

# CLINICAL UPDATE

Advances in the Treatment of Myelofibrosis

## When to Initiate Treatment in Myelofibrosis



Claire Harrison, MD  
Consultant Hematologist and Deputy Director  
Guy's and St Thomas' Hospital  
London, United Kingdom

### H&O What are the characteristics of myelofibrosis?

**CH** The cardinal features of the blood cancer myelofibrosis are splenomegaly, fibrosis in the marrow, and either myeloid proliferation or myeloid depletion (Table). Myelofibrosis reduces duration of life, as well as quality of life. It is generally a disease of older patients. Myelofibrosis can manifest as a primary disorder, and it can also develop after an antecedent chronic myeloproliferative disorder, such as essential thrombocythemia or polycythemia vera.

A myriad of symptoms are associated with myelofibrosis. Patients can develop all of the symptoms expected with bone marrow failure, such as fatigue, bleeding, and risk of infection. There are also other symptoms that are more specific to the disease. Symptoms related to the enlarged spleen include abdominal pain, early satiety, and bowel upset. Symptoms related to cytokine changes or viscosity include fatigue, bone pain, and pruritus, which is very common.

As a general principle, symptoms become more prevalent and severe as the disease progresses. However, patients can develop any of these symptoms at any stage in their disease. Not all symptoms are prognostic. There are patients who clinically have very early-stage disease, but have a very severe disease symptom burden. For example, a patient with low-risk disease can experience terrible pruritus for several hours a day or can be very fatigued and unable to work.

### H&O How long do patients live after a diagnosis of myelofibrosis?

**CH** The median life expectancy is between 5 and 6 years. It has probably improved recently with our understanding of the molecular pathogenesis of myelofibrosis, the

development of targeted therapies allowing Janus kinase (JAK) inhibition, and the more appropriate use of bone marrow transplant.

### H&O What is known about genetic mutations in these patients?

**CH** Increasing evidence is showing that, at the biologic level, the disease is characterized by abnormalities of the JAK/signal transducer and activator of transcription (STAT) signaling. In many patients, myelofibrosis is driven by mutations of *JAK2* or the exon 9 of the calreticulin (*CALR*) gene.

The seminal finding regarding genetic mutations in myelofibrosis occurred approximately 10 years ago, at the laboratory of William Vainchenker, MD, PhD. The *JAK2 V617F* mutation, which leads to constitutive activation of JAK2, was shown to be central to the signaling cascade. Since then, other mutations have been identified. A series of mutations were seen in the transmembrane domain of the myeloproliferative leukemia virus (*MPL*) gene, which is the thrombopoietin receptor. A more recent discovery identified mutations affecting the *CALR* gene. These mutations in *JAK2*, *MPL*, and *CALR* are known as phenotypic driver mutations.

Approximately 10% to 20% of patients remain negative for these 3 mutations. Borrowing a term from breast cancer, we call these patients “triple-negative.” Increasingly, we are starting to understand more about mutations elsewhere in the genome that might be important prognostically. We are also beginning to appreciate how to apply these findings clinically.

Currently, genetic mutation status does not impact disease monitoring or management. It does appear that testing for other genetic mutations (eg, additional sex combs like 1, transcriptional regulator [*ASXL1*]) can be used to slightly improve prognostic stratification.

## H&O What are the components of disease monitoring?

**CH** The key components of disease monitoring are individualized to each patient, depending on the disease features and severity. At one end of the spectrum, I might see a patient once or twice a year, when I perform a blood count, do a physical examination, and view the blood film. At the other end of the spectrum, I might see a patient every week to adjust his or her therapy, administer a transfusion, and refine management as needed.

Currently, myelofibrosis differs from chronic myeloid leukemia in that patients are not monitored through serial evaluation of genetic mutations or mutational loads. In the future, however, this strategy may be used.

## H&O What prognostic tools are used to stratify risk in patients with myelofibrosis?

**CH** Several prognostic scoring systems are available. The most common one is probably the International Prognostic Scoring System, which was introduced in 2009. The core of the scoring systems consists of 5 main clinical features: age of the patient (65 years or younger vs older than 65 years); presence or absence of anemia; leukocytosis, particularly white count higher than  $25 \times 10^9/L$ ; and presence of circulating blasts exceeding 1%. We also evaluate the presence of specific symptoms, notably fever, bone pain, and night sweats. Other considerations include red cell transfusions, thrombocytopenia, and specific cytogenetic abnormalities. This scoring system has been modified over time. The Dynamic International Prognostic Scoring System Plus incorporates prognostic information drawn from the karyotype, platelet count, and transfusion status. More recently, as our understanding evolves, we have begun to consider different mutations and genes, such as *ASXL1*.

