

NCCN Debuts New Guidelines for Myeloproliferative Neoplasms

Presented by Ruben A. Mesa, MD

Abstract

For the first time, NCCN has published guidelines specifically geared toward treating myeloproliferative neoplasms (MPNs). The first set of guidelines was developed for myelofibrosis (MF), and was presented at the NCCN 22nd Annual Conference. Future guidelines will be issued for polycythemia vera, essential thrombocytopenia, and atypical MPNs. Patients with MF can have an unpredictable course, one that is largely dependent on the presence of certain molecular alterations. Models are currently emerging that take into account molecular factors. Only one drug is currently approved for MF, the oral *JAK1/2* inhibitor ruxolitinib, which has been shown to significantly reduce splenomegaly and improve symptoms.

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Inaugural guidelines for the treatment of myeloproliferative neoplasms (MPNs) were unveiled at the NCCN 22nd Annual Conference. The first set of these guidelines discusses treatment recommendations only for myelofibrosis (MF). In 2017, guidelines will also be published for polycythemia vera and essential thrombocytopenia, which will be followed by recommendations for managing atypical MPNs, said Panel Chair Ruben A. Mesa, MD, Chair, Division of Hematology and Medical Oncology, Mayo Clinic Cancer Center.

“Among MPNs, treatment guidelines for MF are the most urgently needed,” Dr. Mesa said. “The new NCCN Guidelines bring consensus and tight evaluation of what has become standard practice and the evidence behind it.”

MPNs are a family of chronic leukemias that can progress to acute myeloid leukemia (AML) and affect patients in a variety of ways. MPNs are largely driven by key molecular abnormalities, and although they share many features with myelodysplastic syndromes

and chronic myeloid leukemia, they warrant their own guidelines, he said.

“If we look across the spectrum of these neoplasias, it’s important to recognize their interdependencies, as well as those aspects that are disease-specific. They are different entities, and our guidelines are different for them,” he advised.

Patient Assessment

For patient assessment, the NCCN MPN Panel drew from the WHO diagnostic criteria. For quantifying the symptom burden, it incorporated the MPN Symptom Assessment Form. For prognosis, clinicians should refer to the International Prognostic Scoring System (IPSS) at diagnosis and the dynamic IPSS (DIPSS) for subsequent risk assessment.

Molecular evaluation is a critical part of the initial assessment. Mutations that activate JAK/STAT (Janus kinase/signal transducer and activator of transcription) signaling are thought to drive the disease process in most patients with primary disease. Approximately 50% to 60% of patients carry the *JAK2* V617F mutation, and an additional 5% carry a mutation in *MPL* (*MPL* W151L/K). Mutations in *CALR*, another gene involved in dysregulated JAK/STAT signaling, are also common. Additional mutations can also be relevant, especially *ASXL1* and *SRSF2*. These mutations often

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New NCCN Guidelines for MPNs

co-occur with the 3 driver mutations, are not exclusive of each other, and may impact prognosis. *ASXL1*, for example, is independently associated with inferior leukemia-free survival and overall survival (OS), Dr. Mesa pointed out.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for MPNs summarize the prognostic significance of approximately a dozen relevant mutations. For example, the *JAK2* V617F mutation conveys an intermediate prognosis and a higher risk of thrombosis compared with a *CALR* mutation. Taking into account these mutations is the mutation-enhanced IPSS,¹ which refines risk stratification within the IPSS categories. According to this model, the presence of one additional mutation in a patient with IPSS intermediate-1 risk will reduce the median OS to 8 years, down from 17 years in the absence of the mutation.¹

“This information is very relevant in distinguishing patients for the various treatments,” he said, “and is a rapidly moving part of the discussion.”

Symptom Burden

Survival in patients with primary MF can range from “close to age-matched controls” to “markedly diminished,” Dr. Mesa said; however, the risk of evolution to AML is not the only concern with primary MF. “Implications for health can be independent of that,” he said. “I’ve known patients with pruritus to commit suicide.”

The potential for a substantial symptom burden is largely driven by inflammation and factors related to splenomegaly (Figure 1). The MPN Symptom Assessment Form helps capture this important part of the picture (Figure 2).

Treatment Selection

“Treatment selection begins with a molecular understanding of the cancer, but does not end with this,” Dr. Mesa commented. Symptom profile, ability to metabolize drugs, psychosocial circumstances, personal beliefs, treatment side effects, treatment expense, and treatment goals are all factors in deciding whether or how to treat. “It’s not solely about the tumor,” he emphasized.

Only one drug, ruxolitinib, an oral JAK1/2 inhibitor, is FDA-approved for the treatment of MF.

