Professional article

MODALITY OF TREATMENT IN ESSENTIAL THROMBOCYTHEMIA

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Essential thrombocytosis (ET) is clonal chronic myeloprolifertive disorder which originates from abnormality of a multipotent hematopoietic stem cell.

It is characterized by an increased platelet count, megakaryocytic hyperplasia and by hemorrhagic or thrombotic tendency. Symptoms and signs may include weakness, headaches, paresthesias, bleeding, splenomegaly, and digital ischemia. ET patients showed equal or slightly shorter survival than age- and sex-matched healthy population. Major causes of death were thrombotic and hemorrhagic complications or malignant progression due to both the natural history of the disease and, possibly, the use of chemotherapeutic agents.

Diagnostic criteria for essential thrombocythemia were proposed in 2005 by the PVSG and demand diagnosis of exclusion.

Myelosuppressive therapy to lower the platelet count usually consists of hydroxyurea, interferon alfa or anagrelide. Hydroxyurea is the most commonly used treatment, because of its efficacy, low cost and rare acute toxicity. Interferon alfa is a biological response modifier. It is not known to be teratogenic and does not cross the placenta, and is often the treatment of choice during pregnancy. Anagrelid suppresses bone marrow megakaryocytes by interfering with the maturation process and decreasing platelet production without affecting other blood cell lines. Low-dose aspirin may be used to control microvascular symptoms.

Recommendations for management of patients with essential thrombocythemia were given by ASH. From a treatment standpoint, hydroxyurea is now confirmed to be the drug of choice for high-risk patients with essential thrombocythemia. Interferon alfa and anagrelide are reasonable second-line agents. Low-risk patients should receive low-dose aspirin alone. For the intermediate-risk patients, a consensus could not be reached on a recommendation for platelet-lowering treatment. *Acta Medica Medianae 2008;47(3):51-55.*

***Key words**: essential thrombocythemia, recommendation, treatment*

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Introduction

Essential thrombocythemia is chronic myeloproliferative disorder, involving clonal hematopoietic stem cells abnormality. It is characterized by an increased platelet count megakaryocytic hyperplasia in bone marrow, and hemorrhagic and thrombotic tendency.

Disease is rare (incidence 1:1000000). It occurs most often after the age of 50, although it can happen in the age between 2 and 90. Disorder occurs slightly more often in women. Etiology of disease is unknown. It occurs because of the abnormality of a multipotent hematopoietic stem cell or CFU-GEMM stem cell myeloid lines. Disease is characterized by highly increased platelet formation (up to 10 times more than normal) while their age is preserved, so their count in peripheral blood could be over 1000/mm^3, while formation of other blood cell lines is within normal range. Because of the increased platelet count, thromboembolic complications occur in venous and arterial blood vessels.

Diagnostic criteria for essential thrombocythemia are controversial, and universal agreement is lacking, thus diagnosis of essential thrombocythemia is established by the method of exclusion. Version of PVSG diagnostic criteria for essential thrombocythemia is shown in Table 1.

Molecular studies suggested new possibilities of diagnostic research. A molecular marker that can be applied to diagnostic evaluation is thrombopoietin receptor c-Mpl. Its reduction was discovered in essential thrombocythemia platelets. Studies have also indicated that percentage of megakaryocytes with Mpl expression in bone marrow provides a means of both distinguishing ET from reactive or secondary thrombocytosis and that it can also provide a means for prediction a tendency toward thrombosis as well as disease progression in polycythemia vera or idiopathic myelofibrosis (1,2).

*Table 1.*Proposed diagnostic criteria for essential thrombocythemia (ET)

A1	Platelet count > 600 × 109 /L for at least 2 months
A2	Acquired JAK2 mutation
B1	No cause for a reactive thrombocytosis - e.g., normal inflammatory indices
B2	No evidence of iron deficiency - stainable iron in the marrow or normal red cell mean corpuscular volumea
B3	No evidence of PV - hematocrit < midpoint of normal range or normal red cell mass in presence of normal iron stores
B4	No evidence of chronic myeloid leukemia - no Philadelphia chromosome or bcr-abl gene rearrangement
B5	No evidence of myelofibrosis - no collagen fibrosis and ≤ grade 2 reticulin fibrosis (using 0–4 scale)
B6	No evidence of a myelodysplastic syndrome - no significant dysplasia - no cytogenetic abnormalities suggestive of myelodysplasia
Diagnosis of ET requires A1+A2+B3–6 (V617F-positive ET) or A1+B1–6 (V617F-negative ET).	