These factors are used to divide patients into 4 risk groups: low, intermediate 1, intermediate 2, and high. Patients tend to be spread evenly among these prognostic groups.

It is difficult to precisely apply prognostic criteria to patients with myelofibrosis arising out of essential thrombocythemia or polycythemia vera, and caution is necessary when doing so. These criteria have not been validated in this population of patients.

## H&O What are the treatment goals for patients with myelofibrosis?

**CH** The treatment goals are individualized to the patient. Unfortunately, in most cases, cure is not the goal. At the present time, the only curative therapy is bone marrow

transplant, which is applicable to a small number of patients. In most patients with myelofibrosis, bone marrow transplant is contraindicated owing to illness from the disease or comorbidities. Prognostic scoring systems are used to judge whether transplant is an option.

Regardless of whether the goal is cure, we try to identify the individual facets of the disease that are most important to the patient. Because the disease is variable in its phenotype, these issues can be very different. Examples include pruritus, weight loss, spleen pain, and anemia.

## H&O What is the current treatment approach for patients with myelofibrosis?

**CH** The first step is to ensure that the diagnosis is correct, which will involve correlation of clinical, laboratory, and molecular features. Several other conditions can mimic myelofibrosis—examples being myelodysplastic syndrome with fibrosis and chronic myeloid leukemia.

Once an accurate diagnosis is ascertained, it is necessary to evaluate the patient's symptoms, assess the prognosis, and consider whether bone marrow transplant, either at present or in the future, might be an option. Then we look at the individual facets of disease that require treatment. For example, a patient with a heavy symptom burden and splenomegaly might be a candidate for JAK inhibition. If anemia is the predominant characteristic, then it should be treated. Many of the current treatments address only 1 or 2 aspects of the disease, and combined-modality therapy is often required.

There are also economic considerations. In the United Kingdom, novel therapies, such as the JAK inhibitors, are reimbursed only for patients who fall into specific prognostic groups.

## H&O What novel therapies are available for myelofibrosis?

**CH** Ruxolitinib (Jakafi, Incyte) is a JAK1/JAK2 inhibitor approved in 2011 for patients with intermediate- and high-risk myelofibrosis. In 2010, a phase 1/2 study showed that ruxolitinib delivered significant reductions in the rather massive spleen size that some of these patients have. Ruxolitinib was also associated with weight gain and reduction in debilitating symptoms. It was relatively well-tolerated, with the main toxicities being anemia and thrombocytopenia.

These data led to phase 3 studies. The most important ones are known as the COMFORT trials (Controlled Myelofibrosis Study With Oral JAK Inhibitor Therapy), which enrolled patients with intermediate 2 or high-risk myelofibrosis. The patients had an enlarged spleen and an adequate blood count. COMFORT-I was conducted in

North America and Australia, and compared ruxolitinib vs placebo. The open-label COMFORT-II trial was performed in Europe, and compared ruxolitinib vs standard therapies, which were a range of different treatments.

In both COMFORT-I and COMFORT-II, the primary endpoint was a reduction in spleen volume by 35% or more, as judged by central, blind review of a magnetic resonance imaging scan or, in some patients, a computed tomography scan. (A 35% decrease in spleen volume equates to a roughly 50% reduction in palpable spleen length.) Other endpoints included symptom control, survival, and toxicity. Both studies demonstrated a highly significant positive outcome in favor of ruxolitinib. The best available therapies were little better than placebo. Ruxolitinib was shown to have significant benefit in reducing spleen size by at least 35%, and it significantly improved symptoms. There was some hematologic toxicity, which was managed by dose modification.

The most recent updates from these studies, with 5 years of follow-up, were presented recently. They showed durable spleen responses. The primary endpoint was maintained for a median of 3 years. Many patients still had durable responses at 5 years.

#### **H&O** Does ruxolitinib appear to impact the bone marrow?

**CH** The primary aim of treatment with ruxolitinib is to reduce the patient's spleen size and symptom burden. There is increasing evidence that patients live longer when treated with ruxolitinib. Some case reports, as well as my own clinical experience, suggest that some patients might have striking responses in their bone marrow. By no means, however, will all patients experience a change in their bone marrow. Monitoring of bone marrow is not usually a component of monitoring treatment with ruxolitinib. It is necessary to learn more about how ruxolitinib might affect the stroma of the bone marrow and why it impacts different patients in different ways.

