Improving Disease Burden in Myelofibrosis: Changing the Natural History of the Disease

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Palliation is a laudable concept and an important goal in the therapy of all patients with malignant disease. Unfortunately, in the current day and age, the adjective “palliative” is being used in a derogatory manner that suggests palliation of suffering somehow lessens the importance or impact that such a therapy has upon individuals with the disease.

Myelofibrosis: A Very Heterogeneous Myeloid Neoplasm

The review by Kremyanskaya and colleagues[1] regarding the utilization of ruxolitinib (Jakafi) in the therapy of myelofibrosis (MF) raises many important issues regarding how we assess drug efficacy in MF, the heterogeneous nature and impact of the disease, the published data regarding utilization of ruxolitinib, and practical advice for potential prescribers. At its core, the key question posed by the authors is, “What is the aggregate benefit of ruxolitinib in MF: palliation or improvement of the natural history of this disease?”

The quite varied natural histories of MF and related chronic myeloid disorders are evidenced by the increasing number of diverse prognostic scores that are available for these ailments (eg, the International Prognostic Scoring System [IPSS][2]; the Revised IPSS developed by the International Working Group for Prognosis in Myelodysplastic Syndrome [MDS IPSS-R][3]; the Dynamic IPSS [DIPSS][4]; and DIPSS Plus[5]). Among MF patients, the survival can vary from an average of a little over 2 years to more than a decade.[2,4,5] The clinical prognostic variables in MF include the degree of cytopenias, the symptomatic burden, and the presence of peripheral blood blasts. Additionally, increasing age is prognostically detrimental, given how much longer the survival can be in younger patients with MF, although increased age may represent the impact of comorbidities (not yet studied as an independent prognostic variable in MF). Cause of death in MF patients[3] is generally the MPN blast phase (around 30% of patients), a comorbidity unrelated to the myeloproliferative neoplasm, or a complication of MF (thrombosis, transfusion reaction, pneumonia, an infectious event). Finally, many (difficult to quantify) patients can die from having the stress of the MF (splenomegaly, cachexia, debilitation, cytopenias) further exacerbate underlying comorbidities.

Heterogeneous Nature of Myelofibrosis-Related Symptom Burden

The heterogeneity of the morbidity associated with MF is further highlighted by the spectrum of symptomatic difficulties that can be seen among patients with the illness. Utilizing the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)[6] and the subsequent analysis of the Total Symptom Scores (TSS).[7] we see that there exists a significant spectrum of symptom burden among patients with MF, from those who are essentially asymptomatic to those who are highly symptomatic. Additionally, we have identified that there are clusters of symptoms that vary among affected patients—eg, the onset and impact of weight loss, and the degree and onset of anemia, fatigue, and bone pain.[8] These observations regarding the spectrum and impact of the symptom burden underscore the heterogeneous natural history of the disease.

Myelofibrosis: Plateaus, Declines, and Causes of Death

How do we make sense of the spectrum of both the prognostic variability that is seen with MF as well as the spectrum of time course and intensity of progression from essential thrombocytopenia (ET) and polycythemia vera (PV) to post-ET and post-PV myelofibrosis?[9] Data on symptomatic burden from the MPN-SAF efforts, coupled with clinical observations of disease course, would suggest that MF is not a disease of continuous progressive decline, but rather is a disease of periods of clinical plateau and clinical decline. Factors that affect whether an individual is in plateau or decline revolve around the three main axes of difficulty that patients with MF can experience, including progressive
or stable splenomegaly, progressive or stable weight loss and constitutional symptoms, and progressive or stable cytopenias. It is therefore very reasonable to suspect that the stepwise correction of one of the axes of decline for MF patients may well improve the trajectory (ie, natural history) of the disease.

Ruxolitinib and JAK2 Inhibition in Myelofibrosis: What Are the Benefits?

The review article highlights clearly the randomized data demonstrating a survival advantage for the successful use of ruxolitinib compared with placebo[10] and “best alternative therapy.”[11] What conclusions can we draw from this? Mainly that individuals eligible for clinical trials, who had intermediate-2 and high-risk MF, survived longer on ruxolitinib than those who initially received either placebo or alternative therapy.[9] At present it is impossible to determine why a survival advantage is observed, yet it is logical to speculate that it results from improvement in performance status, debilitation, and weight loss, all features that potentially lead to increased mortality in patients with MF. Other JAK2 inhibitors (SAR302503,[12] CYT387,[13] pacritinib[14]) have similarly been shown to improve (in earlier nonrandomized phase I and II studies) MF-related splenomegaly, symptoms, and debilitation. Although it is not possible to assess an impact on survival rates in these latter nonrandomized studies, I believe it would not be unexpected for individuals with successful responses while receiving these medications to have improved survival. Similarly, medications that have a significant impact on the anemia of MF (thalidomide,[15] lenalidomide [Revlimid],[16] pomalidomide [Pomalyst],[17] or other therapies efficacious for anemia) may similarly improve survival in individual patients, whether or not there are randomized clinical data to prove that benefit.

Beyond Palliation: Improving the “Natural” History of Advanced Myelofibrosis

Palliation is a laudable concept and an important goal in the therapy of all patients with malignant disease. Unfortunately, in the current day and age, the adjective “palliative” is being used in a derogatory manner that suggests palliation of suffering somehow lessens the importance or impact that such a therapy has upon individuals with the disease. JAK2 inhibitors have improved the major morbidities of MF—splenomegaly, symptomatic burden, a decreased quality of life—and demonstrate improvement in survival. These benefits of JAK2 inhibition should not be viewed as diminished in importance simply because we do not see an improvement in a histological feature of indeterminate prognostic significance, namely reticulin fibrosis. I would conclude, given the current state of evidence, that appropriate use of therapies that impact the burden of MF in affected patients not only palliates the suffering caused by this disease but also improves the natural history of death precipitated by disease burden. Incremental synergy of the medical therapies that might further impact the pathogenetic underpinnings of progression in the marrow may augment the aggregate impact of medical therapy for patients with MF.

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References:

REFERENCES


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