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EDITORIAL

Thalidomide in the Treatment of Plasma Cell Malignancies

THALIDOMIDE, REMOVED from clinical use because of severe teratogenicity, is back.¹ In a comeback that has proceeded with remarkable speed, the drug that adversely affected more than 10,000 infants just over four decades ago now seems to be a lifesaver for patients with advanced plasma cell malignancies.

In a sense, thalidomide never really went away. Shortly after reports of teratogenicity forced the drug off the market, it was found to be effective in the treatment of erythema nodosum leprosum.² The drug has since been available in a limited manner to leprosy patients in many countries. In 1998, the Food and Drug Administration approved the drug for use in erythema nodosum leprosum, with substantial precautions. Over the last 10 years, other uses have emerged, including AIDS-related cachexia and oral ulcers,³ aphthous ulcers in Behcet's disease,⁴ and chronic graft-versus-host disease.⁵

Thalidomide was first studied as an anticancer agent by astute investigators intrigued by its potent teratogenic potential. In 1962, only 4 months after the initial reports of teratogenicity, Woodyatt⁶ treated a woman with malignant mixed mesodermal tumor of the uterus. The interest in studying thalidomide as an anticancer agent led to at least three clinical trials in the early 1960s, including a study by the Eastern Cooperative Oncology Group.^{7,8} These trials did not show any significant activity, and interest in thalidomide as an anticancer agent diminished greatly.

The recent studies of thalidomide in plasma cell disorders were prompted by the growing interest in studying tumor angiogenesis as a novel therapeutic target. Given its compassionate use availability and its anti-angiogenic properties,⁹ Barlogie et al initiated clinical studies with thalidomide in refractory multiple myeloma. Their results, published in 1999 by Singhal et al,¹ demonstrated an overall response rate of 32% in 84 patients with relapsed, refractory myeloma. Considering that 90% of patients in this study had failed autologous stem-cell transplantation, these results

were impressive. The activity of thalidomide in relapsed myeloma with response rates in the range of 25% to 45% has since been confirmed by numerous studies worldwide.¹⁰⁻¹² These studies indicate a median response duration of 9 months to 1 year. Approximately 10% to 20% of patients are free of progression at 2 years. Based on these results, thalidomide is now considered as part of standard therapy for relapsed myeloma, but Food and Drug Administration approval for this indication is pending.

In this issue of the *Journal of Clinical Oncology*, Dimopoulos et al¹³ report activity of thalidomide in Waldenström's macroglobulinemia, a closely related plasma cell malignancy. The study of thalidomide in this disease is certainly warranted given the striking activity seen in advanced myeloma. The authors report a response rate of 25% in an unselected group of patients with Waldenström's macroglobulinemia. Responses seem durable and were associated with improvement in marrow infiltration, hemoglobin concentration, and uninvolved immunoglobulin levels. The study demonstrates proof of principle that thalidomide has activity in this disease. Although the sample size is too small to make definite conclusions, it is worth noting that all responders had received less than 24 months of prior therapy, and none of the patients with refractory relapse responded to therapy.

Two findings made by the authors resonate well with observations made in myeloma trials. First, doses higher than 200 mg to 400 mg are associated with significantly higher toxicity and may not necessarily yield better response rates. Second, the effect of thalidomide is rapid. Patients who do not achieve at least a 25% reduction in monoclonal protein levels in 1 to 2 months are unlikely to respond with continued therapy.

How can we explain the efficacy of thalidomide in plasma cell malignancies? Given its unstable nature (upon absorption it spontaneously and nonenzymatically cleaves into over 20 metabolites), the mechanism of action of

