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How I treat Essential Thrombocythemia and Polycythemia Vera

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Abstract

Polycythemia Vera (PV) and Essential Thrombocythemia (ET) are chronic myeloproliferative neoplasms associated with thrombotic and/or hemorrhagic complications, and increased risk of transformation to myelofibrosis and acute myeloid leukemia. The main goal of therapy is aimed at preventing vascular events that are the leading cause of morbidity and mortality in these patients. Accordingly, risk stratification is the basis for deciding when to treat a patient with cytoreductive therapy. The European LeukemiaNet has developed a series of management recommendations for front-line and second-line therapy in order to provide the optimal treatment for the individual patient. There is still controversy about the efficacy and safety of several modalities of cytoreductive treatment at the long-term in both diseases as well as in the use of antiplatelet therapy in ET. The presence of *JAK2*V617F and *CALR* mutations in ET patients has been related to different thrombotic risk and this fact will probably lead to different therapeutic approaches in a near future. On the other hand, the near normal life expectancy of these patients makes essential a careful analysis of benefits and risks associated to treatment. This review provides our current management strategy of PV and ET patients.

Introduction

Essential thrombocythemia (ET) and polycythemia vera (PV) are classic *BCR-ABL1*-negative myeloproliferative neoplasms (MPN) characterized by overproduction of mature blood cells, an increased risk of thrombosis and/or hemorrhage, and a tendency to transform to myelofibrosis and acute leukemia[1]. Both ET and PV are the most common *BCR-ABL1*-negative MPN and the life expectancy of these patients is only slightly reduced[2]. This fact, together with the relatively low incidence of thrombotic complications, and the remarkable proportion of young patients with ET determine a careful analysis of benefits and risks associated to treatment.

In the present review, I will discuss the different modalities of treatment based in a risk-adapted approach, the rationale of the use of the current options, and some personal views based in my clinical experience.

Goals of therapy

The goals of therapy in ET and PV are similar, including prevention of occurrence and/or recurrence of thrombotic and bleeding complications, control of disease-related symptoms, decrease of the risk of transformation to acute leukemia and myelofibrosis, and management of certain risk situations such as pregnancy and surgery[3].

Thrombotic and hemorrhagic complications are the main causes of morbidity and mortality in PV and ET[4,5]. Transformation to myelofibrosis may form part of the natural history of the disease and acute transformation is generally related to the sequential use of chemotherapy[6]. Unfortunately, although we can reasonably decrease the risk of vascular complications applying treatment based on consensus recommendations, conventional therapies are not able, at present, of decreasing or modifying the risk of transformation to myelofibrosis.

Risk-adapted treatment approach

In PV, the classical or conventional stratification system is based on thrombotic risk and divides patients into high-risk and low-risk categories. Advanced age (> 60 years) and/or history of thrombosis are the two main clinical variables predictive of the

appearance of thrombotic complications. Thus, the existence of at least one of them assigns the patient into the high-risk group, indicating the need for starting cytoreductive therapy[3]. This clinical approach is a pragmatic and easy classification that allows deciding, once the diagnosis has been established, to start cytoreductive therapy.

Regarding ET, most clinicians use the same risk stratification system than in PV to allocate the patient to a risk category of thrombosis. A new prognostic system has been developed to refine this classical stratification system. The IPSET (International Prognostic Score in WHO-ET)-thrombosis model incorporates some clinical and biological variables such as cardiovascular risk factors and the presence of the *JAK2*V617F mutation. According to this system, three risk categories are defined with different thrombosis risk rates (per patients/year)[7] (Table 1). Recent studies have shown that calreticulin (*CALR*)-mutated ET patients present a lower risk of thrombosis when compared to *JAK2*V617F-mutated ET patients[8,9]. In spite of the fact that the mutational status of *CALR* gene does not impact on the IPSET-thrombosis prognostic score[10], probably the observed lower rate of thrombosis associated to *CALR* mutation will modify in a near future our current strategy of treatment of patients with ET. In addition to the IPSET-thrombosis score, an IPSET-survival model has also been generated including leukocyte count $>11 \times 10^9/L$ as a biological parameter beside advanced age and history of thrombosis[11] (Table 1). Both IPSET prognostic systems have been established from retrospective data, so they need to be validated in prospective clinical studies before being accepted as clinical-decision treatment tools. In my clinical practice, the decision to start cytoreductive therapy in the individual patient is based on the conventional stratification system both for ET and PV.

The British Committee for Standars in Haematology (BCSH) suggests a risk stratification system which includes diabetes or hypertension requiring pharmacological therapy as features of high-risk disease, apart from age >60 years and history of thrombosis. On the contrary, low-risk ET is defined as those patients younger than 40 years without features of high-risk disease[5]. Therefore, an intermediate risk category is established comprising patients aged between 40 to 60 years and lacking characteristics of high-risk disease. There is no general agreement among experts about the existence of this intermediate risk category, although in clinical practice this group of ET patients may represent a clinical challenge in terms of treatment. The intermediate risk arm of the PT1 study where this group of patients is randomized to hydroxycarbamide (HC) with aspirin (acetylsalicilic acid, ASA) or HC alone will provide

useful information regarding the optimal treatment for these patients[5]. In general, I do not consider that controlled diabetes or hypertension are for themselves so detrimental to make the decision of starting cytoreduction, but of course, in this setting, the individual clinical judgement is essential.

