

How I treat MPNs.

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Commentary on the season's scientific findings and MPN events.

In this concluding section of diagnosis and treatment of MPNs, four of the world's pre-eminent MPN researchers and clinical specialists combine current thinking from Europe and the United States. Dr. Claire Harrison, Dr. Hans Hasselbalch, Dr. Richard Silver and Dr. Ruben Mesa share their approach to treating the Philadelphia negative myeloproliferative neoplasms, essential thrombocythaemia, polycythaemia vera and myelofibrosis.

Dr. Claire Harrison: How I treat essential thrombocythaemia.

Consultant haematologist and Deputy Director, Guy's and St. Thomas' NHS.

We will review any patient with a platelet count over 450. All will have a clinical evaluation and directed investigation which will always include at least a blood film, inflammatory markers, iron status, JAK exon 14 and MPL exon 10 mutation screen. I almost always do a BMBx with cytogenetics which is reviewed by me along with all the diagnostic information. Even if a patient comes for a second opinion I am likely to request to see all the diagnostic material.

Then I discuss findings and options with the patient.

We discuss the natural history of essential thrombocythaemia with short and medium terms risks of clotting (thrombosis) and bleeding (haemorrhage) events and long term risks of transformation to myelofibrosis (with stiffened bone marrow, enlarging spleen, falling blood counts and aggressive disease course) or acute leukaemia. In particular we discuss that many patients do not suffer any of these complications. This condition is due to abnormal control of blood cell production. In about half of patients this is due to an abnormal sequence in a gene called JAK2; this change causes increased growth and is known as JAK2 V617F. There is no clear difference in the disease of patients who either have or do not have this mutation.

We review treatment strategies for this condition ranging from management of cardiovascular risk factors (control of blood pressure screening for cholesterol problems) and low dose aspirin for patients without increased risk of bleeding. Control of the platelet count with a drug is offered for high risk patients, high risk implying that patients are at high risk of particularly clotting but also bleeding events. Such patients being defined by any ONE of: Age over 60 years, previous clotting or bleeding events or platelet count more than $1500 \times 10^9/l$. Under some circumstances — treated hypertension or diabetes — there is also emerging evidence for an elevated white cell count as a marker of high risk disease.

The three main treatment options and their various side effects are explained in depth as summarised below. Hydroxycarbamide or Hydroxyurea being the "gold standard" therapy supported by trial data showing it reduced clotting (especially in JAK2 V617F positive patients) and bleeding events and potentially slow transformation to myelofibrosis and being associated with few short term side effects — mild stomach upset, some mouth and skin ulceration but carries the potential un-quantified risk of slightly increasing transformation to leukaemia. In comparison Anagrelide does reduce clotting and bleeding but less well than Hydroxycarbamide, it does not slow myelofibrotic transformation but also does not increase the risk of leukaemia. The major side effects of Anagrelide being: headaches, palpitations, diarrhoea, fluid retention. Lastly Interferon given by injection has never been compared formally to the other two treatments but is likely to be similar with some anecdotal reports suggesting reduction or reversal of fibrosis, safety in pregnancy and no risk of leukaemia. The side effects of Interferon being: flu-like symptoms for the first two weeks, and high incidence of fatigue and depression in the long term.

I encourage all patients to have an annual review of weight, blood pressure, cholesterol and diabetes screen. All are encouraged and advised on healthy lifestyle not smoking etc. I tell all patients that this is a form of blood cancer explaining that there is a spectrum of cancers. Then

Low risk ET, age less than 40, platelets less than 1500 (sometimes I allow this to be higher) no risk factors (see paras above) get aspirin alone, Sometimes I do not use aspirin if the patient has a bleeding phenotype or I will stop it if the patient bleeds ++ on aspirin. The results from low risk arm of the PT-1 (Primary Thrombocythaemia 1) trial will be important here to be able to say more definitively what the natural history is. This data is due in 2014.

Intermediate risk ET, age 40-60 platelets less than 1500, no risk factors. There is little evidence for clinical practice here. We are awaiting results of the intermediate risk arm of PT-1 [clinical trial](#)). I explain this to the patient and offer aspirin alone. I would offer more to patients with strong family history of vascular event etc.

High risk ET. In addition to health advice I explain all 3 options and offer the patient a choice, supported by written information. In general I would usually use HU or IFN up front reserving anagrelide for second line where I often prescribe it in combination with HU.

All patients receive written information about their disease and different treatment options. They are also given information about patient support groups (we hold one at least twice a year on behalf of MPD Voice www.mpdvoice.org.uk). All patients are encouraged to bring a friend or relative to the consultations initially.

All patients at diagnosis also see a specialist nurse. All patients receiving treatment beyond aspirin have a structured consent and detailed instruction/review of potential side effects, after starting they get a follow up call within a week from the nurse. All have full access to contacts within the department. We also offer full health psychology support if needed.

