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REVIEW ARTICLE

Treating early-stage myelofibrosis

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Abstract

Myelofibrosis (MF) is a Philadelphia chromosome–negative myeloproliferative neoplasm associated with bone marrow fibrosis, splenomegaly, a high symptom burden, and poor prognosis. Treatment is based on a risk-adapted approach, with treatment guidelines generally recommending allogeneic stem cell transplant or drug-based therapy for patients with higher-risk or more advanced disease and recommending observation or the "watch-and-wait" strategy for those with lower-risk or early-stage MF. With the advent of targeted therapies, such as the Janus kinase inhibitors, many patients have experienced substantial clinical benefits, including reduction in splenomegaly and symptoms and, in some instances, improvement or stabilization of bone marrow fibrosis and reduction of *JAK2* V617F allele burden. These observations raise the possibility of patients in earlier phases of the disease also benefiting from treatment with targeted therapies. In this review, we discuss the current treatment options for patients with early-stage MF and the available evidence supporting the treatment of patients with less-advanced disease. Overall, therapies used to treat patients with early-stage MF will have to be assessed in randomized studies, with the potential benefits balanced against adverse events associated with treatment.

Keywords Myelofibrosis · Janus kinase inhibitors · Allogeneic stem cell transplant · Early myelofibrosis

Introduction

Myelofibrosis (MF) is a chronic myeloproliferative neoplasm characterized by progressively worsening bone marrow fibrosis, cytopenias, progressive splenomegaly, debilitating symptoms, and shortened survival. It may present as primary disease (PMF) or as post–polycythemia vera MF (PPV-MF) or post–essential thrombocythemia MF (PET-MF) [1]. The clinical manifestations in MF are heterogeneous, with up to 30% of patients initially asymptomatic; however, most patients present with constitutional symptoms or symptoms associated with anemia or splenomegaly [2].

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Several prognostic models for survival have been developed for patients with PMF, including the International Prognostic Scoring System (IPSS), which is used at diagnosis [3], and the Dynamic IPSS (DIPSS), which can be used at any time [4] (Table 1). Very recently, a tool was developed for risk stratification in patients with secondary MF (PPV/PET-MF). The Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM) was developed based on a cohort of 685 patients with secondary MF molecularly annotated for Janus kinase 2 (*JAK2*), calreticulin (*CALR*), and myeloproliferative leukemia (*MPL*) mutations. Hemoglobin level < 110 g/L, circulating blasts ≥ 3%, *CALR*-unmutated genotype, platelet count < 150×10^9/L, constitutional symptoms, and increasing age were found to correlate with worse survival [8] (Table 1).

Currently, treatment with JAK inhibitors is typically reserved for patients with intermediate- to high-risk disease with splenomegaly or symptoms. However, recent evidence has suggested that treating patients with early-stage MF may lead to better outcomes. These patients often have a lower symptom burden, less severe splenomegaly, a lower incidence of cytopenias, and less-severe bone marrow fibrosis [9–11]. This review will discuss evidence for the treatment of patients with early-stage MF and explore potential treatment options for these patients.

Table 1 Prognostic factors and scoring systems in myelofibrosis

	Primary myelofibrosis						Secondary myelofibrosis
Risk factor, adverse points[a]	IPSS [3]	DIPSS [4]	DIPSS-Plus [5]	MIPSS [6]	MIPSS70 [7]	MIPSS70-Plus [7]	MYSEC-PM [8]
Age > 65 years	1	1	1	1.5[b]			0.15[c]
Hemoglobin < 100 g/L	1	2	2	0.5	1	1	2[c]
WBC count > 25×10^9/L	1	1	1		2		
Circulating blasts > 1%	1	1	1		1[d]	1[d]	2[c]
Constitutional symptoms	1	1	1	0.5	1	1	1
Unfavorable karyotype			1[e]			3[f]	
Platelet count < 100×10^9/L			1	1[b]	2		1[c]
Transfusion need			1				
Triple-negative				1.5			
JAK2 or *MPL* mutation				0.5			
ASXL1 mutation				0.5			
SRSF2 mutation				0.5			
Absence of *CALR* mutations					1[g]	2[g]	2
HMR category					1	1	
≥ 2 HMR mutations					2	2	
BM fibrosis grade ≥ 2					1		

ASXL1 additional sex combs-like 1, *BM* bone marrow, *CALR* calreticulin, *DIPSS* Dynamic International Prognostic Scoring System, *HMR* high molecular risk, *IPSS* International Prognostic Scoring System, *JAK2* Janus kinase 2, *MIPSS* Mutation-Enhanced International Prognostic Scoring System, *MPL* myeloproliferative leukemia, *MYSEC-PM* Myelofibrosis Secondary to PV and ET-Prognostic Model, *SRSF2* serine–arginine-rich splicing factor 2, *WBC* white blood cell

[a] Risk categories are based on a patient's risk score (i.e., sum of adverse points). Risk categories according to each prognostic system, risk score, and the expected median survival for each category are as follows:

IPSS: low (risk score, 0; median survival, 11 years); intermediate-1 (1; 8 years); intermediate-2 (2; 4 years); high (≥ 3; 2 years)

DIPSS: low (0; 15 years); intermediate-1 (1–2; 6.5 years); intermediate-2 (3–4; 3 years); high (5–6; 1 year)