The risk of bleeding in ET and PV has been associated with the use of aspirin and with extreme thrombocytosis (>1000-1500x10^9/L). In this setting, a decrease or even the absence of large von Willebrand factor multimers may cause a bleeding diathesis compatible with an acquired von Willebrand disease[12]. This acquired syndrome is reversible by reduction of the platelet count to normal. Patients with history of severe hemorrhage attributable to the disease as well as those patients (ET or PV) with platelet counts >1500x10^9/L are candidates for initiating cytoreduction[3].

Control of cardiovascular risk factors (arterial hypertension, diabetes, smoking, and hypercholesterolemia) is a cornerstone of a comprehensive clinical management of ET and PV patients. There are discrepancies among studies about which of them has a more adverse effect in the risk of thrombosis. In a cohort of 126 young (<40 years) ET patients, smoking was associated with higher risk of thrombosis[13]. Irrespective of the risk group, all experts on MPN agree that patients should be encouraged to keep a healthy life-style.

Patients with ET and PV often complain of constitutional or systemic symptoms that may be underestimated by their physician. Recent studies have shown a significant symptom burden and decreased quality of life in MPN patients[14]. The MPN-SAF TSS is a specific symptom burden questionnaire developed and validated in many languages to assess the patient's perception of common symptoms and overall quality of life on a 0 (absent) to 10 (worst imaginable) scales. The symptoms include fatigue, concentration problems, early satiety, inactivity, night sweats, itching, abdominal discomfort, bone pain, weight loss, and fever. This questionnaire is a useful tool to monitor symptom burden and quality of life either at diagnosis or during clinical evolution and should be incorporated into routine clinical practice[15].

Antiplatelet therapy in PV and ET

The use of daily low-dose (75/100 mg) acetylsalicylic acid (ASA) as primary prophylaxis of thrombosis is recommended for all PV patients. The ECLAP study included a total of 518 PV patients in a double-blind, placebo-controlled, randomized

trial to assess the safety and efficacy of prophylaxis with low-dose aspirin. The two primary end points were the cumulative rate of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes and the cumulative rate of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes. Low-dose ASA, compared with placebo, was associated with a 50% to 60% reduction in the risk of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes. In addition, the incidence of major bleeding episodes was not significantly increased in the aspirin group[16]. According to these data, most clinicians recommend low-dose ASA in PV patients who have no contraindications for antiplatelet therapy.

A general practice among clinicians involved in the care of ET patients is to prescribe low-dose ASA irrespective of the risk category. This empiric approach is mainly based in the extrapolation of results from the ECLAP study and in the efficacy of ASA in controlling microvascular symptoms. However, the effectiveness of low-dose ASA in the primary prevention of thrombosis in ET patients has not been assessed in prospective randomized clinical trials and some uncertainties encompass this clinical practice[17].

In order to study whether primary prophylaxis with low-dose ASA plus cytoreduction benefits patients with high-risk ET, the incidence of thrombosis and hemorrhage in 247 patients during the periods of time in which they received combination therapy (cytoreduction+low-dose ASA) or cytoreduction alone as primary prophylaxis of thrombosis was analyzed retrospectively. Patients who had a history of previous thrombosis were excluded from the study. In the subgroup of patients in whom the indication of cytoreduction was age older than 60 years, the addition of low-dose ASA resulted in a lower incidence of thrombosis (0.86 events per 100 person-years) than under cytoreduction alone (2.9 events per 100 person-years). Although the addition of low-dose ASA significantly increased the incidence of bleeding, this increase was much lower than the benefit obtained in thrombosis reduction. Moreover, the interaction analysis showed that among patients older than 60 years, low-dose aspirin yielded the greatest benefit in those patients with cardiovascular risk factors or the *JAK*2V617F mutation[18]. The conclusion of this study was that low-dose aspirin benefits high-risk ET patients older than 60 years receiving cytoreductive therapy as primary prophylaxis of thrombosis.

The use of low-dose ASA in low-risk ET patients is a matter of debate, given the excessive risk of bleeding observed in patients with extreme thrombocytosis mostly

due to acquired von Willebrand disease. In this context, evaluating von Willebrand factor function may help in the identification of those patients at high risk of bleeding. I assess von Willebrand factor function by determining ristocetin cofactor activity in patients with platelet count >1000x10⁹/L managed on a conservative approach without cytoreduction and in all patients presenting ET-related major bleeding. In those cases with ristocetin cofactor activity <20–30 %, I avoid the use of low-dose aspirin as primary prevention of thrombosis[1].

A retrospective study of 300 low-risk ET patients (age <60 years) without thrombosis history showed that the incidence of thrombosis was similar whether they received antiplatelet therapy or not. Of note, the risk of bleeding was five times greater in patients with a platelet count at diagnosis >1000x10⁹/L when treated with antiplatelet therapy. Nevertheless, two subgroups of patients benefited from the addition of ASA resulting in a lower risk of thrombosis; patients with cardiovascular risk factors experienced a lower rate of arterial thrombosis and *JAK2*V617F-positive patients a lower rate of venous thrombosis[19]. Accordingly, in low-risk patients with these features ASA should be indicated as primary prophylaxis whereas patients without them could be managed conservatively, without antiplatelet therapy. The current approach to the use of antiplatelet therapy in ET recommended by the Spanish Group on MPNs is shown in Fig. 1. A recent international retrospective study of the role of antiplatelet therapy in the prevention of thrombosis in patients with *CALR*-mutated low-risk ET has shown that antiplatelet therapy does not provide a clear benefit since the increase in the rate of bleeding may offset the reduction in the rate of thrombosis[20].

