should be strongly considered in MIPSS-70 high risk disease and/or high or very high risk MIPSS70-Plus MF patients.

Recently, a personalized MPN prediction model was developed which incorporates genomic and clinical data in order to provide a more personalized risk stratification and prognosis. A total of 2035 patients (63 genomic and clinical variables) were included in the analysis and outcomes correlated with an independent external cohort. The calculator can be found at: [Link] and may assist physicians in providing a more personalized treatment approach for MF; in particular provide a better understanding for an optimal timeline for consideration of alloSCT[91]. Despite advances in our understanding of molecular markers, and the development of novel prognostic tools, the complete understanding of their relevance for alloSCT remains to be studied prospectively. There are no definite guidelines on integration of these newer scores in clinical practice. Ultimately, many factors need to be considered when proceeding to alloSCT including the Hematopoietic stem cell transplant comorbidity index (HCT-CI) and donor status[92].

It has been demonstrated that pretreatment with JAK1/2 inhibitors has no adverse impact on the outcomes of subsequent alloSCT but rather improves clinical status and symptom burden, particularly reduction of splenomegaly pre-alloSCT. Furthermore, serious adverse events during drug discontinuation appear to be less frequent when JAK inhibitors are continued until close to the conditioning regimen. Patients undergoing alloSCT while responding to JAK inhibitors appear to have better outcomes compared to those with progressive disease[93,94]. It is important to consider timing of alloSCT and recognizing that 50% discontinue at 2-3 years and it is best to proceed with alloSCT before loss of ruxolitinib response[36]. We suggest ruxolitinib use pre-transplant and that it be discontinued at the start of conditioning for alloSCT.

Transplant: *Recommendations*

1. Allogeneic stem cell transplant (alloSCT) is the only curative treatment in MF and should be considered in fit patients with DIPSS Intermediate -2 or higher risk disease. Ultimately fit patients (<75yrs) with expected overall survival less than 5 years are suggested for referral to alloSCT. Younger patients with Intermediate -1 risk disease should be assessed for additional prognostic factors (see below) with consideration for alloSCT as future therapy.
2. Newer scores such as MIPSS70 and MIPSS70-Plus also identify patients with “high” or “very high” risk as being appropriate candidates for alloSCT. Personalized MPN genomic and clinical calculators are also available.
3. Additional factors for early alloSCT consideration include: ineligibility for JAK inhibitor treatment or lack of response to JAK inhibitor therapy, pretreatment transfusion dependence, or presence of HMR mutations.

Emerging Treatments

Anemia is a significant problem among MF patients. A novel class of drugs termed activing receptor type II ligand traps consist of fusion proteins that sequester ligands belonging to the transforming growth factor B (TGFRB) superfamily and therefore inhibit their suppressive effects on terminal erythropoiesis[95]. Sotatercept is the first molecule in its class studied which has had response rates of 40%[78]. In a phase 2 trial in MF patients, 6 of 17 patients (35%) and 1 of 8 patients (12.5%) treated with sotatercept alone and combined with ruxolitinib, respectively, achieved erythroid response, with good tolerance.[113] Likewise, phase 2 study of MF patients (n=74) with anemia were randomized to luspatercept with or without ruxolitinib. Among those patients on ruxoilitinib and transfusion dependant (n=19) , 53% had a $\geq$ 50% reduction in RBC transfusion burden with 32% achieving transfusion independence $\geq$ 12 weeks, Among those on ruxolitinib with anemia that were nontransfusion dependant 57% achieved a mean increase of Hgb level of 15 g/L.[114]

