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## Unpacking Myelofibrosis: Pathogenesis and Management Goals

### Announcer:

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Here's your host, Dr. Gates Colbert.

### Dr. Colbert:

Welcome to ReachMD. I'm your host Dr. Gates Colbert. And joining me to discuss myelofibrosis and the underlying mechanisms that drive this disease is Dr. James Rossetti. He's a hematologist at the University of Pittsburgh Medical Center, UPMC Hillman Cancer Center, at the Mario Lemieux Center for Blood Cancer in Pittsburgh, Pennsylvania. Dr. Rossetti, welcome to the program.

### Dr. Rossetti:

Thank you for having me.

### Dr. Colbert:

To start us off, Dr. Rossetti, can you briefly give us some background on myelofibrosis?

### Dr. Rossetti:

Sure. So, myelofibrosis is a rare myeloproliferative neoplasm, or an MPN, causing bone marrow scarring, underproduction of various blood cells, and constitutional symptoms, all of which can be highly variable.<sup>1</sup> Patients often present with cytopenias, including anemia, splenomegaly, and some constitutional symptoms that may include fatigue, night sweats, pruritis, and weight loss.<sup>1,2</sup>

Progression of myelofibrosis can lead to more extensive bone marrow fibrosis, which is the key feature of the disease.<sup>3</sup> This increase in fibrosis or scarring within the bone marrow further inhibits the production of healthy red and white blood cells.<sup>3</sup> Myelofibrosis also carries a risk of progression to a more aggressive form of hematological disease, including the unfortunate evolution to acute myeloid leukemia, or AML for short, and this occurs in about 20 percent of our patients.<sup>4</sup>

Myelofibrosis, even among the MPNs, is rare, with an incidence of about 1500 newly diagnosed patients in the U.S. per year. In comparison, essential thrombocythemia, or ET, another MPN, has an incidence of about 5000 cases in the U.S. per year. And myelofibrosis has worse survival outcomes than the other MPNs, with a five-year mortality rate of 51 percent and a median overall survival of 3.6 years.<sup>5,6</sup>

### Dr. Colbert:

Now as a follow-up, can you tell us about the molecular pathways that drive myelofibrosis?

**Dr. Rossetti:**

Certainly. Well, back in 2005, the discovery of the JAK2V617F mutation unlocked a new chapter in our understanding of the mechanisms that contribute to the development of myelofibrosis. Overactive JAK-STAT signaling via this and other mutations is what drives myelofibrosis, leading to abnormal megakaryocyte development, cytokine dysregulation, and fibrotic scarring within the bone marrow. All of which ultimately results in impaired blood cell production, accounting for the cytopenias we often see.<sup>7</sup>

The subsequent detection of multiple other mutations of diagnostic and prognostic relevance followed. Understanding the role of constitutively activated JAK-STAT has led to the development of several JAK inhibitors, which are now FDA-approved treatments for patients with myelofibrosis.<sup>4</sup>

So to drive home the importance of JAK-STAT, inhibition of JAK leads to suppression of inflammatory cytokines and myeloproliferation with potential spleen volume reduction and improved constitutional symptoms.<sup>4</sup> While we hope the natural evolution of the disease may be altered, the spleen may stop shrinking or even grow back, symptoms often return, and the disease may continue to progress for some patients.<sup>1</sup> And so myelofibrosis response to this modality can oftentimes be short-lived.<sup>8</sup>

Other pathways involved in the development and progression of myelofibrosis include MAPK, PI3K, epigenetic regulation, and the BCL-2 family.<sup>9,10</sup>

**Dr. Colbert:**

And you mentioned patients who lose their response to therapy, Dr. Rossetti, how then does myelofibrosis progress?

**Dr. Rossetti:**

Progression is complex in myelofibrosis because there are several different definitions, and as clinicians, we can think about it in several different ways.