The role of antiplatelet and anticoagulant treatment as secondary prophylaxis in patients with history of thrombosis is not well-defined. Generally, low-dose ASA is advised indefinitely in all patients who have suffered an arterial thrombosis, whereas anticoagulation is recommended for those patients who have presented a venous thrombosis. In the latter case, the duration of oral anticoagulation is established by guidelines recommended for the specific type of thrombosis in the general population. There is general agreement about the use of lifelong anticoagulation for all these patients (PV or ET) with thrombosis of the intraabdominal veins as well as for those patients who present venous thrombosis recurrences[3]. In a retrospective study of 150 patients with PV and ET treated with vitamin K antagonists (VKA) because of an arterial or venous thrombosis, the incidence of re-thrombosis was 4.5 and 12 per 100 patient-years under VKA therapy and after stopping it, respectively (P<0.0005). After a multivariate adjustment for other prognostic factors, VKA treatment was associated with a 2.8-fold reduction in the risk of thrombotic recurrence. Remarkably, VKA therapy

offset the increased risk of re-thrombosis associated with a prior history of remote thrombosis (thrombosis occurring before the two years preceding the MPN diagnosis). Both the protective effect of VKA therapy and the predisposing factors for recurrence were independent of the anatomical site involved in the first thrombotic event leading to anticoagulant treatment. Treatment periods with VKA did not result in a higher incidence of major bleeding as compared with those without VKA[21].

The concomitant use of ASA and anticoagulants should be avoided if possible because of the increased risk of bleeding and only can be supported after a very careful and individualized weighing of potential benefits against additional risks.

Management of low-risk patients

In my daily routine I follow the European LeukemiaNet (ELN) recommendations for the treatment of PV (Fig. 2). According to these guidelines, the combination of low-dose ASA as primary thromboprophylaxis (discussed previously), control of cardiovascular risk factors and therapeutic phlebotomies is the best approach to manage accurately a low-risk PV patient[3]. Phlebotomy is a keystone of treatment and the CYTO-PV Collaborative Group has demonstrated that in patients with PV, those with a hematocrit (Hct) target of less than 45% had a significantly lower rate of cardiovascular death and major thrombosis than did those with a Hct target of 45 to 50%[22]. So, on the basis of this study, a Hct target <45% should be pursued as a standard of care in all patients with PV, irrespective of the risk category to which they belong. Phlebotomies are usually performed by removing 250 to 500 ml of blood every other day or twice a week until the hematocrit target is reached. Generally they are well tolerated, although some patients may complain of the appearance of symptoms of iron deficiency like restless legs syndrome[23]. A practical tip: I always recommend the patient to eat something before the venesection in order to decrease the risk of possible dizziness.

The treatment of low-risk ET patients is similar to the treatment of low-risk PV patients with the exception of phlebotomies. The use of antiplatelet therapy has been discussed in the section of Antiplatelet therapy in PV and ET. In accordance with the recommendations of use of antiplatelet therapy (Fig. 1), asymptomatic *JAK2*V617F-negative low-risk patients without cardiovascular risk factors can be followed by observation alone without the need of a specific therapy. A major clinical dilemma is the degree of thrombocytosis that allows adopting such conservative strategy. In patients <40 years a platelet count >1000×10^9/L must not be the only criterion to start cytoreduction and even patients with platelet counts between $1000 \text{-} 1500 \times 10^9$/L may benefit from this approach. In such context I recommend to discuss thoroughly the pros

and cons, trying to reassure the patient about this conservative strategy. However, there are no solid recommendations in this difficult issue and personal clinical experience is probably the most useful guiding principle.

Management of high-risk patients

Patients with PV at high-risk of thrombosis must be treated with cytoreductive therapy. In addition to the features defining high-risk, that is, age >60 years and/or history of thrombosis, cytoreductive treatment can be considered, irrespective of the risk category, if the patient presents uncontrolled disease-related symptoms: progressive or symptomatic splenomegaly, severe constitutional symptoms, platelet count >1500x10^9/L, progressive leukocytosis, and poor tolerance to phlebotomy[3] (Fig. 2).

The ELN recommends HC and Interferon (IFN) as first-line cytoreductive therapy (Fig. 2). The experts also advocate that HC should be used with caution in patients <40 years and that busulfan is a feasible approach for PV patients older than 70 years[3].

In my clinical practice I use HC as first-line cytoreductive therapy for all patients above 60 years and IFN is my choice for patients <40 years, if feasible. For patients between 40 and 60 years I discuss in detail the advantages and side effects associated with each one of both alternatives. Of note, IFN is not licensed in Europe for the treatment of patients with MPN and for this reason has to be indicated on a compassionate basis. For patients older than 70 years my personal choice as first-line cytoreduction is HC and I prefer to use busulfan as second line therapy which will be discussed below.

