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Recent Advance in Diagnosis, Pathogenesis and Risk Stratification of Essential Thrombocythemia

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Abstract

In the 2016 version of WHO classification, bone marrow morphology is critical in the distinction between ET and pre-PMF. Reticulin-fiber grading becomes central: grade 1 or less is needed for ET. Furthermore, *CALR* assessment must be performed in all ET patients without *JAK2* mutation. Some prognostic implications have been described for *CALR* mutations, i.e., a lower risk of thrombosis in ET.

Abbreviations: MPN: Myelo Proliferative Neoplasm; WHO: World Health Organization; JAK: Janus kinase; CALR: Calreticulin; bp: base pair; MPL: Myelo Proliferative Leukemia virus oncogene; TPO: Thrombo Protein; RARS-T: Refractory Anemia with Ring Sideroblasts associated with marked Thrombocytosis; PMF: Primary Myelo Fibrosis; IPSET: The International Prognostic Score for Essential Thrombocythemia; WBC: White Blood Cell; LMWH: Low-Molecular Weight Heparin; SVT: Splanchnic Vein Thrombosis

Introduction

ET is a Philadelphia-negative MPN characterized by sustained clonal proliferation of the megakaryocytic lineage in the bone marrow and an elevated platelet count in the peripheral blood [1]. According to the WHO classifications (especially the 2016 version), diagnostic criteria for ET include: major criteria (i) an elevated platelet count (≥ 450 X 10^9/L); (ii) bone marrow biopsy showing proliferation, mainly of the megakaryocyte lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers (iii) failure to meet diagnostic criteria for BCR-ABL1 CML, PV, PMF, myelodysplastic syndromes or other myeloid neoplasms; (iv) demonstration of clonal markers, such as *JAK2*V617F (*JAK2*), *CALR* or *MPL* mutations and a minor criterion: presence of a clonal marker or absence of evidence for reactive thrombocytosis. Diagnosis of ET requires meeting all four of the major criteria above or the first three major criteria and a minor criterion [2]. The incidence rate for ET is 0.2-2.5/100.000 people/year. The prevalence is higher at 38-57/100.000 people, because of the long life expectancy (in excess of 20 years) of ET patients [1].

Pathophysiology: Megakaryocyte progenitor cells in ET are hypersensitive to the action of several cytokines including IL3 and IL6 and possibly TPO. There is controversy regarding spontaneous megakaryocyte formation [3].

Genetic data: Driver mutation (*JAK2*V617F, *CALR* and *MPL* mutations): the frequency of *JAK2*V617F mutation is approximately 50-60%. Most patients with *JAK2*-unmutated ET express *CALR* or *MPL* mutations, with respective estimated incidences of 25-30% and 3-5% [4]. Most *CALR* mutations were deletions and insertions in exon 9, which cause frame shift mutations. Two *CALR* mutations are predominantly associated with ET. Type 1 result from a 52-bp deletion, and is found in approximately 50% of patients and type 2 mutation results from a 5-bp TTGTC insertion, and accounts for approximately 30% of patients [5].

Approximately 15% of patients are wild-type for all 3 mutations (i.e., triple-negative)[6]. However, a few triple negative patients carry activating mutation of *MPL* outside exon 10 [7]. Double-mutant *JAK2*V617F and *CALR* positive, patients make a specific subgroup that might be distinct from the *JAK2*-positive or *CALR*-positive subgroups and require a careful follow-up and management. The frequency of this co-occurrence was below 1%, in one study [8] and 6.8% in Lim et al. [9]study. In the last study, these patients had the oldest age, higher thrombotic events and higher major arterial thrombotic events after diagnosis and more patients were in the high-risk group for thrombo hemorrhagic complications [9]. Rashid et al. [10] (2015) reported 55 year old female ET patient who was in complete remission without cytoreductive therapy until their paper publication [10].

Non driver mutation: In ET, 46% of patients had somatic mutations. The most commonly mutated, non driver genes, included DNMT3A (6%), TET2 (13%), and ASXL1 (11%), SF3B1 (5%), CEBPA (4%), and TP53, SH2B3, EZH2, and CSF3R (2% each). Patients with ASXL1, EZH2, SRSF2, or IDH mutations are considered to have a "high molecular risk" profile and were at risk for premature death or leukemic transformation. However, only ASXL1 mutations remained significantly associated with survival [11]. The number of mutations also matters, the presence of 2 or more mutations predicted for worse outcomes; the reported median survival was 12.3 years for patients without a mutation compared with 2.6 years for those with 2 or more mutations. Those with post-ET-MF were more likely to have ASXL1 and EZH2 mutations, compared with those with post-PV-MF. The order in which mutations are acquired appears to influence clinical features. It was suggested that those patients who acquired *JAK2*V617F prior toTET2 are more likely to present with PV than ET [11].

