Overview of management strategies toward Thrombocythemia

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Abstract:

This article discuss pathogenesis, risk factors and summarizes the current status of ET therapy and emphasizes the importance of a risk-adapted treatment strategy in the management of these patients. MEDLINE, AMED, EMBASE, CINAHL, and the Cochrane Library were searched in details (for articles published up to November, 2017) for relevant articles in English language were included in the review. Search terms as following “thrombocythemia”, “essential thrombocythemia”, “treatment”, “management”, “therapy”. Essential thrombocythemia (ET) is a chronic myeloproliferative disorder of unidentified origin characterized by a persistently raised platelet count, a raised number of megakaryocytes in the bone marrow, and an enhanced danger of thromboembolic and hemorrhagic complications. Therapy in patients with essential thrombocytosis (primary thrombocythemia) need to be individualized on the basis of danger aspects for thrombohemorrhagic complications. Lifestyle modifications should be recommended for all patients with reversible risk factors. These consist of diet and exercise to promote weight loss for obese patients and smoking cessation for smokers.

Introduction:

Essential thrombocythemia (ET), initial recognized as a distinctive entity in 1934 under the term "hemorrhagic thrombocythemia," is a myeloproliferative neoplasm (MPN) characterized by thrombocytosis with bone marrow megakaryocytic hyperplasia and a tendency to develop vascular complications, including thrombosis, microvascular disruptions, and hemorrhage. ET was placed by Dameshek in 1951 within the myeloproliferative problems, together with chronic myeloid leukemia, polycythemia vera (PV), and primary myelofibrosis (PMF) [1].The discovery of the Philadelphia (Ph) chromosome led to coining of the term "traditional" Ph-negative myeloproliferative problems to encompass ET, PV, and PMF, three heterogeneous problems with clonal beginning in a multipotent hemopoietic stem cell that share various clinical, hematologic, and biological features. Change from one disorder to the various other is in some cases observed. In 2005, the discovery of an obtained anomaly in the JAK2 gene in a high percentage of patients with classic Ph-negative MPNs [2] provided a molecular basis for Dameshek's intuitive integration of these entities. ET is the most usual of the three disorders and the one with a more beneficial prognosis, because it affects the patients' quality of life greater than their survival because of the raised occurrence of vascular complications [3]. Evolution to myelofibrosis is observed in 4%-8% of patients at 10 years [4], whereas leukemic modification is rare yet could enhance with using certain cytoreductive medicines [5]. For that reason, ET therapy should be aimed at protecting against apoplexy and bleeding but without increasing the danger of transformation.

This article discuss pathogenesis, risk factors and summarizes the current status of ET therapy and emphasizes the importance of a risk-adapted treatment strategy in the management of these patients.

Methodology:

MEDLINE, AMED, EMBASE, CINAHL, and the Cochrane Library were searched in details (for articles published up to November, 2017) for relevant articles in English language were included in the review. Search terms as following “thrombocythemia”, “essential thrombocythemia”, “treatment”, “management”, “therapy”. Reference lists of all retrieved articles were scanned for further relevant studies.

Discussion:

Pathogenesis

A major milestone for the understanding of MPN pathogenesis was the recognition of the JAK2 V617F anomaly most of PV patients and in 50%-60% of those with ET and PMF [2]. This mutation generates an increased tyrosine kinase activity of JAK2, leading to a cytokine-independent phenotype. Although the JAK2 mutation is crucial for MPN appearance, molecular evaluation has shown that it could frequently occur as a secondary event after the acquisition of other mutations [6].It is additionally intriguing why the exact same molecular lesion generates three different phenotypes. According to the most widely approved concept, the "gene-dosage theory," the mutated allele burden is the more vital contributor to MPN phenotype [6].This concept stems from the observation that the greater JAK2 altered allele worry is discovered in PV and PMF and the lower in ET, whereas homozygosity for the JAK2 mutation is frequent in PV and PMF and unusual in ET. Moreover, experimental studies in animal models parallel the searchings for in human MPNs. As a result, overexpression of JAK2 V617F in mice leads to a picture imitating PV without

thrombocytosis, with additional development to myelofibrosis, whereas low JAK2 V617F expression creates an ET-like condition with thrombocytosis yet not erythrocytosis.12 However, the allele worry is not sufficient to explain the MPN phenotype. It is fairly most likely that aspects, including pre-JAK2 mutation occasions, host genetic factors such as specific polymorphisms, epigenetic factors, additional somatic anomalies not yet determined, and host modifiers such as iron accessibility, add to the final MPN phenotype [6].

