SOHO Supplement 2016

How to Treat Essential Thrombocythemia and Polycythemia Vera

Carlos Besses, Alberto Alvarez-Larrán

Abstract

Polycythemia vera and essential thrombocythemia (ET) are chronic myeloproliferative neoplasms associated with thrombotic 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 to provide the optimal treatment for the individual patient. There is still controversy about the efficacy and safety of several modalities of cytoreductive treatment in the long-term for both diseases and in the use of antiplatelet therapy in ET. The presence of *JAK2*V617F and *CALR* mutations in patients with ET has been related to different thrombotic risks, and this will probably lead to different therapeutic approaches in the near future. On the other hand, the near normal life expectancy of these patients makes a careful analysis of the benefits and risks associated with treatment essential. This review provides our current management strategy of patients with polycythemia vera and ET.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 16, No. S1, S114-23
Keywords: Anagrelide, Antiplatelet therapy, Essential thrombocythemia, Hydroxyurea, Interferon, Polycythemia vera, Ruxolitinib

Introduction

Essential thrombocythemia (ET) and polycythemia vera (PV) are classic *BCR-ABL1*-negative myeloproliferative neoplasms (MPNs) characterized by overproduction of mature blood cells, an increased risk of thrombosis 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 with treatment.

The present review discusses the different modalities of treatment based on a risk-adapted approach, the rationale of the use of current options, and some personal views based on our clinical experience.

Goals of Therapy

The goals of therapy in ET and PV are similar, including prevention of occurrence 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 generally is 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 classic or conventional stratification system is based on thrombotic risk and divides patients into high-risk and low-risk categories. Advanced age (>60 years) or history of thrombosis are the 2 main clinical variables predictive of the appearance of thrombotic complications. Thus, the existence of at least 1 of them assigns the patient to the high-risk group, indicating the need for starting cytoreductive therapy.[3] This clinical approach is a pragmatic and easy classification that allows the decision, once the diagnosis has been established, to start cytoreductive therapy.

For ET, most clinicians use the same risk stratification system as in PV to allocate the patient to a risk category of thrombosis. A new

Hematology Department, Hospital del Mar, Barcelona, Spain

Submitted: Feb 9, 2016; Accepted: Feb 9, 2016

Address for correspondence: Carlos Besses, MD, PhD, Hematology Department, Hospital del Mar, Passeig Marítim 25-29, 08003 Barcelona, Spain
E-mail contact: cbesses@parcdesalutmar.cat

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2016.02.029

prognostic system has been developed to refine this classic stratification system. The International Prognostic Score of Thrombosis in World Health Organization-essential thrombocythemia (IPSET) 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, 3 risk categories are defined with different thrombosis risk rates (per patients/year)[7] (Table 1). Recent studies have shown that patients with calreticulin (*CALR*)-mutated ET present a lower risk of thrombosis when compared with patients with *JAK2*V617F-mutated ET.[8,9] Despite the fact that the mutational status of the *CALR* gene does not affect the IPSET-thrombosis prognostic score,[10] the observed lower rate of thrombosis associated with *CALR* mutation probably will modify our current strategy of treatment of patients with ET in the near future. In addition to the IPSET-thrombosis score, an IPSET-survival model has been generated including leukocyte count $>11 \times 10^9$/L as a biological parameter in addition to 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 myour clinical practice, the decision to start cytoreductive therapy in the individual patient is based on the conventional stratification system for both ET and PV.

The British Committee for Standards in Haematology suggests a risk stratification system that includes diabetes or hypertension requiring pharmacologic 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 aged less than 40 years without features of high-risk disease.[5] Therefore, an intermediate risk category is established comprising patients aged 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 patients with ET may represent a clinical challenge in terms of treatment. The intermediate-risk arm of the PT1 study, in which this group of patients are randomized to hydroxycarbamide (HC) with aspirin (acetylsalicylic acid [ASA]) or HC alone, will provide useful information regarding the optimal treatment for these patients.[5] In general, we do not consider that controlled diabetes and hypertension are themselves so detrimental to make the decision of starting cytoreduction, but of course, in this setting, the individual clinical judgment is essential.

The risk of bleeding in ET and PV has been associated with the use of aspirin and with extreme thrombocytosis (>1000-1500 $\times 10^9$/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 a history of severe hemorrhage due to the disease and patients (ET or PV) with platelet counts $>1500 \times 10^9$/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 patients with ET and PV. 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 patients (aged <40 years) with ET, smoking was associated

Table 1 Risk Stratification of Essential Thrombocythemia

	Risk Stratification of ET						
	Classic		BCSH			IPSET Thrombosis	IPSET Survival
	HR	LR	HR	IR	LR		
Age >60 years[a]	+	−	+			1 point	2 points
Age 40-60 years				+			
Age <40 years					+		
History of thrombosis[a]	+	−	+	−	−	2 points	1 point
History of hemorrhage	+	−	+	−	−		
Cardiovascular risk factors[b]						1 point	
Diabetes or hypertension[c]			+	−	−		
Platelet count $>1500 \times 10^9$/L[d]	+	−	+	−	−		
Leukocyte count $>11 \times 10^9$/L							1 point
*JAK2*V617F mutation						2 points	
						Score (thrombosis risk, patients/year)	Score (median survival)
						LR: <2 (1.03%)	LR: 0 (not reached)
						IR: 2 (2.35%)	IR: 1-2 (24.5 year)
						HR: >2 (3.56%)	HR: ≥3 (13.8 year)

Classic thrombotic risk requires fulfilling at least 1 of the 2 variables: age >60 years or history of thrombosis. History of hemorrhage and platelet count $>1500 \times 10^9$/L are features of high risk of bleeding.

Abbreviations: BCSH = British Committee for Standards in Haematology; ET = essential thrombocythemia; HR = high risk; IPSET = International Prognostic Score of thrombosis in World Health Organization-essential thrombocythemia; IR = intermediate risk; LR = low risk.

[a]High risk of thrombosis.

[b]Smoking, hypertension, or diabetes.

[c]Requiring pharmacologic therapy.

[d]High risk of bleeding.