

## **A Focus on Primary Myelofibrosis**

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It has been more than 100 years since Vaquez and Osler first described what we now call polycythemia vera. In that time much has been learned about this group of diseases that we classify as myeloproliferative neoplasms (MPNs). The 2008 World Health Organization (WHO) classification system includes essential thrombocythemia, polycythemia vera, and primary myelofibrosis as classic MPNs. This review will focus on primary myelofibrosis (PMF).

### **Overview**

Primary myelofibrosis is a myeloproliferative neoplasm characterized by overproduction of malignant pluripotent hematopoietic stem cells and bone marrow fibrosis. The disease is caused by the accumulation of malignant bone marrow cells that trigger cytokine release from megakaryocytes. The resulting inflammatory response stimulates the nonclonal proliferation of fibroblasts scarring the bone marrow and limiting normal hematopoiesis. In this sense the term “primary” MF is a misnomer; however it is useful in distinguishing this disease from PV and ET where fibrosis tends to be absent at the time of initial presentation. This bone marrow scarring encourages extramedullary hematopoiesis, which often results in splenomegaly (enlarged spleen), early satiety, pain, and extreme fatigue both from anemia and inflammatory cytokines. Patients with PMF also have an increased risk of embolic events similar to those with essential thrombocythemia.

### **Diagnosis**

Currently there is no universally accepted medical standard for the diagnosis of PMF. Common findings include megakaryocyte proliferation and atypia (structural abnormality), anemia with extramedullary hematopoiesis, and an absence of criteria to diagnose polycythemia vera, Chronic Myeloid Leukemia (CML), or Myelodysplastic syndromes (MDS). The driver mutation for this disorder is not yet known, however, the demonstration of JAK2 or myeloproliferative leukemia protein (MPL) mutations may assist in the diagnosis.

### **Prognosis**

Oncologists at Norton Cancer Institute employ the International Prognostic Scoring System (IPSS) staging system, which examines several risk factors for estimating survival from time of diagnosis, including age, hemoglobin, leukocyte count, circulating blasts, and presence of constitutional symptoms. Another commonly used scoring system, the Dynamic International Prognostic Scoring System (DIPSS) can be applied at any time in the disease course. The Myeloproliferative Neoplasm Symptom Assessment Form is another guide to help assess symptom burden and can be used as a beneficial tool in clinical practices.

[http://jco.ascopubs.org/content/suppl/2012/10/15/JCO.2012.42.3863.DC1/data\\_supplement\\_JCO.2012.42.3863.pdf](http://jco.ascopubs.org/content/suppl/2012/10/15/JCO.2012.42.3863.DC1/data_supplement_JCO.2012.42.3863.pdf).

The median survival of all PMF patients has been variably reported to be three to five years.<sup>1</sup> The prognostic scoring systems have proven successful in predicting both survival and the transformation into acute leukemia (from less than 1 percent to 30 percent in low and very high risk categories, respectively).<sup>2</sup>

## **Mutations**

Advances in our understanding of somatic mutations may soon provide a new way to diagnose, classify, and treat primary myelofibrosis patients. Since it was first identified in 2005, the JAK2 V617F mutation has been identified in approximately 90 percent of patients with polycythemia vera and in almost 50 percent of those patients with primary myelofibrosis or essential thrombocythemia<sup>3</sup>. This phenylalanine for valine substitution in the regulatory domain results in constitutive kinase activation. In JAK2 V617F mutated patients, the JAK/STAT signaling pathway is upregulated, causing marrow hypercellularity and development of bone marrow fibrosis.

The TET2 gene is involved in epigenetic regulation of transcription in myeloid cells. Loss of TET2 has been identified in patients with primary myelofibrosis, as well as other myeloproliferative neoplasms and myeloid neoplasms. This mutation is present in about 15 percent of myeloproliferative neoplasms, and may co-occur with the JAK2 V617F mutation.<sup>4</sup>

We are learning more about the calreticulin, or CALR mutation. Most recently, calreticulin mutations have been identified in the majority of MPN patients without the JAK2 V617F mutation. Patients with CALR mutation are thought to have a more favorable prognosis and improved overall survival compared with wild-type patients.

We are also beginning to recognize that mutation order may play a role in clinical presentation of myeloproliferative neoplasms. A recent article by a group at Cambridge University sought to determine mutation order in patients with myeloproliferative neoplasms, and how this sequence may affect clinical features. The trial, published in the *New England Journal of Medicine*<sup>5</sup> screened 246 patients with the JAK2 V617F mutation and for mutations in TET2. Of those patients, mutation order could be confidently identified in 24 patients (12 “TET2-first” patients and 12 “JAK2-first” patients). The authors found that patients who acquired the JAK2 V617F mutation first were more likely to present with polycythemia vera than with essential thrombocythemia. These patients were also more likely to develop blood clots, and were thought to be more sensitive to JAK2 inhibitors, such as ruxolitinib.

## **Treatment**

Therapy options for patients with myelofibrosis have evolved over the last decade in large part due to our better understanding of somatic mutations and their impact on survival. Low- or intermediate-risk patients at our facility are typically observed without initiation of therapy, or take a “watch and wait” approach. In our intermediate-2/high-risk patients, therapy is tailored based primarily on symptom management and patient presentation. Hydroxyurea has long been considered the drug of choice for reducing spleen size and control of blood cell counts. Erythropoiesis stimulating agents are often used in symptomatic anemia without splenomegaly. Danazol and other androgen preparations have been shown to be another effective and well tolerated option for treatment of anemia in myelofibrosis patients.

Immunomodulatory agents (lenalidomide, thalidomide) demonstrate antiangiogenic activity and cytokine inhibition in the bone marrow microenvironment, which is thought to induce molecular and pathologic responses in PMF. These agents have been investigated alone, and in combination with corticosteroids, with promising results.

Ruxolitinib is a first in class JAK2 inhibitor indicated for intermediate- or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis. Ruxolitinib has been shown to reduce spleen size, help with relief of constitutional symptoms, and improve anemia in patients with myelofibrosis.

Even with all of these new treatment options, allogeneic stem cell transplantation remains the only curative therapy for primary myelofibrosis. Non-stem-cell-transplant approaches are palliative at best. Advances in non-ablative transplants and better control of toxicities have made transplantation available to older patients.

### **Clinical Trials**

Recent advances in identifying mutations associated with primary myelofibrosis and related myeloproliferative neoplasms have increased the possibility of developing molecularly targeted therapy. At the Norton Cancer Institute, we participate in the Persist-2—a Phase 3 Study of Oral Pacritinib versus Best Available Therapy in Patients with Thrombocytopenia and Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis. Pacritinib (SB1518) is a novel JAK2 inhibitor thought to regulate signaling in pathways necessary for normal cell growth and development, as well as inflammatory cytokine expression and immune responses.

Other clinical trials are underway in hopes of finding more effective treatment options for PMF patients.

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