Mechanisms of Resistance to JAK2 Inhibitors in Myeloproliferative Neoplasms

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KEYWORDS

• JAK2 • Myeloproliferative neoplasms • JAK2 inhibition • Resistance

KEY POINTS

- Resistance of myeloproliferative neoplasm (MPN) cells to JAK2 inhibitors develops based on reactivation of JAK-STAT signaling by JAK heterodimer formation, or protective cytokine effects.
- Acquired *JAK2* resistance mutations have not been observed in patients with MPN so far.
- JAK2 inhibitor–resistant MPN cells remain dependent on JAK2, consistent with incomplete target inhibition by the current type I JAK2 inhibitors.
- Resistance to the current type I JAK2 inhibitors like ruxolitinib is overcome by a novel type of JAK2 inhibition with an alternative binding mode (type II JAK2 inhibition), by HSP-90 inhibitors, or by combined pathway inhibition including Bcl-2/Bcl-xL, PI3K/Akt, or PIM kinase inhibition.
- Intermittent treatment with ruxolitinib could help to manage type I JAK2 inhibitor resistance, but may be complicated by potential flaring of symptoms on pausing ruxolitinib.

INTRODUCTION

Myeloproliferative neoplasms (MPNs) are chronic leukemias occurring at an annual incidence of 0.5 to 1.0 per 100,000.[1] They are hematopoietic stem cell disorders leading to excessive proliferation of mature myeloid cells. The 3 main MPN clinical phenotypes include essential thrombocythemia (ET) with marked thrombocytosis, polycythemia vera (PV) with erythrocytosis often along with neutrophilia and thrombocytosis, and myelofibrosis (MF) with expansion of megakaryocytes, progressive bone marrow fibrosis, and extramedullary hematopoiesis.[2] Splenomegaly and elevated serum cytokine levels are typical and contribute to symptom burden.[3] Myelofibrosis is the rarest (0.47/100,000 annually[1]) and most severe form of MPN with life expectancies limited to a few months in the presence of high-risk features.[4] MF transforms

Conflicts of interest: None.
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Hematol Oncol Clin N Am ■ (2017) ■–■
http://dx.doi.org/10.1016/j.hoc.2017.04.003 **hemonc.theclinics.com**

to secondary acute myeloid leukemia (AML) in 15% to 20% of patients (0.09/100,000 annually) with dismal prognosis or alternatively leads to hematopoietic failure. The sole curative therapy for MPN to date is hematopoietic stem cell transplantation. As MPNs mainly affect the elderly, only a limited subset of patients is eligible showing reduced success rates. Interferon-α has shown disease-modifying activity with molecular responses, but application is limited by poor tolerability.[2] Other therapies focus merely on symptom control and prevention of thromboembolic and hemorrhagic events complicating the disease, without altering the natural course of MPN.

The breakthrough discovery of the V617F gain-of-function mutation in the tyrosine kinase Janus kinase 2 (*JAK2*) in 2005 for the first time denominated a molecular therapeutic target.[5–8] *JAK2*V617F is present in 95% of PV and 50% to 60% of MF and ET. JAK2 is an intracellular non-receptor tyrosine kinase essential for hematopoiesis. It represents the exclusive mediator of cytokine signaling from the thrombopoietin receptor MPL, the erythropoietin and granulocyte-macrophage colony-stimulating factor receptors.[9,10] Hematopoietic cytokines binding to their cognate receptors induce JAK2 dimerization and phosphorylation.[11] Activated JAK2 initiates signaling through several intracellular signaling pathways, including the signal transducers and activators of transcription (STAT)3 and STAT5 transcription factors,[12] the phosphoinositide-3 kinase (PI3K)/Akt pathway,[13] and the mitogen-activated protein kinase (MAPK) pathway,[14] which promote cell proliferation, differentiation, and survival via multiple effectors.[15] Thus, the *JAK2*V617F mutation constitutively activates JAK2 signaling leading to dysregulated myeloid cell proliferation in most patients with MPNs.[16] Further molecular characterization identified *JAK2* exon 12 mutations in most cases of *JAK2*V617F-negative PV[17] and mutations in the thrombopoietin receptor *MPL,* such as *MPL*W515 L and *MPL*W515 K in *JAK2*V617F-negative patients with ET/MF, accounting for 5% to 10% of ET and MF.[18] As *JAK2*V617F, these mutations induce hyperactive JAK2 signaling and uncontrolled growth of myeloid lineages. Recently, acquired mutations in the chaperone protein calreticulin (CALR*)* were identified in most patients with ET/MF who were *JAK2*-unmutated and *MPL*-unmutated, accounting for 25% to 35% of ET and MF.[19,20] There is mechanistic evidence that *CALR* mutations converge on activation of MPL through facilitating binding of mutant CALR to MPL.[21–24] Thus, mutations in *JAK2, CALR,* and *MPL*, as well as rare mutations in negative regulators of JAK2, such as *LNK* and *CBL*, all induce activated JAK2 signaling. They are mutually exclusive, which highlights the JAK2 pathway activation as a shared mechanism of transformation in MPNs. Transcriptional profiling of MPN granulocytes substantiated this notion, showing gene expression profiles consistent with activated JAK2 signaling in all patients with MPNs independent of mutational status and clinical phenotype.[25] Additional genetic lesions, such as mutations in epigenetic modifiers *TET2*, *ASXL1*, *EZH2,* or *IDH1/2,* or in tumor suppressors, such as *TP53*, have also been identified in MPNs and may shape the heterogeneous phenotypes of MPNs and impact the course,[26] whereas JAK-STAT pathway activation represents the central mechanism in the pathogenesis of all MPNs.[25]

The critical role of hyperactive JAK2 signaling in MPN has led to the development of JAK2 inhibitors.[27–31] Conventional JAK2 inhibitors act as ATP mimetics and stabilize JAK2 in the active conformation characterized by paradoxic hyperphosphorylation of the JAK2 activation loop (type I JAK inhibition).[32] They effectively reduce splenomegaly and constitutional symptoms in patients with MPN, which means substantial alleviation of symptom burden.[33,34] A survival advantage has been observed compared with placebo or best available therapy.[35,36] Type I JAK inhibitors are not mutant-selective, meaning that they inhibit both mutant JAK2 as well as activated wild-type JAK2 downstream of mutated *MPL* or *CALR*, providing effective treatment