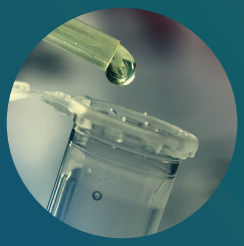

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# Management Strategies in Early Myelofibrosis

## Introduction

Myelofibrosis (MF) is a chronic myeloproliferative neoplasm (MPN), characterized by ineffective clonal hematopoiesis, splenomegaly, worsening bone marrow fibrosis, cytopenias, and transformation to acute myeloid leukemia. It is associated with debilitating and diverse clinical symptoms and shortened survival.[1,2] One-third of the patients are initially asymptomatic; however, constitutional symptoms, and symptoms associated with anemia or splenomegaly are common among the MF patients.[3]

The disease can be classified into primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), and post-essential thrombocythemia myelofibrosis (PET-MF). The management strategies for all the disease categories remain the same.[4]

### *Pathogenesis of MF*

- MF pathogenesis begins with the activation and expansion of stroma that results from the pathologic interactions between hematopoietic progenitor cells and stromal cells. Mesenchymal stem cells produce reticulin and collagen fibers which accumulate and further help in MF pathogenesis. The disease progression involves megakaryocytic over-expression which results from activation of Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway.[5,6]
- Although the exact mechanism is not fully known, several cytokines are secreted from megakaryocytes and are responsible for the abnormal proliferation of fibroblasts, leading to MF. These cytokines include transforming growth factor-beta (TGF-β), basic fibroblast growth factor (bFGF), platelets-derived growth factor (PDGF), and interleukins such as interleukin-1 (IL-1).[7]

### *Mutations associated with MF*

Increasing evidence shows that phenotypic driver mutations are associated with MF.[2] These include:
- mutations in Janus kinase 2 (*JAK2)*
- exon 9 of the calreticulin (*CALR*) gene and
- myeloproliferative leukemia virus (*MPL*) gene

In addition to these driver mutations, mutations in *ASXL1, EZH2, SRSF2, and IDH1/2* are also found in some MF patients. These mutations put them in

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the High Molecular Risk (HMR) category, which is associated with poor prognosis.[8]

Understanding more about mutations and the clinical application of such findings is crucial in the treatment of MF. Though disease monitoring or management is independent of genetic mutations, considering them can be useful in disease analysis.[9]

MF is a result of both genetic mutation and chronic inflammation, however, the exact mechanism is still unclear. As MF is marked by a disruption of the cytokine network balance, cytokine-mediated therapy is being explored in the treatment of MF.[10]

## Risk Classification

### *Different prognostic tools for MF assessment*

The treatment of MF is largely determined by the risk for each patient. Several prognostic scoring systems are available for patients with MF. These include:

- The International Prognostic Scoring System (IPSS)[11]
- The Dynamic IPSS (DIPSS)[12]
- The DIPSS-Plus[13]
- Mutation-enhanced IPSS (MIPSS-70),[14] and MIPSS-70+ version 2.0[15,16]
- Genetically Inspired Prognostic Scoring System (GIPSS)[16]
- Myelofibrosis secondary to polycythemia vera (PV) and essential thrombocythemia (ET) - Prognostic Model (MYSEC-PM)[17]

Several clinical features are considered

*Table 1: Different prognostic tools of myelofibrosis[11-17]*

| Scoring System | Prognostic variable | Points | | | Risk group | Points | Median survival (years) |
|---|---|---|---|---|---|---|---|
| Primary Myelofibrosis (PMF) | | | | | | | |
| IPSS | Age > 65 years | 1 | | | Low<br>Intermediate-1<br>Intermediate-2<br>High | 0<br>1<br>2<br>>3 | 11<br>8<br>4<br>2 |
| | Hemoglobin < 10 g/dL | 1 | | | | | |
| | White Blood Cell count > 25 × $10^9$/L | 1 | | | | | |
| | Circulating blasts > 1% | 1 | | | | | |
| | Constitutional symptoms | 1 | | | | | |
| DIPSS | | **0** | **1** | **2** | Low<br>Intermediate-1 (INT-1)<br>Intermediate-2 (INT-2)<br>High | 0<br>1 or 2<br>3 or 4<br>5 or 6 | 15<br>6.5<br>3<br>1 |
| | Age, (Years) | ≤65 | >65 | - | | | |
| | White blood cell count, x$10^9$/L | ≤25 | >25 | - | | | |
| | Hemoglobin, g/dL | ≥10 | | <10 | | | |
| | Peripheral blood blast, % | <1 | ≥1 | - | | | |
| | Constitutional symptoms, Y/N | N | Y | - | | | |
| DIPSS-PLUS | DIPSS low-risk | 0 | | | Low<br>Intermediate-1 (INT-1)<br>Intermediate-2 (INT-2)<br>High | 0<br>1<br>2 or 3<br>4 to 6 | Not reached<br>14<br>4<br>1.5 |
| | DIPSS intermediate-risk 1 (INT-1) | 1 | | | | | |
| | DIPSS intermediate-risk 2 (INT-2) | 2 | | | | | |
| | DIPSS high-risk | 3 | | | | | |
| | Platelets <100 x $10^9$/L | 1 | | | | | |
| | Transfusion need | 1 | | | | | |
| | Unfavorable karyotype[a] | 1 | | | | | |
| MIPSS-70 | Hemoglobin <10 g/dL | 1 | | | Low<br>Intermediate<br>High | 0-1<br>2-4<br>≥5 | 27.7<br>7.1<br>2.3 |
| | Leukocytes >25 x $10^9$/L | 2 | | | | | |
| | Platelets <100 x $10^9$/L | 2 | | | | | |
| | Circulating blasts ≥2% | 1 | | | | | |
| | Bone marrow fibrosis grade ≥2 | 1 | | | | | |
| | Constitutional symptoms | 1 | | | | | |
| | CALR type-1 unmutated genotype | 1 | | | | | |
| | High-molecular risk (HMR) mutations[b] | 1 | | | | | |
| | ≥2 HMR mutations | 2 | | | | | |

