# Treatment of MF-associated Anemia

## Faculty

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## Learning Objective

Describe the current and emerging strategies under investigation to improve MF-associated anemia

## Introduction

In this activity, Dr. Srdan Verstovsek will discuss management of myelofibrosis-associated anemia. He will provide guidance on thresholds for red blood cell transfusion, criteria for selecting anemia therapy, and current and emerging treatment options for managing anemia, including erythropoiesis-stimulating agents (ESAs), anabolic steroids, corticosteroids, immunomodulatory agents, Janus kinase (JAK) inhibitors, anti-hemojuvelin antibodies, ALK2 receptor inhibitors, and luspatercept.

## How often do patients with myelofibrosis (MF) present with anemia?

An analysis of the characteristics of patients presenting to the Mayo Clinic with MF, as a good reference to address this question, revealed that almost 40% present with significant anemia, defined as hemoglobin (Hb) <10 g/dL.[1]

## Are MF patients typically dependent on red blood cell transfusion (RBC) at diagnosis?

Almost one-fourth of MF patients are receiving RBC transfusion at diagnosis, but not necessarily too often, eg, biweekly transfusions (which we would call a transfusion dependency). After one year, two-thirds of the MF patients are anemic and 45% require RBC transfusion, attesting to the progressiveness of the disease.

## What is the threshold for RBC transfusion?

The usual threshold is Hb <8 g/dL. In the era of COVID-19 and a reduction in the blood supply, many now consider the threshold to be <7 g/dL, which may become normal practice as studies show that patients can live with lower Hb levels with less impairment on their quality of life than previously assumed.

**For those who are not yet dependent on RBC transfusion, how effective are the other established treatments for MF-associated anemia?**

I'll start by saying that no therapies are approved for the treatment of MF-associated anemia. The therapies used are the same regardless of the degree of anemia, but the goal of treatment may differ. In anemic patients who do not require transfusions yet, therapy to increase Hb >10 g/dL to alleviate symptoms such as shortness of breath and fatigue is desirable. The same therapies are used for patients who require transfusions once their Hb level declines to ≤8 g/dL and they start requiring transfusions. In this case, the goal of therapy is to eliminate requirement for transfusions, ie, transfusion independence.

The first step in the management of anemic MF patients is to check the erythropoietin level. According to guidelines from the National Comprehensive Cancer Network (NCCN), if the erythropoietin level is <500 mU/mL, the treatment of choice is erythropoiesis-stimulating agent.[2] Many patients with MF already have high levels of endogenous erythropoietin, so use of erythropoietin is not very common. Unfortunately, even in the setting of a low erythropoietin level, erythropoietin injections are not often effective.

A second option is an anabolic steroid, such as danazol, 400 mg/day to 600 mg/day. Both erythropoietin injections, usually given weekly or every other week, and anabolic steroids, given as pills, are relatively safe.[3]

Others will opt for a short course of a corticosteroid such as oral prednisone. We use a tapered dosing regimen of prednisone over 3 months — 30 mg/day for the first month, tapered to 20 mg/day the second month, and 10 mg/day for the third month.

Immunomodulatory agents (ie, thalidomide, lenalidomide) are often used off-label at a low dose in patients with MF. Thalidomide is usually prescribed at 50 mg/day and lenalidomide at 5 mg/day. Sometimes, immunomodulatory agents are used in conjunction with corticosteroids.

All of the aforementioned therapies change the bone marrow environment to allow production of RBCs for a limited duration. Efficacy is limited too — response rates are typically only up to 25%, and the duration of positive effect for any of the aforementioned treatments is only about 9 to 12 months.[3-12] The median time to onset of their anti-anemic effect is 3 to 4 months.

The JAK1/JAK2 inhibitor ruxolitinib, started at 5-20 mg twice daily, is approved by the US Food and Drug Administration (FDA) for the treatment of symptomatic intermediate-2 or high-risk MF, and the JAK2 inhibitor fedratinib, 400 mg/day, is also approved by the FDA for the treatment of adults with symptomatic intermediate-2 or high-risk primary or secondary MF.

Both approved JAK inhibitors are associated with improvement of symptoms related to MF and a reduction in spleen size (up to 90% of patients will have an enlarged spleen). Both, however, also worsen anemia.[13]

**What are the criteria for choosing among the standard options?**

Ten to 15% of MF patients will have anemia without splenomegaly. For these patients, a therapy to improve the RBC may be the only treatment required. The vast majority, however, have symptoms with an enlarged spleen and poor quality of life in addition to anemia. For them, a combination of medications may be required, one for control of splenomegaly and symptoms (eg, a JAK inhibitor), and one to control anemia.