Follow ups: We offer a range including telephone and face to face. All patients have an annual review including film and spleen examination, skin exam for HU patients, thyroid and liver and depression screen for IFN every 6 months. Most patients on cytoreductive drugs once stable are reviewed every 3-4 months, low and intermediate patients between 4-6-12 monthly depending on disease duration, stability and patient preference.

We offer repeat BMB if indicated, we encourage it for patients on anagrelide every 3-4 years and for young patients. All patients are offered the opportunity to take part in our national sample banking for MPN which involves a blood sample and mouthwash (formally known as buccal sample).

I also discuss the risks of inheritance of this condition with regard to their children. There is a slight increase in risk that first degree relatives of patients with these conditions will develop the same condition. The magnitude of risk however is very low with an overall risk of approximately 1 in 20,000. I would not recommend routine screening of children unless they are due to undergo a high risk procedure or have suggestive symptoms

If appropriate, with regard to pregnancy I discuss the following:

The combined oral contraceptive pill is not an appropriate means of contraception because of the added risk of thrombosis. In terms of pregnancy itself I would imagine that the pregnancy could be managed jointly between local haematologists and obstetricians and that once pregnancy occurs we would send a copy of our latest pregnancy protocol to guide management if that was desired. I would anticipate that pregnancy is likely to be both successful and uncomplicated. However, there is an increased risk of 1st trimester miscarriage possibly between 1:6 and 1:8 pregnancies and of events later in pregnancy such as a growth restricted baby due to blood clotting in the placenta or rarely a late pregnancy foetal death for the same reason. Approximately 70-75% of pregnancies in patients with this condition are successful. During pregnancy low dose aspirin should be given and uterine artery Doppler's determined at the 20 weeks scan repeated at 24 weeks if notching is present. If notching persists then consideration should be given to increased therapy (e.g. adding or increasing the dose of low molecular weight heparin or IFN) and the pregnancy monitored more closely.

In terms of maternal risk this generally occurs in the post partum period, in particular the first six weeks after the baby is born, and relates to an increased risk of clotting. For this reason we would recommend in addition to Aspirin throughout pregnancy six weeks of low molecular weight heparin in the post partum period.

This is an exciting and interesting time for all patients with MPNs. For our patients with ET we need some improvements in risk stratification to better understand the long term effects of many treatments and to safely introduce some of the exciting new therapies for this disease area.

Introduction

Most guidelines and recommendations for the “Goals of Therapy in ET and PV” during the years have aimed at reducing the risk of thrombosis and hemorrhage without increasing the inherent risk of leukemic and myelofibrotic transformation by treating patients with potentially leukemogenic agents according to the concept “Do no Harm to The Patient.” In recent years additional major issues have also been addressed , including quality of life (QoL) of patients with ET and PV.

Several QoL studies in ET and PV have convincingly shown that even in the early MPN stages a subset of patients is heavily disease burdened . Another important issue is the revival and renaissance of interferon-alpha2 (IFN) , being used for decades in the treatment of ET and PV . Recently, IFN has been shown to be able to induce major molecular remissions as assessed by the JAK2V617F allele burden, reducing the risk of thrombosis and hemorrhage and in a subset of patients even reverting disease progression with normalization of bone marrow architecture . This “minimal residual disease “ condition may even be sustained after discontinuation of IFN for several years .

Accordingly, IFN has the potential to modify disease progression in a subset of patients – indeed supportive of the concept of intervention with IFN at the earliest disease stage , when a favourable outcome is likely the very best. Importantly, they also urgently call for new

Standards for therapeutic goals in ET and PV.

When addressing the goals of therapy in ET and PV it is important also to address the burden of ET-and PV- related comorbidities , which actually may heavily influence the QoL of our ET and PV patients. All these comorbidities – eg cardiovascular, pulmonary, renal, skeletal , inflammatory and autoimmune – should be diagnosed and treated at the very early stage of the disease upfront at the time of diagnosis .

The Goals of Therapy in ET and PV

Cure is the optimal goal of treatment of any cancer and if not possible then to convert to a stage of “minimal residual disease.” A prerequisite for achieving these goals is that the cancer is diagnosed at the earliest stage of its development , when the tumor burden is the least at any time and accordingly the chance of a favourable outcome the best. In the context that ET and PV are early stages of myeloid cancers, which untreated may steadily progress to the advanced myelofibrosis stage with myeloid metaplasia comparable to an untreated disseminated cancer , it seems rational to start treatment with IFN at the time of diagnosis. The goal is to minimize and control the disease at the early cancer stage and hopefully inhibit cancer progression.