*Table 1: Different prognostic tools of myelofibrosis[11-17] (continued)*

| Scoring System | Prognostic variable | Points | Risk group | Points | Median survival (years) |
|---|---|---|---|---|---|
| MIPSS-70+ version 2.0 | Severe anemia (Hemoglobin <8 g/dL in women and <9 g/dL in men) | 2 | Very low<br>Low<br>Intermediate<br>High<br>Very high | 0<br>1-2<br>3-4<br>5-8<br>≥9 | Not reached<br>16.4<br>7.7<br>4.1<br>1.8 |
| | Moderate anemia (Hemoglobin 8–9.9 g/dL in women and 9–10.9 g/dL in men) | 1 | | | |
| | Circulating blasts ≥2% | 1 | | | |
| | Constitutional symptoms | 2 | | | |
| | Absence of CALR type 1 mutation | 2 | | | |
| | HMR mutations[c] | 2 | | | |
| | ≥2 HMR mutations | 3 | | | |
| | Unfavorable karyotype[a] | 3 | | | |
| | Very-high-risk (VHR) karyotype[d] | 4 | | | |
| GIPSS | VHR karyotype[d] | 2 | Low<br>Intermediate 1 (INT-1)<br>Intermediate-2 (INT-2)<br>High | 0<br>1<br>2<br>≥3 | 26.4<br>8<br>4.2<br>2 |
| | Unfavorable karyotype[a] | 1 | | | |
| | CALR type 1 unmutated genotype | 1 | | | |
| | *ASXL1* mutation | 1 | | | |
| | *SRSF2* mutation | 1 | | | |
| | *U2AF1* Q157 mutation | 1 | | | |
| Post-PV and Post-ET Myelofibrosis | | | | | |
| MYSEC-PM | Age at diagnosis | 0.15 per patient's year of age | Low<br>Intermediate-1 (INT-1)<br>Intermediate-2 (INT-2)<br>High | <11<br>≥11<br>≥14 and <16<br>≥16 | Not reached<br>9.3<br>4.4<br>2 |
| | Hemoglobin <11 g/dL | 2 | | | |
| | Circulating blasts ≥3% | 2 | | | |
| | Absence of CALR type 1 mutation | 2 | | | |
| | Platelets <150 x $10^9$/L | 1 | | | |
| | Constitutional symptoms | 1 | | | |

[a]Unfavorable karyotype: complex karyotype or sole or two abnormalities that include trisomy 8, 7/7q-, i(17q), 5/5q-, 12p-, inv(3), or 11q23 rearrangement.
[b]Presence of a mutation in any of the following genes: *ASXL1, EZH2, SRSF2*, or *IDH1/2*.
[c]Presence of a mutation in any of the following genes: *ASXL1, EZH2, SRSF2, U2AF1* Q157, or *IDH1/2.*
[d]VHR karyotype: single/multiple abnormalities of –7, i(17q), inv(3)/3q21, 12p–/12p11.2, 11q–/11q23, or other autosomal trisomies not including +8/+9 (eg, +21, +19).

for the IPSS, DIPSS, and DIPSS-Plus scoring systems.

Additionally, DIPSS-Plus incorporates prognostic information considering cytogenetic abnormalities. MIPSS-70 and MIPSS-70+v2 consider clinical and genetic features, MIPSS-70+v2 has an additional cyotegentic factor. GIPSS and MYSECPM are genetically based tools which consider clinical, cytogenetic, and mutation analysis for the scoring of MF.