DIPSS-Plus: low (0; not reached); intermediate-1 (1; 14 years); intermediate-2 (2–3; 4 years); high (≥ 4; 1.5 years)

MIPSS: low (0–0.5; 26.4 years); intermediate-1 (1–1.5; 9.7 years); intermediate-2 (2–3.5; 6.4 years); high (≥ 4; 1.9 years)

MIPSS70: low (0–1; 27.7 years); intermediate (2–4; 7.1 years); high, (≥ 5; 2.3 years)

MIPSS70-Plus: low (0–2; 20 years); intermediate (3; 6.3 years); high (4–6; 3.9 years); very high (≥ 7; 1.7 years)

MYSEC-PM: low (< 11; not reached); intermediate-1 (≥ 11 to < 14; 9.3 years); intermediate-2 (≥ 14 to < 16; 4.4 years); high (≥ 16; 2 years). The final score can be calculated using a discrete/continuous nomogram (available online at https://mysec.shinyapps.io/prognostic_model/)

[b] Age > 60 years; platelet count < 200×10^9 /L.

[c] Any age, 0.15 points per years of age; hemoglobin < 110 g/L; platelet count < 150×10^9 /L; blasts ≥ 3%

[d] Circulating blasts ≥ 2%

[e] Complex karyotype or sole or two abnormalities that include + 8, − 7/7q-, i(17q), − 5/5q-, 12p-, inv.(3), or 11q23 rearrangement

[f] Any abnormal karyotype other than normal karyotype or sole abnormalities of 20q−, 13q−, +9, chromosome 1 translocation/duplication, −Y, or sex chromosome abnormality other than –Y

[g] Absence of *CALR* type 1-like mutation

Prognostic implications of driver and subclonal molecular mutations in PMF

MF is characterized by dysregulation of the JAK/signal transducer and activator of transcription (STAT) pathway [12, 13] at least in part related to three somatic "driver" mutations that directly or indirectly affect JAK activity, specifically the *JAK2* V617F mutation (present in 65% of patients) and mutations in *CALR* (25% of patients) and *MPL* (5–10% of patients) [14–17]. Driver mutations also correlate with prognosis, with patients with type 1/type 1-like *CALR* mutations having better survival probability than patients with *JAK2* V617F, type 2/type 2-like *CALR*, or *MPL* mutations [18–21]. Interestingly, triple-negative patients (i.e., those without mutations in *JAK2*, *CALR*, or *MPL*) also show hyperactivation of JAK-STAT signaling, with triple negativity associated with worst survival [22].

Mutations in *ASXL1*, *EZH2*, *SRSF2*, *IDH1*, or *IDH2* indicate an IPSS- and DIPSS-Plus–independent high molecular risk (HMR) status; patients with HMR status have shorter

survival and higher risk of blast transformation than patients with low molecular risk (LMR) status (i.e., patients without a HMR mutation) [23]. On the basis of these results, presence of driver and subclonal mutations have been integrated in the Mutation-Enhanced International Prognostic Scoring System (MIPSS) [6] and the MIPSS70 [7], two molecular-based prognostic scoring systems (Table 1).

Guidelines for treatment of MF

Current treatment guidelines recommend a risk-adapted treatment approach, which is of utmost importance when choosing to route a patient to allogeneic hematopoietic stem cell transplant (alloSCT) [14, 24] (Fig. 1). AlloSCT is the only curative therapeutic option for patients with MF [27, 28] and can lead to near-complete or complete regression of bone marrow fibrosis, regardless of risk score at transplant [29, 30]. However, it is associated with high treatment-related mortality and morbidity, with an overall survival (OS) of approximately 50% in patients receiving conventional-intensity conditioning alloSCT [31, 32]. Based on guidelines from the European LeukemiaNet (ELN) and European Society for Blood and Marrow Transplantation (EBMT), all patients with intermediate-2 or high-risk disease according to IPSS, DIPSS, or DIPSS-Plus who are < 70 years old should be considered for alloSCT [27]. AlloSCT may also be recommended for patients with intermediate-1–risk disease with either refractory transfusion-dependent anemia, blasts > 2%, or unfavorable cytogenetic abnormalities (as defined by the DIPSS-Plus) [5, 27]. Furthermore, the ELN/EBMT guidelines suggest alloSCT for intermediate-1–risk triple-negative and/or *ASXL1*-mutated patients [24, 27]. However, until future validation occurs, the decision to perform alloSCT in these patients should be evaluated on an individual basis.

Given the risks associated with alloSCT and the advanced median age of patients with MF, most patients with high- or intermediate-risk MF are deemed transplant ineligible and are treated based on their clinical needs. Hydroxyurea is a nonalkylating antineoplastic agent that is commonly used for the control of leukocytosis and thrombocytosis but has limited efficacy on splenomegaly [33, 34]. Ruxolitinib is a JAK1/JAK2 inhibitor that has been approved for the treatment of MF-related splenomegaly and symptoms (with exact indications varying by country). Ruxolitinib showed superiority over placebo and standard therapy in patients with intermediate-2– and high-risk MF in the two pivotal phase 3 studies, Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment (COMFORT)-I and COMFORT-II [35, 36]. In these studies, ruxolitinib led to rapid and durable reductions in splenomegaly and symptom burden, with improvements in quality of life and OS [35–39].

