

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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The New NCCN Guidelines for the Management of Myelofibrosis



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H&O What is myelofibrosis?

RM Myelofibrosis is a myeloproliferative neoplasm, a type of chronic leukemia. Myelofibrosis can evolve from an antecedent polycythemia vera or essential thrombocythemia, or it can manifest as an initial diagnosis. The disease typically presents with anemia and other cytopenias, splenomegaly, and constitutional symptoms. It is diagnosed through assessment of the bone marrow; classic changes include the development of reticulin fibrosis. A more recent component of diagnosis is the presence of a key molecular marker in at least 1 of 3 genes: Janus kinase 2 (*JAK2*), myeloproliferative leukemia (*MPL*), and calreticulin (*CALR*).

H&O What is known about the molecular mechanisms?

RM It is known that the *JAK2* mutation, *MPL*, and *CALR* drive the development of myeloproliferative neoplasms, particularly myelofibrosis. It is less clear how the driver mutations that are present in earlier myeloproliferative neoplasms, such as essential thrombocythemia or polycythemia vera, evolve to the more advanced phases of myelofibrosis. Factors may include epigenetic changes; additional somatic mutations in other genes, such as additional sex combs like 1 (*ASXL1*), ten-eleven translocation-2 (*TET2*), and isocitrate dehydrogenase 1 (*IDH1*) and 2 (*IDH2*); and contributions of the bone marrow microenvironment, particularly in regard to inflammation. It is an evolving science with a variety of potential contributors for progression.

H&O What are the symptoms?

RM Symptoms are common and represent a range of different challenges. They appear to develop at least in part from increased cytokines that arise from the microenvironment owing to clones in the bone marrow. There can be symptoms related to splenomegaly, such as pain, discomfort, and abdominal fullness. Hypercatabolic symptoms include weight loss, night sweats, and fevers. Patients may develop pruritus. Symptoms from high blood counts (either leukocytosis, thrombocytosis, erythrocytosis, or a combination) include headaches, vascular events, and transient ischemic attacks.

Myelofibrosis can also aggravate other disease states, which can lead to less common symptoms, such as ascites.

H&O What are the treatment goals?

RM For appropriate candidates, stem cell transplant can achieve a cure. Stem cell transplant is used primarily in patients with intermediate-risk and high-risk myelofibrosis who are considered to be good candidates based on age, comorbidities, and the presence of a donor. For many patients with myelofibrosis, however, the goal is to decrease the burden of disease, which can include extending survival, decreasing splenomegaly, improving cytopenias, and/or alleviating difficult symptoms.

H&O What are the treatment options to decrease the disease burden?

RM The core treatment is ruxolitinib (Jakafi, Incyte),

which is the only broadly available approved therapy. Ruxolitinib, a JAK inhibitor, can improve splenomegaly symptoms and even prolong survival in patients with intermediate-2–risk and high-risk myelofibrosis. It is also used in patients with symptomatic intermediate-1–risk and lower-risk myelofibrosis.

Several therapies that can be helpful for alleviating anemia are used off-label. Examples include immunomodulatory drugs, such as thalidomide, lenalidomide (Revlimid, Celgene), and pomalidomide (Pomalyst, Celgene); androgens; and erythropoietin-stimulating agents. Hydroxyurea is sometimes used to control high blood counts in myelofibrosis, but its utility is limited.

H&O Does symptom progression indicate disease progression?

RM Symptom progression and disease progression overlap, but they are not necessarily equivalent. Risk assessment of myelofibrosis, using the Dynamic International Prognostic Scoring System (DIPSS) or DIPSS Plus, stratifies patients into low-, intermediate-1-, intermediate-2-, or high-risk disease based primarily on the presence of cytopenias, age, symptom burden, and movement toward acute leukemia (manifested by circulating blasts or abnormal karyotype). There are types of progression that are not associated with worsening symptoms, but could reflect an adverse prognosis. Worsening symptoms along the path of myelofibrosis include a bigger spleen and more cytopenias. However, progression to acute leukemia is not always associated with worsening symptoms; it can be signaled by an abrupt decrease in blood counts that then poses clinical challenges.

H&O How is the Myelofibrosis Symptom Assessment Form used?

RM The modified Myelofibrosis Symptom Assessment Form, version 2 (MFSAF v2.0) asks patients to rate the 7 core symptoms—night sweats, itchiness, abdominal pain, pain under the ribs on the left side, feelings of fullness (early satiety), bone or muscle pain, and inactivity—on a scale from 0 (absent) to 10 (worst imaginable; Table). This form and variants have been used in most of the clinical trials of new agents in myelofibrosis. The MFSAF has been more limited in use in clinical practice because of the need to facilitate incorporation into clinical workflows. Someone in the office must distribute the form, collect it, and input data into the electronic medical record. In our clinic, patients complete this brief form while waiting for their provider visits. Use of the form is now part of the management guidelines from the National Comprehensive Cancer Network (NCCN). In the future, it should be more broadly available and incorporated