Table 1 represents different prognostic tools of MF with their respective scoring systems based on clinical features, risk categories (based on a patient's risk score, i.e., the sum of adverse points), and median survival (years).

## Management of Myelofibrosis

Currently, there is no single effective treatment for all MF patients. For the early stages of MF, the 'watch-and-wait' approach has been employed. MF patients may remain symptom-free for years without treatment.[2] Symptom-directed conventional therapy is considered reasonable in the treatment of intermediate and higher-risk MF patients who are not eligible for either allogeneic hematopoietic stem cell transplantation (allo-HSCT) or investigational drug therapy (Table 2).[11,15,18]

The driver mutation identification in JAK2, *CALR,* and *MPL* enables the scientists to recognize the activated JAK/STAT signaling as the hallmark abnormality in MF. Therefore, management of MF targets the therapeutic agents that inhibit the overactive JAK/STAT signaling

*Table 2: Symptom-directed conventional therapies*[11,15,18]

| Symptoms | Conventional Therapies |
|---|---|
| Anemia | Thalidomide, Danazol, Lenalidomide, blood transfusions, Erythropoiesis Stimulating Agents (ESAs) |
| Splenomegaly | Hydroxyurea, Interferon, radiation, splenectomy |
| Thrombosis | Low-dose Aspirin/ Hydroxyurea |
| Extramedullary hematopoiesis | Radiation therapy |

pathway and provide several clinical benefits including reduction of spleen size, symptomatic improvement, and better survival.[19] Additionally, new therapies are emerging which are clinically effective in the treatment of patients with a significant reduction in MF-induced symptoms.[18] Careful integration of clinical, pathological, and molecular data is very important for the appropriate diagnosis of patients with early MF, since the clinical picture and prognosis of early MF and lower-risk overt MF can overlap. Individualized treatment options may reduce the progression of the disease and alleviate the symptoms in early MF. Effective treatment of anemia and thrombocytopenia is the most challenging part.[2]

## Treatment and Recommendations for Management of MF

*Dr. Gill Harinder Singh Harry MBBS, MD, FRCP (Edin, Glasg, Lond), FRCPath, FHKCP, FHKAM (Medicine) Clinical Assistant Professor, Department of Medicine, The University of Hong Kong*

The major goals of treatment in MF comprise symptom control, spleen size reduction, prevention of disease progression, improving quality of life, and overall survival.[20,21]
The therapeutic approach is based on risk stratification models, patient symptoms, and the patient's clinical needs.[22,21] Allo-HSCT is a potentially curative option for patients with MF.[23,21] Assessment of symptoms in MF patients is generally recommended and is primarily based on Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS).[21] It is performed at baseline and during treatment to assess the common symptoms such as fatigue, poor concentration, early satiety, inactivity, pruritis, bone pain, abdominal discomfort, fever, weight loss, and night sweats.[24,21]
• Observation alone is suggested for both low or intermediate-1 risk MF patients without symptoms,[22] while ruxolitinib is recommended for symptomatic patients.
• Allo-HSCT is recommended for all intermediate-2 or high-risk MF patients.
• Other therapeutic options for cytoreduction include hydroxyurea and interferon alpha (IFNα) preparations.

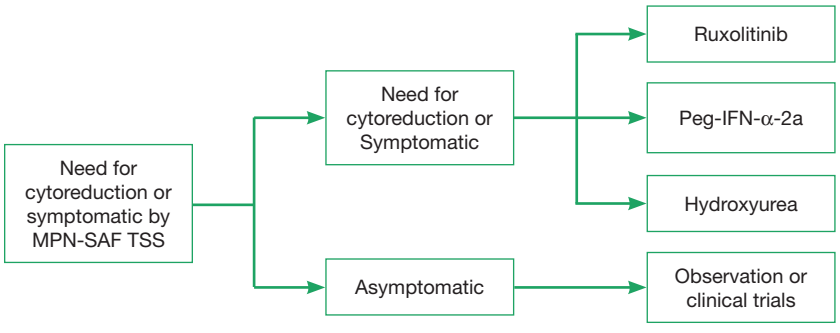
### Recommendations on the management of MF

The IPSS, DIPSS, and DIPSS-Plus remain the most adopted prognostic scoring systems for MF in Asian institutions, as next-generation sequencing (NGS) used for the evaluation of HMR mutations is not widely available. Nevertheless, risk stratification based on molecular markers may help in accurately defining the indications of allo-HSCT in eligible patients.

• DIPSS-plus should be used for treatment decision-making.
• If NGS is available, MIPSS-70+ version 2.0 and the GIPSS are preferred, especially when considering allo-HSCT.
• Symptom burden should be routinely assessed in all patients regularly using the MPN-SAF TSS or other validated quality of life or functional assessment tools.

