THE INCIDENCE OF THROMBOHAEMORRHAGIC EVENTS IN ESSENTIAL THROMBOCYTEMIA. ROLE OF TREATMENT WITH ANAGRELIDE

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Background: Essential thrombocythemia (ET) is a myeloproliferative disorder characterized by persistent thrombocytosis. It is classified among the myeloproliferative disorders (MPDs) along with Polycythemia Vera, chronic idiopathic myelofibrosis, chronic myelogenous leukemia and chronic neutrophilic leukemia ,chronic eosinophilic leukemia and unclassified chronic MPD.

The recent discovery of JAK2-V617F mutation is a major break-through in understanding the molecular pathogenesis of the MPDs.

Despite decades of clinical and laboratory research, relatively little has been accomplished concerning the pathogenesis as well as the identification of risk factors for thrombosis and bleeding in myeloproliferative disorders. In polycythemia vera, the pro-thrombotic effect of an elevated haematocrit is well established. In contrast, thrombocytosis per se has not been similarly incriminated in essential thrombocythemia. In both conditions, advanced age and the presence of a prior event identify thrombosis-prone patients. A substantial minority of affected patients display reduced levels of high molecular weight von Willebrand protein in the plasma during extreme thrombocytosis and it is believed that this might explain the bleeding diathesis of such patients.

Anagrelide is the latest addition to the therapeutic arsenal in platelet lowering therapy in myeloproliferative disorders especially in essential thrombocythemia (ET). Anagrelide selectively reduces the production of platelets by inhibiting megakaryopoiesis. Its efficacy is about a 70% in ET and the response is rapid (in a few weeks).

Aim of the study: the incidence of thrombo-haemorrhagic events at 45 patients with ET in a hemato-oncological center of Timisoara over a period of 3 years and to determine the efficacy and long-term safety of anagrelide.

Methods: We included 45 patients with ET, 24 men and 21 women, with a median age of 39 years. Splenomegaly was present in (16,2%) patients and fibrosis in (22,3%) . The positive diagnosis is sustained by WHO criteria for ET:
-sustained platelets count>450x109/l
-bone marrow biopsy
-demonstration of JAK2- V617F.

45% of patients received a prior treatment with one of two cytostatic agents and 55% received as a first line anagrelide.

Results: The most important thrombo-hemorrahagic events were: splenic thrombosis - 10,01%, cerebral thrombosis – 33,06%, pulmonary thrombosis - 5,21%, portal vein thrombosis – 2,32%, peripheral thrombosis – 9%, cutaneous bleeding – 6,10%, mucosal bleeding – 4%, upper gastrointestinal bleeding – 0,71% At 85 % of the patients treated with anagrelide platelet levels fall below <450x109/l. 25% developed toxic side effects as tachycardia. In the first two weeks of treatment 33% of the patients suffered from nausea and vomiting.

Conclusions: Thrombosis in ET occurs in arterial, venous or microcirculatory locations. In general, arterial events predominate over venous events. Of importance, patients with ET have an unusually high rate of intra-abdominal (portal and hepatic) vein thrombosis and together account for a substantial proportion of identifiable causes of these potentially catastrophic events. Interestingly, young patients appear to be particularly vulnerable to this complication. There is increasing evidence to suggest an additional role by leucocytes that might partly explain the antithrombotic effects of myelosuppressive therapy. Complete remission (defined as a platelet count<400x109/l in symptomatic patients and 600x109/l in asymptomatic patients) was maintained in 75% of patients still treated with anagrelide. Long term efficacy was good, tolerance and safety were satisfactory and the cardiac toxicity was low.No thrombohemorrhagic events after introduction of Anagrelide in treatment of patients.