The Targets of Therapy in Polycythemia Vera and Thrombocythemia

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The most common myeloproliferative disorders (MPDs) include Polycythemia Vera (PV), Essential Thrombocythemia (ET) and Idiopathic Myelofibrosis (IMF).These are clonal diseases resulting from a transformation of a multipotent hematopoietic stem cell that leads to overactive hemopoiesis and bone marrow fibrosis. The clinical course of PV and ET is marked by significant thrombotic complications and a variable risk to evolve into acute myeloid leukemia. Polycythemia vera (PV) and Essential Thrombocythemia (ET) are Chronic myeloproliferative disorders (MPDs) in which morbidity and mortality are more frequently due to thrombohemorragic diathesis and a variable incidence of progression to myelofibrosis (MF) or acute leukemia.

Randomized clinical trials performed in USA and Europe have shown that cytoreductive treatment of blood hyperviscosity, chemotherapy and low-dose aspirin have dramatically reduced the number of thrombo-hemorrhagic episodes and substantially improved survival. However, there is a concern that certain myelosuppressive drugs accelerate the disease progression to acute leukemia. Thus, to minimize this risk, the best strategy in PV and ET is to limit the cytotoxic drugs to patients stratified on the basis of their risk for developing vascular events. The important risk factors are an age of 60 years or more and previous vascular events whereas hemorrhagic complications are paradoxically associated with extreme thrombocytosis.

As compared to PV and ET, IMF has the worst prognosis with a median survival or 3-5 years. A prognostic score system was developed where the presence of leukocytosis, leukopenia or anemia was used to identify three groups of patients with different survival, from 1 to 8 years. Conventional therapy in this disease is palliative and includes many drugs in addition to supportive therapy to improve anemia, thrombocytopenia and progressive splenomegaly. Recently, an experimental approach with hemopoietic stem cell transplantation after a reduced intensity conditioning regimen is offered in the younger patients and the results seem promising.

A new avenue for the treatment of MPDs was opned by the recent identification of an acquired mutation of the JAK2 gene (V617F) in 90% of patients with PV and in about half the patients with ET and IMF. The consequence of this mutation is a constitutive tyrosin kinase activity of JAK2 resulting in proliferative and survival advantage of hematopoietic progenitor cells. This finding is being explored in terms of diagnosis, prognosis and therapy. The mutational status and the allele burden in granulocytes have been correlated with survival, specific disease symptoms and the evolution towards leukemia. The results on its prognostic value are so far inconclusive and do not provide new stratification for therapy. Novel JAK2 inhibitors are being developed and promising results have been obtained with some of these compounds. In this context, it should be mentioned that JAK2V617F is not an essential pathogenetic component for MPDs other than PV and might not be the initial clonogenic event. There are data to admit that other mutations may cooperate to determine the phenotype. Thus, these drugs should be tested in all MPDs and not limited to those with JAK2 mutation. The inclusion criteria for phase II studies should consider high risk patients with poor survival and those with myelofibrosis (primary or secondary to PV or ET) should be the first candidates for testing these experimental drugs.