Interferon alpha (IFN) has been used to treat MF; however, its efficacy is limited, and its use is often associated with intolerable adverse events, including flu-like symptoms, neuropsychiatric symptoms, and autoimmune problems [40].

Early-stage MF as a clinical mimicker for other entities

The clinical picture and prognosis of prefibrotic or early MF can overlap with those of lower-risk overt MF. For this reason, the identification of patients with early-stage MF requires careful integration of clinical, pathological, and molecular data. Even though a precise diagnostic dissection is clearly desirable, both aforementioned scenarios (i.e., prefibrotic MF and lower-risk overt MF) are characterized by a potential prodromal stage and a more advanced common disease phase. In these cases, the best clinical management and prediction of progression to high-risk overt MF are still imprecise.

Prefibrotic or early PMF according to 2017 WHO criteria

The 2017 World Health Organization (WHO) criteria introduced early PMF (i.e., prefibrotic PMF) as a separate clinical and histological entity, distinct from overt MF [1], and defined the criteria for its diagnosis (Table 2). On morphological grounds, it is defined by increased cellularity in relation to age due to granulopoietic and megakaryocytic proliferation, along with precursors' excess of the former and atypia of the latter, with peculiar bulbous-shaped nuclei and frequent formation of clusters. It may be accompanied by mild increase in reticulin fibers defined as grade 0 or 1 on a scale of 0 to 3 according to the European Consensus [41]. Conversely, fibrosis of grade 2 or 3 defines patients with overt MF. The lack of fibrosis in the early phases as well as a clinical onset sometimes characterized by isolated thrombocytosis can lead to prefibrotic MF being misdiagnosed as ET, which may have prognostic implications [42]. Given that bone marrow histology shows different morphological pictures among the different categories of Philadelphia chromosome–negative myeloproliferative neoplasms, its role is crucial in diagnosing MF [1, 42]. In particular, ET differs from PMF in that cellularity is usually preserved, granulopoiesis and erythropoiesis are in regular ratio and not expanded, and megakaryocytes, although significantly increased, show no or only mild atypia, with mature hyperlobulated nuclei.

Patients with MF at lower risk per IPSS

At diagnosis, approximately 50% of patients with PMF are in the lower-risk categories (low risk, 22%; intermediate-1 risk,

