Benefits and risks of JAK inhibition

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On 16 November 2011, the US Food and Drug Administration (FDA) approved ruxolitinib, a small-molecule inhibitor of JAK1/2, for the treatment of patients with intermediate- or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocytemia myelofibrosis. In this issue of Blood, Porpaczy et al report findings of a study showing that JAK1/2 inhibitor treatment is associated with an increased risk for aggressive B-cell lymphomas.¹

The turning point in our understanding of the pathophysiology of myeloproliferative neoplasms (MPNs) was undoubtedly the identification in 2005 of the unique JAK2 (V617F) mutation in most patients with polycythemia vera, essential thrombocytemia, or primary myelofibrosis.² This discovery opened avenues of research, the results of which were soon translated into improvements in clinical practice. After the identification of somatic mutations of MPL in 2006, the discovery of CALR mutations in 2013 defined the full landscape of MPN-restricted driver mutations.² Although through different molecular mechanisms, the 3 mutant genes activate the cytokine receptor/JAK2 pathway and their downstream effectors in hematopoietic cells.

The discovery of JAK2 (V617F) opened the possibility of using specific inhibitors for targeting the activated cytokine receptor/JAK2 pathway with the aim of suppressing the clonal myeloproliferation that characterizes MPNs. This expectation was based on the paradigmatic example of chronic myeloid leukemia, a condition in which the discovery of the BCR-ABL1 fusion gene and its oncogenic properties was translated into a highly successful targeted therapy, with selective suppression of leukemic myeloproliferation and prolongation of survival of affected patients.

In 2010, a phase 1-2 trial of INCBI880242, an orally bioavailable inhibitor of JAK1 and JAK2 currently known as ruxolitinib, showed that administration of this compound was associated with clinical benefits in patients with myelofibrosis.³ Two subsequent phase 3 trials confirmed these benefits, which include reductions in splenomegaly, amelioration of disease-related symptoms, and improvements in quality of life.⁴,⁵ More recently, ruxolitinib has been shown to be effective in lowering the hematocrit, reducing the spleen volume, and improving symptoms associated with polycythemia vera.⁶ On 4 December 2014, the FDA approved ruxolitinib for the treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.

Although the above benefits are important, the studies conducted so far indicate that ruxolitinib, at variance with imatinib in chronic myeloid leukemia, does not selectively suppress the clonal myeloproliferation of MPNs. In fact, although reductions in JAK2 (V617F)-mutant allele burden have been reported, molecular remissions are uncommon. Moreover, a recent evidence-based focused review has concluded that there is insufficient evidence supporting a survival prolongation in patients with myelofibrosis.⁷ Common adverse effects of ruxolitinib include development or worsening of anemia and/or thrombocytopenia and increased incidence of infections; occurrence of nonmelanoma skin tumors has also been reported.⁸ Despite these limitations, ruxolitinib nonetheless represents a useful therapeutic tool for patients with myelofibrosis who have marked splenomegaly and/or severe systemic symptoms. However, the current report on an increased risk for aggressive B-cell lymphomas makes therapeutic decision making more problematic.

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Frequencies of immunoglobulin (Ig) rearrangement in the bone marrow of MPN patients receiving conventional therapy (n = 44) or JAK inhibition (n = 54). In this latter cohort, 3/54 (5.6%) patients developed an aggressive B-cell lymphoma, and all of them had in their bone marrow a preexisting B-cell clone that was later found to be related to the malignant lymphoma. See Figure 1E in the article by Porpaczy et al that begins on page 694.
Because hematologic malignancies are rare disorders, the casual coexistence of a lymphoid and a myeloid neoplasm is expected to be a very rare event. Several studies, however, have previously shown that the risk of developing a lymphoid neoplasm is higher in MPN patients compared with the general population. In the current work, Porphacz et al have defined a new paradigm, that is, an association between JAK inhibition and lymphoma development in MPN patients. In the Vienna cohort of 626 MPN patients, 4 out of 69 (5.8%) patients developed an aggressive B-cell lymphoma upon JAK1/2 inhibitor treatment, whereas only 2 of the remaining 557 patients without JAK inhibition did so. All 4 patients were treated with ruxolitinib, although 1 had initially been treated with fedratinib, a selective JAK2 inhibitor. Based on the above relative frequencies, MPN patients under JAK inhibition would have a 16-fold higher risk of developing an aggressive B-cell lymphoma.

The above 4 patients developed an aggressive B-cell lymphoma with extranodal involvement, high MYC expression, and presence of lymphoma cells in both bone marrow and peripheral blood in 3 cases. Of note, prior to the current work, development of a leukemic B-cell lymphoma was observed in 2 patients with myelofibrosis treated with ruxolitinib. Although there was no evidence of mutations in MPN-driver genes in lymphoma samples in the 4 patients of the current study, clonal immunoglobulin gene rearrangements were found in the bone marrow during the myelofibrosis phase in nearly 16% of patients studied (see figure), and this preexisting B-cell clone was related to aggressive lymphomas in all 3 patients tested. The effects of JAK inhibition were mirrored in a mouse model of abnormal myeloproliferation with the concomitant presence of aberrant B cells. Although these observations are interesting, the mechanism or mechanisms by which JAK inhibition may cause progression from an indolent clonal B-cell proliferation to a leukemic B-cell lymphoma need to be elucidated.

The study by Porphacz et al further underlines the importance of real-world evidence studies for assessing the long-term risks of new treatments in hematologic malignancies. Studies aimed to define the risk of malignant lymphomas following JAK inhibition in real-world MPN patients are now mandatory. However, the crucial question that practicing hematologists are now facing is how to treat the next patient with myelofibrosis in whom ruxolitinib treatment would be indicated. Clearly, the patient should be informed adequately so that he or she can understand the benefit-risk balance of a JAK inhibitory treatment. According to Porphacz et al, patients at risk are essentially those with a preexisting B-cell clone in their bone marrow. A clonal B-cell population can be identified using a polymerase chain reaction technique for detection of immunoglobulin gene rearrangements; flow cytometry immunophenotyping might also be employed provided that bone marrow aspiration yields an adequate sample. If there is no evidence of a clonal B-cell population, one may reasonably assume that ruxolitinib treatment is relatively safe and may start treatment, closely monitoring the patient. However, if there is evidence of clonal B cells, therapeutic decision making is really problematic at present. That is why there is an urgent need of ad hoc studies.

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REFERENCES


Non-zero-sum game of transfusions: EOL in leukemia

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Inability to provide transfusion support to patients with leukemia is a major cause of delays in hospice enrollment for end-of-life (EOL) care. In this issue of Blood, LeBlanc et al explore the relationship between transfusion dependence (TD), time to hospice enrollment, and quality of EOL care in patients with leukemia.

Acute leukemias (acute myeloid leukemia [AML] and acute lymphoblastic leukemia [ALL]) are devastating and often fatal malignancies characterized by an acquired and progressive bone marrow failure. Without treatment, the median overall survival of patients with AML or ALL ranges between 6 and 8 weeks, independent of patient age. In addition, most adult patients with acute leukemia...