Hydroxycarbamide is an oral antimetabolite usually well tolerated and with a dose-dependent action. The recommended starting dose is 15 mg/kg/day (500 mg, twice daily) and then the dose is titrated until achieving normal blood cell counts. In elderly patients I usually start with a lower dose; 500 mg five days and 1000 mg two days per week. A practical approach is to control blood cell count every two weeks during the first two months, every month the following three months, and every three-four months in steady state in responding patients. Macrocytosis and/or a mild macrocytic anemia are frequent. Bone marrow myelosuppression can be observed in some patients. The most common side effects of HC are mostly mucocutaneous as leg ulcers in the perimalleolar area, oral aphtous ulcers, actinic keratosis, and a wide variety of skin lesions[24]. HC has also been associated to an increased risk of skin cancer[25].

Patients may be afraid or be reluctant to use HC when they read in the patient information leaflet about the potential leukemogenic effect of this drug. Concerning this

serious effect, some studies have provided data showing the lack of a strong association between HC and acute leukemia when this drug is used as monotherapy. In two large cohorts of patients with PV, HC was not statistically associated with an increased risk of acute leukemia when used as a single agent[26,27]. On the other hand, in a Swedish case-control study including 162 patients with acute leukemia/myelodysplastic syndrome (AML/MDS) evolved from a cohort of 11,039 MPN patients, 25% of patients who developed AML/MDS had never been exposed to cytotoxic therapy, suggesting an inherent propensity of patients with MPN to progress to AML/MDS[28]. However, the study of the French Polycythemia Study Group randomizing 285 PV patients younger than 65 years to HC or pipobroman showed that the leukemogenic potential of HC might be not so negligible. With a median follow-up of 16 years, the cumulative incidence of AL/MDS at 10, 15, and 20 years, was 6.6%, 16.5%, and 24% in the HC arm and 13%, 34%, and 52% in the pipobroman arm (P=0.004)[29]. As a result of this study, pipobroman is considered clearly leukemogenic and not suitable for first-line therapy in PV patients.

Interferon (IFN) has shown in patients with MPN a wide range of biological actions such as inhibition of erythroid and megakaryocytic colony growth, decrease of bone marrow fibroblasts, inhibition of megakaryocytic proliferation, and ability to target quiescent V617F-positive stem cells, among others[30]. Clinical studies in patients with PV and ET have demonstrated the capacity of IFN to induce clinical, hematological, and molecular responses[31,32]. The main advantages making IFN an interesting option for the treatment of PV and ET when compared to other therapeutic options are absence of leukemogenic effect, reduction of the MPN clone, and persistence of response after discontinuation of treatment. Presently, pegylated IFN (PEG-IFN) is preferred over recombinant interferon because of the convenience of once-a-week dosing and to a lower rate of discontinuation by toxicity. In two studies using PEG-IFN-α2a the percentages of complete hematologic responses, complete molecular responses, and discontinuation rates ranged between 70% to 91%, 14% to 24%, and 10% to 24%, respectively[31,32]. Interestingly, in the French cohort 27% of patients could stop PEG-IFN-α2a and remained in complete response without treatment for a median time of 31 months. In addition, no vascular events were reported and in some patients histological complete remission was observed. However, it must be taken into account that overall, 20% to 40% of all patients treated with IFN discontinue therapy by toxicity[33]. A recent report of the updated results of 43 PV and 40 ET patients treated with PEG-IFN- α2a in the MDAnderson Cancer Center has shown that after a median follow-up of 82 months only 39% are still on study (29% on active treatment).

Discontinuation was due not only to nonhematological toxicity but also to vascular events and progression to MF and AL. Of note, at the moment of the analysis most patients were receiving a dose ≤90 mcg every week or every two weeks[34]. A new next-generation monopegylated IFN-α2b, ropeginterferon alfa-2b with a longer elimination half-life allows administration every two weeks achieving similar rates of responses (hematologic and molecular) than PEG-IFN-α2a[35,36]. We still do not know the rate of responses and tolerance as well as the discontinuation rate of this new formulation at the long-term.

Interestingly, concerning molecular responses, PEG-IFN-α2a not only decreases allele burden in *JAK2*V617F-positive patients but may also decrease *CALR* mutant allelic burden[37]. In both cases, the presence of additional non-driver mutations, such as *TET2* mutations or other mutations may influence the molecular response to treatment[38].

I recommend starting the pegylated formulation at 45 mcg/week and adjust (increase) the dose every 1-2 months according to hematologic values and tolerability. The aim of treatment should be to achieve and maintain a complete hematological and clinical response with the lowest dose in order to ensure patient compliance of treatment and avoid its discontinuation. Flu-like symptoms are usually controlled with acetaminophen premedication.

Concerning the therapy of high-risk ET, the ELN recommends HC as first-line therapy for all patients, with the same nuances than in PV regarding its use in patients younger than 40 years. Likewise, the use of busulfan is also considered for patients >70 years[3] (Fig. 3).

