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ESSENTIAL THROMBOCYTHEMIA

Toni Valković[a,b]

[a]Department of Hematology, University Hospital Rijeka;
[b]Faculty of Medicine, University of Rijeka, Rijeka, Croatia

Summary

Essential thrombocythemia is an indolent clonal hematological neoplasm. The JAK2 V617F mutation can be identified in the half of the patients. However, the detection of new mutations (calreticulin and MPL) and their potential consequences on biological behavior, diagnosis and further treatment approaches should be defined in future investigations and clinical studies. The assessment of the risk for thrombosis continues to be essential for therapeutic approach.

Key words: essential thrombocythemia, mutations, risk factors, management.

INTRODUCTION

Essential thrombocythemia (ET), together with polycythemia vera (PV) and primary myelofibrosis (PMF), is a clonal Ph-negative myeloproliferative neoplasm (Ph-MPN), characterized by thrombocytosis, bone marrow megakaryocytic hyperplasia and a tendency to develop vascular complications [1].

The etiology of the disease is unknown, incidence is 0.6-2.5/100,000 per year and the median age at onset is 65-70 years. ET it is slightly more frequent in males than in females [2].

Pathogenesis

The milestone for the understanding of MPN pathogenesis is identification of acquired Janus kinase2 (JAK2) V617F mutation. The detection of this molecular lesion, from either peripheral blood cells or bone marrow cells, in at least 50-60% of ET patients is important for diagnosis [3]. JAK is a protein involved in intracellular transduction of signals originating from thrombopoetin receptor, predominantly through JAK-STAT pathway [4]. Several studies suggest that JAK2 V617F positive cases share some features with PV such as higher hemoglobin values, higher num-

ber of neutrophils, more thrombotic complications and more frequent incidence of fibrotic marrow transformation [5,6]. It seems that JAK2 allele burden is higher in patients with PV, PMF, or post-PV MF than in those with ET and homozygosity for JAK2 mutation is pretty rare in ET, suggesting that mutated allele burden is an important factor which determines MPN phenotype [7].

Recently, two other molecular lesions have been identified in ET and PMF patients contributing to our understanding of disease pathogenesis, but also to the diagnostic process. The calreticulin (CALR) gene mutation (19p13.2) can be detected in approximately 15-24 % of ET patients, who are usually JAK-2 V617F negative [8]. CALR is a multi-functional Ca2+ binding chaperone localized mostly in the endoplasmic reticulum, but can also be found in nuclei implicating possible role in transcription. In ET, mutant CALR is associated with younger age, male gender, lower leukocyte and hemoglobin values, higher number of platelets and decreased rick for thrombotic events [8,9]. Additionally, MPL (myeloproliferative leukemia gene) mutations occur in less than 5% of patients with ET [10]. These molecular lesions cluster in exon 10 and the most frequent among them is MPLW515L/K mutation [11]. In some investigations, MPL mutations have been associated with older age, female sex, higher number of platelets and lower hemoglobin value [12]. Furthermore, JAK2 and MPL mutations can be detected in other myeloid neoplasms, while other mutations such as TET 2, ASXL1, IDH are sometimes found in ET [13]. Finally, approximately 20% of patients with ET show a triple negative mutation status.

Clinical presentation

The patients are often asymptomatic and the disease is revealed after routine blood tests (complete blood cell count). Arterial or/and venous thrombosis (myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis) occurs in approximately 20 % of patients. Hemorrhagic complications, such as easy bruising, mucosal and gastrointestinal bleeding, as well as prolonged bleeding after surgery, occur in 25 % of patients and sometimes can be life threatening. Common presentation may include microvascular symptoms due to microvascular occlusion such as paresthesia, headache, dizziness, syncope, visual disturbances, atypical chest pain, erythromelalgia (burning sensation, pain and erythema in hands or feet) or livedo reticularis.

Recurrent abortions and fetal growth retardation can also be a part of clinical presentation in fertile women. The constitutional symptoms are not common suggesting possible transformation of disease. Fatigue is not uncommon.

Diagnosis

Complete blood count shows persistent thrombocytosis (platelet count > 450x10^9/L, but may be as high as 4000-5000 x10^9/L), hemoglobin level and white blood count are usually normal, but normocytic anemia or leukocytosis can be present. Blood film shows numerous platelets, variable in shapes and sizes. Neutrophilia and basophila are not uncommon. Bone marrow aspirate is not reliable for diagnosis, however it can show an increased number of atypical megakaryocytes and cluster formation. The bone marrow biopsy is extremely important, showing megakaryocytic hyperplasia with clustering and nuclear pleomorphism. Reticulin in bone marrow is normal or increased. The analysis of JAK2 V617F mutational status and allele burden is mandatory. Cytogenetic and molecular abnormalities characteristic for other myeloproliferative diseases, such as Ph+ chronic myeloid leukemia (Ph+ CML) or myelodysplastic syndrome (MDS), must be tested, especially the bcr/abl fusion gene. Cytogenetic abnormalities occur in 5% of the cases (mainly affecting chromosomes 20, 1, 8, 9).

In the absence of clonal markers the reactive thrombocytosis, caused by many factors (eg. infections, malignant tumors, post surgical, post splenectomy, severe burns, chronic bleeding, hemolysis, rheumatologic disorders, inflammatory bowel disease, Ph+ CML, MDS, etc), must be excluded.

The World Health Organization (2008) criteria for ET [14] are shown in Table 1.

Table 1. World Health Organization Diagnostic Criteria for Essential Thrombocythemia, 2008.