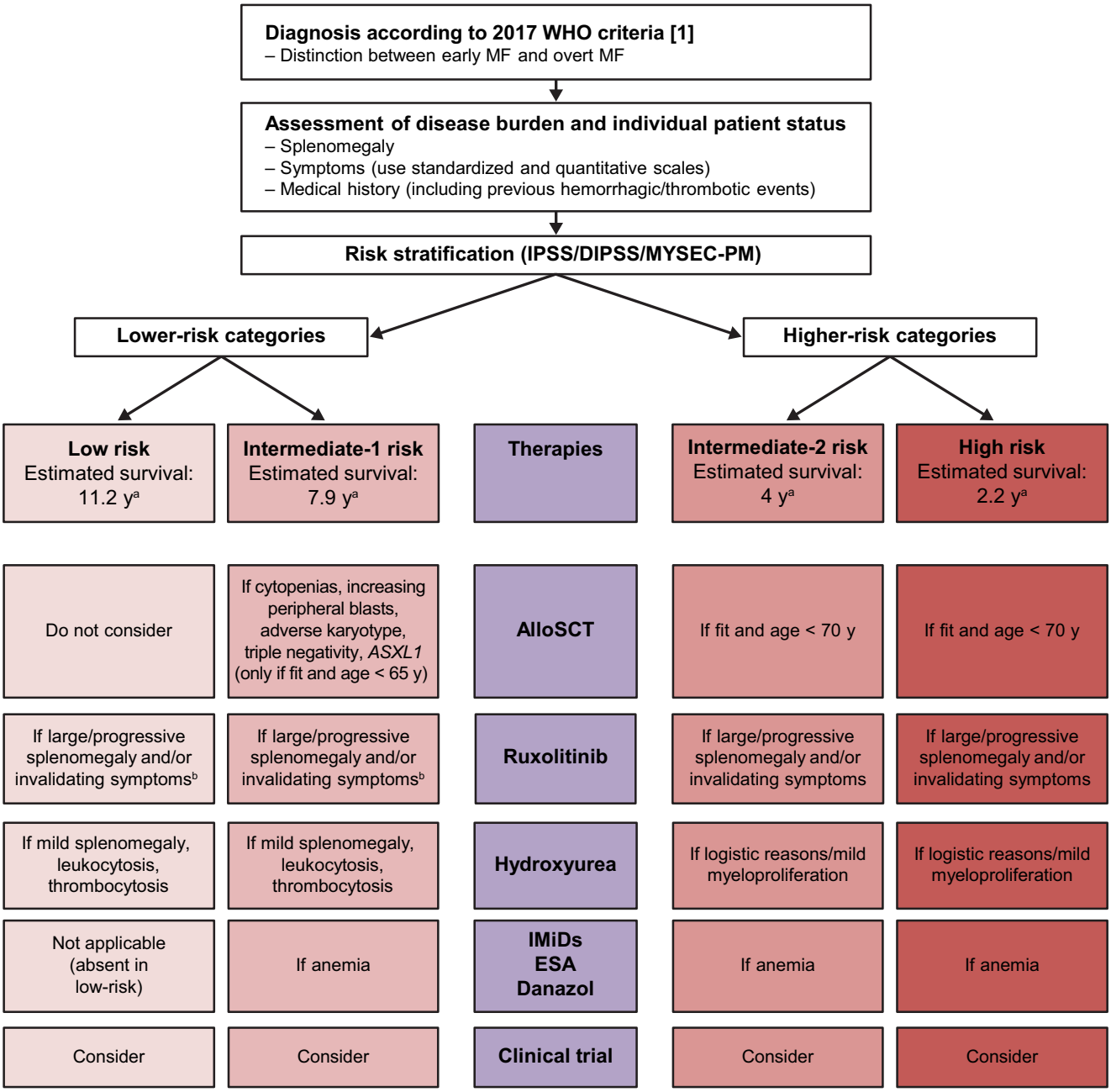


Fig. 1 Risk-adapted approach in myelofibrosis [24–26]. alloSCT, allogeneic hematopoietic stem cell transplant; *ASXL1*, additional sex combs-like 1; DIPSS, Dynamic International Prognostic Scoring System; ESA, erythropoiesis stimulating agent; IMiD, immunomodulatory drugs; IPSS, International Prognostic Scoring System; MF, myelofibrosis; MYSEC-PM, Myelofibrosis Secondary to PV and ET-Prognostic Model; WHO, World Health Organization. [a]Survival estimates are according to the IPSS. [b]Hydroxyurea is recommended as first-line therapy by the European LeukemiaNet in these patients. Ruxolitinib is recommended in those patients with splenomegaly not responding or intolerant to hydroxyurea [24]

29%) according to the IPSS score [3]. When the MYSEC-PM in PPV/PET-MF is used, approximately 60% of patients are found to be in the lower-risk categories (low risk, 19%; intermediate-1 risk, 40%) [43]. These patients are projected to have a median survival > 5 years and therefore are generally considered not eligible for alloSCT. Also, patients with lower-risk MF are usually less symptomatic and have a smaller spleen size than those with higher-risk MF [44]. Overall, these patients are generally considered to be affected by an early-stage MF.

Triggers for early treatment

To date, no specific guideline has been developed—on, for example, the basis of adverse prognostic features—to allow

Table 2 World Health Organization criteria for prefibrotic or early-stage primary myelofibrosis [1]

The diagnosis of prefibrotic or early-stage primary myelofibrosis requires that all three major criteria and at least one minor criterion are met

Major criteria

1. Megakaryocytic proliferation and atypia, without reticulin fibrosis grade > 1, accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and (often) decreased erythropoiesis
2. World Health Organization criteria for *BCR-ABL*–positive chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, myelodysplastic syndromes, or other myeloid neoplasms are not met
3. *JAK2*, *CALR*, or *MPL* mutation or presence of another clonal marker[a] or absence of minor reactive bone marrow reticulin fibrosis[b]

Minor criteria

Presence of at least one of the following, confirmed in two consecutive determinations:

- Anemia not attributed to a comorbid condition
- Leukocytosis $\geq 11 \times 10^9$/L
- Palpable splenomegaly
- Lactate dehydrogenase level above the upper limit of the institutional reference range

[a] In the absence of any of the three major clonal mutations, a search for other mutations associated with myeloid neoplasms (e.g., *ASXL1*, *EZH2*, *TET2*, *IDH1*, *IDH2*, *SRSF2*, and *SF3B1* mutations) may be of help in determining the clonal nature of the disease

[b] Minor (grade 1) reticulin fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or another lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies

identification of patients with early-stage MF who have inadequately controlled disease or who should receive a more personalized or preemptive therapeutic approach. Here, we describe some special situations that may identify patients in need of earlier therapy.

Presence of subclonal mutations

Mutations in any one of the five high-risk genes (*EZH2*, *ASXL1*, *IDH1*, *IDH2*, and *SRSF2*) may be detected in 21.1% and 23.4% of patients with low- and intermediate-1–risk PMF, respectively; having mutations in any of these genes is associated with reduced survival and increased risk of blast transformation compared with having no mutations in these genes [23] (Fig. 2). Furthermore, carrying two or more HMR mutations predicted a worse survival compared with having one or no HMR mutation (2.6 years [hazard ratio {HR}, 3.8 {95% CI, 2.6–5.7}] vs 7.0 years [HR, 1.9 {95% CI, 1.4–2.6}] vs 12.3 years). The presence of two or more mutations was also associated with shortened leukemia-free survival (HR, 6.2 [95% CI, 3.5–10.7]) [45]. Based on these observations, patients with IPSS low- or intermediate-1–risk PMF with HMR mutations, especially mutations in *ASXL1* and *SRSF2* (and possibly only patients with *SRSF2*- or *ASXL1*-mutated PPV- and PET-MF) [46, 47], should ideally receive earlier intervention with treatments able to prevent or delay disease progression or leukemic transformation and potentially improve their survival (Fig. 3).

