

Immunotherapy and essential thrombocythemia

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Abstract

The past few decades have witnessed significant advances in the understanding of the etiology, diagnosis and treatment of essential thrombocythemia (ET), but more detailed insights are required to understand the pathophysiologic mechanism of the disease in ET patients. Identification of the Janus kinase 2 (JAK2)-V617F and MPLW515 mutations in chronic myeloproliferative disorders (MPDs) has led to development of specific inhibitors for clinical use. However, to achieve better patient outcomes such as improved quality of life and for effective therapeutic decisions, possibilities of combining different immunotherapies should be explored.

Abbreviations: ADP: Adenosine Di Phosphate; AMP: Adenosine Mono Phosphate; CINF: Consensus Interferon; CMML: Chronic Myelomonocytic Leukemia; CYP1A2: Cytochrome P450 1A2; EPOR: Erythropoietin Receptor; ET: Essential Thrombocythemia; FDA: Food and Drug Administration; GCSFR: Granulocyte-Colony Stimulating Factor Receptor; IFN: Interferon; JAK: Janus Kinase; JAK-STAT: Janus kinase/signal transducers and activators of transcription; MMM: Myeloid Metaplasia; MPDs: Myeloproliferative disorders; MPL: Thrombopoietin Receptor; MPNs: Myeloproliferative Neoplasms; Pharmacokinetics and Pharmacodynamics (PD/PK); PV: Polycythemia Vera; QoL: Quality of Life.

Introduction/Epidemiology

Myeloproliferative disorders (MPDs) are classified according to the most affected type of blood cells. There are four main types of MPDs, namely, Polycythemia Vera (PV), Essential thrombocythemia (ET), Myeloid metaplasia (MMM), and Chronic myelomonocytic leukemia (CMML). Essential Thrombocythemia (ET) is a rare chronic blood disorder characterized by an increased number of platelets in circulating blood. The disease predominantly affects women and is commonly diagnosed in people aged 60 years and above [1,2]. Globally, studies demonstrate that the incidence rate (newly diagnosed cases) of ET among all races and ethnicities was approximately 2.2 cases per 100,000 person-years. Although, the disorder is mostly diagnosed in adults; occasionally it occurs in older children too. Worldwide estimates show that the prevalence rate (estimated number of people alive on a certain date in a population with a diagnosis of the disease) of ET is approximately 24 cases per 100,000 populations [3].

Etiology/predisposing factors [4-7]

The exact cause of chronic MPDs remains unclear; however, research suggests that the mutation of a particular gene known as Janus kinase 2 (JAK 2) is said to be found in a large proportion of people with MPDs. Although many factors play a key role in the risk of developing MPDs, according to published epidemiological studies the most important risk factors include: age, sex, cancer treatment and exposure to petrochemicals.

Age and sex

ET predominantly affects women and is commonly diagnosed in people ages 60 years and above. On the contrary, PV is more common in men than in women. The condition is rarely seen in people under the age of 40, but a few cases have been diagnosed among children. The risk of CMML increases with age. This disease is rare in those younger than 40, with most cases found in people aged 60 years and above. CMML is about twice as common in men as in women.

Cancer treatment

Prior treatment with chemotherapy seems to increase the risk of CMML. The risk of CMML after cancer chemotherapy, however, is not as high as the risk of other blood problems, such as myelodysplastic syndromes and acute myeloid leukemia.

Exposure to petrochemicals

Benzene and Toluene, and ionizing radiation increase the risk of MMM.

Pathophysiology/molecular basis of ET

JAK2-V617F mutations in ET

Several lines of evidence suggest that there may be differences in the quantitative and/or qualitative signaling by JAK2-V617F in the different myeloproliferative neoplasms (MPNs). First, homozygous JAK2-V617F mutations, which result from acquired uniparental disomy of the chromosomal region (9p24) (which includes JAK2), [8-12] are much more commonly seen in PV than in ET. JAK2-V617F homozygosity is a common pathogenetic event in PV, but not in ET,

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and suggests the possibility that the level of JAK2 activity (high in PV, low in ET) determines the MPN phenotype.

Data suggest that additional genetic and epigenetic factors, including germline modifiers [13] and epigenetic silencing of JAK-STAT pathway genes, contribute to MPN pathogenesis. It is also possible that additional somatic mutations, which remain to be identified, distinguish between JAK2-V617F-positive PV, ET and PMF, and play an important role in instructing the phenotype of JAK2-V617F-positive hematopoietic progenitors. The advent of highly thorough genomic and epigenomic techniques will facilitate investigation into the pathogenesis of ET and allow investigators to elucidate the molecular basis for differences in MPN phenotypes [14].

MPLW515 mutations in ET

A sequence analysis of the exons, encoding the transmembrane-juxtamembrane domains of the erythropoietin receptor (EPOR), the thrombopoietin receptor (MPL) and the granulocyte-colony stimulating factor receptor (GCSFR) led to the discovery of somatic mutations at codon 515 of MPL in JAK2-V617F-negative ET and myelofibrosis [15-17].

An analysis held by Beer and colleagues showed the PT-1 study cohort for MPL exon 10 mutations [18] and identified somatic MPL mutations in 4.1% of all ET patients, including 8.5% of JAK2-V617F-negative ET patients. Notably, this included patients with MPLW515L, MPLW515K and three patients with somatic MPLS505N mutations, which had previously been identified as a heritable disease allele in familial thrombocytosis [19]. Additionally, a screening by Vannucchi and colleagues on 994 ET patients for MPLW515L/K mutations identified MPL mutations in 3% of all ET patients, including 5% of JAK2-V617F-negative ET patients [20].

