

# Novel Thrombopoietic Agents: Preliminary Activity, Potential Benefit

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**S**upportive care for patients undergoing cancer therapy has become a much more varied entity over the past 10 years. The results of clinical trials of erythropoiesis-stimulating agents and colony-stimulating factors have changed the way we manage chemotherapy-induced anemia and neutropenia, and more recently, keratinocyte growth factor and other agents for mucositis have been the focus of clinical investigations as well. No agent is a panacea, but all of them have at least some role in certain patient populations being treated with chemotherapy.

Unfortunately, the progress with cytokines in the management of chemotherapy-induced thrombocytopenia has not yet paralleled that in the treatment of anemia and neutropenia. At this time, the licensed thrombopoietic growth factor interleukin-11 (IL-11; oprelvekin [Neumega]), which is indicated only for the treatment of thrombocytopenia, appears to have limited activity and tolerability in the prevention of chemotherapy-induced thrombocytopenia. Ongoing clinical trials investigating an assortment of thrombopoietic agents, primarily in the management of hematologic diseases such as idiopathic thrombocytopenic purpura (ITP) and myelodysplastic syndrome (MDS) rather than chemotherapy-induced thrombocytopenia, have produced promising preliminary results.

## Novel Agents Making Their Mark

In the treatment of thrombocytopenia associated with the relatively uncommon yet serious ITP, which is characterized by the production of autoantibodies that target platelets and megakaryocytes, encouraging data have been obtained with investigative agents such as AMG 531 and eltrombopag. Patients with ITP not only suffer from increased platelet clearance and inadequate

platelet production; they also experience quality-of-life (QOL) difficulties, such as fatigue, and tend to have lower QOL scores on various health-related measures than does the general population. Ideally, the treatment options that would benefit these patients would work not only to reduce the bleeding risk but also to alleviate symptoms that can complicate the course of ITP.

AMG 531, a novel thrombopoiesis-stimulating peptibody that targets the thrombopoietic receptor, is the only thrombopoietic agent for which long-term use has been reported in patients with ITP or any form of thrombocytopenia. Unlike most other treatments of ITP, which interfere with platelet destruction, AMG 531 increases the production of platelets at a rate that outpaces their destruction by the immune system. Used subcutaneously on a weekly basis, AMG 531 effectively increased platelet counts without causing significant adverse events (Kuter et al, page 78). In most patients, it was generally well tolerated on the long term and permitted concurrent steroid therapy to be decreased or discontinued. According to the researchers, the study now includes 2 years of follow-up data, and the interim results at 48 weeks are promising. Furthermore, in the first reported use of the ITP Patient Assessment Questionnaire to measure treatment effects on health-related QOL, durable platelet responders to AMG 531 showed greater improvement in all 10 scales (encompassing physical and emotional health as well as overall QOL) than did nondurable responders (George et al, page 70). The team concluded that individualized dosing with AMG 531 provides a uniquely effective therapeutic option for managing patients with chronic ITP while improving health-related QOL.

In a retrospective study intending to better describe the background setting of patients with ITP, Mufti et al (page 80) quantitated the amount of reticulin in the bone marrow of patients with ITP. Of the 40 patients evaluated, reticulin was present in the bone marrow of approximately two-thirds of patients, with 15% having greater than grade

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## Novel Thrombopoietic Agents

1 but only 5% having as much as grade 2. Several patients treated with AMG 531 long term developed reversible reticulin fibrosis. It was not clear how many of them might have had bone marrow reticulin present before receiving AMG 531, since bone marrow studies were not performed before and after treatment.

Findings with two oral thrombopoietic receptor agonists also were presented. In the largest randomized, double-blind, placebo-controlled trial ever conducted in patients with ITP, eltrombopag, which stimulates the proliferation and differentiation of megakaryocytes and progenitor cells and ultimately increases the number of circulating platelets, yielded encouraging efficacy and safety results when used for 6 weeks (Bussel et al, page 66). Doses of 50 and 75 mg were both effective in increasing platelet counts and in reducing bleeding. This study was stopped prematurely with 117 patients enrolled due to the efficacy outcomes already observed at the first interim analysis. Very preliminary analysis of a second randomized study supported the findings of the first. With apparently no significant toxicity or tolerability issues reported among over 100 patients in each study, eltrombopag seems poised to take a major stride in the advancement of ITP treatment.

In a phase I trial in healthy volunteers, AKR-501 appeared to be well tolerated, potent, and safe, inducing increases in platelet counts at the 10-mg dose that continued to rise on a dose-dependent basis (Desjardins et al, page 68). The investigators indicated that the drug was well tolerated in both single- and multiple-dose studies, with no serious adverse events reported at any dose. Although this promising agent has only been evaluated in normal volunteers thus far, phase II studies in patients with ITP are planned.

### Unresolved Issues

A noninvasive alternative to splenectomy for adults with chronic ITP is being investigated in a multicenter phase II study. Confirming previous study findings with rituximab (Rituxan) regarding response and toxicity rates, Godeau and colleagues (page 72) found this immunosuppressive agent to be a safe, splenectomy-sparing option, leading to a significant, durable response in 40% of the 60 patients assessed. Initial response correlated significantly with long-term response among the 36 responders.

In a complementary study of rituximab for ITP, the first to evaluate long-term follow-up (more than 1 year), long-lasting benefits were revealed (Patel et al, page 82). Approximately one third of rituximab-treated patients with ITP had a response that lasted at least 1 year. After further follow-up in the current study, two thirds of these responders had lasting responses. The duration of response did not appear to be related to age, gender, time to a platelet count  $> 30 \times 10^9/L$ , or splenectomy status. Indefinite duration responses would be estimated to occur in approximately 20% of patients who started rituximab therapy for ITP. The investigators added that patients who are likely to relapse will do so within the first 2.5 years of treatment, whereas those who do not will have a duration of response 5.5 years or more. However, no clinical variables predict which patients whose response continues past 1 year will remain in remission.

Since there are no reliable data regarding the frequency and clinical consequences of thrombocytopenia in patients with MDS and little agreement as to its optimal treatment, thrombopoietic agents may come to play an important role in managing MDS as well as ITP. Thrombocytopenia and platelet dysfunction contribute to the hemorrhagic complications observed in MDS. According to a systematic review of MDS literature published between 1980 and 2005, thrombocytopenia seems to be more common among patients with MDS than previously thought (Kantarjian et al, page 74). Studies of thrombopoietic agents in patients with MDS and development of novel agents that specifically treat thrombocytopenia are clearly warranted.

### Conclusion

In the future, management of all types of thrombocytopenia will likely be revolutionized by the availability of thrombopoietic agents. They should do for thrombocytopenia what erythropoietin and colony-stimulating factors have done for anemia and neutropenia. It is worth noting that although all three agents are undeniably useful in certain settings, their use is somewhat controversial in chemotherapy-induced cytopenias. This is a particular issue for thrombopoietic agents. Although studies are ongoing, the ultimate utility in chemotherapy-induced thrombocytopenia remains to be determined.