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Optimal Therapy for Polycythemia Vera and Essential Thrombocythemia: A Different Perspective

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Abstract

Recent publications have de-emphasized the importance of recombinant interferon alpha (rIFNα) for the treatment of polycythemia vera (PV) or essential thrombocythemia (ET), favoring the use of phlebotomy and/or hydroxyurea. Here we express our reasons for the use of rIFNα early in the course of PV or ET in the absence of a phase 3 trial.

Recent articles [1,2] have obscured the value of recombinant interferon-alpha (rIFNα) in polycytemia vera (PV) and essential thrombocythemia (ET) either as initial therapy instead of phlebotomy, or because the value of rIFNα has not been established on the basis of phase 3 trials. For high risk PV or ET patients, it is suggested that rIFNα use be limited pending the results of a randomized trial comparing the response of rIFNα to hydroxyl urea (HU) [2]. Concern is also expressed because of the growing popularity of once weekly pegylated interferon-alfa (PEG-rIFNα) for treating PV and ET "off-label" without the results of this slowly accruing phase 3 trial. For "low risk" PV patients (less than 60 years of age and no prior history of thrombosis), we are apprehensive about the recommendation of phlebotomy-only (Ph-O) as definitive treatment [1].

The important issues, therefore, are: 1) In diseases of long duration, can single arm studies of a drug validate therapeutic opinions? What lessons in clinical design can be learned from slowly accruing trials that occur in MPNs? 2) What is the basis for our current treatment recommendations for a patient with PV or ET, especially a younger one, who does not wish to or cannot enter a clinical trial? Why is interferon preferable to phlebotomy or HU in "low-risk" PV patients?

Precedence for the Use of Single Arm Studies

Evaluating response to therapy in diseases of long duration has been considered by the US Food and Drug Administration (FDA) [3]. Consensus indicates that single arm trials can be reserved for serious, life-threatening diseases in which there are relatively few patients, and in which a significant drug effect can be observed. These include symptom relief or change in meaningful biomarkers pending completion of a phase 3 study to confirm survival.

As noted by Dagher et al. [3], patient accrual to treatment studies of rare diseases can be improved by the addition of more study sites, but all studies must have flexibility allowing for protocol modification as new information accrues. Too many sites make protocol modification difficult because of mandatory investigational review board approval. For example, increased accrual to a current study comparing the efficacy of PEG-rIFNα to HU in high risk PV and ET would occur with correction of some of the admission criteria employed in its PV protocol which relies mainly upon increased hemoglobin (Hgb) values, 18.5 gm/dL in men and 16.5 gm/dL in women, representing surrogate markers for an increased red cell mass. These Hgb values fail to diagnose at least 35% of patients. Since most practicing hematologists unfortunately use these criteria rather than the definitive Cr^5 labeled red blood cell technique, approximately 35% of patients are incorrectly excluded from the trial. The scientific error is compounded because of the recognition that patients who are iron deficient at diagnosis have a lower hemoglobin level relative to their corresponding red blood cell count, yielding inappropriate terms such as "masked" polycythemia vera. The disassociation between a low hemoglobin, mean corpuscular volume and red cell value furthermore gives an inaccurate calculated HCT value, a parameter used both for diagnosis and for treatment.

Why should rIFNα be recommended rather than hydroxyurea or phlebotomy-only?

In view of the long and unsuccessful history of treating PV with Ph-O, it is difficult for us to understand why this therapy is still recommended as definitive treatment for low-risk patients after the diagnosis is established. Years ago, many reports documented the impossibility of treating patients with PV with Ph-O because of the resulting severe iron deficiency anemia. Currently the literature is replete with the symptoms and issues associated with iron deficiency *per se* ranging in severity from impaired cognitive function, cheilosis Plummer-Vinson syndrome, to cardiovascular catastrophies [4].

Cytoreductive therapy is often required in PV because of thrombosis, increasing splenomegaly and constitutional symptoms. HU is the drug most often selected because rIFNα is not available in certain countries and because of the misconception regarding side effects of doses used in PV.

The use of HU in clinical practice dates back to the early studies of the Polycythemia Vera Study Group (PVSG) when the Group evaluated a marrow suppressive HU without the leukemogenic potential of radioactive phosphorus or chlorambucil. In the PVSG study, HU controlled the hematocrit and platelet values in 80% of patients, in doses of 15 to 30 mg/kg; 75% were failure-free after 1 year. When HU was discontinued, rebound thrombocytosis occurred. Long term therapy was not contemplated. Multisystem toxicity is seen in patients with MPNs receiving HU for extended periods, not surprising since the drug is a nonspecific cell-poison directly inhibiting DNA synthesis. The carcinogenic potential of HU has been long noted. The frequency of squamous cell cancer is estimated at 20%. Atrophy of the skin and nails, dryness and desiccation, and dermatomyositis are often problems. Although the risk of leukemia is

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less with HU than with alkylating agents, it is unclear there is no risk with long-term therapy. Virtually all studies have been retrospective. We believe leukemogenicity depends upon the dose of HU and its duration. A prospective study comparing patients treated with pipobroman to HU yielded results from the HU arm which was informative [5]. At 10 years, the frequency of patients developing AML or MDS was 6.6%, at 15 years 16.5% and at 20 years 24%. The effect of disease duration *per se* could not be disassociated from the effect of HU. The findings of TET2, ASXL-1 and other molecular abnormalities in normal individuals and in patients [6] with PV and ET are intriguing. Perhaps the use of a cytototoxic agent like HU may predispose to increased clonal evolution, additional cytogenetic abnormalities and the subsequent development of MDS or acute leukemia [6,7].

In contrast to HU, rIFNα has biologic effects on PV stem cells, megakaryocyte proliferation and morphology, marrow cellularity, and fibrosis. Molecular response i.e. reduction in JAK2V617F allele burden in PV is regularly noted and reduction in CALR-mutated ET has been observed. Clinical response is manifested by reduction in phlebotomy rates, prompt symptomatic improvement, especially pruritus, regression of splenomegaly, and normalization of blood counts. Remarkable improvement in thrombosis-free survival has been noted in 4 independent studies, not seen with any other drug. In ET, rapid reduction in platelet number and splenomegaly, if present, is routinely observed with low dosage. rIFNα is the drug of choice for pregnant women with ET requiring treatment. Symptoms of aesthenia and myalgia are uncommon with low-dose interferons. However, significant depression and a history or presence of an auto-immune disease is considered contraindications at any dose.

Considering all the facts, it is no wonder that many patients refuse to enter a clinical trial employing HU. Protocols written years ago ignore the power of the Internet. Importantly, as knowledge accumulates, patients often participate in the decisions pertaining to their illness. In 2015, the PEW Internet Project estimated that more than 65% of all Americans sought health information on-line obtained through search engines such as Google and websites including Wikipedia and WebMed.

While we encourage the randomization of patients in MPN trials, if possible, hopefully in the future, the answers to the questions raised will be found. In the meantime, we will continue to advise those patients not eligible for a clinical trial to receive preferentially interferon because of the evidence presented.

Acknowledgement

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