Whereas the JAK2 V617F mutation is the molecular abnormality more regularly discovered in ET, 3%-5% of patients display mutations in the thrombopoietin receptor genetics or the MPL genetics (from the myeloproliferative leukemia infection oncogene, which causes a PMF-like with thrombocytosis in mice) [7].These mutations (MPLW515L/K) are related to a gain of function and are additionally found in around 5%-10% of PMF patients, yet not in PV. Experiments in mice transplanted with hemopoietic forerunners harboring the MPLmutation show that they develop a swiftly evolving illness with leukocytosis, thrombocytosis, splenomegaly, and BM fibrosis, but not erythrocytosis.

Familial occurrence of MPNs has long been known. Genetic predisposition was sustained by an epidemiological study from Sweden showing an increased occurrence of these diseases amongst relatives of MPN patients [8].Recently, molecular assistance for these clinical observations was provided by the discovery of an enhanced regularity of an unique haplotype of the JAK2 gene, the 46/1 haplotype, in MPN patients and their first-degree family members [9].

Table 1. Diagnostic criteria for ET according to the 2008 WHO classification [10].

1. Sustained platelet count >450 X 109/l
2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes; no significant increase or left shift of neutrophil granulopoiesis or erythropoiesis
3. Not meeting WHO criteria for polycythemia vera, primary myelofibrosis, BCR-ABL1 -positive chronic myelogenous leukemia, myelodysplastic syndrome or other myeloid neoplasm
4. Demonstration of JAK2V617F or other clonal marker, or in the absence of JAK2V617F; no evidence for reactive thrombocytosis

- **Risk stratification according to thrombo-hemorrahagic risk**

Age and previous thrombosis

Age over 60 and a previous thrombotic event were identified as major threat aspects for thrombosis in most studies.The age-related distinctions in the frequency of these occasions is mostly because of the coexistence of vascular illness in older patients. Nonetheless, more youthful patients are not devoid of vascular thrombosis, often in uncommon sites, such as the portal or sagittal veins [11].On the whole, the incidence of thrombotic and hemorrhagic complications in asymptomatic patients with ET younger than 60 years old that had a platelet count of <1500 X 109/l is comparable to a typical control populace [12].

Platelet count and function

Several big accomplice researches have cannot define a relationship in between the regularity of thrombotic difficulties and platelet number. Therefore, a raised platelet matter, per se, need to not be taken into consideration as a sign for a myelosuppressive therapy focused on avoiding thrombotic difficulties. Supporting this view, in a retrospective research of 99 successive young

patients (aged <60 years) who presented with extreme thrombocytosis (platelet count >< 60 years) that presented with extreme thrombocytosis(platelet matter > 1000 X 109/ l) and without a previous history of thrombohemorrhagic complications, the incidences of major thrombosis and hemorrhage throughout the follow-up were comparable between those who were treated with prophylactic cytoreductive treatment and those that did not obtain such treatment [13].

The relationship between regularity of bleeding episodes and high platelet matters is a lot more constant. Many research studies have revealed that the degree and period of bleeding in this patient populace associate with the platelet count. Bleeding events show up to happen when the platelet matters are excessively high and quit when the platelet matter falls to regular. The medical range of bleeding in ET patients closely looks like that observed in von Willebrand condition [13].A rise in the variety of distributing platelets appears to favor the adsorption of bigger von Willebrand multimers into platelet membrane layers, leading to their removal from the flow and their succeeding deterioration. The research laboratory functions of obtained von Willebrand syndrome in ET is characteristic of a kind II deficiency with long term bleeding time, regular aspect VIII C: VWF Ag proportion, reduced ristocetin cofactor activity, and decline or lack of large von Willebrand variable multimers [14].