The rationale of current therapeutic strategy in ET is mainly based in the results of randomized trials comparing face to face treatment modalities. In the first historical trial, Cortelazzo et al randomized high-risk ET patients to HC (n=56) or no cytoreductive treatment (n=58). After a median follow-up of 27 months, the rate of thrombotic complications was 3.6% for HC and 24% for those patients assigned to nonmyelosupressive therapy (*P*=0.003)[39]. The UK-PT1 study randomized 809 high-risk patients diagnosed according to PVSG criteria to HC plus low-dose ASA (n=404) or anagrelide plus low-dose ASA (n=405). With a total observation time of 2,653 patient-years, HC plus ASA was superior to anagrelide plus ASA in terms of reducing the risk of arterial thrombosis, major bleeding and fibrotic progression. Conversely, anagrelide plus ASA was better than HC plus ASA in preventing venous thrombosis. There were no differences between groups in overall survival and death from thrombotic or

hemorrhagic cause or from transformation to myelofibrosis. Platelet count was reduced similarly by both drugs at 9 months and afterwards, but the reduction was higher with HC at 3 and 6 months. The rate of drug discontinuation was higher in the anagrelide arm[40]. *JAK*2V617F-positive patients required lower doses of HC to control their platelet count than *JAK*2V617F-negative patients, an effect not observed in patients receiving anagrelide. In addition, *JAK*2V617F-positive patients receiving anagrelide showed higher rates of arterial thrombosis than those receiving HC, whereas in *JAK*2V617F-negative patients, this difference was not observed[41].

The ANAHYDRET study compared anagrelide with HC in 259 previously untreated WHO-defined high-risk ET patients. With a total observation time of 730 patient-years, no significant difference between anagrelide and HC groups was observed regarding incidences of major and minor arterial and venous thrombosis, severe and minor bleeding, or rates of drug discontinuation. Anagrelide and HC showed a similar platelet-lowering effect at six months and afterwards. Decrease of hemoglobin levels and cardiovascular side effects were more frequently observed in the anagrelide group, whereas mucocutaneous abnormalities were higher in the HC group. The rate of major clinical events was 3.3% per patient-year in the anagrelide group and 3.4% in the HC group[42]. Comparison of results of the UK-PT1 and the ANAHYDRET study is difficult because of differences in the study design (noninferiority comparison study in ANAHYDRET), diagnostic criteria of ET (PVSG *vs*. WHO), and patient treatment characteristics at inclusion (all patients were cytoreductive-naïve in ANAHYDRET *vs*. 1/3 treated with prior cytoreduction in UK-PT-1) and antiplatelet use (not mandatory in ANAHYDRET). However, most clinicians prefer HC rather than anagrelide as first-line cytoreductive therapy for high-risk ET patients.

Anagrelide is recommended by the ELN as second-line therapy for those ET patients who are intolerant or resistant to HC[3]. This is the approved indication in Europe whereas in USA anagrelide can be prescribed as first-line treatment of thrombocytosis associated to myeloproliferative neoplasms. The most frequent side effects of anagrelide are headache, tachycardia, palpitations, diarrhea, and fluid retention that may lead to discontinuation in 10%-40% of patients[43]. In my clinical practice I always inform the patient about these side effects before starting treatment, providing some practical tips as splitting the total daily dose and emphasizing that many of these effects usually decrease over time. In the small group of high-risk ET patients younger than 40 years needing cytoreduction, I also discuss the feasibility of using anagrelide

as first-line therapy in an off-label use. The absence of leukemogenic effect often determines patient's preference to this therapeutic alternative when compared to HC[44].

A general philosophy in the cytoreductive treatment strategy of ET is to normalize the platelet count, but no specific threshold (<400, <600x10^9/L) has been demonstrated to be more protective against thrombosis[45]. However, most clinicians agree to use a normal platelet count target when treating a patient with history of thrombosis. When the patient shows toxicity or serious side effects to cytoreductive treatment, relaxing the platelet count to <600x10^9/L may be justified[46]. A matter of debate is the need to treat an increased leukocyte count. Leukocytosis at diagnosis has been associated to inferior thrombosis-free survival in ET patients[47,48]. In addition, lack of control of the leukocyte count during cytoreductive treatment of ET patients has been correlated with increased risk of hemorrhage and thrombosis, as well as lack of control of thrombocytosis has been related to increased bleeding[49]. As the clinical benefit of strictly controlling this parameter is not yet established, there is no formal recommendation to initiate cytoreductive treatment based on this feature alone.

Management of patients resistant to or intolerant of hydroxycarbamide

Approximately 20% of ET patients develop resistance or intolerance to HC[50]. The ELN proposed a set of criteria to define resistance/intolerance criteria to HC in order to make decisions about when to switch to second-line treatment options[51] (Table 2). A retrospective study of 166 ET patients treated with HC for a median of 4.5 years showed that 20% of patients met at least one criterion for resistance or intolerance. The best discriminating criterion of the appearance of resistance to HC was anemia (Hb <100 g/L). Patients with HC resistance have a poor outcome (median survival of 2.4 years) and a higher incidence of myelofibrosis (47% of patients with resistance to HC *vs.* 3% without resistance)[50].

The ELN recommends anagrelide as second-line therapy if the patient is resistant/intolerant to HC and IFN in selected patients as young females or patients with contraindication to anagrelide[3]. Busulfan may be a good therapeutic alternative for patients with short life expectancy. The Spanish Group on MPN has recently analyzed the results of busulfan as second-line therapy in ET (n=21) and PV (n=15) patients mainly intolerant to HC. Complete hematologic remission (CHR) was achieved in 83% of patients after a median time of 6.7 months. Time to CHR was shorter in patients treated with ≥14 mg of busulfan per week than with lower doses (141 *vs.* 336 days,

P=0.01). With a median follow-up of two years, the probability of survival at two years was 85% and the probability of thrombosis 11%. Transformation to AL/MDS was observed in three patients[52].

