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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, Woodyatt[6] 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 al[13] 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 al[9] 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 al[18] demonstrated that thalidomide-induced birth defects in rabbits can be abolished by pretreatment with the free radical spin-trapping agent alpha-phenyl-N-t-butylnitrone, suggesting free radical–mediated DNA damage as a mechanism of action. Other studies show that thalidomide inhibits tumor necrosis factor alpha (TNFα) activity by promoting the degradation of TNFα mRNA[19] and enhancing the effect of α1-acid glycoproteins that possess intrinsic anti-TNFα effects.[14,20] In addition, it stimulates the proliferation and secretion of interferon gamma and interleukin-2 by cytotoxic T cells[21] 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 al[24] 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 dexamethasone 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 dexamethasone[26] or doxorubicin-based chemotherapy[27] 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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REFERENCES

1. Singhal S, Mehta J, Desikan R, et al: Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 341:1565-1571, 1999
2. Sheskin J: Thalidomide in the treatment of lepra reactions. Clin Pharmacol Ther 6:303-306, 1965
3. Jacobson JM, Greenspan JS, Spritzler J, et al: Thalidomide for the treatment of oral aphthous ulcers in patients with human immunodeficiency virus infection: National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group. N Engl J Med 336:1487-1493, 1997
4. Hamuryudan V, Mat C, Saip S, et al: Thalidomide in the treatment of the mucocutaneous lesions of the Behcet syndrome: A randomized, double-blind, placebo-controlled trial. Ann Intern Med 128:443-450, 1998
5. Parker PM, Chao N, Nademanee A, et al: Thalidomide as salvage therapy for chronic graft-versus-host disease. Blood 86:3604-3609, 1995
6. Woodyatt PB: Thalidomide. Lancet 1:750, 1962
7. Olson KB, Hall TC, Horton J, et al: Thalidomide (N-phthaloyl-glutamimide) in the treatment of advanced cancer. Clin Pharmacol Ther 6:292-297, 1965
8. Grabstad H, Golbey R: Clinical experience with thalidomide in patients with cancer. Clin Pharmacol Therap 6:298-302, 1965
9. D'Amato RJ, Loughnan MS, Flynn E, et al: Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci USA 91:4082-4085, 1994
10. Rajkumar SV, Witzig TE: A review of angiogenesis and anti-angiogenic therapy with thalidomide in multiple myeloma. Cancer Treat Rev 26:351-362, 2000
11. Rajkumar SV, Fonseca R, Dispenzieri A, et al: Thalidomide in the treatment of relapsed multiple myeloma. Mayo Clin Proc 75:897-902, 2000
12. Juliusson G, Celsing F, Turesson I, et al: Frequent good partial remissions from thalidomide including best response ever in patients with advanced refractory and relapsed myeloma. Br J Haematol 109:89-96, 2000
13. Dimopoulos MA, Zomas A, Viniou NA, et al: Treatment of Waldenstrom's macroglobulinemia with thalidomide. J Clin Oncol 19:3956-3601, 2001
14. Stirling DI: Pharmacology of thalidomide. Semin Hematol 37:5-14, 2000
15. Rajkumar SV, Fonseca R, Dispenzieri A, et al: A phase II trial of thalidomide in the treatment of relapsed multiple myeloma (MM) with laboratory correlative studies. Blood 96:168a, 2000 (abstr 723)
16. Rajkumar SV, Hayman S, Fonseca R, et al: Thalidomide plus dexamethasone (Thal/Dex) and thalidomide alone (Thal) as first line therapy for newly diagnosed myeloma (MM). Blood 96:168a, 2000 (abstr 722)
17. Raje N, Anderson K: Thalidomide: A revival story. N Engl J Med 341:1606-1607, 1999
18. Parman T, Wiley MJ, Wells PG: Free radical-mediated oxidative DNA damage in the mechanism of thalidomide teratogenicity. Nature Med 5:582-585, 1999
19. Moreira AL, Sampaio EP, Zmuidzinas A, et al: Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation. J Exp Med 177:1675-1680, 1993
20. Turk BE, Jiang H, Liu JO: Binding of thalidomide to alpha1-acid glycoprotein may be involved in its inhibition of tumor necrosis factor alpha production. Proc Natl Acad Sci USA 93:7552-7556, 1996
21. Haslett PA, Corral LG, Albert M, et al: Thalidomide costimulates primary human T lymphocytes, preferentially inducing proliferation, cytokine production, and cytotoxic responses in the CD8+ subset. J Exp Med 187:1885-1892, 1998
22. Geitz H, Handt S, Zwingenberger K: Thalidomide selectively modulates the density of cell surface molecules involved in the adhesion cascade. Immunopharmacol 31:213-221, 1996
23. Weber DM, Rankin K, Gavino M, et al: Angiogenesis factors and sensitivity to thalidomide in previously untreated multiple myeloma (MM). Blood 96:168a, 2000 (abstr 724)
24. Weber DM, Rankin K, Gavino M, et al: Thalidomide with dexamethasone for resistant multiple myeloma. Blood 96:167a, 2000 (abstr 719)
25. Hideshima T, Chauhan D, Shima Y, et al: Thalidomide and its analogs overcome drug resistance of multiple myeloma cells to conventional therapy. Blood 96:2943-2950, 2000
26. Rajkumar SV, Gertz MA, Witzig TE: Life-threatening toxic epidermal necrolysis with thalidomide therapy for myeloma. N Engl J Med 343:972-973, 2000
27. Osman K, Comenzo R, Rajkumar SV: Deep vein thrombosis and thalidomide therapy for multiple myeloma. N Engl J Med 344:1951-1952, 2001