Figures (1–5) summarize the suggested treatment algorithms based on the conventional and molecularly-inspired prognostic models.
• According to the IPSS, DIPSS, or DIPSS-Plus, allo-HSCT is not recommended in low-/ intermediate-1-risk patients. Nevertheless, the use of molecular markers (e.g. *ASXL1, SRSF2, EZH2, IDH1, IDH2,* and *U2AF1*)[25] in this category may help identify patients who may benefit from allo-HSCT.

*Figure 1. Treatment algorithm for low-risk MF based on IPSS/DIPSS/DIPSS-Plus*




* MPN-SAF TSS: Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score, Peg-IFN: Pegylated Interferon

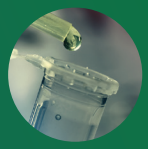
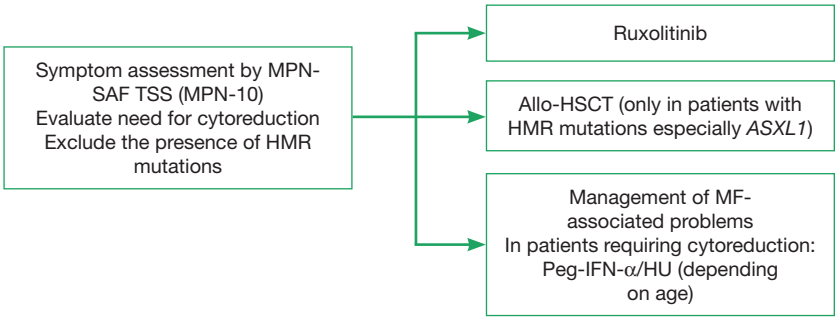
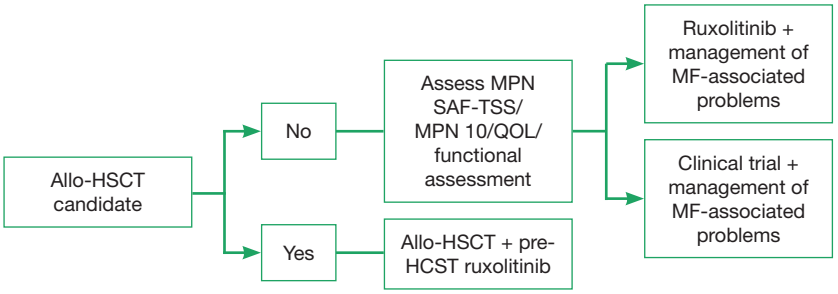


*Figure 2. Treatment algorithm for intermediate-1-risk MF based on IPSS/DIPSS/DIPSS-Plus*




* Allo-HSCT: allogeneic hematopoietic stem cell transplantation; ASXL1: additional sex combs like 1, transcriptional regulator; HMR: High Molecular Risk; HU: Hydroxyurea; MPN-SAF TSS: Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; Peg-IFN: Pegylated Interferon.

*Figure 3. Treatment algorithm for intermediate-2 or high-risk MF based on IPSS/DIPSS/DIPSS-Plus*




* MF: Myelofibrosis; MPN-SAF TSS: Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; QOL: Quality of Life; Allo-HSCT: allogeneic hematopoietic stem cell transplantation

• In advanced MF, a limited efficacy has been obtained with IFN-α preparations.Their use is limited to early MF with a low risk of symptom improvement.[26] Worsening of anemia and symptoms is observed with IFN-α due to intolerance in symptomatic patients with high-risk MF.
• Ruxolitinib is considered the first-line treatment in patients with symptomatic MF and splenomegaly. Its use before allo-HSCT may also improve patient performance status and control splenomegaly before transplantation.[2]
• Low-dose splenic irradiation is reserved as a palliative mean for transplant-ineligible patients who are unresponsive to ruxolitinib and when splenectomy is not feasible.
• Prognostic models (MIPSS-70+/ GIPSS) are preferred for allo-HSCT decisions if NGS is available. The management algorithms of the afore mentioned models are similar. The prognostication and consideration of allo-HSCT do not differ between PMF and secondary myelofibrosis (SMF).
• Transplantation is not recommended in low-/intermediate-risk MF patients.[2]
• Patients with prefibrotic PMF are treated with cytoreduction. In young patients with prefibrotic PMF, pegylated INF-α preparations should be considered given the disease-modifying effects and molecular responses that may be achieved.[26]

Nevertheless, prospective clinical trials are necessary to confirm whether pegylated INF-α preparations may alter the natural history of early/prefibrotic PMF. Specific attention should be paid to the prevention of vascular events in prefibrotic PMF. In prefibrotic PMF with thrombocytosis, the thrombo-hemorrhagic risk is similar to that in essential thrombocythaemia. As a result, cytoreduction and the use of antiplatelet agents are required to reduce the risk of vascular events.

