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CLINICAL TRIALS AND OBSERVATIONS

Comment on Yacoub et al, page 1498

Reducing the burden of MPN

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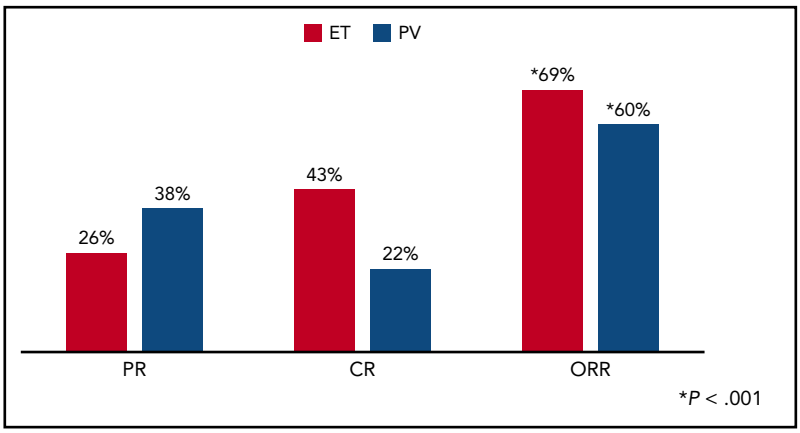
In this issue of *Blood*, Yacoub et al[1] show that pegylated-rIFN-α2a (PEG) is an effective therapy in patients with myeloproliferative neoplasms (MPN) who are hydroxyurea (HU) intolerant or refractory.

In the MPNs polycythemia vera (PV) and essential thrombocythemia (ET), the acquired clone causes excess production of hemopoietic cells. This results in a spectrum of disease characterized by a proliferative bone marrow, increased risk for thromboembolic events and hemorrhage, and in some cases, progression to myelofibrosis and even acute myeloid leukemia. The patients often suffer from a significant symptom burden and detriment of their quality of life. In those who require cytoreductive therapy, the first-line agent is frequently HU. Some patients have an inadequate response to HU so that they do not achieve the targeted reduction in cell counts or they do not tolerate the treatment because of adverse effects. There is evidence that those who are refractory or intolerant to HU have worse outcomes.[2] Therefore, there is a major need for other effective treatments.

Interferon α (IFN-α) has shown disease-modifying activity in MPNs and is clearly nonleukemogenic. IFN-α has to be given by injection and has a notable adverse effect profile; however, pegylated forms are given less frequently and are often better tolerated.[3,4] Molecular responses have been seen in MPNs.[4]

In a global, phase 2, investigator-initiated trial of PEG in high-risk patients with PV and ET who were HU resistant or intolerant, Yacoub et al[1] showed impressive response rates. In a total study of 115 patients at 12 months, overall response rates in PV were 60%, and 69% in ET (see figure). The criteria for assessment used were the 2009 EuropeanLeukemiaNet criteria,[5] which present a high bar to demonstrate response, particularly complete response. In a drug in which adverse effects are a well-recognized issue, the safety profile was acceptable. PEG was well tolerated with discontinuation resulting from adverse events in only 13.9% of patients. The incidence of major thrombotic events at 1 year was 1%, and 5% at 2 years. No major bleeding events occurred during the study. One patient transformed to myelofibrosis during the study, and 1 patient to acute myeloid leukemia within 8 weeks of entering the study. The cumulative incidence of second cancers at 2 years was 4%.



Response rates after 12 months of pegylated interferon alfa-2a in PV and ET. CR, complete response; PR, partial relapse; ORR, overall response rate. See Figure 2 in the article by Yacoub that begins on page 1498.

In MPNs, the symptom burden for the patients in an important issue not always appreciated by medical attendants. In this study, statistically significant decreases in MPN-related symptoms were seen. As expected, PEG-related adverse effects occurred, but in those who tolerated treatment, symptom burden from PEG-related adverse effects remained stable through treatment. Patients who achieved a complete response had significantly better MPN-related symptom scores than those with a partial or no response at 12 months.

