CORRESPONDENCE

Essential Thrombocythemia – Clinical Significance, Diagnosis and Treatment

by Prof. Dr. med. Martin Griesshammer, PD Dr. med. Eva Lengfelder, Prof. Dr. med. Konstanze Döhner, PD Dr. med. Hans Michael Kvasnicka, Prof. Dr. med. Jürgen Thiele, Prof. Dr. med. Hermann Heimpel, in volume 34–35/2007

Increased Myelofibroses

I would like to make the following comments on the outstanding review article of Prof. Griesshammer et al.: to my knowledge, a bone marrow biopsy is not absolutely necessary to diagnose essential thrombocythemia (diagnosis by exclusion sufficient). Moreover, the positive detection of JAK2^{V617F} mutation in half of the patients would rule out reactive thrombocytosis. In the article, I can find no reference to the fact that in a study of Harrison an increased number of myelofibrosis cases occurred after anagrelide therapy. Finally, one question: how can it be explained that the risk of thromboembolism is not increased in secondary thrombocytoses especially since it is still accepted practice to give aspirin in these cases?

DOI: 10.3238/arztebl.2008.0071a

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Tyrosine Kinase Mutation

Although you explain the JAK2^{V617F} tyrosine kinase mutation in your very good article, you do not mention at all the possibility of tyrosine kinase inhibition, as seen for example with imatinib administration in CML. Are there really no new therapeutic strategies for essential thrombocythemia in this area?

DOI: 10.3238/arztebl.2008.0071b

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Mutations in Familial Thrombocythemias

Familial, in most cases autosomal dominant, but also recessive or rarely X-chromosomally inherited forms of essential thrombocythemia (ET) should be recognized and classified as a further, rather heterogeneous entity. Within this group of ET, mutations in the thrombopoietin (Tpo) gene locus, typically in the 5' untranslated region, were identified in a series of patients. These mutations lead to increased translation efficiency of Tpo mRNA and thus to overproduction of Tpo (1). Hematocrit and white blood count are characteristically normal.

Familial thrombocythemias can also be due to mutations in the Tpo receptor (TpoR/c-Mpl). Mutations in the transmembrane domain of TpoR are associated with increased activation of intracellular signal pathways (2).

In contrast, mutations in the extracellular binding domain of TpoR lead to disturbed regulation of Tpo concentrations in plasma. The reduced absorption of Tpo to mutated Tpo receptors on the platelets results in increased circulating Tpo concentrations and causes overstimulation of megakaryopoiesis (3).

However, Tpo or TpoR mutations can be ruled out in more than half of familial thrombocythemias, and therefore other factors must be of pathophysiological relevance. In children and adolescents with familial forms of ET platelet counts are lower (< 1500/nL) than in non-familial forms. Splenomegaly and thrombotic or hemorrhagic complications are very rare. Treatment is only considered for such complications, with preference increasingly being given to anagrelide for the reasons described by Griesshammer et al.

DOI: 10.3238/arztebl.2008.0071c

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Pipobroman Gets Regulatory Approval Outside Germany

Regarding the etiology and pathogenesis of essential thrombocythemia (ET), the authors refer to the fact that clonality analyses only allow the detection of clonal hematopoiesis in about two thirds of all patients. This finding is obtained by detection of the JAK2^{V617F} mutation, which is itself also a marker of clonality, in about 50% of patients. This heterogeneity of ET gives rise to the question whether patients with polyclonal ET are also stratified in terms of risk and hence require medicinal therapy (1).

Polymorphism of the thrombopoietin receptor (Mpl) has been described as one and certainly a rare cause of essential thrombocytosis (2). How would the authors treat such a patient? The tabulated overview of the various therapies for ET raises the question as to which modality is capable of eradicating this cell clone in the presence of the JAK2^{V617F} mutation? In this context, the literature citation offers the possibility of evaluating

pipobroman, which is approved and available – e.g., in Italy and France – for the management of polycythemia and ET. Long-term data on the leukemogenic risk of pipobroman in ET are available and have not shown any increased risk of leukemia in ET (3).

Finally, it should be mentioned that research has already been commenced into the function of platelets and their disorders using proteomic methodologies as a valuable means of further elucidating and describing the genetic changes observed in ET.

DOI: 10.3238/arztebl.2008.0071d

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In Reply:

Prof. Dr. C. Dame reports on the also relevant familial forms of essential thrombocythemia which we have not mentioned for reasons of space. These forms are naturally also to be included in the differential diagnosis.

Dr. Tsamaloukas asks the justified question whether patients with polyclonal ET or polymorphism of the thrombopoietin receptor should be treated differently. Although there is evidence that these patients have a different risk constellation, these constellations have not been included in the risk stratification, with the result that the patients concerned are not treated differently (1). The second question as to which therapeutic modality is capable of reducing the JAK2 mutated clone was answered in a recent publication. However, a reduction of the JAK2 mutated clone is described here only for pegylated interferon-alpha-2a, and only in polycythemia vera (PV) (2). But the molecular response rates do not even approach the magnitudes observed for, e.g., imatinib in CML.

The most recently published WHO criteria also state that bone marrow biopsy is essential for diagnosis of ET (3). Dr. Andreas is right, however, when he says that the conventional PVSG criteria do not state that bone marrow biopsy is mandatory for ET. Making a diagnosis based on the PVSG criteria, however, has the disadvantage that early onset forms of primary myelofibrosis (PMF) or polycythemia (PV) are frequently overlooked and are often erroneously classified as ET. The study of Harrison et al. did indeed describe an increased incidence of myelofibroses after anagrelide therapy. In this connection it should be mentioned that the patient sample in the MRC-PT1 study was a heterogeneous population which was diagnosed not according to the

WHO criteria but the PVSG criteria. Follow-up investigations, for example, showed that a majority of these patients had early-onset forms of primary myelofibrosis (PMF) and not ETs. Furthermore, no sequential biopsies were available for most of the patients, and therefore follow up information is limited. The conventional practice of administering aspirin in secondary thrombocytosis is not substantiated with data. An elevated risk of thrombosis is only actually present in individual cases of secondary thrombocytosis (for example with additional malignancies and/or major surgery) (4).

Since ET has a very good prognosis, experimental therapy with JAK2 inhibitors is without primary value in this context. As Dr. Stern rightly inquires, however, these agents are now being used in initial phase I studies in primary myelofibrosis (PMF) and polycythemia vera (PV) after conventional therapy has failed.

DOI: 10.3238/arztebl.2008.0072

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Conflict of interest statement

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