In the perspective that the MPNs – ET, PV and PMF – are cancers at different stages in the biological continuum from early cancer stage (ET) to the advanced myelofibrosis stage. This last is characterized with metastasis (= egress of CD34+ cells from the bone marrow to seed at extramedullary sites like the spleen and liver). In the following I will argue for the rationale of early intervention with interferon in these cancers instead of a “wait and watch” strategy.

The Wait and Watch Strategy

The goals of therapy in ET and PV are ultimately to improve QoL by reducing the risk of thrombosis and hemorrhage, relieve symptoms and prohibit disease progression towards myelofibrosis and leukemic transformation. The pathway to follow to obtain these goals may differ being dependent upon access to IFN or not. In countries/centres not having access to treat with IFN a large number of patients are followed without cytoreductive therapy according to a risk-adapted treatment approach being founded on the rationale that we shall “Do no Harm “ to our patients.,

Previous cytoreductive therapies (busulphan, piproproman, p 32) were associated with a definite increase in the risk of developing acute myelogenous leukemia (AML). The same concern exists in regard to hydroxyurea (HU) which is the cytoreductive agent being used worldwide to treat patients with ET and PV. Accordingly, at most “non-IFN” centres – ET and PV patients are not considered for cytoreductive therapy, unless categorized as “high risk “ (prior thrombosis > 60 years, platelet counts > 1500 Mia/L).

Importantly, this risk-adapted therapy does not capture the current symptomatic disease burden in the individual patient – the need of the patient – but is highly dictated and influenced by the concern of HU as a leukemogenic agent .

Younger low-risk ET and PV patients (<60 years of age) are left untreated until a major thrombotic event occurs, classifying the patients as high risk and then qualifying for cytoreductive therapy, which in most centres is HU. Unfortunately, however, this agent may be associated with significant skin toxicity , skin cancer, myelodysplasia (MDS) and/or AML after long-term treatment (>10 years) in a subset of patients. Importantly, short term treatment with HU (less than 5-10 years) does not seem to carry an increased risk of MDS or AML . At several centres in Europe and US IFN instead of HU is used routinely for younger patients.

The Early Intervention Concept in The Interferon Era

For decades we have known that IFN is able to induce hematological remissions in patients with ET and PV. In recent years several studies have shown that treatment with IFN is also accompanied by “complete” or major molecular remissions (as assessed by a decline in the JAK2V617F allele burden) in patients with ET and PV. These molecular remissions are associated with normalization of the bone marrow and are sustained after discontinuation of IFN (minimal residual disease/operational cure) in a subset of patients. Taking into account that ET and PV are early cancer stages which – left untreated – may progress to myelofibrosis and AML it seems logical to consider early upfront intervention with IFN in order to prohibit clonal evolution

Despite the huge number of studies displaying excellent response rates on IFN-treatment with IFN is still considered experimental therapy in many MPN-centres of excellence today. The arguments against IFN are many, including (1)a lack of controlled studies to justify the risk of unknown long-term health effects associated with nonconventional therapeutic approaches , (2) the need to reserve IFN-alpha2 for selected categories of patients due to high cost and toxicity, or (3) those who are resistant or intolerant to HU. Finally, there is concern (4) that its use may be governed by local experience with IFN. Thus, several expert reviews and recommendations addressing the issue “how to treat ET and PV ” have been less likely to credit the beneficial effects of IFN in these patients .

Why and when to treat ET and PV with IFN

The MPNs are clonal myeloid neoplasias , in which the JAK2V617 mutation is detectable in virtually all PV patients and in about half those with ET and PMF. These diseases may be considered as a biological continuum from early cancer stage (ET) to the advanced myelofibrotic burnt-out phase. The prognosis of patients in the earliest cancer stage – the ET-population – has been variably reported , five- and 10-year survivals being reported significantly reduced in one study (about 75 % and 60 %, respectively and accordingly significantly reduced mainly attributed to myelofibrotic or leukemic transformation). Other studies have demonstrated better survival curves and today it is generally held that life expectancy of the ET-population does not differ significantly from the general population. However, the QoL even in ET patients may be severely impaired due to a high morbidity rate elicited by thrombohaemorrhagic complications or microvascular occlusive symptoms.

The prevalence of myelofibrotic transformation in ET has been variably reported. Most studies suggest the risk of myelofibrotic transformation increases with disease duration. On average the probability of myelofibrosis is 5 % after 5 years, 10 % after 10 years , 15 % after 15 years and 20 % after 20 years and the median interval from ET diagnosis to development of overt myelofibrosis about 8 years .With the 2008 WHO classification, the ET-population has been subdivided into 2 distinct entities – true ET and early prefibrotic myelofibrosis (epMF)), the latter disease entity having an inferior survival as compared to genuine ET.

