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CORRESPONDENCE

Interferon Alfa in the Treatment of Philadelphia-Negative Chronic Myeloproliferative Neoplasms

TO THE EDITOR: Two important articles that update our knowledge about the pathophysiology and management of myeloproliferative neoplasms (MPNs) were recently published in *Journal of Clinical Oncology*.[1,2] We were privileged to participate as coauthors in the manuscript by Barbui et al.[1] However, we believe there is a dearth of information pertaining to the use of interferon alfa (IFN-α) in Philadelphia-negative MPNs in both articles. We believe that the use of IFN-α in the MPNs polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), post-ET and post-PV myelofibrosis, is no more experimental than other forms of treatment and should not be considered as a second-line drug only, on the basis of the evidence detailed in this letter. We think this information is currently clinically relevant and important and should be brought to the attention of JCO readers.

Since the first report on the use of recombinant IFN-α-2 (rIFN-α-2) in the treatment of MPNs,[3] the long-term efficacy of rIFN-α-2 in patients with PV has been established in several series of patients who were treated with rIFN-α-2b[4-7] or pegylated (PEG) -IFN-α-2a.[8,9] With both preparations, the phlebotomy rate has been significantly reduced, and complete and partial clinical and hematologic remissions occurred in virtually all patients.[10,11] Significant reduction in the Janus kinase 2 allele burden has been recorded after treatment with both PEG-IFN-α-2a[8,9] and PEG-IFN-α-2b.[12] Indeed, some patients may achieve long-lasting complete and molecular remissions, which are sustained in a subset of patients, even after discontinuation of PEG-IFN-α-2b for as long as 24 months.[12] Because of the frequency of secondary acute leukemia recently reported after the use of hydroxyurea therapy,[13-15] and because of its other adverse effects, we believe that rIFN-α-2 is the treatment of choice for patients with PV who are younger than age 60 years, unless there are mitigating factors that contraindicate its use. The most significant of these include a history of severe depression, autoimmune disease, and peripheral neuropathy.[5]

For more than 20 years, the effectiveness of IFN-α-2 in treating ET has been appreciated.[3,10,11] It is routinely used as initial therapy in many treatment centers. In 1996, a review of 273 patients indicated the efficacy of rIFN-α in relieving microcirculatory complaints in induction therapy.[16] During maintenance therapy, a much lower dose of IFN-α-2 could be used. Prolonged remissions of up to 3 years resulted after its discontinuation.[10,11] Likewise, PEG-IFN-α-2a has also resulted in reduction in the Janus kinase 2^{V617F} allele burden.[8] Since the initial review in 1996, results of the treatment of more than 260 patients have been published, confirming the effectiveness of IFN-α-2 in the treatment of ET.[10,11]

In PMF and fibrosis that occur after PV or ET, the statement that IFN-α therapy is "poorly tolerated" and has "limited efficacy"[1] primarily relates to patients who are treated with IFN-α and who have had extensive marrow fibrosis, significant splenomegaly, pancytopenia, and other manifestations of end-stage disease. Universally, the doses of rIFN-α that have been used have been too high for prolonged treatment.[10,11] However, smaller doses in patients with more cellular marrows have resulted in a decrease in spleen size, thereby reducing abdominal pressure, relieving bone pain, and reducing leukocytosis.[4,11] More recently, low doses of IFN-α-2a have been successfully used for treatment during the hypercellular phase of the disease.[17,18] It is conceivable that this may delay progression of the disease. In this regard, most importantly, restoration of normal marrow architecture after prolonged low-dose treatment with rIFN-α-2b has been reported after systematic study,[17] similar to that which has been reported for PV.[12]

The early use of IFN-α-2 as a reasonable treatment strategy in the MPNs has recently been reviewed.[11,19] IFN-α-2 may affect early stem cell proliferation, has immunomodulatory effects, and awakens dormant stem cells to become targets for activated immune cells,[20] which may be among the most important effects of IFN-α-2. This approach may also translate into inhibition of disease progression and development of myelofibrosis.[11,19]

In summary, there is now abundant evidence to indicate that low-dose IFN-α, preferably PEG-IFN-α, is the drug of choice for patients with ET and PV who are younger than age 60 years and certainly should be considered for patients with PMF in its hypercellular phase, post-ET and post-PV myelofibrosis.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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