Diagnosis requires all criteria listed below:
1. sustained platelet count ≥ 450x10^9/L
2. Bone marrow biopsy showing megakaryocyte proliferation with increased numbers of enlarged, mature megakaryocytes, no or little granulocyte or erythroid proliferation.
3. Not meeting WHO criteria for PV, primary myelofibrosis, BCR-ABL positive CML, MDS, or other myeloid neoplasm.
4. Demonstration of JAK2 V617F or other clonal marker, or in the absence of JAK2 V617F mutation, no evidence of reactive thrombocytosis.

Risk stratification

Vascular events are the most frequent, sometimes life threatening complications because of which the risk stratification for thrombosis is essential to decide whether cytoreductive therapy should be initiated or not. For each patient the individual thrombotic risk must be evaluated because it defines the therapeutic approach.

The standard high-risk factors are age over 60 years and prior history of thrombosis [15]. Furthermore, JAK2 V617F mutational status and allele burden [16], as well as standard cardiovascular risk factors [15] can additionally increase the thrombotic risk. Leukocytosis and anemia have also been reported to have a negative impact on survival but only in some studies [17]. All these additional factors should also be considered before making a decision to initiate therapy.

On the other hand, "extreme" thrombocytosis (defined as platelets number >1000x10^9/L for some and > 1500x10^9/L for others) is considered to be a risk factor for bleeding caused by different abnormalities of platelet function or acquired von Willebrand syndrome [18]. Because of this, in this group of patents ristocetin cofactor activity should be tested. Paradoxically, "extreme" platelet number was found to show a protective effect against thrombosis [19].

Treatment

The main goals of the treatment of patients with ET are maintaining the platelet number in normal range through the use of cytoreductive drugs, as well as modulating the platelet function through the use of aspirin, which together reduce the incidence of vascular symptoms and complications.

Currently, there are a few cytoreductive drugs used in every-day practice. Hydroxyurea is a traditional antineoplastic drug used as first line therapy in ET since Cortelazzo et al published the results on its efficiency in reducing the platelet number and vascular complications [20]. There is some concern regarding a possible increased risk of leukemic transformation and teratogenic effect. However, the leukemogenic potential of this drug is not definitely proven. Thus, in many centers hydroxyurea is restricted for patients older than 60 years. Interferon-alpha, standard and pegylated form, was shown to reduce thrombocytosis, and can even induce molecular response [21]. In some studies pegylated interferon also reduced the progression of fibrosis [22]. It is a drug of choice for young patients or pregnant females because, according to our knowledge, it is not teratogenic or oncogenic. Finally, anagrelid is a selective inhibitor of megakaryocyte differentiation which reduces the platelet number. This drug has been approved for treatment of patients with ET based on a single arm study [23]. Harrison et al published the results of a randomized comparison of hydroxyurea and anagrelide in ET patients. In this study hydroxyurea showed to be superior to anagrelide in terms of bleeding incidence, arterial thrombosis and myelofibrotic transformation, but inferior in terms of venous thrombosis [24]. Consequently, anagrelide became the second line therapy for patients in whom hydroxyurea or interferon are inadequate or not tolerated.

The low-dose aspirin is widely used in ET patients because of its potential to reduce thrombotic events in those who don't have contraindications to this drug. In patients with an "extreme" platelet number: ≥1500x10^9/L, an acquired von Willebrand deficit may be present. In these cases cytoreductive therapy should be started before aspirin initiation. The risk-adopted therapy used in our institution is described in Table 2.

Patients should be advised to stop smoking, control body weight, hypertension, hyperlipidemia or diabetes. The regular exercise is recommended.

Several experimental drugs (e.g. JAK2 inhibitors, telomerase inhibitors) are currently being evaluated in clinical studies.

Table 2. Risk Stratification and Risk-Adopted Therapy

Risk category	**Risk factors**	**Therapy**
Low	Age < 60 years and no thrombosis history; platelets < 1000 x 10^9/L	Low-dose aspirin*
High	Age > 60 years and/or thrombosis history; platelets ≥1000 x 10^9/L	Cytoreductive drugs: - hydroxyurea (age ≥ 60 years) - interferon α (age <60 years, in pregnancy) - anagrelide (second line therapy) Low-dose aspirin*

* if there are no: contraindications for aspirin, "extreme" thrombocytosis or acquired von Willebrand deficit

Prognosis

ET is an indolent clonal hematological disorder with good prognosis and in which life expectancy is near normal. However, recent results of Tefferi et al. showed that, despite the very long survival of patients with ET, their life expectancy remained inferior to the age- and sex-matched US population (the median survival was 19,8 years for all patients and 32,7 years for patients younger than age 60) [25].

Risk factors for a shortened survival in both PV and ET include advanced age, leukocytosis, and history of thrombosis [15].

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Sažetak

Esencijalna Trombocitemija

Esencijalna trombocitemija je indolentna hematološka novotvorina. Mutacija JAK2 V617F gena je prisutna u polovice bolesnika. Ipak, otkriće mutacija novih gena (kalretikulin i MPL) te njihova potencijalna uloga u biološkom ponašanju bolesti, njenoj dijagnostici, kao i budućem liječenju tek se mora definirati u nadolazećim istraživanjima i kliničkim ispitivanjima. Procjena rizika za trombozu i dalje je osnova za kreiranje terapijskog pristupa.

Ključne riječi: esencijalna trombocitemija, mutacije, čimbenici rizika, liječenje

Corresponding author:
Toni Valković, MD, PhD
E-mail: toni_val@net.hr