

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Harrison CN, Campbell PJ, Buck G, et al. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. *N Engl J Med* 2005;353:33-45.

Criteria For the Diagnosis of Essential Thrombocythemia:

Platelet count $>600 \times 10^9/L$ on two occasions at least two months apart, and absence of overt polycythemia or polycythemia masked by co-existent iron deficiency.

Exclusions:

Patients were ineligible if they had the t(9;22) translocation or *BCR-ABL* fusion gene, haematological signs of myelodysplasia or myelofibrosis, and known causes of reactive thrombocytosis. Patients were also excluded if they had breathlessness or cardiac pain at rest or on minimal exertion, a myocardial infarction within the previous three months; severe congestive heart failure; severe ventricular arrhythmia; pregnancy or lactation; or leg ulceration.

Diagnostic Criteria

Myocardial infarction was defined by standard clinical and laboratory criteria.

Unstable angina was defined in accordance with the Thrombolysis in

Myocardial Infarction group criteria (18). Stroke was defined as a new focal neurological defect of presumed vascular origin persisting for >24 hours or ending in death within 24 hours, confirmed by computed tomography (CT) or magnetic resonance imaging of the brain. Transient ischemic attack was defined using the criteria of Landolfi et al (19). A diagnosis of deep vein thrombosis required typical clinical features with a definitive radiological investigation.

Pulmonary embolism required relevant clinical findings plus either a high-probability ventilation-perfusion scan or positive CT pulmonary angiogram. Other thrombotic or embolic events were diagnosed in patients with typical clinical syndromes together with unequivocal radiological or histological evidence of thrombosis. Major hemorrhage was defined as an intracranial or retroperitoneal bleed, overt hemorrhage associated with a decrease in hemoglobin $\geq 20\text{g/l}$ or overt hemorrhage requiring a blood transfusion of two units or more. Deaths were included as a death from thrombosis or hemorrhage if they satisfied criteria for one of the above diagnoses immediately ante-mortem, or if they had a post-mortem examination confirming the diagnosis. Sudden death of presumed vascular origin without a post-mortem examination was included as a thrombotic death.

Myelofibrotic Transformation

The definition of myelofibrotic transformation of essential thrombocythemia was a modification of the Italian criteria for primary idiopathic myelofibrosis (20). The diagnosis required at least grade 3 reticulin fibrosis in a bone marrow biopsy (21) (with an increase by at least one grade from presentation or trial entry biopsy, available in 12 of the 21 confirmed cases, 10 and 2 in the anagrelide and hydroxyurea groups respectively) together with at least two of the following: increase in spleen size of at least 3 cm; unexplained decrease in

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hemoglobin by $\geq 20\text{g/l}$; immature myeloid or erythroid cells in the blood smear; tear-drop poikilocytes in the blood smear; or B symptoms (night sweats, bone pain, or weight loss of more than 10% in six months). Standard criteria were used to define transformation to acute myeloid leukemia (22), myelodysplasia (23) and polycythemia vera (24).

Composite Endpoint:

Myocardial infarction, unstable angina, stroke, transient ischemic attack, peripheral arterial thrombosis, splanchnic or limb deep vein thrombosis, or pulmonary embolism.

Conduct of the Trial

The trial was conceived, conducted and analyzed by the investigators on behalf of the UK Myeloproliferative Disorders Study Group and the MRC Adult Leukaemia Working Party. It was conducted under standard MRC clinical governance arrangements (the coordinators reported to the MRC Leukemia Trial Steering Committee with an independent MRC Data and Ethics Monitoring Committee). The Shire Pharmaceuticals Company, manufacturers of anagrelide donated the drug but were otherwise not involved in the design, running, or reporting of the trial. Data collection and analysis were performed by the MRC Clinical Trial Service Unit. The coordinators wrote the paper and had complete control over the data.