First, we think of clinical progression, which I would call classical progression, meaning the patient's symptoms are worsening. This is the most recognizable form of disease progression for the patient and healthcare provider, and many of us who treat myelofibrosis often think of it as a symptoms-driven disease.<sup>11</sup>

Then, there's also splenic progression, and although splenomegaly is commonly seen at diagnosis, the spleen will continue to grow with myelofibrosis progression. The International Working Group for MPNs Research and Treatment, or IWG-MRT for short, defines progressive myelofibrosis disease according to various splenic growth and blast count parameters. While these parameters are often used in clinical trials, clinical practice use of splenic growth assessment for disease progression varies widely.<sup>11</sup>

The third type of disease progression, leukemic progression, can be considered the most serious. This progression indicates a transformation of myelofibrosis to a post-MPN AML, a highly aggressive disease with a poor prognosis. Patients diagnosed with this form of progression typically have a median survival of less than six months.<sup>12</sup>

Now there are a few processes that can cause disease progression in patients with myelofibrosis.<sup>13</sup> One of them is progression of bone marrow fibrosis itself, which can lead to continued symptoms and is often associated with poor outcomes.<sup>3</sup>

Another is increased inflammatory cytokine production, which can lead to ongoing or progressive constitutional symptoms.<sup>2,3</sup> Leukemic progression occurs when immature cells called blast cells proliferate in the blood or the bone marrow, leading to what we call a Blast Phase, which is essentially AML.<sup>12</sup>

**Dr. Colbert:**

Dr. Rossetti, you've mentioned the spleen a few times in discussing myelofibrosis. Can you tell us more about its role in myelofibrosis disease pathogenesis?

**Dr. Rossetti:**

Absolutely. So the spleen is responsible primarily for filtering blood to remove cellular waste, as you know, this gets rid of old damaged blood cells and makes cells that can help fight infections.<sup>14</sup>

In myelofibrosis, the spleen very often presents in an enlarged state because it's compensating as the main center of production of red and white blood cells that the scarred and dysfunctional bone marrow is unable to make.<sup>15</sup> The process here is called extramedullary hematopoiesis leading to an increase in spleen size.<sup>16</sup>

And as the spleen continues to work to produce these blood cells, it enlarges and it can sometimes press against the stomach, causing

abdominal discomfort and even early satiety. So for some patients who have massive spleens, this can be quite debilitating.<sup>17</sup>

Another complication linked with splenomegaly is thrombosis, particularly of the hepatic portal vein, termed portal vein thrombosis. This condition can lead to various clinical effects, including gastrointestinal bleeding, portal hypertension, and further enlargement of the spleen. And individuals with MPNs, such as myelofibrosis, are more likely to experience portal vein thrombosis at higher rates because splenomegaly promotes further thrombosis of the hepatic portal vein.<sup>18,19</sup>

**Dr. Colbert:**

Now let's continue by addressing myelofibrosis management. What are some of the primary treatment goals when dealing with this progressive and often fatal disease?

**Dr. Rossetti:**

Well, some of the current goals for managing myelofibrosis certainly include reduction of spleen volume and improved symptom responses, simply making the patient feel better. As clinicians, we also hope that evolving treatment plans will further reduce the risk of that leukemic progression we spoke of, extend anemia response for longer transfusion-free periods, prolong spleen and symptom response, and ultimately, improve the overall survival.<sup>1,13,20,21</sup>

Now when patients with myelofibrosis were asked their treatment goals in the U.S. MPN Landmark survey, they ranked a better quality of life, healthy blood counts, and symptom improvement as important. However, the most important treatment goal for the surveyed patients was to slow or delay disease progression which supports what we've been discussing earlier.<sup>22</sup>

**Dr. Colbert:**

For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Gates Colbert. And today I'm speaking with Dr. James Rossetti about pathogenesis and treatment goals in myelofibrosis.

So now that we've discussed the importance of spleen in disease pathology, Dr. Rossetti, what role does the spleen have in myelofibrosis goals of therapy? Is this something clinicians—and for that matter, patients—should care about?

**Dr. Rossetti:**

This is an interesting question because there are a few ways of thinking about the importance of shrinking the spleen as a goal of therapy.

Now more broadly, an overarching goal as I have said as a clinician treating patients with myelofibrosis to make sure the patient is feeling better. Of course, ideally, I'd also like to see them to live longer and prevent disease progression, too, and while there is progress there, we're not quite there yet with advanced therapies.<sup>1,21</sup> Also, as a transplant specialist, I have a strong interest in shrinking the spleen as studies have shown that reducing spleen size may improve engraftment outcomes for transplant, which is the only curative treatment option for myelofibrosis to date.<sup>23,24</sup>

In terms of symptoms, as we've said, splenomegaly can lead to abdominal pain, early satiety, general discomfort, especially with ongoing growth, so we want to reduce spleen size, particularly for those who are experiencing related symptoms, which can be quite severe.<sup>17</sup>

Lastly, in terms of clinical significance, there's ongoing research correlating a reduced spleen volume with survival, including investigational studies that set the stage for spleen volume response to be used as an outcome measure in phase three trials of myelofibrosis.<sup>25,26</sup> Although not yet definitive, the evidence summarized here suggests a link between spleen size or volume to survival which should be further investigated.<sup>27-31</sup>

Now that said, it's important to note there has been no *causal* relationship established between decreased spleen size and survival, so more studies are needed to determine whether reducing spleen volumes is directly impacting survival, serving as a marker for an auxiliary, as yet to be discovered deeper mechanism of disease control, or simply indicative of patients who have a better prognosis.

