Mutational Landscape in Myeloproliferative Neoplasms: Implications on Prognosis and Clinical Management

Presented by Aaron T. Gerds, MD, MS

ABSTRACT

Mutations are a critical piece in understanding how myeloproliferative neoplasms (MPNs) occur, specifically the pathobiology of JAK/STAT activation. Mutations play such an important role, in fact, that they are a key part of the diagnostic classification for these diseases. Furthermore, the mutational landscape of MPNs affects both the prognosis and the biology of disease progression. Current research in the field is focused on understanding how and why these mutations occur, as well as how to attack them to address disease at the time of progression or even before disease progression has occurred.

J Natl Compr Canc Netw 2021;19(11.5):1362–1364
doi: 10.6004/jnccn.2021.5102

An estimated 300,000 people in the United States are currently living with a myeloproliferative neoplasm (MPN), a heterogeneous group of hematopoietic stem cell diseases, characterized by activated JAK/STAT signaling and a propensity for evolution to myeloid blast-phase disease. At the NCCN 2021 Virtual Congress: Hematologic Malignancies, Aaron T. Gerds, MD, MS, Associate Professor of Medicine and Deputy Director for Clinical Research, Cleveland Clinic Taussig Cancer Institute, and Medical Director, Case Comprehensive Cancer Center Clinical Research Office, discussed the importance of mutations in the diagnosis, prognosis, and treatment of patients with MPNs. "We are living in the age of molecular analysis and molecular biology," said Dr. Gerds. "It is critically important to understand how and why these mutations occur so we can apply this knowledge to our everyday clinics and develop new therapeutics for the future."

Molecular Markers for Diagnosis and Classification

As Dr. Gerds explained, the classic Philadelphia chromosome (Ph)–negative MPNs include essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis. Furthermore, ET or PV can progress into myelofibrosis, called *post-ET* and *post-PV myelofibrosis*. "These diseases are very closely related," he said, and noted that patients often move from one disease state to another during the course of their disease. "For example, a patient may initially be diagnosed with ET, which transforms into PV within a few years. Patients with PV or ET may then advance to either myelofibrosis or acute leukemia (also known as *accelerated-* or *blast-phase MPN*)."

In 2005, 4 independent research groups identified recurrent mutations in *JAK2* leading to MPN.[1–4] The first mutation identified was *JAK2* V167F, which accounts for disease in approximately 97% of patients with PV and 50% to 60% in those with ET or myelofibrosis. Since then, other mutations that lead to JAK/STAT activation have been discovered, including mutations that recur in *MPL* and *CALR*. "All of these mutations lead to constitutive JAK/STAT activation and upregulation of similar downstream genes," said Dr. Gerds. "That's why multiple different mutations can cause the same phenotype in a population of patients."

The discovery of JAK/STAT-activating mutations led to the development of JAK inhibitors for MPNs. Several of these have failed due to toxicities in early clinical trials, said Dr. Gerds, but 2 JAK inhibitors were ultimately FDA-approved: ruxolitinib and fedratinib. Two additional JAK inhibitors, pacritinib and momelotinib, are currently in phase III trials (ClinicalTrials.gov identifiers: NCT03165734 and NCT04173494, respectively).

As Dr. Gerds explained, mutations are not just important for understanding the biology of the disease; clinicians also rely on them to diagnose PV, ET, and myelofibrosis. According to WHO criteria for the diagnosis of PV, the third major criterion is the presence of *JAK2* V617F or *JAK2* exon 12 mutation. Similarly, for ET, the presence of a *JAK2*, *CALR*, or *MPL* mutation is a key criterion for making the diagnosis and differentiating ET from reactive thrombocytosis. Finally, for myelofibrosis, the

presence of *JAK2*, *CALR*, or *MPL* is a major criterion to demonstrate that disease is not reactive but a true clonal process.

Mutations and Prognosis for MPNs

Historically, clinical factors have been used to understand an MPN prognosis. Both the International Prognostic Scoring System (IPSS) and the Dynamic International Prognostic Scoring System (DIPSS), for example, use age, constitutional symptoms, and blood counts to determine prognosis. "Even without mutation analysis, DIPSS does a pretty good job of stratifying patients," said Dr. Gerds. Patients in the low-risk category with a DIPSS score of 0, for example, live so long that average survival cannot be determined.[5] Conversely, patients with high-risk disease have a median survival of approximately 1.5 years.

Despite its utility in the clinic, however, Dr. Gerds emphasized that the DIPSS can be strengthened with mutational analysis. This was demonstrated in a study of patients with myelofibrosis and JAK/STAT-activating mutations, and patients with *CALR* mutations had improved overall survival (OS) compared with those with *JAK2* or *MPL* mutations.[6]

However, JAK/STAT-activating mutations are not the end of the story. According to Dr. Gerds, there are several recurrent mutations seen in MPNs that are important for both prognosis and targeted therapy. The cumulative incidence of disease progression for *SRSF2*, *EZH2*, *IDH1*, *IDH2*, and *ASXL1*, for example, has demonstrated inferior outcomes for patients with these mutations.[7,8] "The role of mutations is only increasing over time for diagnosis, prognosis, and perhaps treatment in the future," he said. "The key piece for these prognostic models is to figure out how these mutations interact, because we know that clinical factors are often driven by mutations, and these mutations are what drive disease risk."