With regard to PV, roughly 16-24% of PV patients treated with HC develop resistance/intolerance to HC[53]. Similarly as in ET the ELN has produced a series of criteria for defining this clinical situation[54] (Table 3). Briefly, these criteria include the need for venesections to keep Hct <45%, the presence of leukocytosis and thrombocytosis, and failure to control spleen size or spleen-related symptoms after three months of ≥2 g/day of HC. Additional criteria of resistance/intolerance include the appearance of cytopenia/s at the lowest dose of HC required to achieve any type of response, or the appearance of extrahematologic toxicity. In a retrospective cohort of 261 PV patients treated with HC, resistance and intolerance to HC occurred in 11% and 13% of patients, respectively. With a median duration of treatment of 4.4 years and a median follow-up of 7 years, extrahematological toxicity (13%) and cytopenia (9%) were the most frequent categories defining intolerance and resistance, respectively. Patients fulfilling the ELN criteria for resistance, including those with cytopenia, had a 6.8-fold higher risk of hematologic transformation, and a significant shorter survival than patients not developing resistance. Although being a reason to switch to second-line therapy, intolerance did not entail any prognostic significance[53]. In a registry-based study of 890 patients with PV treated with HC, cytopenia at the lowest dose needed to achieve a response was an independent risk factor for transformation to AL and MF[55]. In conclusion, the presence of cytopenia not dose-related in a PV patient treated with HC is the most clinically relevant criterion associated with a worse survival and should alert the clinician about myeloid transformation.

Recently, the *JAK*1/2 inhibitor ruxolitinib has been approved by the FDA and the EMA for the treatment of PV patients with inadequate response/resistant or intolerant to HC based on the results of phase 2 and phase 3 trials[56,57]. The randomized phase 3 clinical study (RESPONSE trial) of ruxolitinib versus best available therapy (BAT) demonstrated that in PV patients with an inadequate response or with unacceptable side effects to HC, ruxolitinib was superior to standard therapy in controlling the Hct, reducing the spleen volume, and improving symptoms associated with PV. In brief, 222 patients were randomly assigned to receive ruxolitinib (n=110) or BAT (n=112). The primary endpoint was a composite of both Hct control between weeks 8 to 32 and at least a 35% reduction in spleen volume at week 32, as assessed by MRI imaging. The combined end point was achieved in 21% of the patients in the ruxolitinib group versus

1% of those in the standard-therapy group (*P*<0.001). Hematocrit control was achieved in 60% of patients receiving ruxolitinib and 20% of those receiving standard therapy; 38% and 1% of patients in the two groups, respectively, had at least a 35% reduction in spleen volume. In the ruxolitinib arm, the probability of maintaining the primary response for at least 80 weeks from time of response was 92%, and the probability of maintaining Hct control was 97% at week 48 and 87% at week 80. A complete hematologic remission was achieved in 24% of patients in the ruxolitinib group and in 9% of those in the standard-therapy group (*P*=0.003); 49% versus 5% had at least a 50% reduction in the total symptom burden score at week 32. Improvement was prominent in the cytokine symptom (fatigue, itching and night-sweats) and splenomegaly (abdominal discomfort) symptom clusters. The most frequent reported nonhematologic adverse events were headache, diarrhea, and fatigue, with very few patients presenting grade 3-4 toxicity. In the ruxolitinib group, grade 3 or 4 anemia occurred in 2% of patients, and grade 3 or 4 thrombocytopenia occurred in 5%; the corresponding percentages in the standard-therapy group were 0% and 4%. Herpes zoster infection was reported in 6% of patients in the ruxolitinib group and 0% of those in the standard-therapy group (grade 1 or 2 in all cases). Thromboembolic events occurred in one patient receiving ruxolitinib and in six patients receiving standard therapy[57]. In spite of the effectiveness of ruxolitinib to control symptoms, hematocrit and spleen size, only long-term follow-up will confirm or not its ability to achieve clinically relevant end-points in PV such as the decrease of vascular complications and transformation to myelofibrosis, that is, the possibility to modify the natural history of the disease.

Management of disease transformation

In PV and ET patients transformation to myelofibrosis (post-PV, post-ET MF) must be suspected when progressive splenomegaly, anemia and leukoerythroblastic picture appear during clinical follow-up. Overall, the clinical, laboratory, and histological features of post-PV/ET MF are alike to those of primary myelofibrosis (PMF) patients. Consequently, treatment should follow the same principles as for patients with PMF. This subject is beyond the scope of this paper and excellent reviews concerning this issue have been published[58]. It is worth noting that prognostic models devised for PMF, such as the IPSS score, may not accurately discriminate different prognostic groups in these secondary forms of MF[59].

Transformation to AL is associated with a dismal prognosis, with median survival of 3 to 5 months[60]. Even patients with a reasonable fitness level show short-lived responses to intensive induction chemotherapy. Patients who respond to chemotherapy and have a suitable donor should be considered for allogeneic hematopoietic cell transplantation (HCT)[61]. However, in the majority of patients HCT is not a feasible option due to advanced age, co-morbidities and poor performance status. In those patients not enough fit for transplant, hypomethylating agents may be an alternative. Decitabine, a hypomethylating drug that can be delivered in an outpatient setting may prolong modestly overall survival with less toxicity and better tolerance than standard intensive chemotherapy regimens[62]. In those patients candidates only to palliative treatment, oral mercaptopurine and transfusion support is a wise approach.