#### **H&O** Do genetic mutations appear to impact treatment response to ruxolitinib?

**CH** Given that ruxolitinib is a JAK1/JAK2 inhibitor, it might be expected that only patients with the *JAK* mutation would respond to treatment. Studies show, however, that patients respond regardless of their phenotypic driver mutation; no particular group responds better or worse. Mutations in other genes, such as enhancer of zeste 2 polycomb repressive complex 2 subunit (*EZH2*), *ASXL1*, and isocitrate dehydrogenase 1 and 2 (*IDH1/2*), might have an impact. A recent study from MD Anderson evaluating use of ruxolitinib in patients with myelofibrosis

found that the number of gene mutations corresponded with a worse outcome. Patients with 3 or more mutations were 9 times less likely to have a spleen response ( $\geq 50\%$  reduction in palpable spleen size) than those with 2 or fewer mutations. In patients with 3 or more mutations, time to treatment discontinuation and overall survival were shorter as compared with patients who had fewer mutations.

#### **H&O** What is the relevance of the *JAK2 V617F* allele burden?

**CH** If a parallel is drawn between the myeloproliferative neoplasms and chronic myeloid leukemia, it might be expected that the *JAK2* allele burden would be important in myelofibrosis. However, we do not yet know the importance of the *JAK2* allele burden in monitoring the disease. Standard practice does not usually include monitoring this aspect. The one setting where such monitoring can be useful is after a bone marrow transplant, when it serves as a highly sensitive test of minimal residual disease. In my clinical practice, this is the only setting in which I perform serial monitoring of the *JAK2* allele burden.

#### **H&O** Do data suggest that patients might benefit from earlier treatment?

**CH** There is no evidence that patients with low-risk disease benefit from earlier intervention with a specific treatment. For patients with intermediate-2 and high-risk disease, data from the COMFORT studies suggest that earlier treatment with ruxolitinib might be beneficial. The 5-year data from COMFORT-I showed that survival was decreased among the patients who received placebo first and then crossed over after 40 weeks, as compared with those who received ruxolitinib earlier. That is powerful evidence that we should consider the use of therapies such as ruxolitinib earlier in the disease course. A specific trial, however, will be required to evaluate treatment in patients with earlier disease.

#### **H&O** How might this field evolve?

**CH** Myelofibrosis is a rapidly growing field, with new data appearing all the time. There is increasing interest in the JAK inhibitors and in therapies that target other facets of the disease. Promising agents include the telomerase inhibitor imetelstat and the pentraxin analogue PRM-151. Molecular aspects may be used to more precisely provide a prognosis. Five-year data from phase 3 studies are also valuable and can inform treatment selection. An important discovery in patients with triple-negative disease is that they have other mutations in *JAK* or *MPL*,

confirming the central importance of JAK2 in the pathogenesis of these conditions.

### Disclosure

*Dr Harrison has received honoraria for speaking and advisory board membership from Shire, Novartis, Sanofi, Gilead, S\*Bio, YM BioSciences, and CTI BioPharma. She has received research funding from Novartis.*

### Suggested Readings

Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. *Blood*. 2009;113(13):2895-2901.

Gangat N, Caramazza D, Vaidya R, et al. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. *J Clin Oncol*. 2011;29(4):392-397.

Harrison C, Kiladjan JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med*. 2012;366(9):787-798.

Harrison CN, Vannucchi AM, Kiladjan JJ, et al; COMFORT-II investigators. Long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs best available therapy for myelofibrosis. *Leukemia*. 2016;30(8):1701-1707.

Mesa RA, Gotlib J, Gupta V, et al. Effect of ruxolitinib therapy on myelofibrosis-related symptoms and other patient-reported outcomes in COMFORT-I: a randomized, double-blind, placebo-controlled trial. *J Clin Oncol*. 2013;31(10):1285-1292.

Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). *Blood*. 2010;115(9):1703-1708.

Patel KP, Newberry KJ, Luthra R, et al. Correlation of mutation profile and response in patients with myelofibrosis treated with ruxolitinib. *Blood*. 2015;126(6):790-797.

Tefferi A, Lasho TL, Begna KH, et al. A pilot study of the telomerase inhibitor imetelstat for myelofibrosis. *N Engl J Med*. 2015;373(10):908-919.

Tefferi A, Vardiman JW. Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organization criteria and point-of-care diagnostic algorithms. *Leukemia*. 2008;22(1):14-22.

Vainchenker W, Delhommeau F, Constantinescu SN, Bernard OA. New mutations and pathogenesis of myeloproliferative neoplasms. *Blood*. 2011;118(7):1723-1735.

Verstovsek S, Kantarjian H, Mesa RA, et al. Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. *N Engl J Med*. 2010;363(12):1117-1127.

Verstovsek S, Mesa R, Gotlib J, et al. Long-term outcomes of ruxolitinib therapy in patients with myelofibrosis: 5-year final efficacy and safety analysis from COMFORT-I. Presented at: 2016 European Hematology Association Congress; June 9-12, 2016; Copenhagen, Denmark. Abstract S452.