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Essential Thrombocythemia: Current Molecular and Therapeutic Insights

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ABSTRACT

Essential thrombocythemia is one of the Philadelphia chromosome negative, clonal myeloproliferative disorders involving the hematopoietic stem cells and is characterized by elevated platelet counts and attendant thromboembolic phenomenon. A point mutation in the Janus-Activated Kinase 2 gene (JAK2V617F) accounts for nearly 50% of Essential thrombocythemia patients while about 10% have mutations in the thrombopoetin receptor (MPL) gene (MPLW515L/K). Several other genes are implicated, clearly indicating the existence of drivers both common and uncommon in the causation of Essential thrombocythemia. Genotyping for mutations will therefore be a useful diagnostic tool for detection of Janus-Activated Kinase 2 negative, MPL negative, Essential thrombocythemia patients. An integrated approach of systematic analysis leading to accurate diagnosis will enable risk stratification and institution of therapy following the World Health Organization guidelines. In addition to Janus-Activated Kinase inhibitors, a combination of agents that has anti-inflammatory properties could help prevention and/or reversal of fibrosis.

Keywords

Essential thrombocythemia; Myeloproliferative neoplasms; JAK2V617F mutation; MPLW515L/K mutation; Calreticulin mutation

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INTRODUCTION

Essential thrombocythemia (ET) arises due to an acquired genetic defect in hematopoietic stem cells leading to clonal myeloproliferation. Hematopietic stem cell (HSC) proliferation, differentiation and apoptotic effects mediated by epidermal growth factor, colony stimulating factor, platelet derived growth factor, interleukin 3 and erythropoietin are regulated via the Janus-Activated Kinase 2 (JAK2)/signal transducer and activator of transcription (STAT) signaling pathway.

ET is characterized by an increase in platelet numbers, which therefore can cause a predisposition to frequent thrombosis and hemorrhagic incidents. The prevalence in the general population is about 30/100000[1], having a slight female preponderance with a ratio of 2:1. Although the disease can occur at any age, the median age for ET is between 65 -70 years. Due to occlusion of the microvessels (arteries/veins) vascular disturbances such as stroke, transient ischemic attacks, headache, lightheadedness and visual disabilities are frequently encountered[2]. Polycythemia vera (PV) and ET are commonly associated with microcirculatory disturbances leading to thrombotic/ hemorrhagic incidents while primary myelofibrosis (PMF) has the propensity to undergo leukemic transformation[3,4]. Evidences indicate that angiogenesis or the process of new vessel formation occurs not only in solid tumors but also in hematological tumors, as noted by the increase in micro vessel density that was more predominant in PMF followed by PV and ET associated with vascular endothelial growth factor (VEGF) expression and in relation to JAK2 mutations[5,6].

Considerable overlap exists with myelodysplastic/ myeloproliferative diseases such as chronic myelomonocytic leukemia and chronic myelogenous leukemia which are usually accompanied with dysplastic and ineffective erythropoiesis and hence it may be difficult to differentiate some cases of ET from reactive disorders[7]. Chronic inflammation is the underlying disorder in myeloproliferative neoplasms (MPNs), which eventually leads to cancerous transformation with poor prognosis and this transformation may be due to acquisition of additional genetic abnormalities[8]. Reticulin fibrosis is associated with increased risk of myeloproliferative changes in ET/PV and in general, MPNs transformed into acute promyelocytic leukemia have very poor prognosis. Precise diagnosis therefore needs to be established according to the World Health Organization (WHO) guidelines and appropriate therapy instituted. An international panel of experts in hematology and hematopathology have proposed a revised criteria for diagnosis in 2007 and this was adopted by the WHO in 2008[9,10]. An integrated approach, including the histomorphological changes, genetic abnormalities and clinical criteria, is essential in the differentiation and management of MPNs.

