Optimal therapy for polycythemia vera and essential thrombocythemia can only be determined by the completion of randomized clinical trials

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Essential thrombocythemia (ET) and polycythemia vera (PV) are chronic myeloproliferative neoplasms (MPNs) associated with an increased risk of developing arterial and venous thrombotic events which are a major cause of early morbidity and mortality.[1,2] These MPNs frequently also evolve to myelofibrosis (MF) and less commonly a myelodysplastic syndrome (MDS) and/or transform to a universally fatal form of acute leukemia (AL). These events represent clonal evolution of these MPNs and are responsible for the majority of deaths that occur several decades after the initial diagnosis. The risk of patients developing thrombotic complications has been related to age over 60 years, a prior history of thrombosis, and the presence of associated cardiovascular risk factors.[1,3,4] Historically, treatment has focused on reducing the risk of developing thrombotic complications by treating patients with low-risk ET/PV with low-dose aspirin and reduction of the hematocrit with therapeutic phlebotomy in the case of PV, while cytoreductive therapy is utilized to normalize the blood counts in patients with high-risk ET and PV.[5] None of the treatment options currently employed has been shown to delay or prevent the evolution of ET/PV to MF, MDS or AL.

Although the immediate goal of treating patients with ET/PV is a reduction in the risk of developing thrombotic events, the real-time assessment of response to treatment is 'normalization' of peripheral blood counts. A recent prospective study provided supportive evidence that maintenance of hematocrit below 45% led to a reduction in the thrombotic risk of patients with PV regardless of whether therapeutic phlebotomy or cytoreductive therapy was used.[6] This hematocrit level has not been universally accepted as the optimal target hematocrit value due to the variance in altitude at which various patients reside.[7] Phlebotomy therapy alone has limitations due to its inability to control systemic symptoms (e.g. pruritus) and progressive symptomatic splenomegaly. Iron deficiency is not unusual in PV and is virtually invariable when repeated therapeutic phlebotomies are instituted. Iron deficiency has been associated with fatigue, cognitive impairment, and increased pulmonary artery pressure.[8] Excessive thrombocytosis in ET patients has, by multivariate analysis, been shown to be related to an increased hemorrhagic tendency, and the degree of elevation of the platelet count at diagnosis or during the patient's clinical course has not been shown to correlate with developing thrombotic episodes.[9,10]

The therapeutic agents currently used by clinicians to treat high-risk patients with ET/PV in 2014 include hydroxyurea (HU), anagrelide, interferon-alpha (IFN-α) and the alkylating agent busulfan that is reserved for patients with significant comorbidities. There have been very few randomized phase III trials to determine the optimal treatment of patients with ET/PV (Table 1).[6,11-16] Such trials have been difficult to perform due to: 1) the prolonged survival of patients with ET/PV (1-2 decades) making prolonged follow up necessary before the beneficial and detrimental effects of a potential therapeutic agent can be fully appreciated; 2) limited access to sufficient numbers of patients at individual centers; and 3) the lack of a sufficiently large group of investigators equipped to perform such trials.

The trial carried out by the Polycythemia Vera Study Group (PVSG) over 45 years ago has had a profound influence on treatment practices even to this day. In order to determine the optimal treatment for PV, 431 previously untreated patients were entered into a prospective, randomized controlled trial between 1967 and 1974. Three treatment regimens were evaluated: phlebotomy alone, chlorambucil supplemented by phlebotomy, or radioactive phosphorus supplemented by phlebotomy.[14] The primary aim of the analysis was to compare the incidence of AL among the three treatment groups. The median duration of follow up at the time of the publication of this trial was more than 6.5 years. At that time, a statistically significant difference in survival among the treatment groups was not observed. However, the risk of AL in patients given chlorambucil was 2.3 times that observed in patients receiving radioactive phosphorus and 13 times greater than that of patients treated with phlebotomy alone. This study had an enormous impact on treatment practices with most clinicians preferring to avoid the use of radioactive phosphorous and chlorambucil in order to minimize the risk of developing AL. Between 1967 and 1978, another phase III clinical trial was performed by the European Organization for Research on Treatment of Cancer (EORTC) in patients with treatment naïve PV.[16] A total of 293 patients were randomized to receive either radioactive phosphorous or busulfan treatment with a goal of maintaining the hematocrit between 42-47%. With a median follow up of eight years, busulfan therapy was shown to be associated with a superior overall survival as a result of a reduction in the rate of vascular complications as compared to the patients receiving radioactive phosphorus therapy. The rate of leukemic transformation was similar in the two groups. The conclusions from these studies led to the search for a non-leukemogenic myelosuppressive agent to treat patients with ET/PV.