In over 50% of patients with essential thrombocythemia mutation V617F JAK has been found, which divides patients in to two different groups. V617F positive patients displayed significantly higher hemoglobin levels, neutrophil counts, bone marrow erythropoiesis and granulopoiesis, more venous thromboses and a higher incidence of polycythemic transformation as well as lower serum erythropoietin and ferritin levels. V617F-negative patients with essential thrombocythemia have more frequent cytogenetic abnormalities, hypercellular bone marrow with abnormal megakaryocyte morphology, PRV1 overexpression, growth of erythropoietin-independent erythroid colonies, and a risk of myelofibrotic or leukemic transformation. These facts demand that essential thrombocythemia should be subclassified as either V617F-positive or V617F-negative. Most recent studies have shown that there is no significant difference between V617F-positive or V617F-negative essential thrombocythemia regarding disease duration or frequency of disease transformation (3,4). Lower percentage of registered mutation-positive patients is the consequence of low method sensitivity and the fact that variable percentage of the granulocytes is derived from the malignant clone. In the case of JAK2 mutation, diagnosis of essential thrombocythemia demands that other myeloproliferative diseases are excluded, as well as reactive thrombocytosis and iron deficiency (5).

The main causes of death of patients with essential thrombocythemia are thrombosis, hemorrhage, and progression to myelofibrosis or acute myelogenous leukemia. Myelosupressive therapy that prevents vascular events in essential thrombocythemia can by itself increase the risk of transformation to myelofibrosis or myeloid leukemia. Challenge in treatment of essential thrombocythemia is to prevent bleeding and thrombosis without increasing the risk (3).

Vascular complications are the most common cause of morbidity and mortality in subjects suffering from ET, bearing in mind very low frequency of transformation to myelofibrosis (6-10%) and acute leukemia. Because of that, studies describe essential thrombocythemia as "benign" disease and show that there is no significant decrease in life expectancy in patients with essential thrombocythemia in comparison to healthy population. Around 40% of patients show tendency towards thrombosis, while 60% show tendency towards bleeding. In one third of patients, functional vasomotor disorders occur (vascular headache, sight disorders, pains in palms and feet, distal paresthesis, akrocyanosis). Numerous risk factors for thrombosis have been identified. High risk for thrombosis is reported in patients over 60 years of age or with previous history of thrombosis. Significance of platelet count is less clear. Major hemorrhages have been more frequent in patients with platelet count higher than 1500×10^9/l. There is an increased risk for thrombosis in patients with platelet count higher than 1000×10^9/l when diagnosis is established or in patients with increased platelet count during therapy. Numerous other characteristics can correlate with thrombotic complications. This includes clonal X chromosome inactivation, decrease of expression of MPL in bone marrow megakariocytes, overexpression of PRV1 in granulocytes of peripheral blood. The increased risk of thrombosis can be combined with antiphospholipid antibodies, heterozygosity for factor V Leiden and numerous cardiovascular risk factors, such as hypertension, diabetes mellitus, smoking and hypercholesterolemia (6,7).

Therapy

The treatment of essential thrombocythemia is still an unsolved clinical issue. Epidemiological studies have shown that patients over 60 years of age or those with previous history of thrombosis are at high risk for thrombosis and should be treated with medications that decrease platelet count. At the same time, there is no correlation between platelet count and thrombosis in essential thrombocythemia, and, paradoxically, patients with extremely high platelet counts of 1500×10^9 show more tendency towards bleeding, while patients with platelet counts less than 600×10^9 show tendency towards thrombosis (8).