Additional Concerns

Blast phase myelofibrosis: Blast phase MF (MPN-BP) is synonymous with acute myeloid leukemia (AML) and is defined by the presence of ≥20% blasts in the blood or bone marrow [96]. The risk of leukemic transformation depends on the MPN variant and is highest in PMF, with an incidence of 10–20% during the first decade[42]. The prognosis is poor with median survival of approximately 3 months which has not improved in 15 years[97,98]. In a recent retrospective study, intensive chemotherapy resulted in complete remission (CR) or CR with incomplete count recovery (CRi) rates of 35% and 24%, respectively. Treatment-specified 3- and 5-year survival rates were 32% and 10% for patients receiving alloSCT (n = 24), compared to 19% and 13% for patients achieving CR/CRi but were not transplanted (n = 24), and 1% vs 1% in the absence of both alloSCT and CR/CRi (n = 200) ($p < 0.01$). Less intensive strategies, such as Azacitidine fail to achieve CR rates however at a dose of 75 mg/m^2 x 7 days on 28-day cycle overall response rate (ORR) of 38% including in 4/7 cases of transformed MF resulted in median survival of 8 months[99]. AlloSCT remains the only curative option in transformed MF but can only be offered to a select few patients. Overall 3-year survival is dismal at 6-11%[98]. Refer to current AML guidelines for further treatment options.

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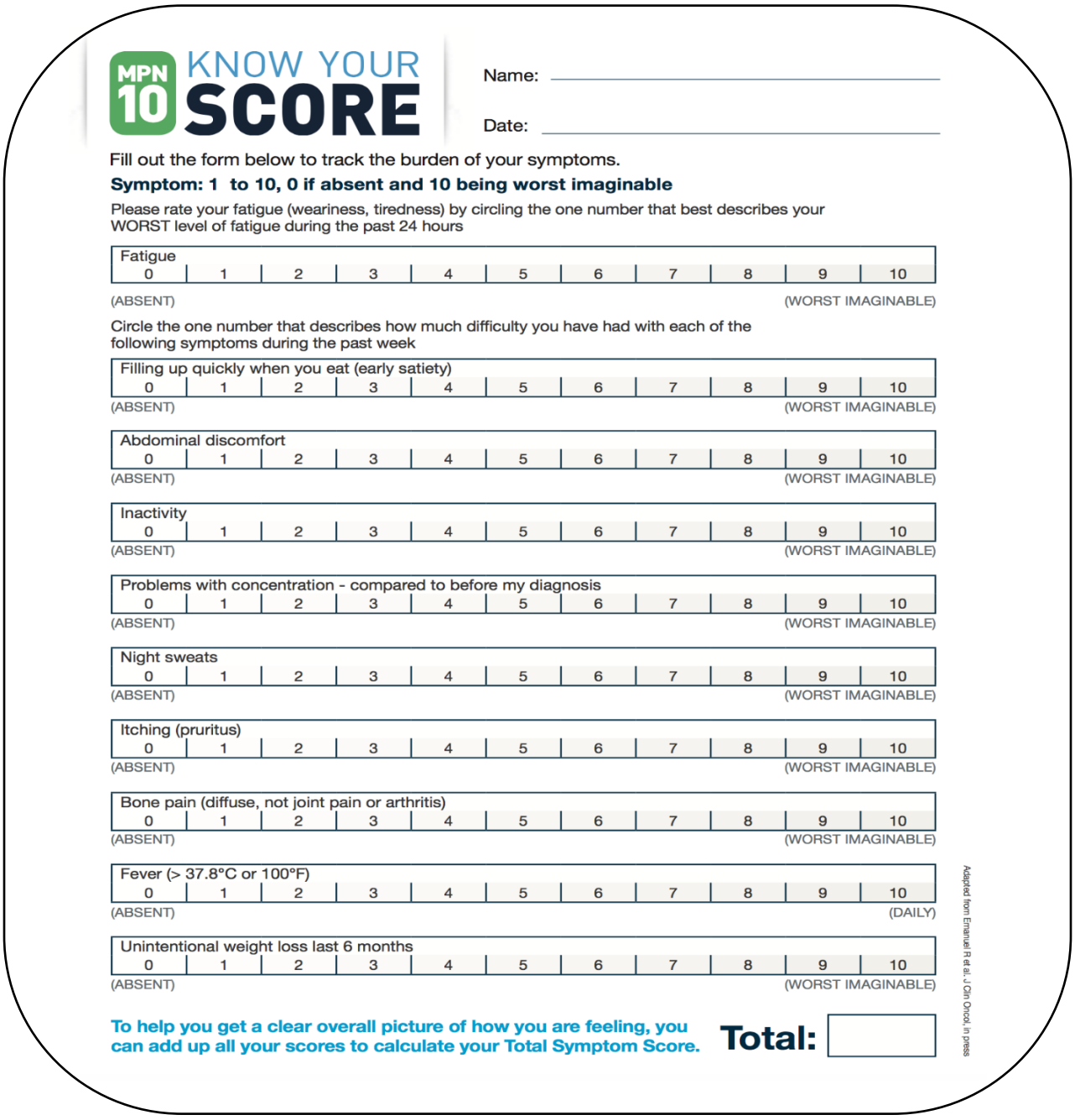
Appendix A: Assessment Tools

Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) MPN-SAF TSS, also known as MPN10, includes 10 items: fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fever. The tool has been validated in a prospective study of over 1400 patients and results correlated with other measures of disease burden. It can be used to: quantitatively assess the burden of symptoms of patients with MPNs, track disease progression and response to treatment[100]. MPN Symptom Assessment Form Total Symptom Score:



MPN 10 KNOW YOUR SCORE

Name: _____

Date: _____

Fill out the form below to track the burden of your symptoms.

Symptom: 1 to 10, 0 if absent and 10 being worst imaginable

Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past 24 hours

Fatigue
0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10
(ABSENT) (WORST IMAGINABLE)

Circle the one number that describes how much difficulty you have had with each of the following symptoms during the past week

Filling up quickly when you eat (early satiety)
0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10
(ABSENT) (WORST IMAGINABLE)

Abdominal discomfort
0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10
(ABSENT) (WORST IMAGINABLE)

Inactivity
0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10
(ABSENT) (WORST IMAGINABLE)

Problems with concentration - compared to before my diagnosis
0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10
(ABSENT) (WORST IMAGINABLE)

Night sweats
0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10
(ABSENT) (WORST IMAGINABLE)

Itching (pruritus)
0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10
(ABSENT) (WORST IMAGINABLE)

Bone pain (diffuse, not joint pain or arthritis)
0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10
(ABSENT) (WORST IMAGINABLE)

Fever (> 37.8°C or 100°F)
0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10
(ABSENT) (DAILY)

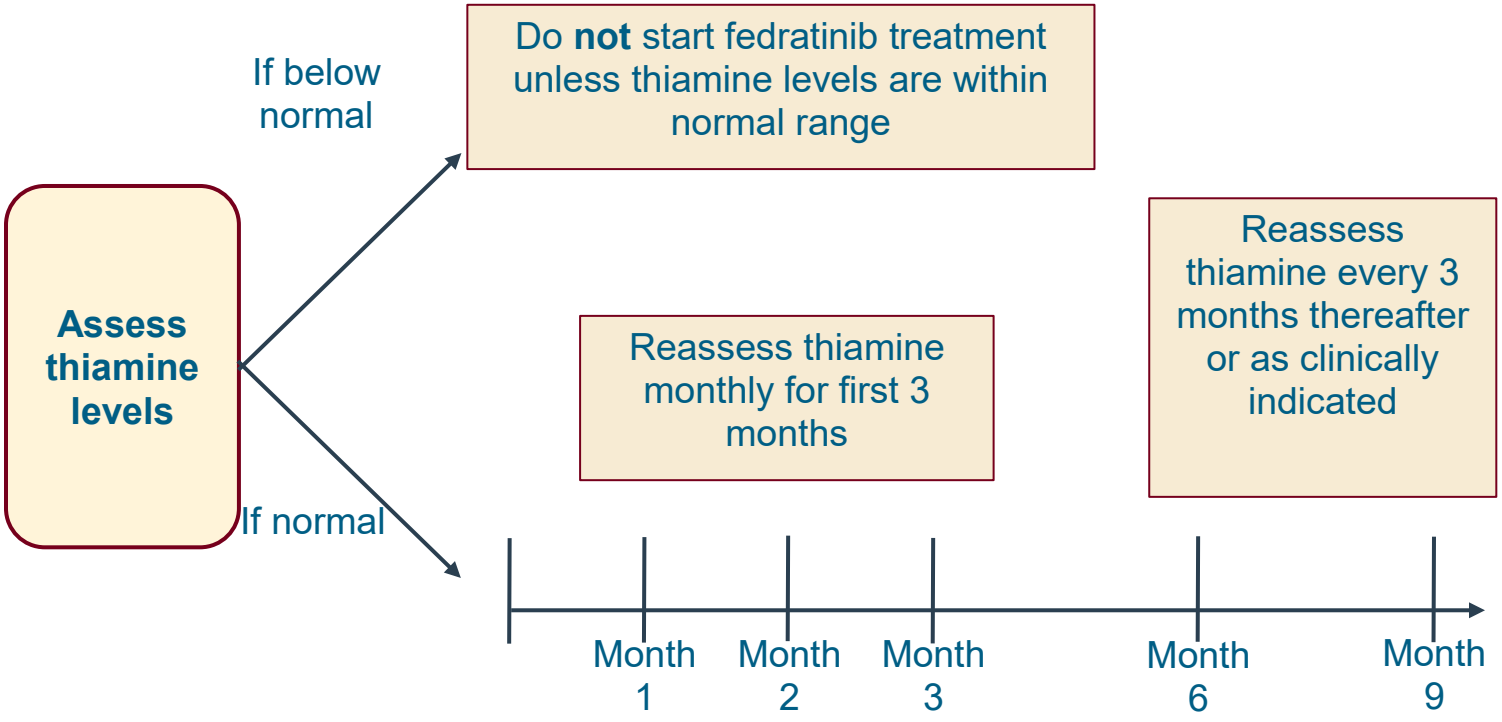
Unintentional weight loss last 6 months
0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10
(ABSENT) (WORST IMAGINABLE)