Disease burden

Recently, the US-based MPN Landmark survey investigated perceptions of disease burden (and treatment management), including overall disease burden, quality of life, activities of daily living, and work productivity in 813 respondents with MPNs (MF, $n = 207$). The study showed that patients with DIPSS lower-risk MF are moderately to highly symptomatic in 44% of the cases, and that the reduction of quality of life and social/working activity was similar in low- and high-risk categories. An increased total symptom score (TSS) was also significantly associated with larger spleen size (> 10 cm: mean TSS, 25.2 vs 30.0, $P = .02$; > 15 cm: 25.5 vs 32.9, $P = .004$) [48]. Analogously, the global MPN Landmark survey completed by 699 patients with MPN (MF, $n = 174$) showed that 83% of patients with MF complained of a reduction in quality of life due to MPN-related symptoms and 41.1% also reported overall impairment at work [49].

Taken together, these studies indicate that disease burden may also be severe in patients in lower-risk categories, and these patients would likely benefit from symptom-based treatment. A cutoff criterion of the worst single symptom being > 5 (of 10) using the MPN10 score has been suggested for predicting increased DIPSS risk score and for identifying patients who will most benefit from symptom-based treatment. Additionally, ruxolitinib was strongly recommended for treating MF-associated splenomegaly in highly symptomatic patients with intermediate-1–risk disease by the ELN guidelines [24]. We, however, believe that the determination of disease burden that warrants treatment with ruxolitinib should also be supported by an individual assessment.

Rationale for earlier treatment in MF

Although patients with lower-risk MF are generally monitored with a watch-and-wait approach, the observations listed below suggest considering rethinking treatment strategy, at least in symptomatic patients.

MF is a progressive disease

Given the progressive nature of MF, a significantly higher percentage of patients have anemia in the year following their MF diagnosis than at the time of their MF diagnosis (58% vs

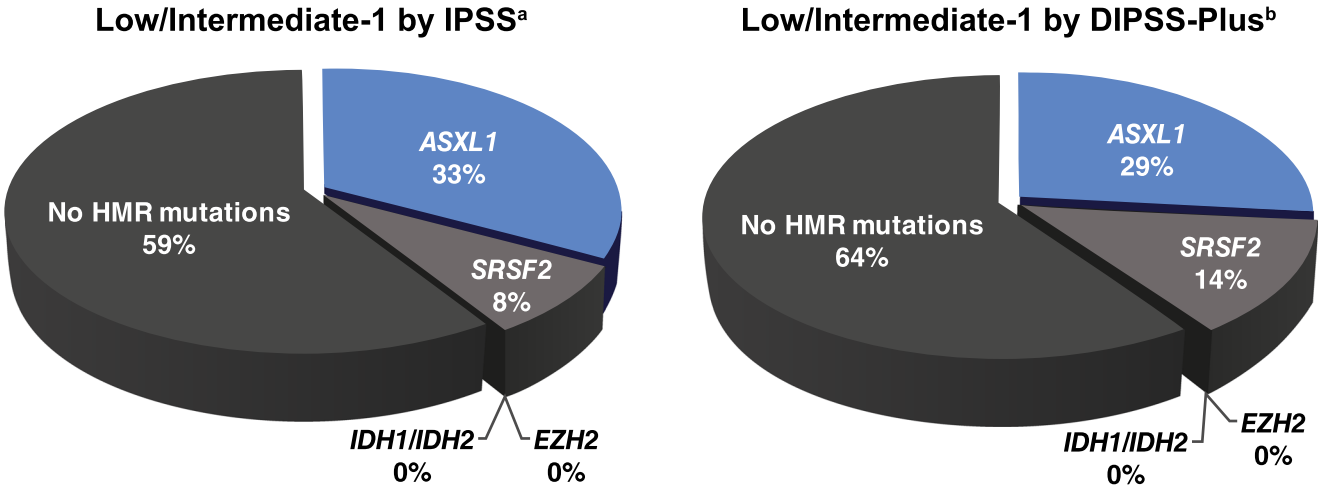


Fig. 2 Frequency of high molecular risk mutations in patients with low- or intermediate-1–risk myelofibrosis [23]. *ASXL1*, additional sex combs-like 1, DIPSS, Dynamic International Prognostic Scoring System; *EZH2*, enhancer of zeste homolog 2; HMR, high molecular risk; *IDH1*/*IDH2*, isocitrate dehydrogenase 1/isocitrate dehydrogenase 2; IPSS, International Prognostic Scoring System; MF, myelofibrosis; *SRSF2*, serine–arginine-rich splicing factor 2. [a]Mutations were analyzed in 68 patients with MF in chronic phase. Overall, 12 patients were considered to have low or intermediate-1 risk by IPSS. *ASXL1* and *SRSF2* mutations were identified in 33.3% (4/12) and 8.3% (1/12) of patients. [b]Mutations were analyzed in 68 patients with MF in chronic phase. Overall, 14 patients were considered to have low or intermediate-1 risk by DIPSS-Plus. *ASXL1* and *SRSF2* mutations were identified in 28.6% (4/14) and 14.3% (2/14) of patients. One patient had two mutations