GENETIC MUTATIONS

JAK2 is widely distributed in the somatic cells and is also involved in the immune system regulation in addition to the hematopoietic signal transduction. The discovery of a point mutation in the JAK2 gene provided the initial molecular basis[11]. JAK2 is an important member of the JAK family which is located on chromosome 9p24. Mutation occurs at base position 1849 in exon 14 and the homozygous G to T transversion results in valine substitution to phenylalanine at residue 617 (V617F)[12]. JAK2V617F mutation is the most common genetic defect associated with ET. PV and PMF also carry JAK2V617F mutation and these disorders together with ET constitute the Philadelphia negative (BCR-ABL1 negative) chronic MPNs according to the WHO classification[9,10,13,14].

JAK2V617F mutation leads to constitutive activation of the thrombopoietin signaling mechanisms leading to ET. Importantly, the burden of JAK2V617F mutation is relatively low in ET and PMF compared to PV, in which the mutational load is high and is almost always present. Nearly 90% - 95% cases of PV have the JAK2V617F mutation while it is only present in about 60% of ET and PMF cases. A small fraction of JAK2 negative patients (about 3% to 7% of ET/PMF) are due to point mutations of the thrombopoietin receptor (MPL) MPLW515L/K[15]. Somatic mutation in the calreticulin (CALR) gene that encodes for CALR are also found in ET or PMF patients who do not harbor either JAK2 or MPL mutations[16,17]. CALR mutations occur in 20% to 25% of MPSs and nearly 40 CALR mutations are reported, with Type I (52 bp deletion) and Type II (5 bp insertion) being the most common[18,19].

The involvement of other genes indicates the existence of many drivers in MPNs all acting via the JAK-STAT signal transduction mechanism. Some of the other genes implicated are ASXL1, TET2, CBL, IDH2, IDH2, EZH2, IKZF1 and LNK[20-26]. High throughput single cell sequencing of cancer genome led to the identification of 8 candidate genes (viz. SESN2, DNAJC17, ST13, TOP1MT, NTRK1, ABCB5, FRG1, and ASNS) as possible drivers of JAK2/MPL negative cases of ET[27]. Screening of SESN2, DNAJC17, ST13, TOP1MT that exhibited the highest score in a cohort of 64 patients diagnosed with ET, found none of the proposed candidate drivers, but led to the identification of a novel mutation in exon 11 of TOP1MT, establishing that this mutation is involved in low frequency in the pathogenesis of JAK2/MPL negative ET (*i.e.,* is recurrently mutated in ET)[28]. Another study, gene expression microarray studies of whole blood from 69 MPN patients, led to the identification of 5 upregulated genes, namely DEFA4, ELA2, OLFM4, CTSG, AZU1 in PMF. Interestingly, hierarchical clustering analysis showed most of these genes were also highly expressed in the transitional stages of ET and PV leading to PMF[29].

Inflammation leads to the production reactive oxygen species (ROS) and interestingly JAK2V617F mutation is associated with increased ROS production in the HSC niche. The Nrf2 gene, which is known to regulate stem cell function and has an anti-oxidant effect, is identified to be downregulated in MPNs[30,31]. All above studies clearly indicate that, apart from the common driver mutations

(JAK2/MPL/CALR), subclonal driver mutations in other genes, cytogenetic aberrations and epigenetic changes may influence disease progression in MPNs.

EPIGENETIC MODIFICATIONS AND ESSENTIAL THROMBOCYTHEMIA

In addition to the role of irreversible changes in the gene sequences viz. mutations, the reversible modifications which affect gene expression pattern, namely the epigenetic modifications viz DNA methylation/histone acetylation are well known to be associated with initiation and progression of various neoplasms. Epigenetic modifications, especially those of DNA methylations have been more identified with hematopoietic neoplasms such as acute leukemia and myelopdysplastic syndromes[32,33].