Platelets in patients with ET have been understood for a significant time to be qualitatively unusual. Although both raised and decreased platelet reactivities have been explained, these findings have not been definitively connected with thrombohemorrhagic complications with two noteworthy exceptions; erythromelalgia, where the timely alleviation of symptoms by cyclooxygenase inhibitors offers direct proof that prostaglandins have a role in the growth of vascular occlusion, and obtained von Willebrand disorder, which is a significant cause of bleeding in patients with ET [14].

Leukocyte number and function

A prognostic function for leukocytosis in ET has been advocated [16] 3 large accomplice researches reported that an increased baseline leukocyte matter was an independent threat factor for both thrombosis and inferior survival. The duty of WBC matter in ET was primarily observed on the occurrence of myocardial infarction, as additionally shown in patients with PV. In 'low-risk' ET patients, (that is, below 60 years and without previous thrombosis) leukocytosis conferred a thrombotic danger equivalent to that of treated 'high-risk' patients without leukocytosis. These findings were not confirmed in a retrospective study of 407 low-risk patients with ET [17].Leukocytosis at the time of diagnosis, specified by a cut-off level of either 15 or 9.4 X 109/ l, did not appear to be anticipating of either arterial or venous thrombosis throughout follow-up. Nevertheless, in an evaluation of 194 low-risk ET patients, the boost in leukocyte matter within 2 years of medical diagnosis (observed in 9% of patients), instead of leukocytosis at diagnosis, was associated with a higher threat of vascular complications throughout follow-up [18].

In ET, an in vivo leukocyte activation has been constantly recorded in association with indications of activation of both platelets and endothelial cells. Remarkably, the existence of the JAK2 mutation is associated with greater platelet and leukocyte activation in these patients. Therefore, platelet and leukocyte activation could have a role in the generation of the pre-thrombotic state that defines ET [19].However, whether leukocytosis should be merely considered a pen for vascular condition or whether raised WBC levels really contribute straight to triggering such disorders must be matter of potential studies.

Other risk factors

The presence of the JAK2V617F mutation in about 60% of ET patients elevated the question whether mutated and non-mutated patients vary in regards to thrombotic risk. The biggest potential research study on 806 patients recommended that JAK2 mutation in ET was related to anamnestic venous but not arterial events. A boosted threat of apoplexy in JAK2-mutated patients was retrospectively observed by various other investigators [19].Nonetheless, the rate of vascular difficulties was not influenced by the existence of the mutation in two fairly large retrospective researches, consisting of 150 and 130 ET patients specifically. An organized literature evaluation was carried out to compare the regularity of thrombosis in between JAK2V617F-positive and wild-type patients with essential thrombocythemia. This study showed that JAK2V617F patients have a two-fold danger of developing thrombosis (probabilities ratio (OR) 1.92, 95% self-confidence period (CI) 1.45 -2.53) but a significant heterogeneity in between researches has been pointed out. Along with the prognostic function of JAK2 mutation for the initial thrombotic episode, current information would show that the anomaly has also a function to anticipate reoccurring thrombotic episodes in patients with ET [20].

Bone marrow histology is very important for an exact morphologic diagnosis of ET according to WHO standards and for predicting survival and hematological changes to myelofibrosis or acute leukemia.1 However, its function as a danger element for thrombosis is controversial. Campbell et al. [21] have identified raised bone marrow reticulin fibrosis at diagnosis as an independent forecaster of subsequent thrombotic and hemorrhagic complications. At variance, a current analysis contrasting 891 patients with WHO identified ET vs 180 patients medically providing like ET yet with an histological photo of prefibrotic PMF did not show any kind of distinction in the rates of arterial (1.2 - 1.4% patient-year, specifically) and venous (0.6% patient-year in both groups)

thrombotic problems.1 Instead, prefibrotic PMF was a considerable predictor of significant bleeding, together with leukocytosis, previous hemorrhage and aspirin usage.

