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Review

Evolving Therapeutic Strategies for the Classic Philadelphia-Negative Myeloproliferative Neoplasms

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ABSTRACT

Despite the emergence of JAK inhibitors, there is a need for disease-modifying treatments for Philadelphia-negative myeloproliferative neoplasms (MPNs). JAK inhibitors ameliorate symptoms and address splenomegaly, but because of the heterogeneous contributors to the disease process, JAK inhibitor monotherapy incompletely addresses the burden of disease. The ever-growing understanding of MPN pathogenesis has provided the rationale for testing novel and targeted therapeutic agents, as monotherapies or in combination, in preclinical and clinical settings. A number of intriguing options have emerged, and it is hoped that further progress will lead to significant changes in the natural history of MPNs.

Contents

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1. Introduction

The Philadelphia chromosome-negative (Ph−) MPNs include clonal disorders of myeloid progenitor cells, such as polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF). The latter can be sub-categorized as either primary (PMF) or as transformed from PV or ET (post-PV/ET MF) (Tefferi et al., 2009a). The incidence of classic Ph− MPNs in Europe is 1.8 cases per 100,000 person-years (Visser et al., 2012). In the US, between 2008 and 2010 (as assessed by a review of two large health plans), the prevalences of PV, ET, and MF were 44–57, 38–57, and 4–6 per 100,000, respectively (Mehta et al., 2012). In general, the MPNs may be associated with an increased risk of morbidity and mortality and may lead to a significant decrement in quality of life (QOL). Generally, MF differs from PV and ET in that it typically carries a worse prognosis and high symptom burden related to elevated cytokine levels, cytopenias, splenomegaly, and extramedullary hematopoiesis, all of which can result in fatigue, early satiety, abdominal discomfort, inactivity, night sweats, pruritus, bone pain and weight loss (Emanuel et al., 2012). Transformation to acute myelogenous leukemia (AML) has been the most feared complication of MPNs, particularly of MF.

Prognosis of MPNs varies greatly based on subtype. ET is associated with a 10-year and 15-year survival of 89 and 80%, leukemic transformation rate of 0.7% and 2.1%, and rate of progression to MF of 0.8% and 9.3%, respectively (Barbui et al., 2011). Among patients with PV, median survival has been shown to be 14.1 years, which is worse than that of the age- and sex-matched control population of the US (Tefferi et al., 2013). Evolution to MDS and leukemia was the main cause of death in a phase 3 study comparing the use of hydroxyurea (HU) to pibobroman among treatment-naïve PV patients under the age of 65 years (Kiladjian et al., 2011) In a large European epidemiological study of PV, 41% of deaths (1.5 deaths per 100 persons per year) were attributable to cardiovascular events (Marchioli et al., 2005). The median survival for patients with MF was shown to be 6.5 years, between years 1996 and 2007, in a European population (Cervantes et al., 2012).

A better understanding of the molecular pathogenesis of Ph− MPNs has been greatly facilitated by the 2005 discovery of the point mutation *JAK*2 V617F, which is present in almost 95% of PV cases and 50–60% of ET and PMF cases (Kralovics et al., 2005; Rampal and Levine, 2014). The mutation leads to constitutive activation of Janus kinase 2 (JAK2), a member of the Janus family of kinases, normally phosphorylated/activated by

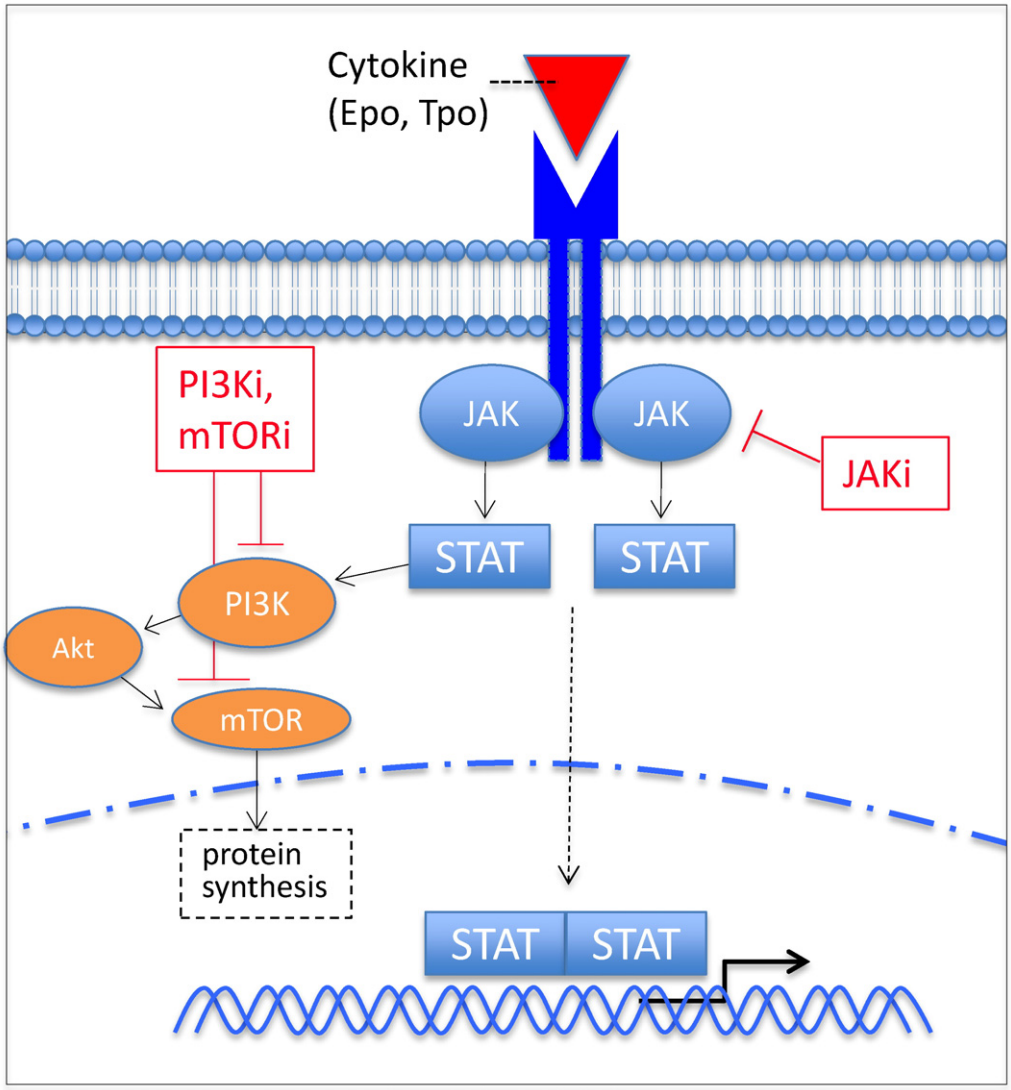

Fig. 1. JAK-STAT signaling contributes to the pathogenesis of MPNs. Unregulated JAK-STAT signaling, leading to STAT-mediated hematopoiesis and activation of the PI3K/Akt/mTOR pathway, may result from a number of aberrations including point mutations JAK2 V617F, leading to constitutive activation of JAK2 kinase, and MPL W515L, an activating mutation of the thrombopoietin receptor. Number small molecule inhibitors of these pathways, including JAK, PI3K, and mTOR inhibitors, are in clinical development. Epo, erythropoietin; JAK, Janus kinase; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide-3 kinase; STAT, signal transducer and activator of transcription; Tpo, thrombopoietin; -i, inhibitor.