Hydroxyurea is the most commonly used medication for reduction of platelet count. It belongs to the group of antimetabolic drugs since it inhibits deoxynucleotide sythesis and thus inhibits cell replications. Hydroxyurea is used as the first therapeutic line in high-risk patients because of its efficiency, low cost and rare acute toxicity. The most common side effects are leg ulcers and other changes on the skin (photosensitivity and solar keratosis) and reversible suppression of bone marrow (9). A common concern

is whether hydroxyurea could be leukemogenic. Some studies have shown that 5-10% of patients treated with hydroxyurea develop AML/MDS. These studies have included small numbers of patients and many of them also received other cytoreductive drugs, so it remained unclear whether it was the drug effect or the consequence of the progression of disease. In contrast, nowadays, numerous new studies have shown that patients with essential thrombocythemia treated only with hydroxyurea have low incidence of AML/MDS i.e. they show that its leukemogenic potential is very low (3-4%) (10, 11).

Interferon-α is myelosuppressive protein product, produced by recombinant DNA technology. The mechanism of antitumor activity is not quite clear, but it is thought that direct antiproliferative effect on malignant cells and modulation of host immune response probably have an important role.

Italian and American researchers have shown their results with interferon-α in patients with essential thrombocythemia. A long-acting form of interferon was applied, which was administered once a week. The largest response was after 3 to 6 months since the start of therapy with global rate of response of 50% to 80%. Toxicity, usually WHO grade II, is expected proportionally to the dosage, but there are no evidence that interferon permanently damages the bone marrow (12).

Interferon-α is effective in reduction of platelet count below 600×10^9/l in 90% of patients. Average dosage is 3 millions of unit per day. It is not know whether it is teratogenic or leukemogenic, but it has been proven that it does not pass the placenta, thus it is often the therapy of choice in pregnancy. Need for parenteral application and its side effects, especially flu-like symptoms, are important problems and lead to the cancellation of application of medication in a significant percentage of patients.

Anagrelide is an imidazoquinazoline derivate which has been originally derived as inhibitor of aggregation of thrombocytes. Later, his efficiency has been detected in lowering the platelet count in 70 to 80% of patients in dosages lower than those that inhibit aggregation of thrombocytes. Around 10% of patients are completely refractory, probably because of inability to generate active metabolite of the medication. Anagrelide inhibits activity of anti-cyclic AMP phosphodiesterase. It selectively inhibits the maturation of megakariocytes with minimal effect or with no effect on other blood cell lines. It also acts as vasodilator, having a positive inotrope effect. PT-1 study has shown that anagrelide is not so effective and well tolerated as hydroxyurea, so it should not be used as first therapeutic line in high risk patients (13).

Up to now only two prospective randomized studies of treatment of patients with essential thrombocythemia have been done. The first study included 114 patients, older than 60 years of age or had one previously verified thrombosis. They were divided in two groups, one that has been treated with hydroxyurea and other without cytoreductive therapy. After a median follow-up of 27 months, thrombosis developed in 3.6% of treated patients as opposed to 24% of untreated patients which had one or more thrombotic events. Then, it was clearly shown for the first time that cytoreductive therapy reduced thrombotic events in patients with essential thrombocythemia (14).

The second randomized study included over 800 of high risk patients with essential thrombocythemia, which had previous thrombosis, age over 60 or platelet count of more than 1000×10^9/l. Two groups of patients were compared, one that had been treated with hydroxyurea and aspirin and the other that had been treated with anagrelide and aspirin. The median follow-up was 39 months. The results showed several main differences between those two groups. The group treated with hydroxyurea and aspirin, as opposed to the group treated with anagrelide and aspirin, had greater frequency of arterial thrombosis, significant hemorrhages, myelofibrotic transformation and cancellation of treatment, but decrease of percentage of venous thromboembolism. Platelet count control and incidence of leukemia was similar in both groups (15).