## Early intervention in the Management of MF

### *Progressive disease*

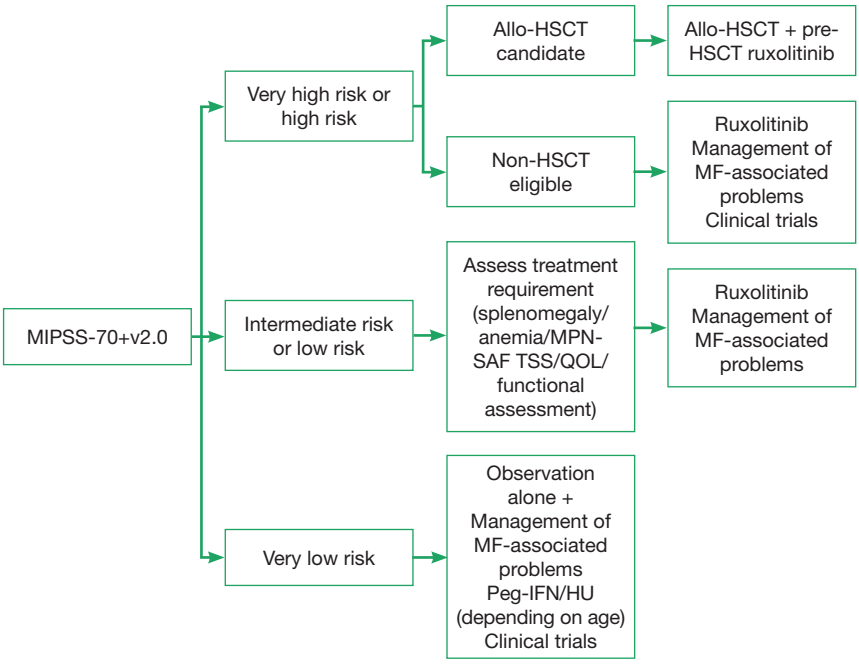
As MF is a progressive disease with a significant disease burden, the treatment strategy should evolve beyond the 'watch-and-wait' approach in lower-risk MF patients. The therapeutic approach should include some novel strategies to minimize the symptoms of the patient.[27]

Anemia, thrombocytopenia, circulating blasts, transfusion requirement, constitutional symptoms, splenomegaly >10 cm, and an unfavorable karyotype were found to increase significantly among patients in the year following their MF diagnosis than at the time of their MF diagnosis.[28] Expression of more pronounced disease symptoms, adverse mutation profile, and the worse outcome were revealed as grades of fibrosis increased in MF (Overt vs Pre PMF). Longer median survival was found in patients with prefibrotic PMF than in patients with overt PMF.[14,2] All these findings indicate the progressive nature of MF.

### *Disease burden*

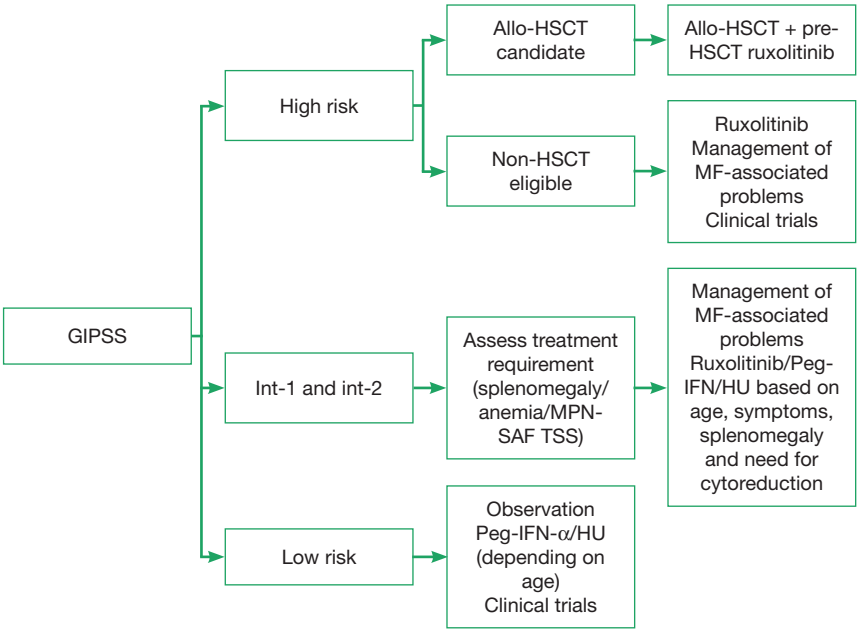
The perception of the disease burden of MF should consider assessing the quality of life, daily-life activities, and work productivity. The US-based MPN Landmark survey reported reductions in all three above-mentioned outcomes due to MPN-related symptoms even in respondents with low DIPSS risk scores (813 respondents with MPNs; MF, n=207). The study also showed an association between increased total symptom score (TSS) and larger spleen size.[29] Another parallel study based on the global MPN Landmark survey

