Prognosis of Primary Myelofibrosis in the Genomic Era

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Abstract

Currently, prognostication in primary myelofibrosis (PMF) relies on the International Prognostic Scoring System (IPSS), dynamic IPSS (DIPSS), and DIPSS-plus, which incorporate age, blood counts, constitutional symptoms, circulating blasts, red cell transfusion need, and karyotype. Although the *JAK2* V617F mutation was discovered a decade ago and *MPL* mutations shortly thereafter, it was the recent discovery of *CALR* mutations in the vast majority of *JAK2/MPL*-unmutated patients and recognition of the powerful impact of *CALR* mutations and triple-negative (*JAK2/MPL/CALR*-negative) status on outcome that set the stage for revision of traditional prognostic models to include molecular information. Additionally, the advent of next-generation sequencing has identified a host of previously unrecognized somatic mutations across hematologic malignancies. As in the myelodysplastic syndromes, the majority of common and prognostically informative mutations in PMF affect epigenetic regulation and mRNA splicing. Thus, a need has arisen to incorporate mutational information on genes such as *ASXL1* and *SRSF2* into risk stratification systems. Mutations in yet other genes appear to be important players in leukemic transformation, and new insights into disease pathogenesis are emerging. Finally, the number of prognostically detrimental mutations may affect both survival and response to ruxolitinib, which has significant implications for clinical decision making. In this review, we briefly summarize the prognostic models in use today and discuss in detail the somatic mutations commonly encountered in patients with PMF, along with their prognostic implications and role in leukemic transformation. Emerging prognostic models that incorporate new molecular information into existing systems or exclude clinical variables are also presented.

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Introduction

Primary myelofibrosis (PMF), the most aggressive of the classic Philadelphia chromosome—negative (Ph−) myeloproliferative neoplasms (MPNs),[1] is a clonal stem-cell disorder clinically characterized by anemia, splenomegaly, extramedullary hematopoiesis, a variety of constitutional symptoms, and relatively short survival.[2] In a Swedish population-based study of 9384 individuals with Ph− MPNs diagnosed from 1973 through 2008, survival was found to have improved significantly over time; however, the improvement was less pronounced after the year 2000 and was confined to patients with polycythemia vera (PV) and essential thrombocythemia (ET).[3] Another European study examined survival trends among patients diagnosed with PMF between 1980 and 1995 (n = 434) and between 1996 and 2007 (n = 368), and found a significant improvement in median survival between the 2 eras (4.6 vs. 6.5 years); however, reduction in disease-specific mortality was restricted to the lower risk categories, with no improvement in survival of intermediate-2 or high risk patients.[4] Recently, the Janus kinase (JAK)-1/2 inhibitor ruxolitinib, approved by the US Food and Drug Administration for the treatment of patients with intermediate or high risk PMF or with post-PV or post-ET myelofibrosis (MF) has demonstrated a survival benefit for these poor risk categories of patients in randomized controlled clinical trials[5,6] compared to matched historical controls,[7,8] as well as in a meta-analysis of pivotal registration trials in the United States and Europe.[9]

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Current Prognostic Classification Systems in PMF

Although a number of prognostic scoring systems have been used over the years,[10] robust prognostic modeling in PMF began with the publication of the International Prognostic Scoring System (IPSS) by the International Working Group for Myelofibrosis Research

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and Treatment (IWG-MRT) in 2009.[11] This simple and widely used system uses 5 clinical variables: age > 65 years, constitutional symptoms, hemoglobin < 10 g/dL, leukocyte count > 25×10^9/L, and circulating blasts ≥ 1%, each assigned 1 point, to delineate 4 prognostic categories: low, intermediate-1, intermediate-2, and high. The respective median survivals in these 4 categories were 135, 95, 48, and 27 months in the original cohort of 1054 consecutively diagnosed PMF patients.[11] In the IPSS data set, patients without splenomegaly at diagnosis survived longer than those with splenomegaly, but the difference did not reach statistical significance, and including splenomegaly at diagnosis as a variable did not improve the prognostic model.[11]

The IPSS risk factors were then validated at later time points, leading to the development of the Dynamic IPSS (DIPSS), which can be used at any time point in the patient's clinical course.[12] Anemia (hemoglobin < 10 g/dL) was assigned 2 points in this model, with the other IPSS clinical variables receiving 1 point each. Median survivals were not reached, 14.2, 4, and 1.5 years for low, intermediate-1, intermediate-2, and high risk patients, respectively.[12] Importantly, the DIPSS has also been shown to predict progression to blast phase (BP) in PMF.[13] Additionally, its usefulness in predicting outcomes after allogeneic hematopoietic cell transplantation has been shown.[14]