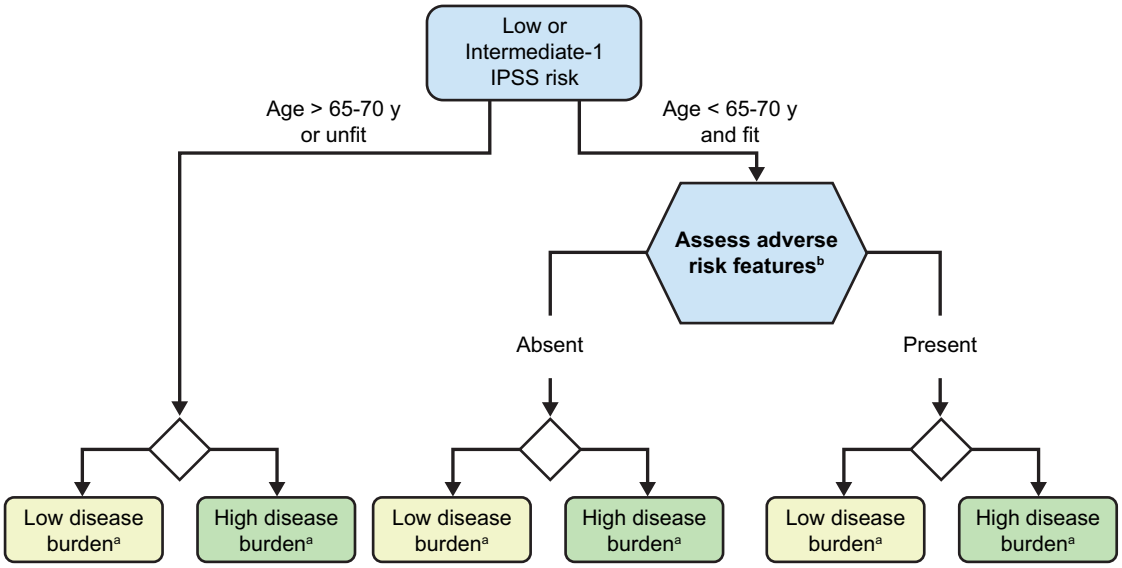
38%); this is also true of thrombocytopenia (28% vs 18%), circulating blasts (54% vs 45%), transfusion requirement (46% vs 24%), constitutional symptoms (38% vs 29%), splenomegaly > 10 cm (46% vs 22%), and an unfavorable karyotype (18% vs 13%) [50]. According to the WHO 2017 criteria, patients with overt PMF (vs prefibrotic PMF) were more frequently classified as being at higher risk (48.0%), with 44.4% of patients having HMR mutations (two or more mutations, 13.6%) [51]. Median survival was significantly longer in patients with prefibrotic PMF (14.7 years vs 7.2 years; $P < .0001$). HMR status was prognostic for survival in both patients with prefibrotic PMF (HR, 1.8 [95% CI, 1.1–3.0]; $P = .03$) and those with overt PMF (HR, 2.5 [95% CI, 1.8–3.4]; $P < .0001$), as was the presence of two or more HMR mutations (HR, 9.3 [95% CI, 4.5–19.0] and 3.4 [95% CI, 2.1–5.3], respectively; $P < .0001$).

Ruxolitinib treatment is associated with survival benefits in MF

Analyses of the COMFORT studies have shown that ruxolitinib is associated with survival benefits in patients with intermediate-2– and high-risk MF. In a 5-year follow-up analysis of COMFORT-II, there was a 33% reduction in the risk of death in patients randomized to ruxolitinib compared with that in patients treated with conventional therapy (HR, 0.67 [95% CI, 0.44–1.02]; $P = .06$), with a crossover-corrected HR of 0.44 (95% CI, 0.18–1.04; $P = .06$) [52]. In the 5-year follow-up analysis of COMFORT-I, patients in the ruxolitinib group had prolonged OS compared with patients in the placebo group (median OS: ruxolitinib group, not reached; placebo group, 200 weeks; HR, 0.69 [95% CI, 0.50–0.96]; $P = .025$), and patient risk of death was reduced by approximately 30% in the ruxolitinib group compared with that in the placebo group [53]. In pooled analysis data of the COMFORT-I and COMFORT-II studies, the risk of death was reduced by 30% in patients randomized to ruxolitinib compared with that in patients in the control group (median OS: ruxolitinib, 5.3 years [95% CI, 4.7-NE]; control, 3.8 years [95% CI, 3.2–4.6]) [54]. Despite the survival advantage observed with ruxolitinib in patients with higher-risk disease, the crossover design of the phase 3 COMFORT studies prevents a definitive demonstration of a survival benefit. Therefore, the ELN does not currently recommend ruxolitinib solely for prolonging survival [24, 39]. Notably, upon treatment with ruxolitinib, median OS in patients with high-risk MF was comparable to that seen in patients with intermediate-2–risk disease in the control arms [55, 56]. Survival from the time of diagnosis was also improved in patients from COMFORT-II who had received ruxolitinib compared with that in a cohort of comparable patients categorized using DIPSS who had received only standard therapy (HR, 0.61 [95% CI, 0.41–0.91]; $P = .0148$) [57]. This suggests that earlier treatment with ruxolitinib positively impacts survival and, conversely, that delayed switching to ruxolitinib has a negative impact. However, any survival advantage in patients with lower-risk disease remains to be seen.