If the erythropoietin level is low, erythropoietin injections weekly or every other week would be used first. Few patients have side effects from erythropoietin injections. The second choice is usually anabolic steroid followed by corticosteroids, and then immunomodulatory agents as response wanes. The safety profiles are unique for each.

Corticosteroids are usually used for only 3 months. During that time, energy level is generally improved but there is a risk of edema and insomnia, and blood sugar levels may increase in patients with diabetes.

Thalidomide can cause peripheral neuropathy, constipation and fatigue, and birth defects from thalidomide use are well known. Lenalidomide may paradoxically reduce RBC count in some patients and is associated with rash and diarrhea. The proportion of patients who discontinue due to intolerability is high with the immunomodulators.

The disease is progressive and patients will become more anemic and more likely to require transfusions, and they become transfusion dependent over time. Once they cycle through the established therapies, clinicians may want to suggest that patients consider enrollment into a clinical trial of an investigational agent.

**What is the pathogenesis of anemia in MF?**

Bone marrow fibrosis in MF is progressive. The fibrotic stroma displaces medullary erythropoietic tissue and limits the proliferation and production of RBCs. Splenomegaly induced by extramedullary erythropoiesis results in sequestration of circulating RBCs in the spleen. In addition, a proinflammatory environment develops from an abundance of inflammatory cytokine expression in the bone marrow to disrupt erythrogenesis.

For example, prednisone works by limiting the production of inflammatory cytokines which suppress the growth of bone marrow cells. Through its anti-inflammatory action, prednisone allows for more RBC production.

The JAK inhibitors currently approved for the treatment of MF—ruxolitinib and fedratinib—are also anti-inflammatory, thereby improving symptoms. They control night sweating and low-grade fever, resolve cachexia, and promote weight gain. However, at the same time, they are antiproliferative, which is why they actually decrease the RBC count and cause anemia.

**When would you resort to splenectomy?**

Refractory anemia is one of the indications for splenectomy. Splenectomy is indicated as the ultimate last resort for helping patients with anemia when the medications we've discussed stop working. With splenectomy, RBCs remain in circulation rather than collecting in the spleen.

**What are some of the emerging agents for the treatment of MF-associated anemia, and how far along are they in development?**

The JAK inhibitor momelotinib is in development as anti-anemia medication.[14,15] Unlike the JAK inhibitors approved for the treatment of MF, momelotinib can increase RBC count through its modification of hepcidin, which is a protein that is important for iron metabolism. Hepcidin expression is very high in MF. It is produced in the liver and is secreted in response to iron loading and inflammation. Hepcidin overexpression leads to functional iron deficiency, and the hope is that inhibition of hepcidin could enhance iron availability from the reticuloendothelial system for erythropoiesis.

It appears that momelotinib modulates hepcidin through direct inhibition of the protein ACVR1, also known as activin receptor-like kinase-2 (ALK2).[16] It is being studied in a phase 3 blinded, randomized study versus danazol, in the second-line setting after ruxolitinib or fedratinib failure. It is known that patients are more anemic in the second- line than in the first-line setting. One possible explanation is exacerbation of anemia through ruxolitinib's and fedratinib's action, as explained before. The other explanation is that the disease, MF, is just more aggressive after failure of first-line JAK inhibitors, causing more anemia. The understanding of possible mechanism of action of momelotinib will potentially open a new chapter in a development of anemia drugs, through modification of iron metabolism. Momelotinib is a JAK inhibitor and ACVR1 modulator. More specific drugs are being developed that target only iron metabolism and nothing else. A small-molecule inhibitor of the ALK2 receptor is currently in phase 1 clinical trials; this is a pill taken daily.

Another preclinical investigational agent that specifically targets iron metabolism is anti-hemojuvelin antibody.[17] Hemojuvelin is another protein directly involved in hepcidin expression.

TGF-beta is an inflammatory cytokine that suppresses RBC and exacerbates symptoms. Luspatercept is a recombinant fusion protein. It acts as a trap for the ligands that attach to activin receptors, thereby reducing TGF-beta signaling. This action enhances terminal erythropoiesis, allowing more erythrocytes to go through the maturation process. A recent phase 3 randomized study led to its FDA approval as a therapy for patients with myelodysplastic syndrome with ringed sideroblasts who are anemic.

The same concept is likely applicable in MF, and so luspatercept is being investigated in a phase 2 study as a therapy for patients with MF who are anemic, including patients who are on a stable dose of ruxolitinib and require transfusions.[18] At the most recent update in December 2020, the need for transfusion has been eliminated in about 30% of luspatercept recipients.

A phase 3 study has been announced in which patients with MF on a stable dose of ruxolitinib who require transfusions to treat their anemia will be randomized to luspatercept or placebo.

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