Clinical picture: ET is an indolent myeloproliferative neoplasm [7]. The median age at diagnosis is 60 years. There may be higher prevalence in younger women (approximately 2:1). Many patients are asymptomatic at presentation [3]. The prevalence of constitutional symptoms is relatively high [7]. Patients might also have micro vascular symptoms such as headaches, acroparesthesia, erythromelalgia, peripheral ischemia, transient ischemic attacks, amaurosisfugax or scotom as [1]. Patients may present with splenomegaly (20%), thrombosis and bleeding. Hemorrhagic event, mostly from GIT is experienced in 13 to 37% of patients while thromboembolic events in the major vessels or microvasculature are experienced in 22-84% of patients [3].

Female patients in the child bearing period may experience: live birth rates of 50% to 70%, and spontaneous abortion rates of 25% to 50%, mostly during the first trimester. Age, parity, thrombophilia, platelet count, WBC count, and hemoglobin level have not been found to be predictive of pregnancy outcome in ET. Pregnancy complications in women with ET are associated with a higher risk of subsequent thrombosis [7].

Thrombotic risk factors: IPSET is a score which provides prognostic information on risk of thrombosis. It is based on widely accepted risk factors for thrombosis which are age ≥60 years (2 points), WBC count ≥11X10^9/L (1 point), and history of thrombosis (1 point) [7]. *JAK2* (V617F) plays a major role in the pathogenesis of thrombosis, whereas CALR or MPL mutation and triple negativity identify patients with lower thrombo embolic risk [7]. Elevated platelet count (>1,000×10^9/L) was associated with lower arterial thrombotic risk [12].

Comparison of clinical and hematological features of patients with *JAK2* mutation and *CALR* mutation: *CALR*-mutated ET patients had a lower risk of thrombosis than *JAK2*-mutated ET patients [6].Thrombotic events occurred in 26% of *JAK2*-mutated ET patients versus 7.7% of *CALR*-mutated ET patients. Genetic background such as race may influence the risk of thrombosis [12]. Previous studies have shown higher platelet counts and lower hemoglobin, leukocyte counts and granulocyte counts in *CALR* mutant compared with *JAK2* mutant patients [6]. In addition, platelet counts are higher in type 2 *CALR* mutant compared with type 1 mutant patients [6]. *CALR*-mutated ET displaysa phenotype favoring megakaryopoiesis [12].

CALR-mutated ET patients had a longer survival compared with those with *JAK2*V617F mutation. A higher rate of post-ET-MF transformation was reported in *CALR*-mutated patients versus *JAK2*-mutated patients. Interestingly, no *CALR*-mutant ET patient evolved to PV [11].

Outcome: ET may transform into PV, MF, AML or MDS. However, ET is generally considered a benign illness because it is associated with prolonged survival and a low risk of leukemic transformation [13]. The 15-year cumulative risk of progression to myelofibrosis is about 10% on average, higher in type 1 *CALR*-mutant than in *JAK2*-mutant ET while the 15-year cumulative risk of leukemic transformation is about 3% on average [7].

Diagnostic Consideration

a) Screening for BCR-ABL1 is important in the diagnostic approach of ET patients to rule out chronic myeloid leukemia and atypical MPN associated with both BCR-ABL1 rearrangement and CALR mutation [7].

b) Assessment of *JAK2* mutational status is mandatory in case of unexplained thrombocytosis [14].

c) *CALR* assessment must be performed in all patients without *JAK2* mutations followed by MPL if *CALR* is absent. These mutations does not replace the need for BM morphologic examination in [1] confirming the diagnosis in triple-negative ET and [2] distinguishing ET from other MPN that share the same mutations, including masked PV and early/ prefibroticmyelo fibrosis [6].

d) *JAK2* (V617F) assessment is recommended in patients with SVT because it may be the first marker of a latent MPN. Although, the incidence of *CALR* exon 9 is low in patients with SVT, CALR assessment can now also be included in the workup of these subjects. Genetic and acquired thrombophilia, in particular the presence of anti-phospholipid syndrome, should be studied in all cases of ET with SVT because ET patients with genetic or acquired thrombophilia are at high risk of recurrent thrombosis [7].

e) At present, there is little evidence to suggest the incorporation of testing for non driver mutation in routine clinical care of ET patients [11].

f) Von Willebr and factor antigen level and ristocetin cofactor activity have to be performed when platelet count is >1000 x 10^9/L or when an acquired von Willebrand syndrome is anyhow suspected [7].

