Platelet Increases Hold Fast

By Ruben Mesa, MD

Intravenous immunoglobulin, accessory splenectomy, high-dose steroids, androgens, and immunosuppression — these were the recommendations made by the ASH ITP practice guidelines for adult patients with refractory ITP *(George, et al. Blood, 1996)*. Since those guidelines were published more than a decade ago, rituximab and several newer immunosuppressive medications have been added to the roster of treatments for refractory ITP. Unfortunately, these therapies are all frequently ineffective. The Plenary Session yesterday highlighted a new therapeutic option for ITP, and potentially for other thrombocytopenic disorders.

Dr. Terry Gernsheimer, the principal investigator, presented the abstract titled "Evaluation of AMG 531 Efficacy in Splenectomized Patients with Chronic Immune Thrombocytopenic Purpura (ITP) in a Randomized Placebo Controlled Phase 3 Study." This trial examined the efficacy of the thrombopoietin receptor (TPO-R) agonist AMG 531 in patients with refractory ITP. In this multi-center, international phase III trial, 63 previously splenectomized ITP patients were randomized in a blinded fashion to receive either placebo or subcutaneously administered AMG 531. Patients were allowed to be enrolled with stable doses of other ITP therapies (i.e. corticosteroids or androgens). Responses were observed in 78 percent of the patients receiving AMG 531, and 38 percent had a durable response (platelets $>50 \times 10^9/L$ for ≥ 6 of the last 8 weeks without need for a rescue therapy). There were no responses in the placebo group. All patients in the treatment group were able to decrease or stop their other ITP medications. The drug appeared well tolerated, but one patient experienced thrombosis and one developed increased reticulin in the bone marrow.

AMG 531 is a "second generation" TPO-receptor agonist, explained Dr. James Bussel in the ASH Education Session on Platelet Disorders over this past weekend, and as published in his recent study of the agent in non-splenectomized ITP (*NEJM 2007;357:2237)*. Dr. Bussel described the evolution of thrombopoietin from the early recombinant analogs (which ceased clinical development due to development of anti-TPO auto-antibodies), to the current second generation of TPO-R agonists, which include AMG 531, eltrombopag, and AKR501. The rationale for investigating these agents in an autoimmune destructive thrombocytopenia, such as ITP, is the recent evidence suggesting inadequate TPO levels in ITP patients, explained Dr. Bussel. Initial phase I/II clinical trials of AMG 531 were successful in improving the most refractory ITP cases.

In addition to Dr. Gernsheimer's study results, at today's simultaneous session on Novel Therapy for ITP from 1:30 to 3:30 p.m., several clinical updates on the TPO-R agonists will be presented. Dr. David Kuter will present data from a placebo-controlled AMG 531 trial (Abstract #2660) carried out in non-splenectomized ITP patients (steroid failures or dependent), where significant platelet improvements were seen. Additionally, two abstracts (#5259 and #4633) will provide data on the long-term safety profile of eltrombopag and AMG 531, respectively.

The clinical consequences of severe thrombocytopenia are significant and extend well beyond ITP, as recently shown in the treatment of thrombocytopenia by eltrombopag in hepatitis C cirrhosis by Hutchison et al. (*NEJM, 2007;357:2227)*. These exciting developments regarding TPO-R agonists in ITP may ultimately be extended to other challenging clinical scenarios, such as improving platelet recovery times after induction chemotherapy for leukemia or after stem cell transplantation, and in treating patients with myelodysplastic syndrome who are platelet transfusion-dependent.