Diagnosing and Assessing Risk in Myelofibrosis

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MediCom recently spoke with a leading expert to discuss challenges in the diagnosis of myelofibrosis, as well as the evolving risk stratification scoring systems that have emerged over the last several years.

What are some of the challenges associated with diagnosing myelofibrosis (MF)?

Dr. Vachhani: There are a few different challenges in the path towards a diagnosis of MF. First, there are the symptoms, which are often vague and non-specific. Patients may or may not report constitutional symptoms such as weight loss, fatigue, pruritus, bone pain, thrombosis, and bleeding, as well as hepatosplenomegaly. Especially when these symptoms are mild, patients tend to ignore those symptoms or attribute them to other causes. There are also the laboratory parameters of MF, which can be difficult to distinguish from other myeloproliferative disorders like polycythemia vera (PV), essential thrombocytopenia (ET), myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML), et cetera. It takes skill and expertise to accurately differentiate between these disorders, which have many overlapping features.

What are the features of MF that are required for an accurate diagnosis?

Essentially, a diagnosis of MF should meet the World Health Organization (WHO) diagnostic criteria while failing to meet the criteria for an alternate myeloid malignancy.[1] Major criteria for pre-fibrotic/early primary MF (PMF) under the WHO diagnostic schema include:

- Megakaryocytic proliferation and atypia, without reticulin fibrosis > grade 1, accompanied by increased age-adjusted bone marrow (BM) cellularity, granulocytic proliferation and often decreased erythropoiesis
- Failure to meet WHO criteria for *BCR-ABL1 +* CML, PV, ET, MDS, or other myeloid neoplasm
- Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker or absence of minor reactive BM reticulin fibrosis

Minor criteria for pre-fibrotic/early PMF include one or more of the following: anemia not attributable to a comorbid condition; leukocytosis ≥11x10^9/L; palpable splenomegaly; lactate dehydrogenase (LDH) level above the upper limit of the reference range.

For overt PMF, major criteria include:

- Megakaryocyte proliferation and atypia accompanied by either reticulin and/or collagen fibrosis (grade 2 or 3)
- Failure to meet WHO criteria for *BCR-ABL1 +* CML, PV, ET, MDS, or other myeloid neoplasm
- Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence, the presence of another clonal marker or absence of evidence for reactive BM fibrosis

Minor criteria for overt PMF include all of those for pre-fibrotic/early PMF plus leukoerythroblastosis.

For example, a case might include a person in their mid-fifties or early sixties, who develops mild anemia, a slightly elevated platelet count, and a blood analysis revealing a *JAK2* mutation. To confirm a diagnosis of MF, this patient would require a bone marrow (BM) biopsy with findings of megakaryocyte changes and reticulin or collagen fibrosis. Bone marrow fibrosis in PMF is usually associated with JAK2, CALR, or MPL mutations, with common karyotype features including +9, del(13q), del(20q), and chromosome 1q duplication or other chromosome 1 abnormalities. Pre-fibrotic MF could be distinguished from ET through evidence of tight clusters of megakaryocytes demonstrating abnormal maturation. This distinction is an essential aspect of disease analysis, as it is prognostically relevant. MDS could be ruled out through the absence of dyserythropoiesis or dysgranulopoiesis. The presence of dwarf megakaryocytes raises the possibility of CML and should be pursued with BCR-ABL1 cytogenetic or molecular testing.

Additionally, performing a broad NGS panel can help to both identify driver mutations and allow for risk stratification of patients. Prognostically important mutations include SRSF2, ASXL1, IDH1/2, EZH2, U2AF1, TP53, and CBL, all of which confer poorer outcomes. Patients with these mutations are less likely to benefit or maintain their benefit from therapy and are more likely to progress to the leukemic phase of the disease. Higher risk molecular gene mutations would tell us that the patient is at greater risk for progression or poor response to therapy, and therefore allow us to change the treatment course and maybe even refer them to transplant earlier rather than later.

What are the available risk stratification schemas that can be applied to MF patients?

Risk stratification scores have evolved significantly in the last few years. The International Prognostic Scoring System (IPSS) was developed over a decade ago for risk stratification of MF.[2] This score assigned risk based on five independent predictors of inferior survival: age > 65 years; hemoglobin (Hb) <10 g/dl; leukocyte count >25 × 10^9/L; circulating blasts ≥1%; and presence of constitutional symptoms. The presence of 0, 1, 2 and ≥3 adverse factors defined low, intermediate-1, intermediate-2 and high-risk disease, with corresponding median survivals being 11.3 years, 7.9 years, 4.0 years, and 2.3 years, respectively.