The impact of reticulin grade at diagnosis has recently been addressed in the ET-population (the PT-1 ET –trial) , showing that the reticulin grade represents an independent prognostic marker. Furthermore, reticulin grade has been shown to correlate positively with white blood cell and platelet counts. Finally , in the same study elevated reticulin levels at presentation predicted higher rates of arterial thrombosis, major hemorrhage , and myelofibrotic transformation independently of known risk factors .

Leukemic transformation in ET has been shown to increase with disease duration , with an incidence of 1-2.5% in the first decade after diagnosis, 5-8% in the second decade and thereafter continuously rising . A most recent multicenter study of 1.104 “ET” patients with the aim of investigating the clinical relevance to distinguish between “true” ET and “false” ET (= epMF) dissected the“ ET-population” into these 2 subgroups – “false” ET (epMF) and “true ET”, the latter category having a better survival than the “false” ET-population .Importantly, however, the 5-year cumulative incidence of thrombosis in “true” ET compared to epMF was 8.7 % and 6.6 %, respectively, the 10-year cumulative incidence of thrombosis in “true” ET compared to epMF was 16.2 % and 17.9 %, respectively and the 15-year cumulative incidence of thrombosis in “true” ET compared to epMF was 21.5 % and 25.4 %, respectively.

Accordingly, the incidences of thrombotic complications were similar between the two groups. Of note, the 15-year myelofibrosis transformation rate in “true” ET compared to epMF was 9.3 % and 16.9 %, respectively. Anemia and a higher leukocyte count (> 11 MIA/L) were risk factors for inferior survival . Also, in epMF patients a higher leukocyte count has been reported to correlate with an increased risk for total thrombosis and in particular, with an increased risk for arterial thrombosis and a lower hemoglobin level was associated with an increased risk for venous thrombosis .

For all the above reasons it is timely to rethink and reconsider if it is still, in 2013, appropriate to base decision-making on when to treat ET patients on risk stratification systems which are based upon age (< 60 years) and the acquisition of a potentially life-thrombotic event which then qualify for cytotoxic treatment. Importantly, induction of “complete” hematological /major molecular remissions during IFN treatment may be associated with a decline in the occurrence of thrombotic and hemorrhagic complications . This latter observation has not yet been demonstrated in a prospective randomized study , but hopefully the MPN-Consortium Study may yield useful information on this topic.

The morbidity of patients with epMF is partly explained by an increased risk of arterial thrombosis but also progression to overt myelofibrosis with huge splenomegaly and ultimately leukemic transformation. The increased risk of thrombosis may be explained by the leukocytosis , which accompanies most patients with epMF since leukocytosis per se is a thrombogen factor in MPNs – akin to the general population . Supporting the viewpoint that both platelet and leukocyte counts should be normalized in ET are the findings in a most recent study that a platelet count outside of the normal range during follow-up was associated with an immediate risk of major hemorrhage, but not thrombosis and an elevated leukocyte count during follow-up was associated with thrombosis and major hemorrhage .The authors (Need a citation here) concluded that the aim of cytoreduction in ET should be to keep the platelet count, and arguably also the leukocyte count within the normal range. Since IFN may normalize elevated leukocyte and platelet counts , induce a definite decline in the tumor burden at the molecular level (JAK2V617F) and – in addition – has the potential to revert bone marrow reticulin and reduce enlarged spleens in MPNs – it seems rational and timely to treat with IFN instead of HU or anagrelide .

JAK2V617F: positive ET or indolent incipient PV ?

A controversial issue in the JAK2V617-positive ET-population concerns the fact that a considerable proportion of JAK2V617F positive ET patients (up to about 60 % ?) indeed has PV as assessed by the historical “golden standard” for a diagnosis of PV – an increased red cell mass (RCM) and an increased plasma volume . This has most recently been emphasised and recognized but irrespective of the overt misclassification of a high proportion of PV patients as ET without measurement of RCM this investigation is not performed in several MPN-centres of excellence. By ignoring the impact of such a misclassification, the clinical phenotype, the rate of thrombohemorrhagic complications, the prognosis in regard to clinical, biochemical and histopathological findings and comorbidities and the associations to the JAK2V617F allele burden in the “ET-population” have been erroneously described in several studies. This occurs when the ET population is mixed with patients in a more advanced disease stage (PV) within the biological continuum from ET over PV to myelofibrosis.

Therefore, RCM estimation should ideally be performed in all “JAK2-positive ET patients” at the time of diagnosis in order to identify the PV patients amongst JAK2V617F-positive ET patients, patients who otherwise would not be treated with phlebotomies and accordingly be at risk of thrombosis due to the expanded RCM .