Ruxolitinib treatment is more effective in patients with lower burden of the disease

In a post hoc analysis of COMFORT-I, patients who initiated ruxolitinib therapy with less-advanced MF achieved a better



Observation	Yes		Yes	Yes, after thorough discussion with pt	
Hydroxyurea	Yes		Yes		Yes
Interferon	Yes		Yes		Yes
Ruxolitinib	Yes		Yes		Yes
Clinical trial	If available	If available	If available	If available	If available
AlloSCT				Consider in Int-1 after thorough discussion with pt; otherwise, strict follow-up, consider if progression	Consider in Int-1

Fig. 3 Integrated treatment algorithm for patients with low- or intermediate-1–risk myelofibrosis. alloSCT, allogeneic hematopoietic stem cell transplant; Int-1, intermediate-1 risk; IPSS, International Prognostic Scoring System; pt, patient; *SRSF2*, serine–arginine-rich splicing factor 2. [a]Disease burden includes symptoms, splenomegaly, and previous vascular events. [b]Includes anemia, increasing peripheral blood blast count, triple negativity, high molecular risk status (and possibly *SRSF2* status in patients with post–polycythemia vera and post–essential thrombocythemia myelofibrosis), and adverse cytogenetics

clinical status than patients with more-advanced disease, as determined by lower absolute spleen size and symptom severity [58]. This analysis suggests that initiation of ruxolitinib in patients with less-severe splenomegaly and symptoms may contribute to improved patient outcomes, including prolonged survival, as confirmed by a pooled analysis of the COMFORT-I and COMFORT-II studies [56].

A recent retrospective study ($N = 408$) assessing predictors of response to ruxolitinib in a "real-world" setting found that disease severity and a delay in initiation of ruxolitinib therapy led to poorer outcomes [59]. Spleen length ≥ 10 cm, delaying ruxolitinib initiation by ≥ 2 years from MF diagnosis, and IPSS intermediate-2– or high-risk disease negatively correlated with spleen response, whereas a baseline total symptom score > 20 negatively correlated with symptom response. These findings suggested that treating patients with ruxolitinib at an earlier stage of their disease leads to better patient outcomes and possibly a survival advantage.

Medical treatment may reduce mutation load and marrow fibrosis

In the 5-year follow-up analysis of COMFORT-II, approximately one-third of evaluable patients had a > 20% reduction from baseline in absolute allele burden, and ≥ 75% of patients had no increase in allele burden (however, sequential

Table 3 Ruxolitinib in intermediate-1–risk vs intermediate-2–/high-risk myelofibrosis

Clinical trial	Spleen response at week 24, %	Incidence of grade 3/4 anemia, %	Incidence of grade 3/4 thrombocytopenia, %	Incidence of infections, %	Discontinuation rate, %
COMFORT-I ($n = 155$) [35, 53, 77]	41.9	45	13	≈ 50	21
COMFORT-II ($n = 146$) [36, 63]	32	42	8	≈ 50	38
JUMP (intermediate-1–risk patient subgroup) ($n = 163$) [66]	56.9	24.5	11	40	19.6
Palandri F, et al. ($n = 70$) [68]	54.7	21.7	2.9	17.1	17.1

COMFORT-I Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment-1, *COMFORT-II* Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment-II, *JUMP* JAK Inhibitor Ruxolitinib in Myelofibrosis Patients

information on mutation load in non–ruxolitinib randomized patients was not provided). Additionally, patients with less-severe disease and shorter disease duration had greater allele burden reductions, suggesting that patients may benefit from receiving earlier treatment. However, it remains unclear whether, and to what extent, an allele burden reduction correlates with patient benefit.

Ruxolitinib also led to stabilization or improvement in bone marrow morphology in patients with MF [60, 61], with some studies reporting resolution of fibrosis [62, 63]. Compared with an independent cohort of patients who received best available therapy (BAT), higher proportions of patients who received ruxolitinib in study 251 had improvement or stabilization in their bone marrow fibrosis grade after 4 years of treatment (improvement, 24% vs 2%; stabilization, 50% vs 46%, respectively) [61]. Patients who received BAT were more likely to have worsened fibrosis after 4 years than patients who received ruxolitinib (BAT, 75%; ruxolitinib, 31%; odds ratio, 0.16 [95% CI, 0.06–0.46]) of treatment. Similarly, improvements in fibrosis were also observed with long-term ruxolitinib treatment in COMFORT-II [63].

Data concerning use of ruxolitinib in early-stage MF

In the phase 2 UK ROBUST study ($N = 48$), similar improvements in splenomegaly and symptoms were observed across risk groups, including in patients with intermediate-1–risk disease ($n = 14$) [64]. At week 48, 50% of all patients and 57% of patients with intermediate-1 risk achieved a ≥ 50% reduction in palpable spleen length and/or a ≥ 50% decrease in the MF-SAF TSS, with no significant difference between risk groups ($P = .599$). All patients with intermediate-1–risk MF showed a reduction in spleen length at the last available visit.