It is very informative to compare these results with Italian study. Statistical rate of the first thrombosis in two years was 4%, 8%, 26%, for the patients who were treated with hydroxyurea and aspirin, with anagrelide and aspirin, or got no cytoreductive therapy, respectively. Italian study has shown that percentage of venous thrombosis was significantly lower in the group treated with anagrelide and aspirin, as opposed to the partial prevention of arterial thrombosis. The frequency of venous thrombosis in untreated patients with high risk essential thrombocythemia is unknown, as it is not clear whether percentage is rising for the treatment with hydroxyurea and aspirin or decreasing for treatment with anagrelide and aspirin. Optimal treatment of patients with previous venous thrombosis depends on individual circumstances, bearing in mind that arterial thrombotic events are more than 3 times more frequent than venous thrombotic events in essential thrombocythemia. Researchers concluded that hydroxyurea and aspirin are superior in comparison with anagrelide and aspirin in patients with essential thrombocythemia that have high risk of vascular events, since that therapy leads to significant decrease of arterial and venous thrombosis (16).

The study has also shown that platelet count control alone should not be taken as a measure of efficiency of treatment for essential thrombocythemia, since there is an increase of vascular events in the anagrelide group as opposed to the reduction of platelet count that has been similar to reduction in hydroxyurea group. Probable explanation for this discovery is widened myelosupressive activity of hydroxyurea that influences both leukocytes and erythrocytes. There is an ever increasing number of evidence that these cells play an important role in patho-genesis of thrombosis in essential thrombocythemia.

Anagrelide and low dosage of aspirin seem to have synergy effect in increase of the risk for

hemorrhagic complications. Simultaneous administration of these two medications probably leads to inhibition of platelet function. To the contrary, combination of hydroxyurea and aspirin provides protection from thrombosis with a minimal risk of bleeding.

Some studies have shown that progression to myelofibrosis is three times more often in the group with anagrelide compared to the group with hydroxyurea. The evolution to myelofibrosis is a part of the natural history of essential thrombocythemia and can be met in approximately 3% of patients after 5 years, 8% after 8 years, 15% after 15 years. The risk of myelofibrosis can be distinguished by the basic characteristic of the bone marrow. It is very low in the so-called real essential thrombocythemia in which bone marrow does not have histopathological characteristics of myelofibrosis, and is higher when bone marrow shows prefibriotic stage of myelofibrosis. Transformation to acute myeloid leukemia has been found in similar numbers in group with hydroxyurea and in group with anagrelide.

For now, hydroxyurea and aspirin should be standard therapy for patients with essential thrombocythemia, that have high risk of thrombosis.

The largest last two trials about anagrelide for the treatment of essential thrombocythemia included more than 9000 patients each. Studies involved patients that were refractory and did not stand other therapy for lowering platelet count. Anagrelide proved to be efficient in lowering platelet count in more that 78% of patients (64% complete remission CR, 12% partial remission PR) in first, while there were 77% of responses in other study (66% CR, 11% PR). With daily dosage of 2.0 mg up to 2.5 mg, response time was average 70 days in each study and without difference for patients with extreme thrombocytosis (platelet count larger than 1500×10^9/l). Reduction of platelet count was accompanied by decrease of thrombotic and hemorrhagic events. Side effects of the medication were headache, palpitations, diarrhea, edema, anemia and they led to the cancellation of treatment in about 25% of patients (17,18).

New way in treatment of essential thrombocythemia and other myeloproliferative diseases is opened by recent identification of mutation of JAK2 gene in majority of patients with polycythemia vera, and in around half of patients with essential thrombocythemia or myelofibrosis. Consequence of this mutation is constitutive tyrosine kinase activity of JAK2 that results in proliferation and survival of hematopoietic progenitor cells. New inhibitors of tyrosine kinase are developed with the aim to discover aimed therapy for this disease.

Recommendation scheme of ASH (American Society of Hematologists) for treatment of essential thrombocythemia is shown in Table 2.