Chronic inflammation as the driving force of clonal evolution

In the perspective, that chronic inflammation may be an important contributing factor in MPN pathogenesis, it seems rational to interrupt clonal evolution at the earliest disease stage – ET – thereby aiming at reducing or eliminating all potential factors which might contribute to morbidity and mortality. In the ET-population these factors include elevated leukocyte and platelet counts but – in addition – circulating leukocyte-platelet aggregates elicited by in vivo leukocyte and platelet activation and being sustained and perpetuated by inflammatory products released from the malignant clone

Furthermore, in the context of chronic inflammation as a potential promoter of cancer development and progression and given that ET and PV patients indeed have an increased risk of second cancer – both hematological and non-hematological — it is also for these reasons important to alleviate the chronic inflammatory drive. Chronic inflammation and a deregulated immune system with impaired tumor immune surveillance may be important factors in the pathogenesis and progression of MPNs . Accordingly, a rational therapeutic approach may include immune-enhancing

treatment with IFN at the time of diagnosis when the tumor burden is the least and consequently the outcome of IFN likely the very best.

In the context that data generated from a large number of studies during the last 25 years convincingly have shown IFN to normalize elevated leukocyte and platelet counts in concert with a decrease in spleen size and a reduction in the JAK2V617-allele burden – thereby alleviating all conventional factors of disease burden (leukocyte count, platelet count, spleen size and JAK2V617F mutational load) and of significance for thrombosis and bleeding – early intervention with IFN may likely also prohibit clonal expansion and myelofibrotic and leukemic transformation .

How to treat with IFN-alpha2 in myelofibrosis ?

Essential thrombocythemia and PV may progress to post-ET myelofibrosis or post-PV myelofibrosis , the risks being the highest in “ET” patients with epMF and in PV-patients with an increased amount of bone marrow reticulin at the time of diagnosis . About 50 % of patients with primary myelofibrosis (PMF) harbor the JAK2V617F-mutation, the large majority being homozygous, reflecting the heavy “ tumor burden” in advanced myelofibrosis with massive splenomegaly. Indeed, most likely all patients with newly diagnosed JAK2V617F-positive PMF have had undiagnosed MPN-disease for decades with disease evolution from early stage (JAK2V617F-positive ET) over PV to myelofibrosis .

During the last 30 years several studies have convincingly and repeatedly shown that even patients with myelofibrosis and large spleens may benefit from IFN-alpha2 by a reduction in elevated leukocyte and platelet counts in concert with resolution of huge splenomegaly and alleviation of hypermetabolic symptoms, bone pain and even improvement in anemia. Most recently, these early observations have been substantiated by several important papers showing that patients with hypercellular myelofibrosis may actually greatly benefit from IFN-alpha2 being able to normalize elevated blood cell counts in concert with a reduction of spleen size and – importantly – regression of bone marrow fibrosis.

Treatment with IFN-alpha2 in myelofibrosis may be associated with more side effects than when treating ET and PV-patients. Although the most recent series conclude that IFN-alpha2 was well tolerated in the large majority it is a clinical experience that “inflammation symptoms” (fatigue, fever , weight loss , muscle and joint pains) may temporarily increase during the first months of therapy. Actually , these symptoms may reflect the outcome of immune cells attacking the huge “tumor burden.” Very often , combining IFN.-alpha2 with prednisolone (50 mg per day in 2 weeks and afterwards during the following weeks gradual dose reduction to about 10 mg /day) may promptly alleviate the symptoms . In addition – a rise in Hb-concentration is usually seen . The dosage of IFN-alpha2 is as given above for ET and PV-patients with supplementary paracetamol according to the same schedule

Conclusions

ET , PV and myelofibrosis are clonal myeloid neoplasias in a continuum from early disease stage to advanced burnt-out myelofibrosis , reflecting increasing genomic instability and complexity with a steady accumulation of mutations of importance for disease progression . One single agent – IFN – has been shown to induce complete hematological and deep molecular remissions in a large proportion of ET and PV patients with reversal of disease progression, being sustained off therapy for several years in a subset of PV patients.

IFN is able to revert abnormal bone marrow architecture with regression of bone marrow reticulin fibrosis, even in patients with hypercellular myelofibrosis . An increase in bone marrow reticulin in ET implies an inferior response to IFN (assessed by fewer patients with complete hematological remissions after about 1 year compared with those patients without excessive bone marrow reticulin) and an increased risk of thrombosis and myelofibrotic transformation.

IFN-alpha2 treatment of ET and PV is associated with a decrease in the frequency of thrombosis and bleeding – the major determinants of symptomatic disease burden in MPNs – and a decrease in reticulin fibrosis. Initial bone marrow reticulin fibrosis in ET and PV exerts an impact on clinical outcome with a propensity to develop post-ET and post-PV myelofibrosis .

Leukocytosis is a risk factor for thrombosis, associated with vascular complications and an inferior survival in ET and PV as in the general population . And, finally, treatment with IFN in the early disease stage may be associated with a better treatment response, likely explained by a lower JAK2V617 mutation load and the absence of additional mutations. All these observations are supportive and argue for early intervention with IFN in ET and PV, the goal being to normalize elevated thrombogenic cell counts and block the otherwise predictable path towards myelofibrotic and leukemic transformation .