The global JAK Inhibitor Ruxolitinib in Myelofibrosis Patients (JUMP) study also showed reductions in spleen length and symptom burden in patients with DIPSS low−/intermediate-1– ($n = 893$), intermediate-2– ($n = 754$), and high-risk ($n = 193$) MF who received ruxolitinib [65]. DIPSS status was determined in 1840 of 2233 enrolled patients who started treatment ≥ 1 year before the data cutoff. Overall, 68.2% of patients experienced a ≥ 50% reduction from baseline in palpable spleen length at any time by week 72. Most patients (74.8%) who achieved a ≥ 50% reduction in spleen length at any time were in the low−/intermediate-1–risk group, followed by 63.1% of patients in the intermediate-2–risk group and 57% of patients in the high-risk group [65]. Additionally, ruxolitinib led to symptom improvement, with approximately 40% to 54% of patients experiencing improvements at each time point, as assessed using the Functional Assessment of Cancer Therapy Lymphoma total score. Importantly, the safety profile of ruxolitinib in patients with intermediate-1–risk MF was consistent with that seen in patients with higher-risk MF in the JUMP [65, 66] and COMFORT studies [35, 36].

A retrospective review of medical records conducted in the USA demonstrated that patients with low- ($n = 25$) or intermediate-1–risk ($n = 83$) MF experienced improvements in splenomegaly and symptoms with ruxolitinib treatment [67]. Overall, 68% of patients with low-risk MF had a decrease in spleen size from initiation of ruxolitinib treatment to best response; 55% of patients with intermediate-1 risk had a corresponding response.

A recent retrospective analysis of data from 71 patients with intermediate-1–risk MF treated with ruxolitinib in routine clinical practice showed that the rates of spleen and symptom response were 54.7% and 80% in 64 and 65 evaluable patients, respectively, at 24 weeks. More importantly, the study reported the incidence of adverse events related to ruxolitinib administration. At 12 weeks, ruxolitinib-induced grade 3 anemia and thrombocytopenia occurred in 40.6% and 2.9% of evaluable patients, respectively, with 11 patients (15.9%) experiencing at least one infectious event ≥ grade 2. Notably, most patients (82.6%) were still on therapy after a median follow-up of 27 months [68].

Findings from these studies suggest that patients with lower-risk MF derive clinical benefit from treatment and that ruxolitinib may be an effective treatment option for these patients without unexpected early toxicities. However, more long-term follow-up is necessary, given that infections [69, 70] and nonmelanoma skin cancer [71, 72] have been observed in some patients treated with ruxolitinib.

Data concerning use of IFN in early-stage MF

IFN may be effective in patients with early-stage MF who have no or minimal splenomegaly (Fig. 3) [73–75]. IFN has also been shown to result in improved bone marrow morphology in patients with early-stage MF [11, 75]. However, little improvement in the fibrosis grade was observed in six patients who initiated treatment with IFN during early transformation to secondary MF [76]. Despite the lack of improvement in bone marrow fibrosis in these patients, IFN led to improved hemoglobin levels and reduced splenomegaly after an initial increase in spleen size, suggesting some efficacy in patients with early transformation to secondary MF. However, these findings were from small studies, some of which were retrospective, and do not allow for definitive conclusions on the use of IFN for the treatment of early-stage MF.

Balancing the pros and cons of early treatment

Patients treated in the early phases of MF are projected to have a longer survival than those in higher-risk categories and are therefore likely to receive treatment for longer. The potential for an increased risk of long-term toxicity should therefore be taken into account when long-lasting drug administration is expected. Overall, the safety profile of ruxolitinib in patients with early-stage MF [64, 65, 67, 68] was consistent with that seen in patients in the COMFORT studies [35, 36], with anemia and thrombocytopenia being the most common adverse events (even if apparently less frequent in ruxolitinib-treated patients with IPSS intermediate-1–risk MF than in those with intermediate-2- or high-risk MF). In addition, the rates of nonhematologic adverse events were similar to those seen in the phase 3 studies, with no reports of herpes zoster, hepatitis B, or tuberculosis [64, 65, 67, 68]. Of note, patients in the randomized studies all had IPSS high- and intermediate-2–risk MF and significant splenomegaly, possibly the two main risk factors for infections in patients with MF [69].

Overall, rates of adverse events in lower-risk patients were similar to those in higher-risk patients, and in some cases lower, suggesting that earlier use of ruxolitinib does not increase short-term toxicity in patients with MF (Table 3). It is, however, important to mention that follow-up of ruxolitinib-treated patients with lower-risk MF is still relatively short. This is of particular relevance in the evaluation of events that may be associated with longer treatment exposure, such as second cancers.

Conclusions

The incorporation of ruxolitinib into routine clinical practice has transformed the treatment landscape and outlook for many patients with MF. However, questions remain regarding its use in patients with early-stage MF. Several studies conducted in patients with lower-risk MF suggest that ruxolitinib could benefit patients in earlier phases of the disease. Additionally, current findings suggest that ruxolitinib treatment may also lead to improvements in morphology, possibly leading to delayed progression in these patients. However, no studies evaluating ruxolitinib vs a watch-and-wait strategy have been conducted, and future studies will be needed to determine whether drug-based therapy is appropriate in patients with early-stage MF. Findings from randomized studies will be crucial in shaping and validating the treatment strategy for patients with MF, including those with early phases of the disease.

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Compliance with ethical standards

Conflicts of interest Francesca Palandri has received an honorarium from Novartis; Elena Sabattini has received honoraria from Novartis for educational events. Margherita Maffioli has no conflict of interest.

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