To help you get a clear overall picture of how you are feeling, you can add up all your scores to calculate your Total Symptom Score.

Total: _____

Adapted from Emanuel R et al. J Clin Oncol, in press

Appendix B: Algorithm to Monitor Thiamine Levels with Fedratinib



Development and Revision History

This guideline was reviewed and endorsed by the Alberta Hematology Tumour Team. Members include surgical oncologists, radiation oncologists, medical oncologists, hematologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Tumour Teams, external participants identified by the Working Group Lead, and a knowledge management specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2020 and revised in 2021.

Maintenance

A formal review of the guideline will be conducted in 2022. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

alloSCT, allogenic stem cell transplant; AML, acute myeloid leukemia; BAT, best available therapy; BID, twice daily; BM, bone marrow; CALR, calreticulin gene; CBCD, complete blood count with differential; CR, complete remission; Cri, CR with incomplete count; CML, chronic myelogenous leukemia; CMML, Chronic myelomonocytic leukemia; DIPSS, Dynamic International Prognostic Scoring System EMH, extramedullary hematopoiesis; EPO, Erythropoietin; ESAs, erythropoietic stimulating agents; ET, essential thrombocytosis; FACT-LYM, Functional Assessment of Cancer Therapy-lymphoma; GHVD, graft versus host disease; GPSS, genetics-based prognostic scoring system; HCT-CI, Hematopoietic stem cell transplant comorbidity index; Hgb, hemoglobin; HMR, High-molecular risk; IPSS, International Prognostic Scoring System; IMiDS, immunomodulators; IWG, International Working Group; IWG-MRT, International Working Group for MPN Research and Treatment; LDH, *Lactate dehydrogenase*; LFS, leukemia free survival; MDS, myelodysplastic syndromes; MF, myelofibrosis; MIPSS, Mutation-enhanced International Prognostic Scoring System; MK, megakaryocyte; MPL, thrombopoetin receptor gene; MPN, myeloproliferative neoplasm; MPN-BP, Blast phase MF; MYSEC-PM, Myelofibrosis Secondary to PV and ET-Prognostic Model; NGS, next generation sequencing; ORR, overall response rate; OS, overall survival; PFS, progression free survival; PMF, primary myelofibrosis; PR, partial remission; PV, polycythemia vera; rIFN-α, recombinant interferon-α; TGFRB, transforming growth factor B superfamily; TTF, time to treatment failure; WBC, white blood cell; WHO, world health organization.

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

Dr. Sonia Cerquozzi reports personal fees, non-financial support and other from Novartis, personal fees, non-financial support and other from Celgene, personal fees from Pfizer, outside the submitted work.
Derek Tilley has nothing to disclose.