Dr. Richard Silver: How I treat PV with interferon.

Professor of Medicine and Director of the Leukemia and Myeloproliferative Center at New York Presbyterian-Weill Cornell Medical Center.

Focus on recombinant interferon-alpha2b (rIFN- α 2b, Intron®) induces complete hematologic remissions in patients with myeloproliferative neoplasms (MPNs) but its use has been limited by side effects owing to relatively high doses used. Now, low dose rIFN- α is stressed, starting relatively early in the course of the MPNs. In polycythemia vera (PV) this has resulted in significant clinical, hematological, morphologic and molecular response manifested by reduction in the JAK2^{V617F} allele burden, sustained even after discontinuation of rIFN. In essential thrombocythemia (ET), platelet count reduction is prompt and durable without treatment. In hypercellular primary myelofibrosis (PM), rIFN- α has restored normal blood counts, reduced splenomegaly and induced morphologic marrow remissions.

rIFN- α 2b Intron® was most commonly used in clinical practice prior to the introduction of the PEG-rIFNs. The pegylated forms of rIFN are universally used in Europe, but not in the USA where insurance issues frequently affect selection of treatment. It has been suggested that rIFN- α 2b may be associated with more side effects than the pegylated forms because of its shorter half-life, resulting in fluctuating blood levels. The efficacy, safety and toxicity profiles of rIFN- α 2b and PEG-rIFN- α 2 have not been compared in patients with MPNs. However, such a trial has most recently been launched in Denmark. It has recently been suggested that differences observed may be a matter of dose.

Treatment of Polycythemia Vera with Interferon

The clinical effectiveness of rIFN- α 2b was demonstrated nearly a quarter of a century ago in PV in the United States and almost simultaneously in ET patients by French and Austrian groups. Approximately 400 patients with PV have been included in nearly 20 trials using different preparations of rIFNs, usually with small numbers of patients, the largest consisting of 55 patients. Reduction in PHL [phlebotomy] rates have ranged from 47 to 100% in 12 of 17 trials, with complete response in 5, depending upon the dose and tolerance of the patient. Discontinuation rates have ranged from 14% to 40% depending upon the dose. It is impossible to state whether one form of rIFN- α 2 is superior to another with respect to clinical results, but recent reviews would suggest differences are quantitative rather than qualitative. Heterogeneous response criteria have been used to evaluate efficacy including those of the PVSG and the European LeukemiaNet (ELN). Agreeing on standard criteria for use in MPNs will help avoid conflicts in interpretation of results in the future. However, these studies have convincingly shown that rIFN- α 2 relieves pruritus, rapidly normalizes elevated white blood and platelet counts in the large majority of patients, and is accompanied by a reduction or elimination of the need for PHLs. With longer treatment (> 6-12 months), splenomegaly is reduced or eliminated and in some cases marrow can be normalized and regression of fibrosis, if present, can occur. We have found treating marrow fibrosis in PV more satisfactory and facile than in PM. It is of considerable interest that in our patients treated with rIFN- α 2, thrombosis-free survival has been remarkably good, perhaps explained by both the cytoreductive effect of rIFN- α 2 per se and/or our meticulous attention to target hematocrit levels.

Although rIFN- α 2 will predictably lower the white blood cell count and platelet count rapidly (1-4 weeks) after initiation of treatment, it will not substantially reduce the RBC count for which PHL is required. Accordingly, we advocate an initially vigorous PHL program as an adjunct to rIFN therapy to reduce whole blood viscosity which together with leukocytosis and thrombocytosis plays a role in the pathogenesis of thrombosis. Our Italian other colleagues have recently confirmed the importance of a hematocrit less than 45% in men (and we require less than 42% in women).

These data initially implied that overall survival for patients treated with PHL-O was superior to those treated with either ^{32}P or chlorambucil based on the old Polycythemia Vera Study Group analysis. Consistently overlooked was the fact that the large majority of patients in the PHL-O arm were rapidly removed from study following an unacceptably high rate of thrombosis during the first 5 years, and were thereafter treated with other drugs, including hydroxyurea, and ^{32}P . Unfortunately, these patients were not followed systematically but allegedly had the lowest morbidity rate and the best survival. The number of patients who could be treated throughout with PHL-O were few indeed based upon a French study. Moreover, abundant data exist that chronic iron deficiency state which results after repeated PHLs is associated with a wide variety of impairments ranging from Plummer-Vinson syndrome to decreased cognitive function, cardiac impairment and stroke. The use of rIFN- α 2 in PV corrects even the worst hypochromic/microcytic indices by suppressing erythroid activity in the marrow.