*Figure 4. Treatment algorithm for MF based on MIPSS-70+ v2.0*




*Allo-HSCT: allogeneic hematopoietic stem cell transplantation; HU: Hydroxyurea; MF: Myelofibrosis; MPN-SAF TSS: Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; Peg-IFN: Pegylated Interferon; QOL: Quality of Life

*Figure 5. Treatment algorithm for MF based on GIPSS*




*Allo-HSCT: allogeneic hematopoietic stem cell transplantation; HU: Hydroxyurea ; MF: Myelofibrosis; MPN-SAF TSS: Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; Peg-IFN: Pegylated Interferon; QOL: Quality of Life

reported that while more than 80% of the patients complained about MPN-related symptoms-induced reduction in quality of life, overall impairment at work was found to be among 41.1% of the patients (699 patients with MPN; MF, n=174).[30]

### *Impact of sub-clonal mutation*

Effective early MF management and treatment using ruxolitinib largely depends on the sub-clonal mutation in genes, including *EZH2, ASXL1, IDH1, IDH2,* and *SRSF2.* Though ruxolitinib is a JAK1/JAK2 inhibitor, when treated with the same, patients respond regardless of their phenotypic driver mutation. Low- and intermediate-1-risk PMF is associated with mutations in more than 1/5$^{th}$ of the patients in any one of the five high-risk genes (*EZH2, ASXL1, IDH1, IDH2,* and *SRSF2*).[31] Association of no or one HMR mutation predicted better survival in comparison with two or more HMR mutations. Shortened leukemia-free survival was found among patients with two or more HMR mutations.[32] Moreover, early intervention and treatments are recommended in IPSS low- or intermediate-1-risk PMF patients with *ASXL1* and *SRSF2* mutation. It may be beneficial in delaying the progression of the disease or in preventing leukemic transformation and prospectively improving the survival of the patients.[25]

## Significance of Early Intervention

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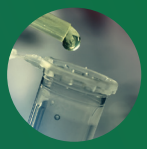
Early MF is a confusing term and needs a proper definition. It is clinically and prognostically heterogeneous.



Unfortunately, there is currently no consensus on the definition.

Currently, risk scores predict the survival of patients with MF but do not necessarily correlate with disease burden or stage of illness. What does early MF mean? Is it defined by the time of diagnosis, or prodrome of disease i.e. pre-MF as defined by WHO 2016? Does it mean a lack of clinical features such as splenomegaly and cytopenias? Or does it mean low-risk disease as assessed by risk stratification using the risk scores?

In low-risk symptomatic patients, the Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment (COMFORT) trials have shown that early treatment with ruxolitinib reduces spleen size and MF symptoms, such as fatigue, more effectively. Currently, data for other JAK2 inhibitors is still lacking in lower risk MF, but we will likely see more data in the coming years as the trial results are published.

There are arguments to be made for the treatment of early MF. It is a progressive disease with a high symptom burden even in the early stages. COMFORT trials and patients with larger spleens have worse survival and respond less well to ruxolitinib. Finally, ruxolitinib has been shown to prolong survival in intermediate-2/high-risk patients with MF, so the assumption is that it may prolong survival if used earlier. The counter-arguments are that there is a scarcity of conclusive data regarding disease modification with the use of ruxolitinib and the median response duration is about 3 years. The use of ruxolitinib also causes anemia and thrombocytopenia, and increased costs to the healthcare system.

We need to consider individualized treatments for patients with early MF. Each patient should be treated with their goals of care, improvement of symptoms, and quality of life. The prognosis is linked to MF risk scores, but there is also the burden of disease that the patient faces, such as splenomegaly, symptoms, and cytopenias. Therefore, treatment with a JAK2 inhibitor in low-risk but symptomatic MF patients should be considered.

On the other hand, in low-risk asymptomatic patients, there is a lack of understanding of the disease progression. We need to learn more and classify the heterogeneity of the disease and have a better understanding of why and how patients progress. Novel biomarkers can be used to monitor the disease progression. These MF biomarkers can direct the need for early treatment.

## Ruxolitinib in Early Management of MF

Ruxolitinib, a potent and selective oral inhibitor of both JAK2 and JAK1 protein kinases, was the first drug to be approved by the Food and Drug Administration (FDA) for PMF, PET-MF, and PPV-MF.

