Optimal therapy for polycythemia vera and essential thrombocythemia: Preferred use of interferon therapy based on phase 2 trials

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Objectives: To determine the value of recombinant interferon-alfa (rIFNα) in the treatment of polycythemia vera (PV) and essential thrombocythemia (ET) based on its biological activities and phase 2 clinical studies, pending completion of phase 3 trials; to determine importance of the Internet in patient decision-making in treatment selection.

Results: The value of rIFNα in PV and ET is based upon its biological effects on PV stem cells and megakaryocyte proliferation. Single-arm trials are useful for life-threatening diseases when there are relatively few patients to evaluate endpoints, such as rIFNα treatment of PV and ET. Proper diagnostic criteria are mandatory; for PV, the current World Health Organization criteria emphasizing increased hemoglobin values exclude approximately one-third of eligible patients.

Importance of these data: Single-arm studies in diseases exemplified by rIFNα in PV require updated diagnostic criteria for research and for clinical practice. The influence of the Internet on patient decisions for treatment is noteworthy.

Conclusion: The biologic basis for selecting therapy is exemplified by rIFNα in treating PV and ET. Current single-arm studies of rIFNα in PV and ET are relevant and acceptable. The importance of the Internet in patient decision-making is important.

Introduction

Recent articles published in leading medical journals have obscured the value of recombinant interferon-alfa (rIFNα) as initial therapy¹ in polycythemia vera (PV) and essential thrombocythemia (ET)² because its value has been established only on the basis of phase 2 trials.² For high-risk PV or ET patients, it has been suggested that rIFNα use be limited pending the results of a randomized trial comparing the complete hematologic response of rIFNα to hydroxyurea (HU).³ Concern has been expressed regarding the growing popularity of pegylated interferon-alfa (PEG-rIFNα) for treating PV and ET ‘off-label’ without the results of this slowly accruing ongoing phase 3 trial.³ For ‘low-risk’ PV patients, i.e. these defined as less than 60 years of age and no prior history of thrombosis, we are apprehensive about the recommendation of phlebotomy-only (PH-O) for maintenance therapy.¹ Although we agree in general, that randomized trials remain the gold standard, we should recognize that even large well-planned phase 3 randomized trials do not always provide timely answers. Just consider, for example, the ongoing arguments regarding the value of routine mammography in breast cancer.³,⁵ Moreover, it is well known that only approximately 3% of eligible patients enter clinical trials for one reason or another; this figure probably applies to PV and ET as well. Therefore, we are obliged to offer our opinions regarding our treatment recommendations for those patients unable to enter such trials and for so-called low-risk PV patients.

The important issues to resolve are: (1) in diseases of long duration, is there a precedence for the use of single-arm studies of a drug to validate therapeutic opinions? What lessons in clinical design can be learned from slowly accruing trials that often occur in Myeloproliferative Neoplasms (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 (PH) or HU as a treatment for PV in so-called low-risk patients?

Methods
We reviewed the Food and Drug Administration (FDA) consensus document regarding phase 2 studies and the basis for them. We analyzed the reason for slow accrual to the current randomized trial of the Myeloproliferative Disease Consortium comparing rIFNα to HU. We reviewed the importance of the intent of patient decisions. We review the biological basis for the use of rIFNα in PV and ET and why we believe it is superior to HU in PV and ET or PH-O in PV.

Results
Evaluating response to therapy in diseases of long duration has been considered in depth by the US FDA.6 Consensus has been reached indicating that single-arm trials can be reserved for serious or life-threatening diseases in which there are relatively few patients, but in which a significant effect can be observed. It was decided that novel investigative agents should demonstrate clear evidence of clinical activity on surrogate endpoints with acceptable safety. These include symptom relief or change in meaningful biomarkers pending completion of a definite phase 3 study to confirm the ultimate purpose of treatment, survival. Thus, complete responses have been accepted as evidence of benefit in malignant diseases when responses to treatment have been associated with established clinical benefit parameters.

As noted by Dagher et al.,6 patient accrual to treatment studies of rare diseases can be improved by the addition of more sites where a drug may not be available. All studies must have flexibility allowing for protocol modification as new information accrues. On the other hand, too large a number of sites makes protocol modification difficult or impossible because of subsequent mandatory Investigational Review Board (IRB) approval. For example, there is a current study comparing the efficacy of PEG-intron to HU in high-risk PV and ET conducted by the Myeloproliferative Disease Research Consortium.7 Improved patient accrual would occur with modification and correction of some of the diagnostic criteria currently employed in its PV protocol which relies mainly upon increased hemoglobin values, 18.5 g/dl in men and 16.5 g/dl in women. These represent surrogate markers for defining an increased red cell mass which fail to diagnose at least 35% of patients.8-12 Since most practicing hematologists unfortunately use these hemoglobin values rather than the definitive Cr5 labeled red blood cell technique, approximately 35% of patients are incorrectly excluded from the trial. The scientific error in this world-wide study is also 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,12,13 yielding inappropriate terms such as ‘masked’ PV.14,15 This basically ignores the physiology of the disease because PV is a disease of increased red cells, not hemoglobin concentration. The disassociation between low hemoglobin and red cell values furthermore gives inaccurate HCT values,13 a parameter currently used both for diagnosis and for treatment.