Models such as MIPSS70 (Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients With Primary Myelofibrosis), which incorporates molecular markers in addition to clinical factors, have come to the forefront of prognosis and now may outperform the DIPSS, said Dr. Gerds (Figure 1).

Disease Progression and Mutational Profile

Mutational analysis is also starting to influence treatment selection in myelofibrosis. Patients classified as having low-risk disease according to DIPSS score, for example, would be reclassified as high risk after detection of *IDH* or *EZH2*. Clinicians might then consider earlier transplantation or using JAK inhibitors in these patients based on treatment algorithms. "These mutations can reclassify low-risk disease to high-risk disease and ultimately change the way you think about treatment for that given individual, in particular referral for transplantation," said Dr. Gerds.

This is true for PV and ET, as well. Mutations in *SRSF2* tend to be associated with worse OS in PV, whereas *SRSF2*, *SF3B1*, *U2AF1*, and *TP53* mutations tend to be predictive of survival in ET.[9] "Patients with one of these mutations should be watched more closely for disease progression, because it is best to intervene before the disease becomes more difficult to treat," said Dr. Gerds.

Although JAK inhibitors can help control symptoms and improve OS, Dr. Gerds cautioned that these agents do not lead to deep remissions or cure. Unlike chronic myeloid leukemia, he said, there is not one mutation that

Parameter	IPSS	DIPSS	DIPSS-Plus	MIPSS70	MIPSS70+ v2.0	MYSEC-PM
Age	✓	✓	✓			✓
Constitutional Sx	✓	✓	✓	✓	✓	✓
Leukocytosis	✓	✓	✓	✓		
Anemia	✓	✓	✓	✓	✓	✓
Peripheral blasts	✓	✓	✓	✓	✓	✓
Thrombocytopenia			✓	✓		✓
RBC transfusion			✓			
Post-PV/ET MF						✓
Fibrosis grade				✓		
Karyotype			✓		✓	
CALR mutation				✓	✓	✓
High-risk mutations				✓	✓	

Figure 1. Risk stratification in myelofibrosis. The choice of a prognostic model is determined, in part, by the type of information available such as clinical (green box), bone marrow biopsy findings (blue box), and molecular analysis (red box).
Abbreviations: DIPSS, Dynamic International Prognostic Scoring System; IPSS, International Prognostic Scoring System; MIPSS70, Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients With Primary Myelofibrosis; MYSEC-PM, Myelofibrosis Secondary to PV and ET Collaboration-Prognostic Model; post-ET MF, essential thrombocythemia that progressed to myelofibrosis; post-PV MF, polycythemia vera that progressed to myelofibrosis; Sx, symptoms.

can be blocked for long-term disease control. Pooled data from the COMFORT studies, the randomized trials that led to the approval of the JAK inhibitor ruxolitinib for myelofibrosis, showed improved OS with ruxolitinib, but did not halt disease progression.[10] "On average, OS after JAK inhibitors is 18 to 24 months, but patients with more abnormal clones that arise at the time of JAK inhibitor discontinuation do more poorly than those who do not," explained Dr. Gerds. "Clearly, clonal evolution is a mechanism of disease progression and resistance to JAK inhibitors, and it's a key piece of the evolution of the disease going forward."

According to Dr. Gerds, the emergence of a *TP53* mutation is a "sentinel event" in patients with MPN, transforming it into a more aggressive disease. Future research should focus on targeting this mutation in "patients who are teetering on disease progression," he said. "The better we understand the factors that lead to disease progression—whether it's a susceptible genome, environmental pressures, disease-related inflammatory pressures, or genomic instability overall—the better we can address them," Dr. Gerds concluded.

Disclosures: Dr. Gerds has disclosed receiving consulting fees from AbbVie, Inc., Bristol-Myers Squibb Company, CTI BioPharma Corp., Kartos, Novartis Pharmaceuticals Corporation, PharmaEssentia, and Sierra Oncology.

Correspondence: Aaron T. Gerds, MD, MS, Cleveland Clinic, 9500 Euclid Avenue, CA-60, Cleveland, OH 44195.
Email: gerdsa@ccf.org

References

1. Kralovics R, Passamonti F, Buser AS, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med 2005;352:1779–1790.
2. Levine RL, Wadleigh M, Cools J, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. Cancer Cell 2005;7:387–397.
3. James C, Ugo V, Le Couédic JP, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. Nature 2005;434:1144–1148.
4. Baxter EJ, Scott LM, Campbell PJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet 2005;365:1054–1061.
5. 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;115:1703–1708.
6. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. N Engl J Med 2013;369:2379–2390.
7. Vannucchi AM, Lasho TL, Guglielmelli P, et al. Mutations and prognosis in primary myelofibrosis. Leukemia 2013;27:1861–1869.
8. Tefferi A, Lasho TL, Guglielmelli P, et al. Targeted deep sequencing in polycythemia vera and essential thrombocythemia. Blood Adv 2016;1:21–30.
9. Tefferi A, Guglielmelli P, Lasho TL, et al. Mutation-enhanced international prognostic systems for essential thrombocythaemia and polycythaemia vera. Br J Haematol 2020;189:291–302.
10. Verstovsek S, Gotlib J, Mesa RA, et al. Long-term survival in patients treated with ruxolitinib for myelofibrosis: COMFORT-I and -II pooled analyses. J Hematol Oncol 2017;10:156.