Genetic Risk Assessment in Myeloproliferative Neoplasms

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CME Activity

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Learning Objectives: On completion of this article, you should be able to (1) describe cytogenetic abnormalities in myeloproliferative neoplasms (MPN); (2) list mutations in MPN; and (3) discuss prognostic relevance of cytogenetic abnormalities and mutations in MPN.

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Abstract

The World Health Organization classification system recognizes 4 variants of *JAK2* mutation–enriched myeloproliferative neoplasms (for expansion of gene symbols, use search tool at www.genenames.org): essential thrombocythemia (ET), polycythemia vera (PV), primary myelofibrosis (PMF), and prefibrotic PMF. All 4 disorders are characterized by stem cell–derived clonal myeloproliferation with mutually exclusive driver mutations, including *JAK2*, *CALR*, and *MPL*. The median survival is approximately 20 years for ET, 14 years for PV, and 6 years for PMF; age is the most important determinant of survival with the corresponding median of 33, 24, and 15 years in patients younger than 60 years. Genetic information is the second most important prognostic tool and includes karyotype, driver mutational status, and presence of specific other mutations. Karyotype has been shown to carry prognostic relevance in PV (abnormal vs normal) and PMF (unfavorable vs favorable abnormalities). Driver mutational status is prognostically most relevant in PMF; type 1/type 1-like *CALR* vs other driver mutational status has been associated with superior survival. In ET, arterial thrombosis risk is higher in patients with *JAK2* or *MPL* mutations whereas *MPL*-mutated patients might be at risk for accelerated fibrotic progression. *ASXL1* and *SRSF2* mutations have been associated with inferior overall, leukemia-free, or fibrosis-free survival in both PV and PMF, and a recent targeted sequencing study has identified additional other adverse mutations in

both these disorders, as well as in ET. Further enhancement of genetic risk stratification in myeloproliferative neoplasms is possible by combining cytogenetic and mutation information and developing a prognostic model that is adjusted for age.

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Myeloproliferative neoplasms (MPN) constitute one of several categories of myeloid neoplasms according to the World Health Organization (WHO) classification system for hematopoietic tumors.[1,2] The 2016 WHO MPN category includes chronic myeloid leukemia, which is invariably associated with the *BCR-ABL1* mutation (for expansion of gene symbols, use search tool at www.genenames.org); the *JAK2* mutation-enriched MPN, which include polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), and prefibrotic PMF; and other less frequent clinic-pathologic entities including chronic neutrophilic leukemia, chronic eosinophilic leukemia—not otherwise specified, and MPN—unclassifiable. The *JAK2* mutation—enriched MPN are characterized by stem cell—derived clonal myeloproliferation with mutually exclusive *JAK2*, *CALR*, and *MPL* mutations.[3,4]

Polycythemia vera is almost always associated with a *JAK2* mutation, primarily the *JAK2*V617F mutation. *JAK2*V617F is also the most frequent mutation in ET and PMF, with an incidence of 50% to 70% in both. About 40% of the patients with either ET or PMF harbor *CALR* (20%-25%), *MPL* (3%-8%), or none of the 3 driver mutations (ie, are triple negative). Accordingly, the presence, absence, or specific type of driver mutations cannot be used for diagnostic distinction among the different MPN, which is based primarily on bone marrow morphology and peripheral blood counts.[2]

PHENOTYPE

Phenotypically, PV is defined by clonal erythrocytosis, ET by clonal thrombocytosis, and PMF by characteristic bone marrow morphology. In addition, all 3 disorders might be associated with hepatosplenomegaly (PMF>PV>ET), leukocytosis (PMF>PV>ET), thrombocytosis (ET>PMF>PV), microvascular symptoms (PV>ET>PMF), constitutional symptoms (PMF>PV>ET), thrombohemorrhagic complications (PV>ET>PMF), and variable risk of leukemic transformation (PMF>PV>ET), or fibrotic progression (PV>ET).[5] Patients with PV or PMF might also experience intractable pruritus, whereas increased rates of first trimester miscarriage have been reported in ET[6,7]; in a recent study, approximately 59% of 292 patients with WHO-defined ET were women and 58% of the study population was younger than 60 years.[8] Additional clinical manifestations in PV include symptoms of hyperviscosity and in PMF, progressive anemia, leukoerythroblastosis, extramedullary hematopoiesis, recurrent splenic infarcts, peripheral edema, early satiety, cachexia, and symptoms of portal hypertension, including ascites and variceal bleeding.

Driver mutations might also influence MPN phenotype.[4] For example, *JAK2*V617F-mutated patients with ET or PMF are usually older and display higher hemoglobin and leukocyte counts and lower platelet count.[9] *JAK2* exon 12—mutated patients with PV are younger and often display predominantly erythroid myeloproliferation. In contrast, *CALR*-mutated or triple-negative patients with ET are younger and display male preponderance, higher platelet count, and lower hemoglobin and leukocyte counts. *CALR*-mutated patients with PMF are also younger and present with higher platelet count and lower frequencies of anemia and leukocytosis. The risk of arterial thrombosis in ET is significantly higher in *JAK2*- or *MPL*-mutated patients than in *CALR*-mutated or triple-negative patients; the same might be true in terms of vascular risk in PMF.[10] In regard to phenotypic correlates of mutations other than *JAK2*, *CALR*, or *MPL*, the most notable so far has been the impressively significant correlation between *U2AF1* mutations and anemia in patients with PMF.[11,12]

CLINICAL COURSE

Life expectancy of patients with MPN is worse than that of the sex- and age-matched control population, and the median survival is estimated at 20 years for ET, 14 years for PV, and 6 years for PMF[8]; the corresponding