More work needs to be done here as it would be *very helpful* to have a reliable clinical marker to measure meaningful treatment success.

**Dr. Colbert:**

Now you've talked about ongoing research that may correlate with reduced spleen volume with survival, but is there any link between symptom reduction and survival?

**Dr. Rossetti:**

As for symptoms, there's been limited data correlating improvement in symptoms to improved survival. In contrast to spleen volume, for the few studies that have been done, the data are more mixed when trying to link symptom improvement to survival.<sup>27,32</sup> Nevertheless, symptom management remains essential to those of us treating myelofibrosis.

Symptom etiology is challenging in that symptoms can arise from the disease itself, from the side effects of therapy, or from co-morbidities that patients may have. So linking something with multifactorial causes, such as symptoms, to survival can be very difficult.<sup>33</sup>

But again, symptom management is still critical as a goal of therapy for healthcare providers like myself. In the future, as clinicians, we hope to expect deeper and more meaningful disease improvement without sacrificing symptom management.

**Dr. Colbert:**

And can you explain what it means when you say, future goal of deeper disease improvement?

**Dr. Rossetti:**

Absolutely. I think it would be ideal to have the ability to treat patients with myelofibrosis beyond simply managing their symptoms. Recently, there's been a discussion of so-called quote-unquote disease modification to capture the essence of this idea.

Disease modification itself is a novel concept in myelofibrosis, so there isn't a consensus on its definition or measurements of assessment. That said, Dr. Naveen Pemmaraju and others in 2022 proposed the following.<sup>21</sup> Pemmaraju and colleagues defined disease modification in myelofibrosis as evidence of clinically meaningful impact on survival outcomes and/or restoration of normal hematopoiesis in conjunction with improved bone marrow fibrosis through a substantial and durable reduction in the clonal burden of disease.<sup>21</sup>

To break that down, I think it's clear that an improvement in survival would indicate some deep disease changes.<sup>21</sup> Additionally, we know that impaired hematopoiesis is a crucial component of myelofibrosis,<sup>34</sup> while bone marrow fibrosis is the primary characteristic that distinguishes myelofibrosis from other MPNs.<sup>13</sup> Lastly, reducing the malignant clone burden that gives rise to myelofibrosis would suggest a foundational alteration of the disease<sup>35</sup> that hopefully translates into some of the benefits above.<sup>3,21,36</sup>

**Dr. Colbert:**

As we're almost out of time today, Dr. Rossetti, what key takeaways would you like to leave with our audience?

**Dr. Rossetti:**

Yes, so I think there are three points worth emphasizing.

First, myelofibrosis is a rare and oftentimes debilitating blood cancer that can progress to AML, primarily driven by the JAK-STAT pathway and marked by increasing bone marrow fibrosis, splenomegaly, and constitutional symptoms. These can adversely impact the quality of life for patients with the disease.<sup>1,4,7</sup> And what defines disease progression is highly variable.<sup>21</sup>

Secondly, the current goals of therapy for treating myelofibrosis are focused primarily on reducing symptom burden and spleen size.<sup>1,4,20,21</sup> And while emerging data is showing that reduced spleen size may correlate with improved survival, this is harder to demonstrate as it relates to symptom control.<sup>27-29,32</sup>

Lastly, I look forward to continued research in our field addressing the need for more meaningful improvement in all measurable outcomes for our patients with myelofibrosis. We hope that newer strategies might not only halt the disease process but perhaps even reverse some of the processes that lead to progression in this often-fatal disease.<sup>21</sup>

**Dr. Colbert:**

These points give us a lot to consider as we round out our discussion today. I want to thank my guest, Dr. James Rossetti, for his insights on myelofibrosis and what drives this rare disease.

Dr. Rossetti, it was great speaking with you today.

**Dr. Rossetti:**

It's been a pleasure, and I thank you for exploring this disease along with me.

**Announcer:**

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