We believe* that all alkylating agents should preferentially be avoided due to their leukemogenic potential, clearly

evidenced in several prospective trials including one recently of pipobroman, still used in several European countries but not in the US. With respect to long-term treatment with hydroxyurea and the risk of developing myelodysplastic syndrome and/or acute myelogenous leukemia: there has been no randomized control trial (RCT) demonstrating an increased leukemogenic potential of hydroxyurea. Of note, these secondary malignancies occur many years after exposure, and in our opinion, only prospective trials with a median follow-up longer than 10 years can accurately estimate the true leukemic risk. The only control with a follow-up of this duration compared hydroxyurea with pipobroman in PV, and clearly showed that pipobroman is leukemogenic. However, the cumulative incidence of leukemic events in the hydroxyurea arm was 16.5% and 24.2%, after 15 and 20 years follow-up, respectively. Such numbers could conceivably reflect the rate of transformation of an MPN in the very long term, and not necessarily be indicative of the effect of a cytotoxic agent such as hydroxyurea. Of great clinical importance, there is no evidence that rIFNs are teratogenic or leukemogenic.

* Dr. Silver is referring to work he has done with Dr. J.J. Kiladjian and Dr. H.C. Hasselbalch,

Dr. Ruben Mesa: How I treat myelofibrosis.

Ruben A. Mesa, M.D. Professor and Chair Division of Hematology and Medical Oncology, Deputy Director, Mayo Clinic Cancer Center.

Let me begin by saying it is a great pleasure to have been invited by Zhenya Senyak to be able to contribute to this edition of *MPN Forum Quarterly Journal*. I think the first comment I would make in terms of “**how I treat myelofibrosis**” is to recognize that patients with myelofibrosis are a very heterogeneous group of individuals. Having seen over a thousand people with this disease over the years, people can range from being in their 30s, typically at the very youngest end, to being in their 80s, 90s, and really no upper cut-off in terms of age limit. People can range from having disease that severely affects them from the moment they are diagnosed to having an accidental finding of a mildly enlarged spleen at the time of a general physical. People can range from a disease that clearly is life threatening to them to a disease that will not necessarily impact their lives to a great degree. So, with all of these caveats, I would say:

Make sure I have an accurate diagnosis of myelofibrosis.

Having an accurate diagnosis of myelofibrosis is essential to make sure that:

1. It truly is a bone marrow disease.
2. It is not another bone marrow disease in which we also see scarring in the bone marrow, such as myelodysplastic syndrome with fibrosis, chronic myeloid leukemia with fibrosis, or the uncommon but still possible secondary cause of myelofibrosis, whether it be autoimmune disease or other marrow trauma. I would refer you to the MPN Forum sessions discussing **how I diagnose an MPN**.

Once the diagnosis is established, there are three groups of individuals with myelofibrosis, those with primary myelofibrosis, those in which we find the disease as the first diagnosis, or those that clearly had a pre-existing polycythemia vera or an essential thrombocythemia and have subsequently progressed to myelofibrosis. Although there are three groups of individuals, at this point in time, there is not a major difference in terms of selection of therapy or intensity of therapy based on which of the types of myelofibrosis is most accurate.

Determine the risk to the patient of their myelofibrosis.

There are many ways of estimating risk in myelofibrosis, but the most important is to truly get an impact of how life threatening the disease might be and, with this, there have been many different papers and studies that have been conducted, but probably some variation of the Dynamic International Prognostic Scoring System is the most helpful – the DIPSS or the DIPSS plus. With these, several features are assessed to see how the disease is impacting the patient. The presence of anemia — with an even greater concern if there is red cell transfusion dependence or need for continual transfusions of red blood cells; the presence of a high white blood cell count, over $25 \times 10^9/L$ cells; the presence of a low platelet count of $<100 \times 10^9/L$; age over 65; significant constitutional symptoms; blasts in the peripheral blood; and certain chromosomal changes. All of these are important in terms of predicting how life threatening the disease. With individuals who have none of these features, we expect they might live many years and sometimes in excess of 10 years or more with the disease. Those that have three or more, their risk for the disease is significantly greater and could mean that the disease could be life threatening in even just a handful of years. With this, we then generate the myelofibrosis risk score, whether they be low risk, intermediate 1, intermediate 2, or high risk.

Determine the symptomatic burden of the disease.

Utilizing the questionnaires that are now available on-line that our group helped develop – The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF), we get an overall sense of the symptomatic impact of the disease on the patient, including issues such as fatigue, night sweats, weight loss, fevers, chills, enlargement of the spleen and symptoms from the spleen. For individuals with significant symptomatic burden this is a major decision point regarding therapy. For individuals who have no symptoms it is likewise a factor in determining therapy or perhaps lack of need for therapy.

Determine the possible role and timing of stem cell transplantation.

