

[6] The Medical Research Council PT1 Trial in Essential Thrombocythemia. Session Type: Plenary Session

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Essential thrombocythemia (ET) is associated with arterial and venous thrombosis, hemorrhage and transformation to acute leukemia and myelofibrosis. Cytoreduction with hydroxyurea (Hu) reduces thrombotic risk, but concerns about potential toxicity have led to the widespread use of a newer agent, anagrelide (Ag) as first-line therapy. However, no randomized trials comparing the efficacy and safety of Ag with Hu have been performed.

The MRC PT1 trial is an international, multi-centre, randomized controlled trial comparing Ag with Hu in patients with ET at high-risk of vascular events (based on age, platelet count or cardiovascular risk factors). The trial was independently conceived, conducted and analysed by the investigators on behalf of the UK Myeloproliferative Disorders Study Group and the MRC Adult Leukaemia Working Party. Patients (newly diagnosed or previously treated) were randomized to receive either Ag plus aspirin (Ag+asp) or Hu+asp. Clinical end-points together with blood and bone marrow morphology were assessed centrally by experts blinded to treatment allocation. With 809 patients randomized and median follow-up of 39 months, it is the largest and most comprehensive randomized study of ET performed to date.

Patients in the Ag+asp arm were significantly more likely to reach the primary end-point and several secondary end-points. Intention-to-treat log-rank analyses of time to event indicate that Ag+asp patients were significantly more likely than Hu+asp patients to reach the composite primary end-point of arterial thrombosis, venous thrombosis or major hemorrhage (55 v 36 events; odds ratio 1.57; 95% CI 1.04-2.37; $p=0.03$). Ag+asp was also associated with increased rates of arterial thrombosis (37 v 17 events; OR 2.16; 95% CI 1.27-3.69; $p=0.004$) and major hemorrhage (22 v 8 events; OR 2.61; CI 1.27-5.33; $p=0.008$) but, interestingly, decreased venous thrombosis compared to Hu+asp (3 v 14 events; OR 0.27; CI 0.11-0.71; $p=0.006$). Myelofibrotic transformation, the diagnosis of which required new clinical and/or laboratory features in addition to grade III/IV reticulin fibrosis, was significantly increased in the Ag+asp arm (16 v 5 events; OR 2.92, CI 1.24-6.86, $p=0.01$).

Transformation to MDS/AML was comparable between the two arms (4 Ag+asp v 6 Hu+asp), although the small number of transformations and short follow-up prevent firm conclusions about leukemogenicity. Overall survival was not statistically different. Ag+asp was more poorly tolerated than Hu+asp. In the Ag+asp arm significantly fewer patients remained on their allocated treatment ($p<0.00001$) and there were significantly greater rates of cardiovascular ($p<0.0001$), gastrointestinal ($p=0.02$), neurological ($p<0.0001$) and constitutional ($p<0.001$) side effects. Long-term control of the platelet count was comparable between the two arms.

These results demonstrate that, compared to Hu+asp, Ag+asp is associated with an excess rate of arterial thrombosis, major hemorrhage and myelofibrotic transformation but decreased venous

thrombosis, and suggest that Hu should remain first-line therapy in patients with ET at high risk for vascular events.

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Plenary Session (1:30 PM-4:00 PM)