Table 2. Recommendations of ASH for management of patients with essential thrombocythemia (ET)

1. All patients: • manage reversible cardiovascular risk factors aggressively (e.g., smoking, hypertension, hypercholesterolemia, obesity.
2. High-risk patients (prior thrombosis or age > 60 years or platelets > 1500 × 109 /L): • low-dose aspirin plus hydroxyurea (anagrelide or interferon-α second line.
3. Intermediate-risk patients (age 40–60 years, no high-risk features): • either enter into randomized trial (e.g., PT-1 intermediate risk arm) • or low-dose aspirin (consider cytoreduction if other cardiovascular risk factors present)
4. Low-risk patients (age < 40 years and no high-risk features): • low dose aspirin

Up to date studies have shown that hydroxyurea should be first therapeutic line for majority of patients with high risk disease. Interferon-α and anagrelide are reserved as second therapeutic line. Decision whether to use aspirin demands potential risk and benefits assessment for each patient. Optimal treatment of patient with previous venous thrombosis would depend of individual circumstances, bearing in mind that arterial thrombotic events are more than three times more often than venous thrombosis in essential thrombocythemia. Also, there is a general consensus that patients with low risk of thrombotic events (younger than 40, without high risk characteristics), should get only low dosages of aspirin. For medium risk patients, (aged between 40 and 60, without high risk characteristics), there is no universal guide for therapy since it is not clear whether cytoreduction is useful. There are recommendations that such patients should be included in randomized studies such as intermediate risk PT-1 (hydroxyurea and aspirin versus aspirin only). However, patients aged between 40 and 60 years with high risk characteristics (platelet count larger than 1000×10^9/l, family thrombophilia or present cardiovascular risk factors) should be treated with cytoreductive therapy.

In addition, there are guidelines for the treatment of essential thrombocythemia in pregnancy. It is advisable to limit the usage of platelet-lowering agents in patients considered to be at high risk for thrombosis, and partially in patients with history of previous thrombosis or fetal loss. Anagrelide and hydroxyurea should be avoided because of the possibility of teratogenic effects, although there have been reports of normal pregnancies despite exposure to hydroxyurea. Interferon-α is generally regarded as the treatment of choice and should be combined with heparin in patients particularly at high risk, with treatment continuing for several weeks postpartum.

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MODALITY OF TREATMENT IN ESSENTIAL THROMBOCYTHEMIA

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Esencijalna trombocitemija (ET) je hronično mijeloproliferativno oboljenje koje nastaje zbog poremećaja multipotentne matične ćelije hematopoeze.

Karakteriše se porastom broja trombocita, hiperplazijom megakariocitne loze u kostnoj srži, sklonošću ka krvarenju i trombozama. Simptomi i znaci uključuju slabost, glavobolju, parestezije, krvarenje, splenomegaliju i digitalnu ishemiju. Bolesnici sa esencijalnom trombocitemijom imaju isto ili nešto kraće preživljavanje nego zdrava populacija istih godina i pola. Glavni razlog smrti su trombotične i hemoragične komplikacije ili transformacija bolesti, bilo kao prirodni tok bolesti ili kao posledica upotrebe citostatika.

Dijagnostički kriterijumi za esencijalnu trombocitemiju su predloženi 2005. godine od strane PVSG i zahtevaju dijagnozu isključivanjem.

Mijelosupresivna terapija za smanjenje broja trombocita sastoji se od hidroksiureje, interferona alfa ili anagrelida. Hidroksiureja je najšire korišćen lek, zbog svoje efikasnosti, niske cene i retke akutne toksičnosti. Interferon alfa je modulator biološkog odgovora. Nije poznato da je teratogen i ne prolazi kroz placentu pa je često tretman izbora tokom trudnoće. Anagrelid suprimira megakariocite kostne srži remeteći proces sazrevanja i smanjujući produkciju trombocita, bez efekta na druge ćelijske linije. Niske doze aspirina mogu biti korišćene u kontroli mikrovaskularnih simptoma.

Preporuke za lečenje bolesnika sa esencijalnom trombocitemijom su date od strane ASH. Sa stanovišta terapije, hidroksiureja je sada potvrđena kao lek izbora za lečenje visoko-rizičnih bolesnika sa esencijalnom trombocitemijom. Interferon alfa i anagrelid su prihvaćeni kao lekovi druge linije. Nisko-rizični bolesnici trebalo bi da dobijaju samo niske doze aspirina. Za bolesnike sa intermedijarnim rizikom nije postignut koncenzus o preporukama za trombocitoreducirajući tretman. *Acta Medica Medianae 2008;47(3):51-55.*

***Ključne reči**: esencijalna trombocitemija, preporuke, tretman*