Stem cell transplantation (bone marrow transplantation, allogeneic stem cell transplantation), all synonyms of one another, where we fundamentally give a significant dose of chemotherapy to clean out the bone marrow and give patients bone marrow from someone else who is a match. This is the only therapy in 2013 that can cure myelofibrosis. That being said, it is a therapy that has a significant up-front risk, a therapy that requires a match donor, and a therapy that typically is only even a consideration if an individual is 70 or below with rare exceptions of people in their early 70s being considered. It is a therapy, that although it can cure the disease, also brings in a risk that a complication can arise from transplantation, which could be life threatening or life shortening for a patient who undergoes it. The timing of transplantation and the choice of transplantation is probably one of the most medically complex decisions a physician and patient can make together. All of these caveats being said, I do think it is one of the first initial discussion points. Whether transplant is something that should be considered immediately for people who have incredibly high risk or are moving toward acute leukemia, for people who should never be considered for transplant because of age, because of having too many other medical problems, or because of their choice, or finally the group that is probably the largest—somewhere in the middle. In other words, if their disease were to progress, then transplant might be considered. In individuals who fall in the category of transplant that might be considered in the future—if they progress, if medical therapy doesn't work, if they move toward acute leukemia, I do advise obtaining HLA (human leukocyte antigen) typing on the patient around the time of diagnosis, so we have a sense of whether any of their siblings are potential donors and that way if the patient progresses unexpectedly, we can move forward with a transplant in a rapid fashion.

Discuss JAK inhibitor therapy.

Ruxolitinib (Jakafi) is now FDA approved for the therapy of myelofibrosis and was specifically done so on the basis of improving symptoms, splenomegaly, and even survival in those individuals with intermediate and high-risk disease. This has become the standard of care for myelofibrosis, in particular with individuals with a big spleen with lots of symptoms who are severely affected. This is the standard of care, in particular, for people who have these difficulties and are not moving towards stem cell transplantation. There are clinical trials ongoing now using a JAK2 inhibitor prior to stem cell transplantation to see if outcomes might be further improved. People who have low-risk myelofibrosis, JAK inhibitor therapy might be considered for individuals with very significant symptomatic burden. Additionally, interferon has been used with success, both pegylated interferon and standard interferon in low and intermediate-1-risk myelofibrosis to hopefully try to delay disease progression and improve the status of these patients. This is also undergoing current clinical trials. People who primarily have difficulties with great anemia in myelofibrosis are in a slightly different category. Those for whom anemia is the main driver of the disease are excellent candidates for clinical trials trying to improve anemia. Outside of the clinical trial setting, we will consider drugs from the immunomodulatory class, thalidomide and lenalidomide being commercially available. Pomalidomide has recently completed a phase III clinical trial and may be FDA-approved in the future for treating anemia in patients with myelofibrosis.

Patients with progressive myelofibrosis – those that have increasing blasts, those who moved into acute leukemia or are coming close to acute leukemia.

This is where the disease is particularly difficult and we have used therapies that are proven in myelodysplastic syndrome for people with increased blasts — azacytidine and decitabine — sometimes to try to help prevent disease progression. Patients in this setting, if they are eligible for stem cell transplant, that is a strong consideration, sometimes with a need for chemotherapy such as induction chemotherapy in advance.

Future directions.

In the future, many more options are going to be added to this list. Several other JAK2 inhibitors are being investigated

of which there are several in phase III clinical trials. The furthest along is fedratinib (SAR302503) of which the phase III results will be presented at the American Society of Hematology and may, on the basis of these results, be FDA approved somewhere in the near future. Others undergoing clinical trial testing in phase III include pacritinib (SB1518) which may have less negative impact on causing anemia or low platelet count, and momelotinib (CYT387) which may not only have less negative impact on low blood counts, but it may be helpful for anemia. These two drugs need to complete their phase III trials before any assessments can be made. Many other JAK2 inhibitors are undergoing testing including LY2784544, NS-018, and results are expected with great enthusiasm. Additionally, there are many combination studies ongoing of combinations of ruxolitinib with many agents to see whether further activity (along with anti-fibrosis drugs such as PRM-151, or drugs to aid anemia such as danazol) can be augmented by the use of this drug; in particular, in helping anemia or reducing further impact of fibrosis.

Conclusion

I have tremendous hope for my patients with myelofibrosis and for the future. We are at a moment where there has never been a greater emphasis, a greater number of clinical trials, or a greater number of investigators working together to try to better understand the biology of myelofibrosis, but also to try to come up with better therapies that truly have a great meaning and impact in patients with the disease. Additionally, we are fortunate that regarding the issue of stem cell transplantation, our colleagues in that arena continue to investigate new ways to make that process safer and more effective from everything from better support of care measures, such as better antibiotics and immunosuppression, to better ways of preparing patients for that process.

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