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EDITORIAL COMMENT

Acute Myocardial Infarction and Chronic Myeloproliferative Neoplasms

Friend and Enemy, Depending on Circumstances*

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Chronic myeloproliferative neoplasms (MPNs), which include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), originate from hematopoietic multipotent stem and progenitor cells in the bone marrow that acquired a clonal proliferative advantage. They manifest with increased numbers of mature blood cells in the circulation, preferentially of red cells in PV and platelets in ET, with opposite changes in PMF including patients who present with cytopenias and are burdened by systemic manifestations and variable enlargement of the spleen (the preferred site of extramedullary hematopoiesis).[1,2] Their grouping together in a single disease family, on the basis of the hypothesis by William Dameshek that they express a common abnormality of the bone marrow cells, dates back to 1951.[3] Yet the first recurrent mutation in the gene encoding for JAK2 (*JAK2*V67F) was not described until 2005. This was followed by the discovery of mutations in the gene encoding for thrombopoietin receptor (*MPL*) and the reticulum-associated protein calreticulin (*CALR*).[4] All these mutated proteins affect the activation of JAK/STAT signaling, a key intracellular pathway involved in cell proliferation, survival, commitment, and maturation, as well as in the regulation of, production of, and response to a vast array of inflammatory proteins, growth factors, and chemokines by different cellular subtypes. Inhibitors of JAK2-driven signal have been approved for patients with MF and PV.

Survival with ET is almost superimposable to the general population, as long as those with ET are accurately differentiated from those with the prefibrotic PMF variant, which presents with a similar clinical picture but has unique bone marrow histopathology features and a different clinical course.[5] In contrast, median survival is 13 to 15 years with PV and 5 to 7 years with PMF; in the latter, survival is highly variable depending on clinical, hematologic, cytogenetic, and molecular features incorporated into current prognostic models.[6,7] Causes of death after MPNs include an increased risk for infections, clinical deterioration with features resembling neoplastic cachexia, and hematologic progression to a very aggressive acute myeloid leukemia. Other frequent complications with MPNs are thrombosis, bleeding, and other secondary malignancies. Thrombosis, either arterial (mainly acute myocardial infarction [AMI] and stroke) or venous (deep vein thrombosis, pulmonary embolism, and thrombosis in unusual sites such as splanchnic veins, retinal central vein, and cerebral sinus), is one of the major clinical issues given the significant morbidity and mortality, although this may be decreasing in more recent years.[8] Information from a large population-based study from a Swedish registry indicated HRs of 3.0 (95% CI: 2.7-3.4) and 9.7 (95% CI: 7.8-12) for arterial and venous events, respectively, among patients with MPNs compared with matched control subjects from the general population, within 3 months of diagnosis, without major differences among MPN subtypes.[9] In particular, the HR for AMI was 2.5 (95% CI: 2.1-2.9) at 3 months and 1.4 (95% CI: 1.2-1.4) at 5 years,

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indicating persistently increased risk. However, the decrease in this risk over time might also potentially suggest an effectiveness of thromboprophylactic and cytoreductive interventions for MPNs, which include low-dose aspirin and cytoreduction with hydroxyurea and/or phlebotomies (in PV, to maintain hematocrit at <45%).[10]

Therapy is dictated by thrombosis risk scores: in PV, patients are categorized as low risk and high risk on the basis of the presence of at least 1 of older age (>60 years) and previous thrombosis, while for patients with ET and PMF, the International Prognostic Score of Thrombosis in Essential Thrombocythemia includes also the presence of the *JAK2*V617F mutation.[11] In general, pharmacologic cytoreduction is reserved for patients within the high-risk category with the aim of reducing the rate of recurrence, globally estimated at 5.7% patients per year in a pooled analysis of 1,500 patients with MPNs.[12] Thrombosis is multifactorial, with contributions from higher mutation variant allele frequency of *JAK2*V617F[13,14] and decreased leukocyte to lymphocyte ratio,[15] particularly for venous events, increased peripheral myeloid cell count, and local and systemic inflammatory activation of endothelium, platelets, and leukocytes. Inflammation may also contribute to the development of atherosclerosis.[16] Intriguingly, clonal hematopoiesis of indeterminate potential has recently been recognized as an important trigger of systemic inflammation responsible for the increased predisposition to thrombosis and cancer in otherwise healthy individuals and may additively contribute to the higher risk in patients with MPNs.[17] Notably, the HR for clonal hematopoiesis of indeterminate potential for coronary heart disease risk is of the same magnitude as those for traditional risk factors.[18]

In this issue of *JACC: CardioOncology*, Leiva et al[19] report on their interrogation of the National Inpatient Sample database of more than 1.6 million admissions for AMI to identify 5,374 patients with concurrent diagnoses of MPNs, accounting for 0.3% of the total, who were then compared with patients without MPNs after propensity score weighting for main clinical characteristics. The primary message of the study is that patients with MPNs had a significantly lower risk for in-hospital death or cardiac arrest but a higher risk for bleeding. However, as a temporal trend of in-hospital death and cardiac arrest was found, unexpectedly, to increase for patients with MPNs unlike control subjects, there remain important unanswered questions about the optimal management of patients with MPNs and AMI. Furthermore, because diagnoses of ET and PMF emerged as a risk factor for those outcomes, in contrast to PV, one possible interpretation is that the current management recommendations for PV (aspirin and hematocrit target at <45%) are more effective compared with the other 2 diseases in preventing and minimizing complications in the setting of an AMI, although a more complete understanding of the mechanisms remains elusive. In addition, patients with ET and those with PMF were found to be more prone to bleeding than patients without MPN, particularly gastrointestinal and procedural bleeding at the time of invasive management. Such increased hemorrhagic tendencies might be ascribed to the well-known role of thrombocytosis and the associated acquired von Willebrand disease and to intrinsic functional defects of platelets, which may then be further exacerbated by exposure to prophylactic aspirin. Trials exploring the impact of different antiplatelet drugs and/or prophylactic measures in patients with MPNs and AMI should be prompted by these findings. One last important result of the study concerns the significantly increased proportion of patients with MPNs and AMI hospitalized from 2006 to 2018, which rose from 0.19% to 0.32%. Although the explanation for this could be chance, it might also reflect improved knowledge of MPNs and the fact that many patients now receive earlier diagnoses, particularly after the implementation of mutation assays and the refinements of diagnostic criteria over the past decade, which could contribute to a measured increased incidence for these rare hematological neoplastic disorders.

In summary, the study of Leiva et al,[19] although having some limitations related to its retrospective design and those intrinsic to database studies and sole use of International Classification of Diseases codes, nonetheless adds novel, clinically relevant, and overall reassuring information on the short-term outcomes of patients with AMI and MPNs, despite the increased risk for thrombosis and bleeding. Not all that is bad causes harm, at least not always.

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Prof Vannucchi has been involved with advisory boards and lectures for Novartis, Incyte, GlaxoSmithKline, Bristol Myers Squibb, and AOP Orphan Pharmaceuticals AG. Dr Guglielmelli has been involved with advisory boards and lectures for Novartis and GlaxoSmithKline.

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