Hydroxyurea (HU), an oral chemotherapeutic agent that inhibits ribonucleotide reductase, selectively inhibiting DNA synthesis and impairing the process of DNA repair, was evaluated in a phase II PVSG trial in patients with PV. HU was found to be effective in reducing the rate of thrombotic events when compared to results from historical controls treated with phlebotomy alone. A higher rate of leukemic transformation was noted in the HU-treated patients, but this trend was not statistically significant.[17] HU has been subsequently evaluated in 3 randomized trials involving patients with ET. HU therapy was found to be superior to patient observation in reducing the number of subsequent thrombotic events in one study, superior to anagrelide in reducing life-threatening thrombotic sequela in another study, while in a third study, HU and anagrelide therapy were reported to have equivalent therapeutic activity.[11-13]

Table 1. Randomized controlled studies of myelosuppressive agents in essential thrombocythemia and polycythemia vera.

N. of subjects	Study population specifics	Treatment arms*	Duration of follow-up	Outcome	Ref
114	Age >60 and/or history of thrombosis and platelet count <1.5 x 10^9/L	HU *versus* n. cytoreductive agent	Median follow up 27 months	HU associated with reduced risk of major thrombosis	(11)
809	Age >60, platelet count ≥1 x 10^9/L, or history of ischemia, thrombosis, bleeding, hypertension or diabetes requiring therapy	Anagrelide *versus* HU	Median follow up 39 months	HU associated with superior reduction in risk of arterial thrombosis and anagrelide with venous thrombosis	(12)
259	Treatment naïve, age ≥60 years, platelet count ≥1000×10^9/L or increase ≥300×10^9/L within 3 months, HTN, DM, and/or a history of thrombosis/bleeding	Anagrelide *versus* HU	Observation period of 730 patient-years	No difference in rates of thrombosis or bleeding	(13)
431	Treatment naïve	Phlebotomy alone *versus* chlorambucil *versus* radiophosphorus	Median follow up 6.5 years	Phlebotomy alone associated with increased risk of thrombotic complications, myelosuppressive therapy associated with increased risk of leukemia and other malignancies	(14)
285	First line; <65 years	HU *versus* pipobroman	Median follow up 16.3 years	Pipobroman associated with leukemic transformation	(15)
293	Cytoreductive therapy naïve	radiophosphorus *versus* busulfan	Median follow up 8 years	Busulfan associated with reduced risk of thrombosis and superior overall survival	(16)
365	All-comers	Goal HCT <45% *versus* goal HCT 45-50%	Median follow up 31 months	Intensive control of HCT associated with lower thrombotic risk and rate of cardiovascular death	(6)

**The use of aspirin prophylaxis was allowed regardless of treatment arm in each of these trials. HU: hydroxyurea; HTN: hypertension; DM: diabetes mellitus; HCT: hematocrit.*

HU therapy was not associated with a higher rate of leukemic transformation in these 3 trials, and, in fact, was associated in one study with a lower rate of transformation to MF as compared to patients treated with anagrelide.[12] It is also important to note that the anagrelide was associated with increased incidence of serious hemorrhage compared to HU therapy.[12] There is scant but sometimes conflicting *in vitro* data to indicate that HU is mutagenic or genotoxic. In fact, in a phase III randomized trial comparing HU to placebo in infants with sickle cell disease, evidence of HU-induced genotoxicity was not detected.[18] However, others have reported that the type of PV-directed therapy that individual patients receive may influence the pattern of karyotypic abnormalities observed in PV-related AL.[19]

Hydroxyurea has, for the last 30 years, been adopted as the myelosuppressive agent of choice for patients with high-risk ET/PV. HU is associated with myelosupression, leg ulcers, hyperpigmentation, fever, alopecia, and an increased risk of developing squamous cell carcinoma. The widespread practice of considering HU the standard of care for patients with high-risk ET/PV can be attributed to the initial PVSG studies evaluating HU, its ease of administration, opinions articulated by thought leaders in this field, teachings that were provided during the training of many practising hematologists, and the lack of evidence of increased rates of AL in sickle cell patients who have been receiving HU for decades. The leukemogenic potential of HU therapy in patients with ET/PV continues to be a topic of debate in the literature and remains untested based on data generated with an MPN prospective clinical trial.[11,12,17] However, perceived or real, this concern is shared by many treating hematologists and patients alike, and has contributed to a culture of polarization of belief that HU is leukemogenic and that an alternative myelosuppressive agent is needed.