Table. Questions in the Modified MFSAF V2.0^a

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| 1. During the past 24 hours, how severe were your worst night sweats (or feeling hot or flushed) due to MF? |
| 2. During the past 24 hours, how severe was your worst itchiness due to MF? |
| 3. During the past 24 hours, how severe was your worst abdominal discomfort (feeling uncomfortable, pressure, or bloating) due to MF? |
| 4. During the past 24 hours, how severe was your worst pain under the ribs on the left side due to MF? |
| 5. During the past 24 hours, what was the worst feeling of fullness (early satiety) you had after beginning to eat due to MF? |
| 6. During the past 24 hours, how severe was your worst bone or muscle pain due to MF (diffuse pain, not joint or arthritis pain)? |
| 7. During the past 24 hours, what was the worst degree of inactivity (including work and social activities) you had due to MF? |

^aEach question is answered according to a 10-point scale, from 0 (absent) to 10 (worst).

MF, myelofibrosis; MFSAF, V2.0, Myelofibrosis Symptom Assessment Form, version 2.0. Adapted from Mesa RA et al. *J Clin Oncol*. 2013;31(10):1285-1292.

into electronic medical records to assist patient care.

H&O What are the components of the NCCN Guidelines in myeloproliferative neoplasms?

RM In October 2016, the NCCN published inaugural guidelines for myeloproliferative neoplasms (MPNs). They cover the diagnosis, treatment goals, and prognosis in essential thrombocythemia, polycythemia vera, and myelofibrosis. Treatment guidelines were provided for myelofibrosis, and are forthcoming for essential thrombocythemia and polycythemia vera. The treatment guidelines for myelofibrosis focus mainly on the assessment of risk and symptom burden, and provide a stratified approach based on these factors in how to select medical therapy and when to initiate it, as well as when to consider stem cell transplant. Key areas of emphasis are to assess the evolution of the disease over time, to continually evaluate utilized therapies for efficacy and toxicity, and to strongly encourage enrollment in appropriate clinical trials at each stage when possible.

H&O In patients with low-risk, intermediate-1 disease, what types of symptoms indicate the need for treatment?

RM To some degree, this very issue—which symptoms

mandate therapy—is an active discussion between patients and their treating physician. The decision is somewhat predicated on how well the therapy in question is tolerated. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF), a 10-symptom assessment score, uses an escalating range of 0 to 100. Statistical analysis has shown that patients with a cumulative symptom score higher than 20, or with a single item higher than 5, will likely benefit from therapy. I consider treatment when a symptom is problematic for the patient and limits functioning, and if therapy will have a significant impact and be well-tolerated.

H&O Can treatment prevent symptoms from worsening over time?

RM Experience has shown that symptoms can be prevented from worsening over time with effective therapies such as ruxolitinib, interferon, hydroxyurea, or treatments used for controlling proliferative symptoms. Patients can experience stability or regression of their symptoms for many years. The progression of symptoms is frequently viewed as either a sign of disease progression or development of resistance or intolerance to a medication. Serial assessment of symptoms is helpful in tracking disease stability and the efficacy of therapy.

H&O Can early medical intervention attenuate disease progression?

RM I believe so. We still do not have a strong surrogate marker of progression, so assessment can be challenging. However, there are indications that effective early therapy, whether with interferon, JAK inhibition, or potentially other agents in development, might have an impact on delaying disease progression.

H&O Are there any other therapies in development for myelofibrosis?

RM There are many important therapies in development. The JAK inhibitors pacritinib and momelotinib are currently in advanced, phase 3 studies. These agents may well become available in the near future, with the potential for use in patients with cytopenias. Other therapies include the telomerase inhibitor imetelstat and the antifibrosing agent PRM-151. These 4 drugs are fairly advanced in their testing for myelofibrosis. If approved, they will impact decisions regarding treatment.

H&O Could you please describe the MPN Landmark study?

RM The MPN Landmark study surveyed patients and

physicians to identify any disconnects between patients' perceptions of how their disease was being managed and practices as reported by physicians. The goals were to assess communication between patients and physicians and to identify any sociologic burdens associated with the disease.

The survey identified 2 key discrepancies: one regarding treatment goals and the other concerning disease burden. For patients, the primary treatment goal was to delay progression of the disease or, when possible, reverse the disease. For physicians, the treatment goals evolved based on the efficacy of available therapies and therefore focus on avoiding thrombotic events, decreasing splenomegaly, and improving symptoms. Although patients still found those benefits of value, their main concern was to avoid disease progression.

The survey showed that the burden of disease can be significant and sometimes not fully appreciated by the treating team. In particular, MPNs can lead patients to retire early, choose employment positions with lower pay, and take a leave of absence owing to medical disability. There are a variety of ways in which the diseases are more morbid sociologically than is frequently discussed. An example is the need to limit activities outside of employment-related activity, such as hobbies and other desired activities, owing to disease burdens.

Disclosure

Dr Mesa is a consultant for Novartis, AOP, Shire, Ariad, and Galena. He has performed research for Incyte, Gilead, CTI, Promedior, and Celgene.

Suggested Readings

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