Ruxolitinib was found to be clinically effective in the alleviation of MF-associated symptoms,[33] improvements in quality of life,[34] and overall survival of the patients.[35] Stabilization of bone marrow morphology in patients with MF was also established followed by ruxolitinib treatment.[36]

## Efficacy of Ruxolitinib

Several studies investigated the efficacy of ruxolitinib in treating early MF. The findings of these studies suggest a reduction in palpable spleen length,[37,38] improvements in the MF-SAF TSS,[37] and reduction in the symptoms.[17] Additionally, the Functional Assessment of Cancer Therapy Lymphoma total score indicates symptom improvement followed by ruxolitinib treatment with a consistent safety profile in patients with intermediate-1-risk.[17,39]

### *Phase II UK ROBUST study[37]*

ROBUST, a UK-based, open-label, phase II study, evaluated the safety and efficacy of ruxolitinib in MF patients, including intermediate-1 risk patients (n=48). The composite endpoint of 'treatment success' was defined as a ≥50% reduction in palpable spleen length and/or a ≥50% improvement in symptom scores.

- Among patients with intermediate-1 (n=14), intermediate-2 (n=13), and high-risk (n=21) disease, 50%, 15%, and 48% respectively, achieved a reduction in spleen length ≥50% at week 48.
- Improvements in MF symptom assessment were seen in 80.0%, 72.7%, and 72.2% of intermediate-1, intermediate-2, and high-risk patients, respectively.

Clinical benefit from ruxolitinib treatment was established in the majority of patients, including patients classified as intermediate-1 risk and those without splenomegaly.

### *The global JAK Inhibitor Ruxolitinib in Myelofibrosis Patients (JUMP) study[39]*

JAK Inhibitor Ruxolitinib in Myelofibrosis Patients (JUMP) study is a large, single-arm, open-label, Phase 3b trial, including IPSS intermediate-1- (n=893), intermediate-2- (n=754), and high-risk (n=193) MF patients, who have been treated with ruxolitinib.

- At weeks 24 and 48, 56.9% and 62.3% of evaluable patients, respectively, achieved ≥50% reduction in palpable spleen length from baseline.

Approximately half of the patients experienced rapid and clinically significant improvements with consistent safety and efficacy profiles in intermediate-1-risk patients in comparison with the overall JUMP population and the previously reported intermediate-2- and high-risk patients.

### *The controlled myelofibrosis study with oral JAK inhibitor treatment (COMFORT) trial*

COMFORT trials were a series of two phase-III, open-label, randomized, crossover trials, that notably demonstrated the superiority of ruxolitinib over the best available therapy (BAT) as a long-term finding with a 33% reduction in the risk of death.

- Better clinical status as determined by lower absolute spleen size and symptom severity were observed in patients with less-advanced MF compared to more-advanced disease after the initiation of ruxolitinib therapy in the COMFORT I (n=155) trial analysis.[40]
- A pooled analysis of COMFORT I (n=155) and COMFORT II (n=146) trials found that early treatment of MF with ruxolitinib improved the clinical outcomes and overall survival with fewer incidences of cytopenia and splenomegaly. Additionally, it also improved renal functions affected by MF.[35]

### *The SIMPLIFY trials*

The SIMPLIFY trials were phase III, randomized trials (n=432) comparing momelotinib (n=215) and ruxolitinib (n=217) in JAK inhibitor-naïve patients with MF. The study demonstrated that ruxolitinib showed better control of MF-induced symptoms over momelotinib in JAK inhibitor-naïve patients with MF.[41]

## Safety

Ruxolitinib was well-tolerated by intermediate-1-risk patients. It demonstrated an adverse effect in intermediate-2- and high-risk MF patients. The most common hematologic adverse events were anemia and thrombocytopenia which led to treatment discontinuation in only a few cases. The most common non-hematologic adverse events were grade 1/2, and included diarrhea, pyrexia, fatigue, and asthenia. The rates of infections were low in grade 1/2, and no new or unexpected infections were observed.[2,39]

## Real-World Assessment of Clinical Outcomes in Patients with MF Receiving Treatment with Ruxolitinib

### *Patients with lower-risk MF receiving treatment with ruxolitinib*

A retrospective, observational study evaluated the clinical benefit of ruxolitinib treatment among low-risk MF patients to assess changes in spleen size and constitutional symptoms. A significant reduction in spleen size was observed in 78% of the patients with low-risk MF during ruxolitinib treatment. General fatigue, night sweat, and early satiety were the three most common symptoms among low-risk MF patients. A distribution of symptom severity from more to less was observed followed by ruxolitinib treatment.[38]

### *Ruxolitinib experience in intermediate-risk MF*

The safety and efficacy of ruxolitinib were evaluated in a retrospective cohort of 57 intermediate-risk MF patients. Clinical improvements were detected followed by ruxolitinib treatment in more than 60% of the patients with manageable hematological side-effects. Symptom response was observed after ruxolitinib treatment among 21.7% of the patients. A 26.3% treatment discontinuation rate indicated a better real-life safety profile of ruxolitinib than those in clinical trials.[42]

## Interferon (IFN) in early MF

Patients with early-stage MF showed improved bone marrow morphology with IFN.[43] An improvement in the fibrosis grade,[44] hemoglobin levels, and reduced splenomegaly were also reported.[43,44] A direct cytotoxic effect of IFN is reported on malignant stemcells and enables immunemodulation to promote beneficial effects in early MF patients. However, low tolerability and an inconvenient dosing schedule, balance its beneficial effects in treating early MF. The findings of these studies were small to draw any definitive conclusions on the use of IFN for the treatment of early-stage MF.