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Differential diagnosis: The most common cause of isolated thrombocytosis is a reactive (or secondary)causes [7] due to infections, acute or chronic inflammatory diseases, smoking, iron deficiency, chronic bleeding, postsurgical states, malignancies, hemolysis, rebound after immunosuppressive chemotherapy, and use of drugs (corticosteroids, adrenaline, and TPO mimetics [14].

a. Other clonal myeloid neoplasms [7].

b. Hereditary thrombocytosis and familial ET. Recent reports have described cases of hereditary thrombocytosis associated with non-canonical germ line mutations of *JAK2*. In familial ET, *JAK2* (V617F) is always a somatically acquired event [7].

c. RARS-T, in which *JAK2*V617F mutational frequency has been reported to be as high as 50% [6]. Most patients have a combination of SF3B1 mutation (as a driver genetic lesion) and *JAK2*, *MPL*, or *CALR* mutation (as a subclonal genetic lesion); however, up to one-third of patients may have wild-type SF3B1 [7].

d. PV when the hemoglobin/hematocrit level is diagnostically equivocal (as in "masked" PV) [6].

e. Prefibrotic/early prePMF with a high platelet count. Leukocyte count, hemoglobin level, platelet count, serum LDH level, incidence of palpable splenomegaly and circulating CD34 cell count, all are greater in prePMF than ET. In ET, there is no or minor (grade 1) increase of reticulin fibers. The 2016 WHO classification allows the presence of reticulin fibrosis grade 1 in ET, but this is a very rare presentation [14]. On the other hand, age, gender distribution and *JAK2*V617F mutational frequencies were similar between both groups. The survival rates, leukemic transformation rates, and rates of progression to overt myelofibrosis were significantly worse in prePMF than in ET [15].

Treatment

Treatment of ET is based on risk stratification: Age >60 years, history of vascular complications (thrombosis or major bleeding), and platelet count ≥1500x10^9/L are the 3 risk factors used to classify patients with ET into low (no risk factors) and high risk (1 or more risk factors). Low-risk ET patients have an incidence of thrombosis similar to that of a healthy control population [7].

The indication for and goals of therapy: are to reduce the risk of life-threatening complications, such as venous or arterial thrombosis or severe bleeding, rather than induce remission or disappearance of the neoplastic clone. Treatment may also help to control vasomotor symptoms [1]. Treatment of ET is based on aspirin in the vast majority of ET cases and cytoreductive therapy [7].

Low-dose aspirin: All ET patients should be managed with low-dose aspirin if micro vascular disturbances are present. In low-risk ET, anti-platelet therapy reduces the incidence of venous thrombosis in *JAK2*-mutated patients [7] and the rate of arterial thrombosis in those with cardiovascular risk factors, with no effect on the risk of bleeding. By contrast, in *CALR*-mutated patients, anti-platelet therapy did not affect the risk of thrombosis whereas it was associated with a higher incidence of bleeding. In high-risk ET patients, anti-platelet therapy should be administered to all patients except those with extreme thrombocytosis (>1500 x 10^9/L) [7].

Cytoreductive therapy: Extreme thrombocytosis is frequently associated with acquired von Willebrand syndrome [7]. So, A platelet count >1500x10^9/L represents an indication to cytoreductive treatment [7] with hydroxyurea, or interferon, or an agrelide when indicated or ruxolitinib when inadequate response to hydroxyurea occurs [14].

Treatment of pregnant females: Aspirin is safe for both mother and fetus. It is recommended for all pregnant women with ET, unless contraindicated. Low-dose aspirin is effective in preventing preeclampsia [7]. LMWH is added to low-dose aspirin in case of previous major thrombosis or severe pregnancy complication. Consider interferon α if the platelet count is >1500 x109/L or in case of previous major bleeding. The optimal time to discontinue anti-platelet treatment is generally about 2 weeks before delivery for any possible instrumental delivery and epidural or spinal anesthesia. After delivery, treat all women with ET with LMWH for 6 weeks to prevent deep vein thrombosis [7].

Cytoreductive therapy and natural history of disease: Hydroxyurea does not specifically target the mutant clone and is therefore unlikely to modify the natural history of disease. Pegylated interferon α-2a has been shown to induce sustained complete molecular response in a subset of patients with *JAK2* (V617F)-mutant ET. In addition, recent reports describe the positive effect of interferon α in patients with *CALR*-mutant ET [7]. Those with additional mutations had poorer molecular responses compared with those with *CALR* alone. Analyses of mutation type also suggested a differential effect from IFN-α on mutated clones, because some patients experienced a decrease in the *CALR* burden but an increase in the clonal burden of other somatic mutations [11]. These observations do not necessarily mean that interferon α can modify the natural history of disease but they at least indicate that this drug can target the myelo proliferative clone [7].

Future therapy: Whether JAK inhibitors can provide beneficial effects in patients with ET remains to be established in ad hoc clinical trials, but ruxolitinib has already proved to be effective in patients with a relatively aggressive disease [7]. A novel ET treatment concept involves telomerase inhibition. Response was seen regardless of the mutational profile, although more pronounced in those with *JAK2* mutation. Mutant allele burdens were also reduced by 15% to 66% in those with MPL or *CALR* mutations [11].

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Conclusion

There is a tremendous scientific advance in the last decade in diagnostic capability, and disease pathogenesis of essential thrombocythemia. However still there are unanswered questions especially as regards progression of disease.

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