thalidomide has not been easy to elucidate.¹⁴ It has complex effects on tumor angiogenesis, the immune system, and various cytokines and adhesion molecules. Using the rabbit cornea micropocket assay, D'Amato et al⁹ determined that thalidomide had potent anti-angiogenic properties, probably by blocking the action of angiogenic cytokines such as basic fibroblast growth factor and vascular endothelial growth factor. In the myeloma trials, no statistically significant differences have been observed in posttreatment microvessel density (MVD) change between responders and nonresponders, and pretreatment MVD is not a predictor of response.^{1,15,16} Because MVD is a crude measure of bone marrow angiogenesis, the lack of a consistent decrease in bone marrow MVD after thalidomide therapy does not fully exclude an anti-angiogenic mechanism of action for this agent. However, it is clear that other properties of thalidomide may play a role in its anticancer activity.^{10,17} Recently, Parman et al¹⁸ demonstrated that thalidomide-induced birth defects in rabbits can be abolished by pretreatment with the free radical spin-trapping agent alpha-phenyl-N-t-butylnitron, suggesting free radical-mediated DNA damage as a mechanism of action. Other studies show that thalidomide inhibits tumor necrosis factor alpha (TNF α) activity by promoting the degradation of TNF α mRNA¹⁹ and enhancing the effect of α 1-acid glycoproteins that possess intrinsic anti-TNF α effects.^{14,20} In addition, it stimulates the proliferation and secretion of interferon gamma and interleukin-2 by cytotoxic T cells²¹ and may modulate the expression of cell surface adhesion molecules that allow myeloma cells to interact with the bone marrow microenvironment.²² We are convinced that elucidation of the mechanism of action of thalidomide in plasma cell malignancies will provide significant insights into tumor biology and will open the door to the development of other novel therapies.

Where do we go from here? At present, there is a need to test thalidomide in early-stage plasma cell disorders. Two recent studies with thalidomide in untreated patients with indolent or smoldering myeloma indicate a response rate of approximately 35% to 40%.^{16,23} Because the standard approach to these patients is observation without therapy, randomized trials are needed to determine whether thalidomide at low doses can delay progression to active symptomatic disease. Another critical question is the benefit of combining thalidomide with other active agents. Weber et al²⁴ have observed responses in 24 (52%) of 47 patients with resistant myeloma using a combination of thalidomide and dexamethasone. Many patients (46%) in this trial had previously failed dexa-

methasone and thalidomide as single agents, suggesting a synergistic effect when the two agents are combined. Preliminary results from a Mayo Clinic study using this combination as initial therapy for previously untreated myeloma indicate promising activity with a response rate of over 75%.¹⁶ Laboratory studies also support the presence of synergistic interactions between thalidomide and dexamethasone.²⁵ The efficacy of thalidomide administered in combination with other chemotherapeutic agents is being addressed by ongoing randomized clinical trials at the University of Arkansas for Medical Sciences. Although results with thalidomide in combination with other active agents in early-stage disease seem promising, we recommend caution until further safety and efficacy data are available. This is important, considering the risk of irreversible neuropathy with long-term thalidomide therapy and the observation of unexpected added toxicity in studies combining the drug with dexamethasone²⁶ or doxorubicin-based chemotherapy²⁷ for newly diagnosed myeloma.

The main limitations of thalidomide are the risk of teratogenicity and side effects such as drowsiness, fatigue, constipation, rash, and neuropathy. Although adverse effects are usually mild, they can be troublesome and severe in a small proportion of patients. To overcome this, analogs of thalidomide (immunomodulatory drugs) are being developed and tested in clinical trials. These analogs have the promise of improved efficacy with fewer side effects. One such analog, CC-5013, has significantly more potent effects against human myeloma cells and less adverse effects than thalidomide. Based on promising preclinical data, two phase I studies with CC-5013 have been initiated in relapsed myeloma, and a larger multi-institutional phase II trial is expected to open early next year.

Thalidomide has emerged as an effective agent in the treatment of relapsed myeloma. It seems to have activity in Waldenström's macroglobulinemia and merits further study. As an anticancer agent, thalidomide may prove useful in the treatment of other cancers. Preliminary data suggest activity in myelodysplastic syndrome, myelofibrosis, gliomas, and renal cell cancer. Further studies should focus on its mechanism of action, ideal dosing schedule, duration of therapy, and role in maintenance therapy. Finally, patients and physicians must continue to exercise caution when using thalidomide to avoid teratogenic complications.

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