Epigenetic modifications, especially the DNA methylation, is evident only during the transformation to acute leukemia, while differential methylation pattern is not prevalently found in PMF, ET or PCV[34]. Minimal incidences of DNA methylation changes were evident in MPNs compared to control samples, but no differences were noted between ET, PCV or PMF[34,35]. Apart from playing a role in causation, these epigenetic modifications may also affect the response of a drug leading to incomplete suppression or eradication of the altered HSCs[36,37]. This was clearly evident in a subset of patients who continued to have TET2 clones while JAK2 mutant clones were eradicated following therapy with pegylated interferon alpha 2a (PEG-IFN-2αa)[38]. A long term follow up of 40 ET patients on phase 2 clinical trial with PEG-IFN-2αa demonstrated complete molecular remission of JAK2V617F mutations in 17% and complete hematologic responses in 77%[39]. Interestingly, those patients who failed to have complete molecular response to PEG-IFN-2αa therapy had higher frequency of mutations outside the JAK2-STAT signaling pathways, thereby suggesting the role of alternative players in the causation and therapeutic outcome of ET.

CLINICAL FEATURES

Many patients may remain asymptomatic and thus never be diagnosed with ET unless seen by a physician for an unrelated illness. Patients with ET are at increased risk for arterial and venous thromboembolic events. Arterial thromboses are reported 3 times more often than venous thromboses. Arterial ischemic complications occur in about 35% (Table 1).

CONCLUSIONS AND FUTURE PERSPECTIVES

Recent research has identified involvement of many new genes either in the causation or transformation of Philadelphia negative MPNs. It is essential to consider reactive disorder and chronic myeloid disorders before making a diagnosis of ET. Powerful technologies have contributed to allow accurate diagnosis in a cost-effective manner. Agents that target the aberrant JAK-STAT signaling such as the small molecule ruxolitinib (FDA approved), momelotinib (CYT387) have demonstrated good clinical efficacy. However, resolution of marrow fibrosis or molecular remissions has not been successful, indicating clonal hematopoiesis may continue to persist due to alternative disease alleles. Therefore additional clinical and molecular testing will be necessary to enable detection of the sensitivity/resistance as well as to allow development of more targeted therapies.

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كثرة الصفيحات الدموية:دراسة للجزيئات والعلاج الحالي

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مركز الملك فهد للبحوث الطبية والطب التجديدي، مركز التميز لبحوث الجينوم الطبية، و[٢]قسم أمراض الدم، و[٣] كرسي الشيخ سالم بن محفوظ لعلاج هشاشة العظام عن طريق الخلايا الجذعية بقسم جراحة العظام بكلية الطب جامعة الملك عبد العزيز، جدة - المملكة العربية السعودية

المستخلص.

تعتبر زيادة عدد الصفائح الدموية واحدة من اضطرابات التكاثر النقوي السلبي لكروموسوم فيلادلفيا وتنطوي على الخلايا الجذعية المكونة للدم. تسبب هذه المشكلة ظاهرة الإنصمام الخثاري، والتي قد تؤثر على متوسط العمر المتوقع ولقد لوحظت الطفرة الجينية Jake-2 في ٥٠ في المائة من حالات زيادة عدد الصفائح الدموية، في حين حوالي ١٠ في المائة توجد لديهم طفرات جينية في مستقبلات (MPLW515L/K) (MPL) وبعض الجينات الاخرى مثل كارتيكيلن (-CALR, Asxl1, TET2,CBL,IDH2,EZH2,IKZF1) وايضاً LNK. وهذا يدل بوضوح على وجود أسباب جينية اكثر شيوعا وأقل حدوثا، وتعتبر الطفرات الجينية مفيدة للكشف عن هذا المرض، كما أن وجود منهج متكامل للتشخيص يؤدي الى الدقة في تشخيص هذا المرض ووضع خطة واضحة ومتدرجة للعلاج. وإضافة لما سبق ، فإن مزيجا من مضادات الالتهاب قد تعكس او تمنع التليف.

مفاتيح الورقة العلمية:

زيادة عدد الصفائح الدموية، JAK2V617F MPLW515L/K Calreticulin الطفرات الجينية.