The role of inflammation amongst the possible prognostic factors in MPN has been recenly highlighted [21].Barbui et al. correlated vascular complications with plasma degrees of high-sensitivity C-reactive healthy protein and pentraxin-3 in 244 ET and PV patients. Major thrombosis rate was higher in the highest C-reactive healthy protein tertile (P 1/4 0.01) and reduced at the greatest pentraxin-3 levels (P 1/4 0.045). These organizations remained substantial in multivariable evaluation and suggest that these inflammatory biomarkers individually and in contrary methods regulate the threat of cardiovascular occasions in patients with MPN [22].

In conclusion, a clinically drivened plan is recommended to stratify patients with ET in a 'risky' or 'low-risk' category inning accordance with their age and previous history of thrombosis (Table 2) [23].Suppositional novel variables, such as leukocytosis and JAK2V617F mutational standing, may be included in the risk category, possibly permitting better meaning of the low-risk group, once more info is readily available when they have been eventually verified in potential studies.

Table 2. Risk stratification in ET based on thrombohemorrhagic risk

Risk category	Age >60 years or history of thrombosis
Low	NO
High	YES
Extreme thrombocytosis (platelet count 41000 109 /l) is a risk factor for bleeding, not for thrombosis. Increasing leukocyte count and JAK2V617F mutation have been identified as novel risk factors for thrombosis, but confirmation is required.	

- **Management of low-risk patients**

The demonstration in the European Collaboration on Low-dose Aspirin in Polycythemia Vera study that the risk of thrombosis was decreased by antiplatelet treatment with low-dose aspirin, along with the fact that mix of the last with hydroxyurea was established as the selection treatment

for risky ET by the outcomes of the PT-1 research, [24] fostered the extensive use of low-dose aspirin as primary treatment of thrombosis in low-risk ET. Nevertheless, the proof for the role of such a strategy in ET is weak. In fact, in some research studies, the incidence of thrombosis in neglected patients did not vary from that observed in a healthy control populace [25].A current research has provided some guidance for indications for low-dose aspirin in low-risk ET. The investigators retrospectively analyzed the outcomes of antiplatelet treatment (mainly low-dose aspirin) or mindful monitoring in 300 low-risk ET patients with a follow-up of 802 and 848 person-years, respectively, showing that antiplatelet treatment reduced the risk of venous thrombosis in JAK2-positive patients and the threat of arterial thrombosis in those with cardiovascular danger aspects, whereas it was connected with an excess of bleeding episodes in patients with platelet counts above 1000 × 109/L. The retrospective nature of the research study and the fact that antiplatelet treatment was based on the physician's finest reasoning present some limitations to the outcomes of the above research study. Nevertheless, the high variety of patients assessed and the lengthy follow-up make its conclusions of value. As a result, although the easiest approach could be to administer low-dose aspirin to all low-risk ET patients in the absence of a significant contraindication, an affordable approach could be to offer low-dose aspirin to low-risk patients other than those with contraindication for aspirin or with platelet counts greater than 1000 × 109/L to reduce the danger of hemorrhage.

- **Management of high-risk patients**

As pointed out formerly, there is general agreement on the management of cytoreductive treatment to all patients with risky ET. Hydroxyurea became the first-line medicine of selection after a randomized test revealed that it produced a substantial reduction in thrombotic occasions. Because research, 114 high-risk patients were randomly assigned to receive hydroxyurea or no cytoreductive treatment and, after a mean follow-up of 27 months, thrombosis rate was 3.6% in