Recently, several publications have shed further light on this important question. The International Working Group (IWG), composed of seven centers, submitted diagnostic and follow-up information on 1545 patients with PV.[20] Advanced age, an abnormal karyotype and a leukocyte count of 15x10^9/L or over, as well as exposure to pipobroman, radioactive phosphorous, or chlorambucil, but not HU or busulfan, were associated with a higher risk of leukemic transformation. In addition, an analysis of population-based data from Sweden to assess the role of MPN treatment on the risk of developing MDS/AL demonstrated an association between the risk of leukemic transformation and therapeutic exposure to radioactive phosphorous and alkylating agents, but not with HU.[21] Importantly, this study showed that 25% of patients with MPNs who developed MDS/AL had never been exposed to cytotoxic therapy, supporting the concept that AL is part of the natural history of such MPNs. The French Polycythemia Study Group randomized 285 patients with PV under the age of 65 years to HU or pipobroman as first-line therapy.[15] In the final analysis of this prospective study, with a median follow up of approx-

imately 16 years, a statistically significant improvement in median survival in favor of HU and a clear increase in development of MDS/AL with pipobroman were demonstrated. Data from this unique randomized trial indicate that evolution to MDS/AL is the leading cause of death in PV, and that pipobroman is leukemogenic and is not an appropriate option for front-line therapy. The incidence of evolution to MDS/AL with HU was higher than previously reported. Whether this is merely a consequence of the natural history of PV and was detected in this study due to the extraordinary long-term follow up or whether it is a consequence of HU therapy is impossible to determine since a phlebotomy alone group was not included in the study. This high rate of leukemic transformation is, however, consistent with those findings in the Scandinavian population-based study indicating that 25% of PV patients who do not receive any myelosuppressive therapy go on to develop AL.

Interferon alpha (IFN-α) has been reported in multiple studies carried out over the last two decades to be an effective agent in treating patients with ET/PV.[22-24] More recently, phase II studies evaluating the efficacy and toxicity of a pegylated form of IFN-α for the treatment of ET/PV have demonstrated potent clinical activity and a possible reduced toxicity profile.[25-27] Complete hematologic response rates ranged from 75-95%, and complete molecular responses as defined by an inability to detect *JAK2V617F* have been reported in approximately 15-20% of patients with ET/PV.[27-30] In fact, IFN-α remains the only reported treatment approach that can reproducibly induce molecular responses including complete responses, although its significance as a biomarker for prolonged survival remains untested.[31] While the exact anti-neoplastic mechanism of action is unclear, IFN-α appears to be active at the level of the hematopoietic stem cell and to be capable of depleting *JAK2V617F*-positive stem cells.[32] While pegylated IFN-α therapy is better tolerated than IFN-α, it is not without toxicity and has been associated with myelosuppression and non-hematologic toxicity that can lead to discontinuation in approximately 15-25% of treated patients with ET/PV.[25,28,33,34] The serious side-effects associated with IFN-α use include an increased risk of depression, exacerbation of autoimmune diseases, neuropathy, hypothyroidism, retinitis, and reversible left heart failure. Long-term toxicity data on patients being treated with pegylated IFN-α beyond two years are not available.

Enthusiasts of the use of IFN-α have concluded that this recombinant cytokine effectively eliminates the risk of developing thrombotic episodes, reduces the rate of transformation to MF, and evolution to AL in patients with ET/PV. Based upon such claims, some investigators and patient advocacy groups have lobbied third party payers to make pegyated IFN-α, which is a parenteral agent and much more costly than HU, available to MPN patients. The proposed effects of IFN-α therapy on rates of thrombosis, development of bone marrow fibrosis, and evolution to MDS and AL are based upon results from phase II studies which included limited numbers of patients followed for a relatively short period of time. Since ET/PV can be associated with additional cytogenetic abnormalities and acquired mutations which can persist perhaps even after the elimination of the JAK2V617 mutation following IFN-α therapy, the use of the JAK2V617F allele burden as a surrogate biomarker for disease activity requires careful study and validation.

Randomized controlled trials represent the gold standard for evaluating the effectiveness of different novel interventions. Adopting new interventions without a rigorous assessment of the potential for harm is in conflict with the basic principles and philosophy of evidence-based medicine. Unfortunately, phase III trials are often difficult to perform due to the heterogeneity of the participating patient population, difficulties with selection bias depending on inclusion criteria, physician perception of the effectiveness of the drugs being studied, and patient willingness to participate in the randomization process.