Although MPL mutations are identified only in a subset of JAK2-V617F-negative ET patients, the identification of mutations upstream of JAK2 in ET/PMF patients demonstrates that the activation of JAK-STAT signaling contributes to the pathogenesis of JAK2-V617F-positive and JAK2-V617F-negative ET. However, it remains to be seen whether there are additional mutations in the JAK2 pathway of JAK2/MPL-negative MPN. Moreover, a reduced STAT3 phosphorylation has been observed in JAK2-V617F-negative ET, [21] suggesting that alternate signaling pathways may be involved in the pathogenesis of this subset of ET.

Immunotherapy in ET

Phosphodiesterase inhibitors

Anagrelide (Agrylin) [22]: It is approved by the US Food and Drug Administration (FDA) for the treatment of ET. A synthetic quinazoline derivative, Anagrelide reduces platelet production through a decrease in the megakaryocyte maturation. Anagrelide inhibits cyclic adenosine monophosphate (AMP) phosphodiesterase, as well as adenosine diphosphate (ADP) and collagen-induced platelet aggregation. It does not influence white cell counts or coagulation parameters. Anagrelide is used for the treatment of ET to reduce elevated platelet counts and the risk of thrombosis.

Indication and uses: Anagrelide is a platelet reducing agent indicated for the treatment of thrombocythemia, secondary to MPNs, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms, including thrombo-hemorrhagic events.

Pharmacokinetics and pharmacodynamics (PD/PK): The dose proportionality was found to be in the dose range of 0.5 mg to 2.5 mg. The gastrointestinal tract absorbed 70% after oral administration, metabolized by Cytochrome P450 1A2 (CYP1A2) to the active metabolite, 3-hydroxy-anagrelide, which was subsequently metabolized by CYP1A2 to the inactive metabolite, RL603 and eliminated with plasma half-lives of approximately 1.5 hours.

Contraindications: None

Warning: Cardiovascular toxicity and risk of bleeding.

Adverse events: The most common adverse reactions are headache, palpitations, diarrhea, asthenia, edema, nausea, abdominal pain, dizziness, pain, dyspnea, cough, flatulence, vomiting, fever, peripheral edema, rash, chest pain, anorexia, tachycardia, malaise, paresthesia, back pain, pruritus and dyspepsia.

Cytokine therapy

Interferon α (IFN α) [23]: It is an analogue of consensus interferon, which contains an additional methionyl amino acid residue. Consensus interferon (also known as interferon alfacon-1, rCon-IFN and CIFN) is a genetically engineered synthetic interferon created from the most common amino acid sequences from the naturally occurring alpha interferons. Alpha interferons bind to specific cell-surface receptors, resulting in the transcription and translation of genes whose protein products have antiviral, antiproliferative, anticancer and immunomodulating effects.

Indication and uses: IFN α suppresses the proliferation of hematopoietic progenitors, has a direct inhibiting effect on bone marrow fibroblast progenitor cells, and antagonizes the action of platelet-derived growth factor, transforming growth factor- β and other cytokines that may be involved in the development of myelofibrosis.

PD/PK: The effectiveness in the induction therapy of patients with ET is demonstrated in 11 international studies, including 212 patients. The response rate was about 90% with an average dose of about 3 million IU IFN daily. Further, studies investigated the practicability and the success of IFN maintenance therapy, which show that IFN can effectively control platelet counts over a period of several years.

Contraindications: IFN is contraindicated in the patients with thyroid and/or mental disorders.

Adverse events: The most common adverse effects associated with IFN are weakness, myalgia, weight and hair loss, severe depression, and gastrointestinal and cardiovascular symptoms.

Kinase inhibitors

Momelotinib (non-FDA approved drug) [24]: It is an orally bioavailable small-molecule inhibitor of Janus kinases 1 and 2 (JAK1/2) with potential antineoplastic activity. Momelotinib competes with JAK1/2 for ATP binding, which may inhibit the JAK1/2 activation and the JAK-STAT signaling pathway. So, there is an induction of apoptosis and tumor cell proliferation in JAK1/2-expressing tumor cells is reduced.

Indication and uses: Essential thrombocythaemia; Myelofibrosis; Myeloproliferative disorders; Pancreatic cancer; Polycythaemia vera.

Table 1. Non-FDA Approved kinase inhibitors.

	Clinical trial identifier no.	Phase	Study Design	Target
Momelotinib	NCT01998828	Phase II	Randomized, Safety/Efficacy study, open label	JAK1/2

Conclusion

The success rate in treating hematological malignancies is increasing and advancing day-by-day with the enhancing knowledge on the function of the immune system. The identification of the JAK2-V617F mutations in chronic MPDs has stimulated a great deal of effort in screening and developing specific inhibitors for clinical use. It is certain that the next few years will bring further developments in this fast-evolving field. Researchers are still challenged when exploring innate and adaptive immune systems. Immunotherapy is a promising development in the field of cancer. The recent activities have increased our understanding of the tumor microenvironment, various immunotherapeutic modalities or combination therapies (like chemotherapy with immunotherapy). The effects of such modalities in combination with immunotherapy in cancer patients are still in the exploratory phase. The complete perspective of immunotherapy treatment has not been realized and/or utilized. Proper preclinical and clinical designs are the important pillars in understanding the future of immunotherapy in treating cancer patients.

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