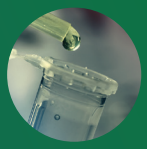
Pegylated IFN has a better safety profile than standard IFN despite frequent side effects including fatigue, myalgia, and neuropsychiatric effects like depression. Hematological abnormalities like leukopenia, anemia, thrombocytopenia, and elevated liver function tests are also seen with pegylated IFN. Hypothyroidism, vasculitis, or hepatitis occur as late autoimmune toxicities. RopegIFN-α-2b was developed to improve the tolerability and is currently under evaluation.[26]

## Newer Treatment Options in MF

Newer treatment options in MF are emerging, but these studies are restricted to intermediate-2 and high-risk patients. Studies in low-risk and early MF are still lacking.

- Fedratinib, an oral selective inhibitor of JAK2, is effective in treating adult patients with intermediate-2 or high-risk primary or secondary MF. It was approved by FDA in 2019.[45,46]
- Imetelstat, a short oligonucleotide telomerase inhibitor, is clinically effective in the overall survival of MF patients.[47]
- Everolimus, a mammalian target of rapamycin (mTOR/Akt) pathway inhibitor is also clinically effective in the reduction of splenomegaly, pruritis, and associated symptoms of MF.[48]
- TGF-β receptor ectodomain-IgG Fc fusion protein (AVID200), a potent transforming growth factor-β (TGF-β) trap, is clinically effective in MF with anti-tumor ability.[49]
- The protein, Aurora kinase A, is over-expressed in MF. Megakaryocytes and its inhibitor can potentially rescue transcription factor, GATA-binding factor 1 (GATA1) expression and prevent megakaryocyte abnormality.[50]

The above-mentioned clinical/preclinical trials are not based on early MF patients. However, formulations of recombinant



IFN-α are emerging as an alternative and clinically effective treatment option in early MF with a reduction in spleen size, decreased constitutional symptoms, and better drug tolerability.[51]

## Novel Approaches Including JAK Inhibitor in Combination

• Scientists should consider novel strategies that alone, or in combination with JAK inhibition, can enable disease remissions and the reversal of bone marrow fibrosis in MF. Molecular abnormalities in MF should be scrutinized more critically to improve the MF risk models by considering both clinical and genetic factors.[1,52]
• Targeting the nuclear factor-kappa B (NF-kB) pathway and members of the Bromodomain and Extra-Terminal (BET) family of proteins in mice with MF has resulted in the reduction of cytokine production, spleen volume, and bone marrow fibrosis. CP-610 is a BET inhibitor that is currently under clinical trials to evaluate its efficacy alone, or in combination with ruxolitinib.[53]
• P-selectin inhibitors are hypothesized to rescue GATA1 expression in MF and have a good rationale for use alone, or in combination with ruxolitinib.[54]

## Conclusion

Several gene mutations are observed in MF, which is a hostile MPN. It is associated with a poor quality of life and lower life expectancy. There is an on-going debate on the early interventions for low-risk MF patients.

According to Dr. Yap, early intervention with JAK2 inhibitors, reduced the spleen size and improved the symptoms. For the asymptomatic cases, he believes that a deeper understanding of disease heterogeneity, when and why it progresses, and diagnosing with novel biomarkers might help in directing the need for early interventions.
Dr. Gill suggested that the therapeutic approach to the management of MF should be based on risk stratification. For low- or intermediate-1-risk MF patients without major symptoms, Dr. Gill recommends monitoring the patients closely, while for symptomatic patients, he recommends using ruxolitinib.
Ruxolitinib is emerging as a useful drug in routine clinical practice and in early and low-risk MF treatment over conventional therapy with delayed disease progression, improved disease burden ability, and reduction in splenomegaly. The reduction of symptoms and lower risk of mortality in the COMFORT trials, when compared with placebo/best available therapy, also indicates the efficacy of ruxolitinib in treating MF. Furthermore, ruxolitinib has been shown to prolong the overall survival in patients with intermediate-2 or high-risk MF.

However, the overall assessment of prognostic and individual clinical factors should be considered in drug-based therapy with early MF. The gap between the ability to analyze the disease progression at the molecular level and applying such knowledge in clinical practice should be minimized for optimization of the treatment benefit.

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