To the editor:

Efficacy and safety of long-term use of hydroxyurea in young patients with essential thrombocythemia and a high risk of thrombosis

The optimal treatment of young patients with essential thrombocythemia (ET) at high risk of thrombohemorrhagic complications is uncertain. Storen and Tefferi[1] recently reported on the long-term use of anagrelide, a platelet-lowering agent without myelosuppressive activity. In a population of 35 young ET patients (median age, 38 years; range, 17-48 years) followed for a median of 10.8 years (range, 7-15 years), rates of 20% for thrombosis, 20% for major bleeding, and 24% for anemia were observed. Hydroxyurea (HU) may be a more effective agent, because a significant reduction in the incidence of thrombotic complications was demonstrated in a randomized clinical trial including ET patients of all ages.[2] However, long-term exposure to this agent may increase the rate of leukemic transformation, and it is presently unknown how this benefit-risk ratio applies to younger patients.

To address this issue, we examined a consecutive cohort of 25 ET patients aged younger than 50 years (median age, 42 years; range, 18-49 years) who started on HU therapy before January 1, 1997, and were previously untreated. Hydroxyurea was given for platelet count persistently higher than $1\,500 \times 10^9$/L (12 cases; 48%) or the occurrence of a major vascular event, such as ischemic stroke (5 cases), myocardial infarction (3 cases), portal vein thrombosis (2 cases), peripheral arterial thrombosis (2 cases), or pulmonary embolism (1 case). Patients with thrombosis were given standard antithrombotic prophylaxis with aspirin (100 mg/d) if arterial, or warfarin to a target international normalized ratio of 2.5 if venous. No cytoreductive drugs other than HU were used. The median platelet count at the start of HU was 933×10^9/L (range, 426-3 200×10^9/L). The aim of therapy was to maintain platelet count less than 600×10^9/L, or less than 400×10^9/L in those patients who had thrombosis with platelet count between 400 and 600×10^9/L. Patients were checked every 3 months, or more frequently if indicated, and, at the last control, the target range of platelet counts was achieved in 20 patients (80%) (median, 450×10^9/L; range, $312\text{-}698 \times 10^9$/L). After 8 years median follow-up (range, 5-14 years), no patient had to withdraw the drug for intolerance or adverse effects. One case (4%) of transient ischemic attack but no major thrombosis or severe bleeding was recorded. Most important, no case of leukemic or neoplastic transformation or death occurred.

This indirect comparison of long-term cohort studies suggests that HU is more effective than anagrelide in preventing thrombosis in the young, apparently without an increase in leukemic risk. There are theoretic reasons to support the superiority of HU as an antithrombotic drug, besides its platelet-lowering effect. As a general myelosuppressive agent, HU also affects polymorphonuclear leukocytes (PMNs) and red blood cells counts, and there is growing evidence in the literature that these cells play a major role in the pathogenesis of thrombosis, also in ET patients.[3] Further data come from the widespread use of HU in children with sickle cell disease to reduce the frequency of vaso-occlusive events. Recent works indicate that the clinical efficacy of the drug in this setting is related to the correction of abnormal interactions between PMNs and vascular endothelium, thus preventing reduced blood flow, microvascular occlusion, and vascular damage.[4] Interestingly, after more than 10 years of use, no leukemia has been related to HU treatment in these children.

Randomized clinical trials are needed to accurately compare the efficacy and toxicity of platelet-lowering agents in ET. However, it is foreseen that these studies will give reliable information mainly on short-term clinical end points, such as drug toxicity and early vascular complications. Long-term outcomes, such as leukemogenesis, can hardly be evaluated in randomized trials and remain to be investigated in appropriate cohort studies such as those reported herein. To date, our long-term results support the use of HU also for younger patients with ET, if they carry a high risk of life-threatening thrombohemorrhagic complications due to a previous thrombotic history or persistent very high platelet count.

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To the editor:

The transcobalamin codon 259 polymorphism should be designated 776C>G, not 775G>C

We read with great interest the recent article by Miller et al[1] that examined the transcobalamin (TC) genetic polymorphism encoding proline or arginine at codon 259 in the *TC* gene (Pro259Arg) and its possible influence on indices of vitamin B12 status in healthy older adults. Based on serum levels of holoTC (the B12-TC complex) that were significantly higher in individuals who were