Many investigators, physicians, and patients alike have already concluded that IFN-α shows superiority in the setting of Philadelphia chromosome-negative MPNs. For the moment, these conclusions remain premature and not substantiated by data from phase III trials. We feel that it remains important to establish the long-term safety, tolerability, and durable efficacy of IFN-α in terms of hematologic, cytogenetic, and molecular response, as well as reduction in thrombotic risk and improvement in survival, before this drug is indiscriminately used by the hematology community. In order to rigorously and scientifically evaluate the true efficacy of IFN-α in the setting of ET/PV, a large, multi-centered clinical trial is essential. This approach is of increasing importance since oral pan JAK1/2 inhibitors are being used with increasing frequency off label to treat PV; an approach that is for the moment supported by a single phase II study.[35]

The Myeloproliferative Disorders Research Consortium (MPD-RC) 112 trial (*clinicaltrials.gov identifier: 01259856*) will provide long-term follow up of ET/PV patients receiving either Pegasys (pegylated IFN-α 2a) or HU and will allow a direct comparison of these two agents in terms of tolerability, adverse event profile, rates of hematologic, cytogenetic, and molecular response rates, thrombotic complications, and risk of progression to MF/MDS/AL. At a time when commercial access to IFN-α is increasingly available for many patients with ET/PV in the United States, and many expert hematologists have already drawn conclusions about this agent, it is both challenging and paramount to move the scientific field forward with rigorous evaluation of these two therapeutic options within clinical trials. Opinions on optimal therapeutic approaches can change as our understanding of the biology and genetics of ET/PV advance, but clinical trial data generated through well constructed and rigorously performed phase III trials are still required in order to generate objective clinical evidence with which to identify the optimal therapeutic approaches. This systematic approach is obviously time consuming and utilizes important clinical resources, but is the only way to identify the superiority of one agent over another. These concepts have been validated innumerable times when evaluating novel treatment options for hematologic malignancies that have more aggressive clinical courses, but have not been universally accepted for the MPNs which are associated with less aggressive, more protracted yet ultimately progressive clinical courses. Ultimately, the biggest winners from the pursual of this approach will be the patients with ET/PV who will have renewed confidence in the manner in which MPN therapeutic agents are being evaluated and

greater confidence in the treatment options that they are being offered.

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A Master Class for European Hematology

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Background

As already highlighted in previous articles,[1-3] successive European Commission educational grant support has created and consolidated a platform for harmonizing training and increasing the level of competence among young hematologists across Europe. This direction of travel began in 2002 with the European Council for Accreditation in Hematology (ECAH) project. Challenged by results then of significant heterogeneity in specialty training offered to future hematologists across Europe, one of the deliverables was the establishment of a pan-European network of champions in the individual national societies of hematology to provide grassroots support and act as linkers in standardizing training. Another key deliverable was the establishment of a European Curriculum Passport (CVP) to promote mobility. Utilized as the basis for the EU-supported grant in 2008-2011 entitled European Network for Harmonization of Training in Hematology (H-Net), the CVP underpinned the proposal to implement strategies of the Life-long Learning Programme. This will further progress towards improved, harmonized hematologic training to raise standards of patient care and public health. H-Net also focused on identifying and mapping educational needs at an individual, nation state and European level. The roadmap would then enable development of a comprehensive and contemporary suite of educational tools to address educational needs.

In addition to existing tools within the EHA educational portfolio, e.g. tutorials, pod and webcasts, a missing element was a more personalized educational approach that could be tailored but yet converge knowledge and enhance professionalism. Development of a European Master Class in Hematology (EHA Master Class) appeared as the most relevant tool in leveling up competency and enhancing safety for the patient with hematologic disorders.

Conventional master classes

There are many reported formats and styles of master classes. These can range from textbooks coupled to online slide shows to face-to-face courses with experts presenting specific topics and taking place in one location. There are pros and cons of different formats but location-specific events would require considerable investment in transport-related costs and are unlikely to provide cost-effectiveness if frequent and regular events are necessary across Europe. There again, there are formats for different purposes, e.g. for short-term targets of passing examinations, or those that are more centered on life-long professional development. In general, master classes offer an opportunity to learn, in particular from a master but also in the presence of peers.[4] As such, the student or trainee is likely to feel under some pressure to make a favorable impression and the impact of the setting can present fresh perspectives that could accelerate the learning process. In non-medical settings, students' perceptions of master classes are generally positive with over 80% agreeing that these form an important part of the curriculum.[5]

The pilot EHA Master Class

The pilot Master Class was developed as part of the H-Net project on the principles of providing both cost-effective and sustainable solutions to personalized training for each trainee in any broad area in hematology that was identified as a gap or weakness in the Harmonized European Hematology CVP. It was planned with expert educational input as an on-line group learning experience with building of professional and social networks to share knowledge and experience on complicated real-life clinical scenarios devel-

Table 1. Key themes of the EHA Master Class.

• Online peer-group supported learning
• Emphasis on knowledge refinement and professionalism
• Social networking format
• Mentoring from a distance
• Transferable value

Table 2. Future EHA Master Class developments.

• Topic specific or bite-sized Master Classes
• Increasing multi-disciplinary application
• Patient enrichment of educational materials
• Research skills Master Class
• Continued professional development opportunities