treated patients versus 24% for neglected patients. This monitoring was further supported by the outcomes of the PT-1 trial, a randomized study that compared hydroxyurea plus aspirin versus anagrelide plus aspirin in 809 patients with high-risk ET [24].After a typical follow-up of 39 months, the results demonstrated the superiority of hydroxyurea plus low-dose aspirin in avoiding vascular events total and change to myelofibrosis, although anagrelide proved to be remarkable in avoiding venous thrombosis. Because anagrelide was just as efficient in minimizing the platelet counts, the superiority of hydroxyurea may be ascribed to its ability to suppress not only the platelets but additionally the leukocytes. Conversely, although there have been worries about the possible mutagenic impact of hydroxyurea, such an effect has not been convincingly proven. In fact, most of the cases of transformation to acute leukemia or myelodysplasia occurred in patients who had also obtained other drugs, whereas organic research studies have failed to demonstrate an increase in DNA mutations in MPN patients receiving hydroxyurea. However, it seems prudent to avoid hydroxyurea as long as feasible in patients under the age of 40 years, given the staying uncertainties about its leukemogenic capacity in the long-term. The starting hydroxyurea dosage is 500 mg two times daily, with further adjustment to keep typical platelet counts (without prompting scientifically relevant neutropenia or anemia) and to eliminate the symptoms and signs of the condition. Strict standards of feedback were defined by a panel of specialists from the European Leukemia Net for their application in clinical trials [26].However, it is uncertain whether accomplishment of such rigid criteria converts into superior patient benefit in medical technique [27].At the normal dose, hydroxyurea is generally well endured, yet intolerance can establish, consisting of anemia, leukopenia, and the appearance of oral or leg abscess, skin lesions, or gastrointestinal signs and symptoms.

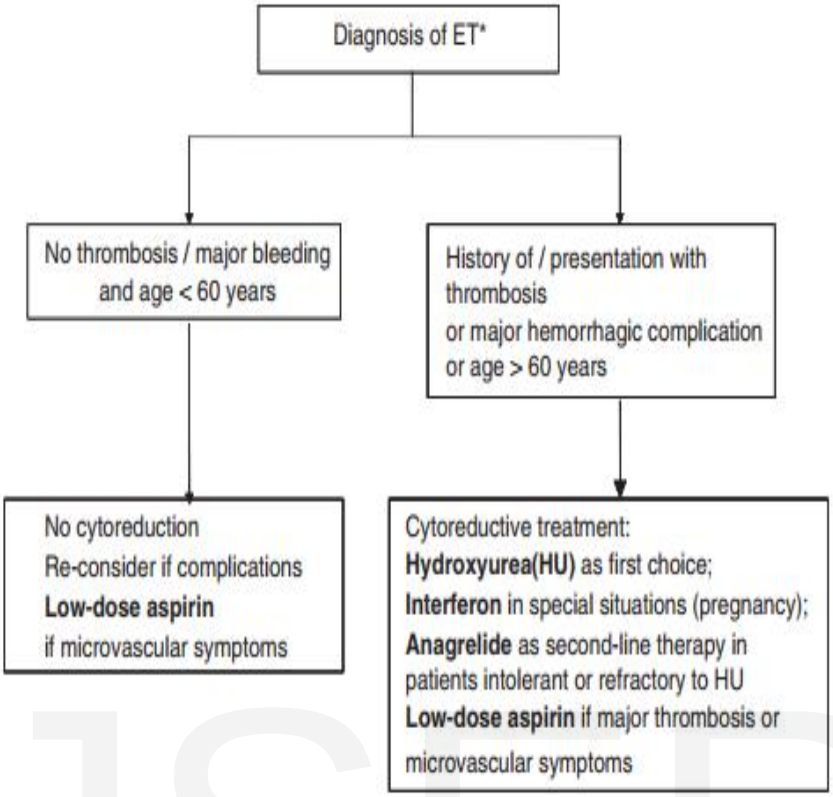

Figure 1. How to manage patients with ET [10].

Conclusion:

Essential thrombocythemia (ET) is a chronic myeloproliferative disorder of unidentified origin characterized by a persistently raised platelet count, a raised number of megakaryocytes in the bone marrow, and an enhanced danger of thromboembolic and hemorrhagic complications. Therapy in patients with essential thrombocytosis (primary thrombocythemia) need to be individualized on the basis of danger aspects for thrombohemorrhagic complications. Risk factors consist of the following: Age 60 years or older, history of thrombosis and obesity, cardiovascular risk factors such as smoking cigarettes, hypertension, and hypercholesterolemia. Cytoreductive therapy needs to be used to reduce the platelet count in high-risk patients. Hydroxyurea is usually considered the first-line drug for cytoreductive treatment in essential thrombocytosis. Lifestyle modifications

should be recommended for all patients with reversible risk factors. These consist of diet and exercise to promote weight loss for obese patients and smoking cessation for smokers.

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