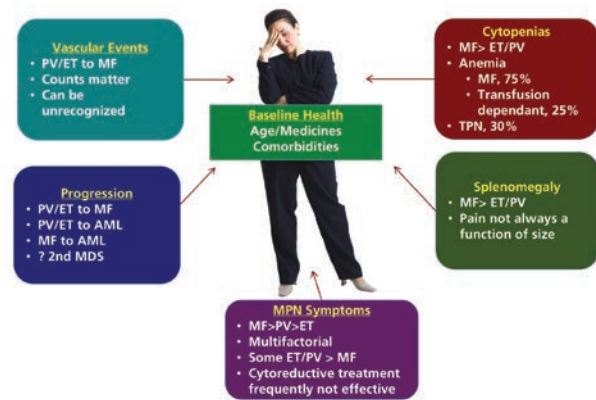


Figure 1. Assessing MPN burden: WHO diagnosis does not tell the whole story.

Abbreviations: AML, acute myeloid leukemia; ET, essential thrombocytopenia; MDS, myelodysplastic syndrome; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythemia vera; TPN, thrombocytopenia.

In the phase III COMFORT-I trial, 41.9% of ruxolitinib-treated patients achieved the primary endpoint ($\geq 35\%$ reduction in spleen volume) compared with 0.7% of the placebo group ($P < .001$). Symptom scores in the ruxolitinib group were also significantly improved ($P < .0001$).² In a recent 5-year update, responses were durable and median OS was not reached with ruxolitinib, but was 200 weeks with placebo.³

The NCCN Guidelines position the use of ruxolitinib among the various risk groups and treatment settings: low and intermediate-1 risk; high and intermediate-2 risk; and progressive disease.

For intermediate-1–risk and low-risk patients, those who are asymptomatic can be monitored or enrolled on a clinical trial; symptomatic patients can receive ruxolitinib or interferon (experimentally) or enter a clinical trial. Intermediate-2–risk or high-risk patients are indicated to undergo allogeneic hematopoietic transplantation if appropriate; nontransplant candidates are assessed for platelet count and treated with ruxolitinib (or enrolled in a frontline trial) if the platelet count is $> 50,000$ mL, or enrolled on a trial if the count is $< 50,000$ mL. If patients are symptomatic only in terms of anemia, a parallel algorithm is provided in the guidelines.

Patients with disease progression to advanced-phase AML undergo bone marrow assessment and more molecular testing. These patients then generally follow treatment recommendations for leukemia.

The NCCN Guidelines also discuss the measurement of treatment response, which is complex in

Mesa

MYELOPROLIFERATIVE NEOPLASM SYMPTOM ASSESSMENT FORM
TOTAL SYMPTOM SCORE (MPN-SAF TSS-10 ITEMS)
 (Recommended for monitoring symptoms during the course of treatment)

Circle the one number that describes how, during the past week how much difficulty you have had with each of the following symptoms

Filling up quickly when you eat (early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration-compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Numbness/Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

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Figure 2. Myeloproliferative neoplasm symptom assessment form: total symptom score.

this disease, and the management of anemia, which can be difficult in this patient population.

New Drugs in Development

Several drugs are in development for MF, including 2 JAK inhibitors. Furthest along in development is pacritinib, which specifically targets patients with intermediate- or high-risk MF with low platelet counts (<50,000 mL), for which ruxolitinib is not approved. A hold was placed on the drug in February 2016 for safety reasons, but was lifted in January 2017 based on PERSIST-2.⁴ Results demonstrated that 18% of patients achieved a $\geq 35\%$ reduction in spleen size with pacritinib compared with 2% receiving best available care ($P < .001$). With twice-daily dosing, 32% of patients had a $\geq 50\%$ reduction in symptoms com-

pared with 14%, respectively. Serious cardiac events and bleeding, which had been a concern, were relatively rare and comparable between all groups.

“Additional studies are required—and they are enrolling soon—trying to identify the minimum effective dose of pacritinib that will achieve an optimal balance of safety and efficacy,” Dr. Mesa said.

The future is less certain for momelotinib, the other JAK2 inhibitor currently under development, which yielded mixed results compared with ruxolitinib in the Simplify 1 and Simplify 2 trials.⁵ Phase II studies are underway for the antifibrosing agent, PRM-151, and the telomerase inhibitor, imetelstat. Research efforts are also focused on boosting the activity of ruxolitinib with a second agent, such as histone deacetylase inhibitors and PI3K inhibitors. None of these combinations are recommended yet in the NCCN Guidelines.

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