ManagingMPN

Ruxolitinib Failure or Moving On from First Line Therapy

What does progressive disease look like and what does that mean to my outcomes?

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"Patient-centered communication is critical to patient and caregiver engagement in treatment decision making, treatment adherence, monitoring and mitigation of disease and treatment related adverse events."

Optimally, patient and caregiver educational strategies should evolve parallel to efforts to educate clinicians. The evolving understanding of myeloproliferative neoplasms (MPNs) at a molecular level along with a growing number of novel agents moving toward approval at a fast pace has brought into question the utility of existing models for risk stratification and risk-adapted treatment selection. The complexity of clinical decision making has naturally increased.

Given the heterogeneity of the myelofibrosis (MF) patient population, tailoring education to the individual patient at each point in their disease trajectory is essential. Effectively describing MF as a hematologic malignancy, then reviewing treatment options and the criteria for selecting treatment at each phase to a patient requires a level of knowledge on the part of the clinician such that they can tailor that description in a way that is understandable for the patient and their caregivers. For clinicians, even those with a subspecialty in hematology, assimilating the constant scientific developments across disease states is a growing challenge.

Consensus statements and clinical guidelines provide a synopsis of key scientific findings that warrant a change in practice. As the complexity of scientific data for MPNs increases, the application of these data to practice is in its early phase. Articulating clinical recommendations to establish guidelines and treatment recommendations becomes increasingly challenging, often changing frequently as clinical trial data mature.

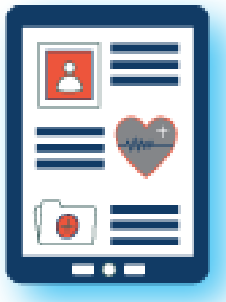
"What is often missing from these published guidelines is the art of clinical decision making, finessing clinical management strategies, and deploying patient and caregiver communication strategies that allow for shared decision making and maximizing each treatment option."

This is particularly true of treatment decision making in the setting of ruxolitinib failure or intolerance in patients with MF. A lack of clarity in the definitions for ruxolitinib resistance or failure and evolving criteria defining disease progression have added to the challenges in clinical decision making.[1]

Understanding the recent evolution of treatment options outside ruxolitinib is necessary to adequately frame these challenges. Transplant remains the only potentially curable treatment option, but is sometimes not an option for most patients with MF due to age or other medical problems and for those eligible, associated with substantial risk of morbidity and mortality.[2] Ruxolitinib (approved November 16, 2011) was the only Janus kinase (JAK) inhibitor commercially available for eight years and provided the foundation for disease modifying treatment of MF.[3] Efforts to optimize ruxolitinib treatment for as long as possible have been the focus of clinical management guidelines given the poor survival estimates after ruxolitinib failure ranging from less than four months to just over two years dependent on chronic phase vs. blast phase at the time of progression.[4-7] On August 19, 2019, fedratinib obtained FDA approval for patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF) offering the first alternative JAK inhibitor. Most recently, pacritinib (approved in March 2022), represents a third in class JAK inhibitor with an indication specific to patients with concurrent thrombocytopenia. However, the FDA defined indications do not provide sufficient guidance for clinicians contemplating the best option for each patient, regardless of prior ruxolitinib treatment. Rather, most clinicians base their treatment selection on familiarity with each agent, information obtained from educational sessions, published literature, or through consultation with MF experts.

With just three years of real-world clinical experience with JAK inhibitors other than ruxolitinib and anticipated approvals for additional agents with varied mechanisms of action, consensus statements, guidelines and clinical pearls will be essential to provide the structure for informed treatment decision making, including discussions with patients. Many of these agents are being evaluated as add-on options for patients on ruxolitinib underscoring the need to better define ruxolitinib resistance or failure.[1,8] All agents are available only because patients have participated in clinical trials. Continued consideration of clinical trials for eligible patients should remain a primary consideration in treatment decision making.

The Dynamic IPSS (DIPSS) and the DIPSS-Plus provide objective measures for describing disease characteristics with prognostic significance including spleen size, blood counts over time, and other pertinent clinical findings.[3,9] Reduction in symptom burden is a primary outcome for all MF clinical trials to date. However, neither tool includes measures for overall symptom burden, present in more than 90% of patients with MPNs.[10,11] Quantifying symptom burden is much more nebulous than quantifying clinical measures, yet essential to describing the potential impact of disease or treatment related symptoms and the potential for symptom burden improvement with treatment. The tools used to measure symptom burden have evolved over time based on identified gaps in adequate measures of key symptoms, particularly fatigue, the most reported symptom across all patients with MF.[12] Although the Myeloproliferative Neoplasm Symptom Assessment Form - Total Symptom Score (MPN-SAF TSS), was used in early MPN clinical trials, gaps in reporting and inclusion of key symptoms have required an evolution of these tools.[12,13] The 18-item MPN-SAF-TSS was simplified to a 10-item MPN-10 tool with an item from the Brief Fatigue Inventory (BFI) to include a measure of fatigue.[13] Most recently, a myelofibrosis specific tool, the MFSAF v4, has been validated to effectively measure symptom burden, including fatigue and is the preferred tool for ongoing clinical trials specific to MF.[12,14]



Quantifying the patient's experience is an elusive target fraught with the nuances of patient reported outcomes. This requires clinicians to evaluate changes in symptoms over time to apply this information to treatment decision-making. The challenge of effective communication across clinicians and over time requires integrating validated tools into clinician's workflow within a patient visit and within the electronic health record (EHR). Validated tools used in clinical trials are rarely imbedded into the EHR. Trends over time are difficult to discern unless vigilant clinicians incorporate this information into the EHR such that it is visible across team members and specialties. Unfortunately, barriers remain in actualizing this workflow, limiting the application of these validated tools into mainstream clinical practice. Familiarity with each question used to solicit patient reported outcomes is essential for clinicians to effectively integrate symptom burden assessment into their patient-clinician interactions and patient education. The items used to measure self-reported MF symptoms in previous MF trials is summarized by Gwaltney et al. in the supplementary materials at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8207823/[14]

Registry trials measuring the patient experience over time including the MPN Landmark study and the MOST study, have added a dimension of understanding of the lived experience of patients with MPNs, including MF. Discordant perceptions of the effectiveness of communication between clinicians and patients underscores the need to better engage patients and their caregivers in developing patient-facing decision tools that facilitate patient-clinician communication and shared decision making.

"Producing plain language summaries that describe key findings of clinical trials, basic science discoveries, and how these findings impact treatment decision making are critical to effective integration of clinical trials data into practice."

The basic principles of patient centered communication are at the core of successfully engaging the patient and their caregivers in shared-decision making. This concept will be discussed in greater detail in forthcoming segments of this series. The basic concepts of setting expectations at each visit with the goal of extending survival and achieving optimal quality of life by incorporating the individual patient and caregiver goals of care within the context of appropriate treatment options should guide treatment decision making at each phase of treatment.

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