Later, the dynamic IPSS (DIPSS) was developed, which was intended to be used at any point in the patient journey, rather than limited to time of diagnosis.[3] This included much of what is in the IPSS, but with more weight on anemia; the DIPSS assigned 2 (rather than 1) adverse points for Hb <10 g/dl. With this change, risk was categorized into low (0 adverse points), intermediate-1 (1 or 2 points), intermediate-2 (3 or 4 points) and high (5 or 6 points) subsets. The respective median survivals were: not reached; 14.2 years; 4 years; and 1.5 years.

The DIPSS was further refined by the DIPSS-plus,[4] which modified the previous prognostic scoring systems with the addition of independent risk factors, including karyotype, transfusion dependency and platelet count <100 × 10^9/L. These factors, combined with age, constitutional symptoms, WBC count, hemoglobin, and peripheral blood blasts, are combined into a 6-point scoring system, where 0 points is low-risk, with a median survival estimated at 180 months, while ≥4 points is high risk, with a median survival estimated at 16 months.

Newer risk stratification schemas that utilize genetic data are the MIPSS70 (mutation-enhanced IPSS70) and the MIPSS70+ version. These scoring tools combine symptoms and blood count values with high molecular risk gene mutation data to allow for more accurate risk stratification. The most recent iteration is the MIPSS70+ v2.0,[5] which has refinements in degrees of anemia, cytogenetics, and high molecular risk (HMR) category, based on the presence of prognostically detrimental mutated genes. The components of this score are summarized in the following table:

Component	Point
Very high risk (VHR) karyotype - single or multiple abnormalities of −7, inv(3)/3q21, i(17q), 12p-/12p11.2, 11q-/11q23, autosomal trisomies other than +9 or +8	4
Favorable karyotype - Normal karyotype or sole abnormalities of 20q-, 13q-, +9, chromosome 1 abnormalities including 1q duplication, loss of Y chromosome or other sex chromosome abnormality	0
Unfavorable karyotype (neither VHR nor favorable)	6
≥2 HMR mutations	3
1 HMR mutation	2
Absence of type 1/like *CALR* mutation	2
Constitutional symptoms	2
Severe anemia (Hb <8 g/dL in women or <8 g/dL in men)	2
Moderate anemia (Hb 8-9.9 g/dL in women and 9-10.0 g/dL in men)	1
Circulating blasts ≥2%	1

The risk categories for MIPSS70+ v2.0 include: high risk (5–8 points); intermediate risk (3–4 points); low risk (1–2 points); and very low risk (zero points). In patients aged 70 years or younger, the corresponding 10-year median survival rates were 1.8 years (<5%), 4.1 years (13%), 7.7 years (37%), 16.4 years (56%) and “median not reached” (92%).

Additionally, there is now the MYSEC-PM Prognostic Model Risk Calculator.[6] This online calculator is intended for use in patients who have post-PV or post-ET MF (ie, secondary MF). Research has demonstrated subtle but important differences in patients who evolve from PV or ET to MF; these patients typically have more normalized Hb and platelet counts compared with primary MF, and the absence of anemia may have different indications. I typically utilize this tool in my secondary MF patients.

These scoring tools have helped to clarify anticipated patient outcomes and response to therapy. They have allowed for more precise treatment selection and guided clinical trial design and enrollment. It is essential that all practicing providers utilize these tools correctly as a means of improving treatment and – ideally – outcomes for patients with MF.

References

1. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016 May 19;127(20):2391-405.
2. Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. *Blood*. 2009 Mar 26;113(13):2895-901.
3. Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). *Blood*. 2010 Mar 4;115(9):1703-8.
4. Gangat N, Caramazza D, Vaidya R, et al. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. *J Clin Oncol*. 2011 Feb 1;29(4):392-7.
5. Guglielmelli P, Lasho TL, Rotunno G, et al. MIPSS70: Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients With Primary Myelofibrosis. *J Clin Oncol*. 2018 Feb 1;36(4):310-318.
6. Passamonti F, Giorgino T, Mora B, et al. A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis. *Leukemia*. 2017 Dec;31(12):2726-2731.

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