The revitalization of thalidomide

Thalidomide was first introduced in 1953 as an oral sedative-hypnotic [1], and was used to ameliorate nausea and vomiting during pregnancy. Limb malformations and abnormalities of internal organs in newborns resulted in the withdrawal of thalidomide from the market in 1961 [2]. Owing to its efficacy in the treatment of the acute cutaneous manifestations of erythema nodosum leprosum (ENL), thalidomide was approved by the Food and Drug Administration for the treatment and prevention of ENL [3]. Interest in the mechanisms of thalidomide-induced phycocytia and activity in ENL led investigators to study the effects of thalidomide on angiogenesis, cytokine pathways, and lymphocyte activation [4].

*In vivo* studies demonstrated that thalidomide inhibited basic fibroblast growth factor (bFGF)-induced angiogenesis in a rabbit cornea micropocket assay [5], and inhibited vascular endothelial cell growth factor (VEGF) in a murine model of corneal vascularization [6]. Thalidomide also inhibited tumor necrosis factor alpha (TNF-α), a cytokine known to be elevated in several malignancies [7-10]. TNF-α enhances neo-angiogenesis, and interacts with other proliferative cytokines such as interleukin-6 (IL-6), known to be involved in the pathogenesis of multiple myeloma [11]. Thalidomide also inhibits monocyte IL-12 production, enhances synthesis of IL-2, and inhibits IL-6 directly [12-14]. Other immunomodulatory effects include differential CD8+ T-cell stimulation resulting in decreased CD4/CD8 ratio, shift from Th1 to Th2 T-cell responses, and inhibition of proliferation of stimulated T-cell lymphocytes [15-18]. These purported immunomodulatory and putative anti-angiogenic effects sparked clinical trials of thalidomide in solid tumors and hematologic malignancies known to be responsive to immune modulation or inhibition of angiogenesis, such as multiple myeloma.

Singhal et al. [19] initially reported a response rate of 32% in 84 previously treated patients with relapsed or refractory myeloma, a remarkable finding considering most patients had received high dose chemotherapy. Responses were characterized by at least 25% reduction in the serum myeloma protein or urine Bence Jones protein levels. Reductions in the percentage of plasma cells in the bone marrow were observed in some of the responders. An update by Barlogie summarized the Arkansas experience with single agent and combination therapy in over 300 myeloma patients, reporting the activity of thalidomide monotherapy in an additional 85 patients [20].

In this issue of *Annals of Oncology*, Bertolini et al. [21] and Dimopoulos et al. [22] confirm the encouraging activity of thalidomide in refractory or relapsed multiple myeloma. Bertolini et al. report a 41% response rate in 17 previously treated patients who had failed conventional chemotherapy. Combination programs incorporating other anti-myeloma agents are being studied, and Dimopoulos et al. report efficacy of thalidomide and dexamethasone in 44 previously treated refractory myeloma patients, despite resistance to prior dexamethasone-based combinations in over three-fourths of the patients. The intention-to-treat response rate was 57% with the Singhal [19] definition of response, confirming earlier reports of increased activity with the combination when compared with single-agent administration of thalidomide, although randomized trials are needed to confirm superiority [23].

Preliminary activity has been reported in other hematologic malignancies including Waldenstrom's macroglobulinemia [24], myelofibrosis [25], and myelodysplastic syndrome [26]. Raza et al. [26] reported that 17 of 25 evaluable patients (68%) with myelodysplastic syndrome responded to thalidomide with improvements in cytopenias observed in at least one lineage; trilineage responses and transfusion-independence were seen in some patients. Bertolini et al. also report transfusion-independence and reduction in transfusion requirements after thalidomide exposure in two of five patients with previously treated early myelodysplastic syndrome, suggesting further study is warranted [21]. Based on these observations, additional confirmatory phase II and III trials with single-agent thalidomide are being conducted.

Attempts to correlate the probability of response with the biologic effects of thalidomide remain tenuous. Bone marrow microvessel density assessments prior to and after treatment did not correlate with response in the Singhal myeloma trial, although reductions in vascularization were observed [19]. Paradoxically, responders in the myelodysplastic syndrome trial had lower serum levels of TGF-β or TNF-α, and less pretreatment marrow apoptosis compared with nonresponders [27]. Bertolini et al. performed serial assessments of plasma VEGF and bFGF levels and measured changes in activated bone marrow endothelial cells; reductions were observed at the time of best clinical response compared with pretreatment values [21]. Although the patient numbers are small, the authors observed that responders had the highest pretreatment levels of VEGF and bFGF.

Challenging questions remain unanswered in the saga of thalidomide. Although several biologic effects of thalidomide have been delineated, the specific mechanism of action responsible for its anti-myeloma or anti-leukemic effect is currently not known. The optimal
dose, schedule, and duration of therapy remains unclear. A direct dose-response relationship has not been established, since responses may be seen with even 50–100 mg of continuous daily thalidomide. Strategies for combination therapy remain empiric at best, with limited data available regarding synergism with other agents. Tolerance to the sedative and neurotoxic effects of thalidomide appears age- and dose-related; however, they remain unpredictable [28].

The remarkably wide spectrum of activity of thalidomide has led to development of two classes of analogues designed to increase efficacy and reduce toxicity (e.g., lack of teratogenicity and decreased sedation) [29, 30]. The first class of compounds are Immunomodulating Drugs (1MiDs™), which inhibit TNF-α with a 10,000-fold increased potency compared with the parent compound. 1MiDs™ resemble thalidomide in their ability to inhibit IL-1β, IL-6, and IL-12 and enhance IL-10, IL-2, and IFN-γ. The second group of thalidomide-related TNF-α inhibitors are the Selective Cytokine Inhibitory Drugs (SelCIDs™). These agents inhibit phosphodiesterase-4 (PDE-4), an enzyme which influences the overproduction of TNF-α. Phase I and II trials of these agents are ongoing, while the enigma of thalidomide remains.

D. A. Thomas & H. M. Kantarjian
Department of Leukemia
M.D. Anderson Cancer Center
Houston, Texas, USA

References