Recognition that unfavorable cytogenetic abnormalities,[15-18] red blood cell transfusion dependence,[19] and thrombocytopenia[15,17] affect prognosis in PMF led to the refinement of the DIPSS into the DIPSS-plus,[20] which adds these 3 adverse features to DIPSS risk. Thus, 1 point each is assigned to DIPSS intermediate-1 risk, unfavorable karyotype (defined as complex karyotype, or single or 2 abnormalities including +8, −7/7q−, i(17q), −5/5q−, 12p−, inv(3), or 11q23 rearrangement), platelets < 100×10^9/L, and red blood cell transfusion need.[20] DIPSS intermediate-2 and high risk are assigned 2 and 3 points, respectively. Low (0 points), intermediate-1 (1 point), intermediate-2 (2-3 points), and high (4-6 points) risk patients had median survivals of 180, 80, 35, and 16 months, respectively.[20] A model that assigns 2 points to very high risk cytogenetics (monosomal karyotype or inv(3)/i(17q)) and 1 point each to circulating blasts ≥ 2% and platelets ≤ 50×10^9/L to classify patients as being at low (0 points), intermediate (1 point), or high (≥ 2 points) risk for leukemic transformation (LT) has been proposed by the IWG-MRT, with 3-year LT rates of 3%, 10%, and 35%, respectively.[21]

Driver Mutations in Ph− MPNs

A driver mutation is one that confers a selective advantage to a cell with self-renewal capacity, leading to the formation of a clone of mutated cells.[22] Driver mutations can be founding (initiating) mutations, which give rise to the initial clone of a malignancy, or subclonal (cooperating) mutations, which occur in an already established clone and generate subclones carrying both the founding and the newly acquired mutation.[22] Subclonal mutations are commonly associated with disease progression.[22] In the case of Ph− MPNs in particular, an important concept is that the founding driver mutations, while largely driving disease phenotype, are not necessarily the first somatic mutations leading to the development of these disorders.[22]

JAK2 *Mutations*

The observation that acquired uniparental disomy (UPD) of chromosome 9p (loss of heterozygosity due to mitotic recombination) was a frequent stem-cell defect in PV[23] set the stage for the discovery in 2005 of the activating *JAK2* V617F mutation,[24-27] found in approximately 95% of patients with PV and 50% to 60% of patients with ET and PMF. This mutation in the pseudokinase domain of JAK2 is unique to myeloid malignancies and removes its inhibitory influence on the catalytic domain, leading to constitutive activation of the kinase.[28] A specific constitutional *JAK2* haplotype, designated 46/1 (GGCC), confers MPN susceptibility by preferentially acquiring the V617F mutation,[29,30] as does a germ-line *JAK2* single-nucleotide polymorphism, rs10974944.[31] In addition to the well-known canonical actions of JAKs in transducing signals from membrane-bound cytokine and hematopoietic growth factor receptors, both wild-type and mutant JAK2 translocate to the nucleus and phosphorylate histone H3 to regulate gene expression.[32] Furthermore, mutant JAK2 phosphorylates the protein arginine methyltransferase PRMT5 with much greater affinity than wild-type JAK2, leading to decreased methyltransferase activity and increased myeloproliferation.[33]

Expression of *JAK2* V617F in mice induces a PV-like disease with secondary myelofibrosis,[34-38] although experimental manipulation of the *JAK2* V617F allele burden can result in ET- or PMF-like phenotypes.[39,40] *JAK2* V617F homozygous mice develop a severe hematopoietic stem cell (HSC) defect, suggesting that additional lesions are needed to sustain clonal expansion.[41] While homozygosity for *JAK2* V617F is most common in patients with PV, the mutant allele burden in patients with PMF is often equally high.[42] In fact, the *JAK2* V617F allele burden is extremely low in HSCs from PV and ET patients at diagnosis, rising only at late stages of hematopoiesis,[43,44] whereas it is much higher in HSCs from patients with PMF or post-PV/ET MF.[45,46] The *JAK2* V617F mutation appears to provide only a minor advantage to HSCs, such that on its own, it would cause disease with a very long latency.[47,48] Therefore, cooperation with other genetic events modifying HSC biology would greatly facilitate the development of the MPN phenotype.[49] It has been suggested that JAK2 V617F-bearing HSCs remain harmless for a long time, until genetic or environmental changes such as hematopoietic stress or aging allow clonal dominance and MPN emergence.[49] Indeed, PMF has been considered to be an accelerated phase of the classic Ph− MPNs.[49,50] Finally, there is considerable evidence to support the acquisition of *JAK2* V617F as being a late event in at least some patients with Ph− MPNs,[51-54] and nullizygosity for the *JAK2* 46/1 haplotype has been associated with shortened survival, regardless of the presence or absence of the V617F mutation.[55] Taken together, these observations point to the underlying genomic complexity of Ph− MPNs, particularly PMF, and suggest that other genetic lesions are also involved in disease pathogenesis, consistent with the 2-hit theory of leukemogenesis.[49]

A low, rather than high, *JAK2* V617F allele burden has been associated with inferior survival and leukemia-free survival (LFS) in PMF.[56,57] While some studies have linked *JAK2* V617F positivity to poorer survival and a higher risk of LT in PMF,[58,59] others have not,[60] and the mutation is often lost upon progression to BP.[61,62]