At the time of the analysis, small but significant reductions in the *JAK2*V617F allele burden were seen in those in complete response compared with those with no response. A similar pattern was seen with *CALR* mutations, but did not reach statistical significance, as numbers were small. However, *CALR* driver mutations were associated with a superior clinical response. In those in which a sample was available for independent histological review, some histopathological remissions were seen.

This trial showed that PEG was an effective therapeutic option, even when using stringent response criteria, in this group of high-risk patients previously treated with HU. In what is a very rare group of patients, this study required an extensive international effort to complete the trial. It represents an important therapeutic advance for this patient group.

It must be recognized that this trial was not randomized. In randomized trials, the difficulty has been treatment options for those who are already HU resistant/intolerant, affecting the results of trials. However, in the light of this trial, the final results of the related phase 3 trial from the Myeloproliferative Neoplasms-Research Consortium (MPN-RC), MPN-RC 112 randomizing between HU and PEG, once treatment is necessary, will be of interest.[6] Long-term follow-up of these patients, particularly those who continue long-term on PEG, will also be of great interest. The accompanying small study of patients with MPN with prior splanchnic vein thrombosis who were not necessarily previously treated with HU had an overall response rate with PEG of 70%,[7] another important result.

The planned study recruitment was curtailed because of limitations of the PEG drug supply, and the drug supply will be an issue going forward. However, these results are still important, given that another pegylated interferon, ropeginterferon alfa-2b, has been shown to be effective in the treatment of PV[8] and is now approved. Ruxolitinib is another therapeutic agent that has been used to treat HU-resistant or HU-intolerant PV and ET. Significant responses have been seen in PV,[9] but it was not superior to best available therapy in ET.[10] It is unlikely that it will be possible to compare ruxolitinib with PEG directly; nevertheless, the therapeutic armamentarium for patients with MPN has now expanded.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Xavier-Ferrucio et al, page 1547

A fork in the road

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In this issue of *Blood*, Xavier-Ferrucio et al provide new insights into the mechanisms responsible for the well-documented finding of thrombocytosis in patients with iron deficiency anemia. By using mouse and human models, they document that a low iron content in the bone marrow environment affects the megakaryocyte-erythroid progenitors (MEPs). This occurs because of induced alteration in their metabolism, attenuation of ERK signaling, slowing of cell proliferation, and biasing of the MEPs toward megakaryocyte commitment, which ultimately results in thrombocytosis and anemia.[1]

Iron deficiency is the most prevalent cause of anemia worldwide and is estimated to affect 1.5 billion people globally, primarily women and children.[2] Iron deficiency anemia is associated with impaired neurocognitive development and immune dysfunction in younger children. Although nutritional deficiency has long been recognized as the primary cause of iron deficiency, recent studies have shed new insights into the regulation of iron homeostasis, which can also affect iron balance.[3]

Although anemia has long been recognized as the dominant clinical feature of iron deficiency, it has also been noted that patients often have elevated platelet counts.[4] It is well known that inadequate access to iron for the synthesis of heme leads to a decrease in red cell hemoglobin content and red cell volume. In marked contrast, our understanding of the mechanistic basis for thrombocytosis in iron deficiency and the pathophysiological sequelae of this increase are less well defined.

In the generally accepted model of hematopoiesis, hierarchical differentiation of the self-renewing pluripotent hematopoietic stem cell (HSC) leads to the production of stem cells with limited capacity for self-renewal (short-term HSCs), which in turn give rise to multipotent progenitors that can commit to either the myeloid lineage or the lymphoid lineage. Ongoing work is shedding new light on the relative contributions of cytokines, growth factors, cell-cell interactions, transcriptional factor networks, epigenetics, and cell metabolism in determining cell fate decisions.[5-7] Significant technical advances during the last decade, including the identification of