Management of unusual and risk situations

Pregnancy

ET is the commonest MPN in women of childbearing age and very few cases of pregnancy in PV patients have been reported. The live birth rate in pregnant women with ET is around 65-75% and roughly 25-40% of pregnancies end in fetal loss. Apart from this complication, late pregnancy loss occurs in 10%, and placental abruption and intrauterine growth retardation in 3-5% of cases. Pre-eclampsia rates are similar to the normal population. Maternal complications are estimated to occur in 8-11% of patients[63]. A recent analysis of 155 pregnancies that occurred in 94 patients with ET has not shown a strong correlation of mutational status and pregnancy complications. However, the presence of *JAK*2V617F mutation was associated with late pregnancy losses, whereas the presence of *CALR* mutations was associated with a trend to a better outcome[64].

In ET females receiving cytoreduction who desire to be pregnant, cytoreductive treatment must be stopped at least three months before conception (wash-out period). High-risk pregnancy is defined when the patient has suffered previous maternal thrombotic or hemorrhagic events and/or previous severe pregnancy complications[65]. Treatment should always be adjusted to pregnancy risk. In low-risk pregnancy low-dose ASA throughout pregnancy is a practical and reasonable option, although is not evidence-based. In high-risk pregnancies additional treatment including IFN-α plus low molecular weight heparin (LMWH) is recommended[63,66]. During the postpartum period strict control of platelet count and Hct is required and LMWH at prophylactic doses is

always indicated for at least six weeks postpartum, irrespective of the risk group. Definitely, the management of pregnancy in ET must be carried out by a multidisciplinary team, including an obstetrician experienced in high-risk pregnancies.

Surgery

Approximately 7% of ET and PV patients undergoing surgery show hemorrhagic or thrombotic complications[67]. Antiplatelet drugs should be stopped for at least one week before surgery and reintroduced after the surgical procedure according to the individual clinical setting. The risk of bleeding associated to the type of surgery should be evaluated individually and treatment measures tailored accordingly. Hemorrhage is much more frequent in those patients with uncontrolled blood cell counts before surgery.

For patients who are receiving cytoreduction, blood cell count should be optimized preoperatively and cytoreduction reinitiated as soon as possible. In patients who do not receive cytoreduction I recommend a shortened treatment with HC before surgery and/or phlebotomies if required in order to normalize blood cell count. Postoperative thromboprophylaxis should proceed according to standard protocols.

Conclusion

Cytoreductive drugs and low-dose ASA are the most widespread therapy addressed to prevent thrombotic complications. However, some uncertainties still encompass the optimal use of antiplatelet therapy. On the other hand, current therapy does not decrease the risk of transformation to myelofibrosis. A better knowledge of the underlying mechanisms involved in this complication will lead to the design of new drugs able to interfere with fiber formation. The introduction of next-generation sequencing techniques will most likely refine and individualize the current prognostication systems used in PV and ET.

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Figure legends

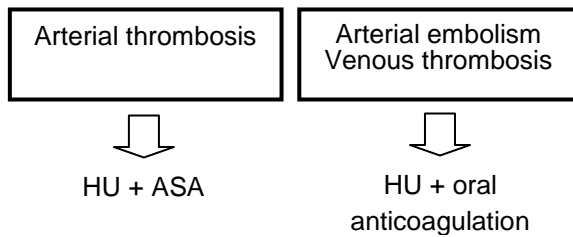**Figure 1:** Antiplatelet Therapy in ET

Figure 2: Recommendations for First-Line Therapy in PV

Figure 3: Recommendations for First-Line Therapy in ET

Figure 1

Antiplatelet Therapy in ET

Secondary prophylaxis of thrombosis

Arterial thrombosis	Arterial embolism Venous thrombosis

⇩   ⇩

HU + ASA   HU + oral anticoagulation

Contraindications to low-dose ASA

- Platelets >1500x10^9/L
- History of bleeding
- Active bleeding
- Allergy to ASA
- Children <12 years (Reye syndrome)

HU: Hydroxyurea
ASA: Acetylsalicylic acid
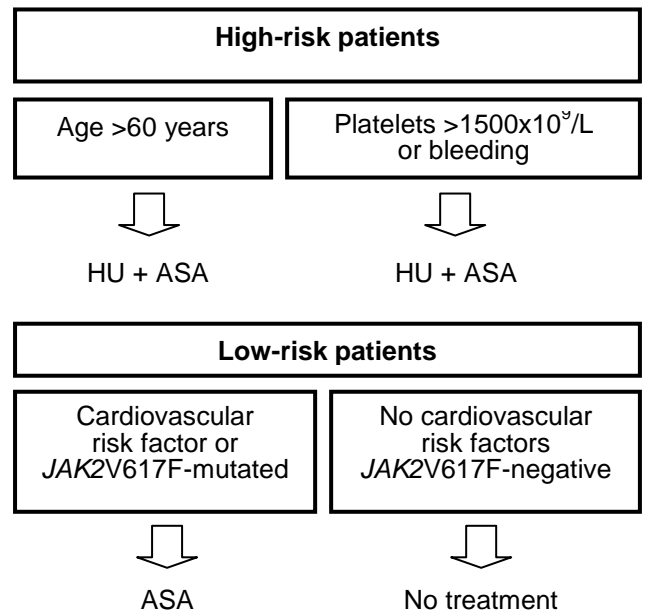
Primary prophylaxis of thrombosis