Protocols conceived and written years ago ignore the current power of the Internet. Importantly, as new knowledge accumulates, patients more often participate in the medical decisions pertaining to their own illness. As noted recently, the internet has become more significant each year as patients react to information related to their health.16 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.16 Undoubtedly, patients are making their own decision about the relative benefit of one treatment compared to another. Moreover, the randomized trial comparing HU to rIFNα in patients with PV is jeopardized because HU, an easily obtainable drug, can be purchased at a reasonable cost; thus, there is less incentive for a patient to join a trial with its attendant protocol burdens.

Why should rIFNα be recommended?
In view of the long and unsuccessful history of the treatment of PV with PH-O, which leaves patients with a plethora of symptoms, poorly controlled by conventional therapy,1 it is difficult for us to understand how this therapy can still be recommended as definitive treatment for so-called low-risk patients after the diagnosis is established to maintain the HCT at 45% or less in both men and women. More than 60 years ago, Wasserman referred to patients treated with PH-O as ‘phlebotomy cripples’ and Berlin17 noted that entirely missing from the literature were data pertaining to the difficulty of maintaining patients on a PH-O regimen particularly as it relates to patient well-being, now subsumed under the term of ‘quality of life’. Najean and Rain18 carefully documented that it was impossible to treat patients with PV with PH-O because of the production of severe iron deficiency anemia and its attendant symptoms.19 Currently the literature is replete with the symptoms and issues associated with iron deficiency per se ranging in severity from impaired cognitive function,
Cytoreductive therapy, nevertheless, is often required in PV because of thrombosis, increasing splenomegaly, and constitutional symptoms and HU is the drug most often selected. This selection is abetted because interferon may not be available in certain countries, because of the preference for oral pills rather than subcutaneous injections (usually once weekly) and because of the misconception regarding its side effects which were significant when used in higher doses in patients with melanoma or chronic myeloid leukemia compared with the lower doses used in PV.

The popularity of HU in clinical practice dates back to the studies of the Polycythemia Vera Study Group (PVSG) in which the Group evaluated a marrow suppressive without the potential leukemogenic lethality of radioactive phosphorus or chlorambucil. In the PVSG study, HU controlled the hematocrit and platelets in 80% of patients, with a dose of 15–30 mg/kg; 75% were failure-free after 1 year. However, when HU was discontinued, rebound thrombocytosis to potentially dangerous levels occurred. The PVSG emphasized that the drug should only be used in patients with ‘good compliance’. Long-term therapy was not contemplated. Toxicity of many kinds is seen in patients with MPNs receiving hydroxyurea for extended periods. This is not surprising since the drug is a non-specific cell-poison directly inhibiting DNA synthesis owing to its effects on ribonucleotide reductase. Its cytotoxicity affects the cell cycle specifically during S phase. An increased incidence of chromosome abnormalities is seen in vitro and in cultured cells. The carcinogenic potential of HU has been long noted. Thus, the frequency of squamous cell cancer has been estimated at 20%. Other skin toxicities include atrophy of the skin and nails, dryness and desiccation, violaceous papules and dermatomyositis.

Mild gastrointestinal toxicity and mucositis and transient abnormalities of renal function have been consistent. Although the risk of leukemia is less with HU than with alkylating agents, it is not clear there is no risk with long-term therapy. Virtually all studies have been retrospective. In our opinion, leukemogenicity depends upon the dose of HU and its duration. It was not thought leukemogenic in the ECLAP study, but the median time of observation was only 2.8 years. A prospective French study of patients treated with pipobroman compared to HU did not yield data indicating HU was unequivocally leukemogenic; however, the results from the HU arm were informative. 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 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 with PV and ET are intriguing. It is not unreasonable to suggest that the use of a cytotoxic agent such as HU may predispose to increased clonal evolution, additional cytogenetic abnormalities, and the subsequent development to MDS or acute leukemia. The use of hydroxyurea in the MPNs has been encouraged because of the absence to date of significant leukemogenesis in patients with sickle cell disease (SCD). However, the studies are short-lived, extending only for a period of approximately 6 years. Interestingly, potential malignancy due to HU has in fact been cited as a possible barrier to its use in SCD and high rates of non-compliance to HU make the effect of dose and duration difficult to evaluate. Moreover, SCD is not a malignant disease with a predisposition to cytogenetic abnormalities.

In contrast to HU, rIFNa can be recommended to patients because of its biologic effects on PV stem cells, megakaryocyte proliferation and morphology, documented regression of marrow cellularity, and reversal of marrow fibrosis. In addition, molecular responses, i.e. reduction in JAK2V617F allele burden in PV, are regularly noted and effects on calreticulin in two patients with ET have been observed. These biological properties support the clinical use of rIFNa in PV and ET. Clinical response is manifested by reduction in PH rates, prompt symptomatic improvement, especially relief of pruritus, regression of splenomegaly, normalization of blood counts, and meaningful reduction and even elimination of the JAK2V617F allele burden. Remarkable improvement in thrombocytosis-free survival has been noted in four independent studies, an observation not seen with any other drug. In ET, rapid reduction in platelet number and splenomegaly, if present, is routinely observed with low-dosage rIFNa and it is the drug of choice for pregnant women with thrombocytosis requiring treatment. Symptoms of asthenia and myalgia are uncommon with low-dose pegylated interferons. However, significant depression and a history or presence of an auto-immune disease are considered relative contraindications at any dose. Considering all these facts, it is no wonder that many patients refuse to enter any clinical trial employing HU.

Conclusion

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, based on our present knowledge, we continue to advise that those patients not eligible for a clinical trial preferentially receive pegylated interferon because of the biological basis for its use. We also...
conclude that healthy scientific dialog will result in the ultimate goal upon which we all agree and seek: improved patient care.  

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Ethics approval
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