High-risk patients

Age >60 years	Platelets >1500x10^9/L or bleeding

⇩   ⇩

HU + ASA   HU + ASA

Low-risk patients

Cardiovascular risk factor or *JAK*2V617F-mutated	No cardiovascular risk factors *JAK*2V617F-negative

⇩   ⇩

ASA   No treatment

Figure 2

Recommendations for First-line Therapy in PV

- Manage cardiovascular risk factors
- Low-dose aspirin to all[1]

Phlebotomies only[2]	Low risk
Hydroxyurea[3]/Interferon-α + phlebotomies	**High risk:** - Age >60 years - Previous history of thrombosis • Poor tolerance to phlebotomy • Symptomatic/progressive splenomegaly • Severe disease-related symptoms • Platelet count >1500×10^9/L • Progressive leukocytosis
Busulfan	Elderly[4]

[1] except if major bleeding or allergy/intolerance
[2] target hematocrit <45%
[3] use with caution in patients <40 years
[4] >70 years

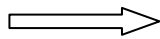**Figure 3**

Recommendations for First-Line Therapy in ET

• Manage cardiovascular risk factors • Low-dose aspirin (if microvascular symptoms)

No therapy	**Low risk**

High risk:

Hydroxyurea[1] $\Longrightarrow$

• Age >60 years • Previous history of thrombosis • Platelet count >1500x10^9/L

Busulfan[2]	Elderly

[1] use with caution in patients <40 years
[2] >70 years

Table 1. Risk Stratification of ET

	Risk stratification of ET						
	Classical		BCSH			IPSET-thrombosis	IPSET-survival
	HR	LR	HR	IR	LR		
Age >60 years[1]	+	–	+			1 point	2 points
Age 40-60 years				+			
Age <40 years					+		
History of thrombosis[1]	+	–	+	–	–	2 points	1 point
History of hemorrhage	+	–	+	–	–		
Cardiovascular risk factors[2]						1 point	
Diabetes or hypertension[3]			+	–	–		
Platelet count >1500×10^9/L[4]	+	–	+	–	–		
Leukocyte count >11×10^9/L							1 point
*JAK*2V617F mutation						2 points	
						Score (thrombosis risk, patients/year) LR:<2 (1.03%) IR: 2 (2.35%) HR: >2 (3.56%)	Score (median survival) LR: 0 (not reached) IR: 1-2 (24.5 years) HR: ≥3 (13.8 years)

HR: high-risk, IR: intermediate-risk, LR: low-risk
[1] high-risk of thrombosis, [2] smoking, hypertension, or diabetes, [3] requiring pharmacological therapy, [4] high-risk of bleeding
Classical thrombotic risk requires to fulfil at least one of the two variables: age >60 or history of thrombosis.
History of hemorrhage and platelet count >1500×10^9/L are features of high risk of bleeding

Criteria for Resistance/Intolerance to Hydroxyurea in ET

1. Platelet count >600x10^9/L after 3 months of at least 2 g/day of HU (2.5 g/d in patients with a body weight >80 kg), **OR**

2. Platelet count >400x10^9/L and WBC count <2.5x10^9/L at any dose of HU, **OR**

3. Platelet count >400x10^9/L and hemoglobin <100 g/L at any dose of HU, **OR**

4. Presence of leg ulcers or other unacceptable mucocutaneous manifestations at any dose of HU, **OR**

5. HU-related fever

The definition of resistance/intolerance requires the fulfillment of at least one criterion

HU: Hydroxyurea

Table 3. Definition of Resistance/Intolerance to Hydroxyurea in Patients with PV

Definition of Resistance/Intolerance to Hydroxyurea in PV

After 3 months of ≥2 g/day of HU, any one of the following	OR	At the lowest dose of HU required to achieve a CR or PR[1], any one of the following:	OR	At any dose of HU
• Need for phlebotomy to keep Hct <45% • Uncontrolled myeloproliferation: platelet count >400x10^9/L **AND** WBC count >10x10^9/L • Failure to reduce massive[2] splenomegaly by >50% by palpation **OR** resolve splenomegaly-related symptoms		• ANC <1.0x10^9/L • Platelet count <100x10^9/L • Hb <100 g/L		• Presence of leg ulcers or other unacceptable HU-related nonhematologic toxicities[3]

ANC: absolute neutrophil count, Hct: hematocrit, Hb: hemoglobin, HU: hydroxyurea, WBC: white blood cell count.

[1] Complete response (CR) was defined as Hct <45% without phlebotomy, platelet count ≤400x10^9/L, WBC count ≤10x10^9/L, normal spleen size on imaging, and no disease-related symptoms. Partial response was defined as Hct <45% without phlebotomy or response in ≥3 other criteria (Barosi *et al*, Blood 2009,113(20):4829-33.

[2] Spleen extending >10 cm from the costal margin.

[3] Mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever