Current Status of Thalidomide in the Treatment of Cancer

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In his comprehensive review, Dr. Rajkumar provides a summary of the current status of thalidomide (Thalomid) therapy in cancer. As discussed in the article, it was the teratogenic effects, particularly phocomelia, that prompted researchers to examine thalidomide's antitumor activity in the 1960s. Although, the results of early phase I trials of thalidomide as an anticancer agent were disappointing, they clearly demonstrated that thalidomide is neither a cytotoxic agent nor a mutagen. The mystery of its teratogenic effect began to unfold after D'Amato et al observed that thalidomide is an inhibitor of angiogenesis.[1] This finding renewed enthusiasm for studying thalidomide as an anticancer agent in the last several years.

The Potential of Combination Therapy

Dr. Rajkumar reviews the clinical trials that established thalidomide as an effective anticancer agent in relapsed or previously untreated multiple myeloma, either as a single agent or in combination therapy. However, contrary to its success in myeloma, single-agent thalidomide has very limited antitumor activity in most solid tumors (see Dr. Rajkumar’s Table 3). In animal models, the combination of an antiangiogenic agent and cytotoxic therapy can be curative, whereas either agent alone is only inhibitory.[2] These data suggested that therapy directed against both the endothelial cell and tumor cell components of a tumor is more effective than therapy targeting tumor cells alone.

Weber et al conducted a study of the combination of dexamethasone and thalidomide in patients with refractory myeloma.[3] As single-agent therapy, dexamethasone or thalidomide had failed in approximately half of the 47 previously treated patients; 24 patients had responded. The improved activity of the combination suggests that the synergistic activity of these agents can overcome drug resistance in myeloma patients. Using the same scenario, the combination of standard chemotherapy and the antiangiogenic agent thalidomide may be more effective in chemoresistant solid tumors.

Preliminary results of several phase II studies have shown that thalidomide is safe and well tolerated when combined with chemotherapy.[4-6]. Numerous trials have been initiated to study thalidomide in combination with standard chemotherapy in various solid tumors, and only preliminary results are currently available. Govindarajan and colleagues conducted a pilot study of thalidomide in combination with irinotecan (Camptosar) for metastatic colorectal cancer.[7] They were encouraged by the observation that thalidomide had almost eliminated the dose-limiting gastrointestinal toxicities associated with irinotecan, especially diarrhea and vomiting. Thus, eight of nine treated patients were able to complete the therapeutic course without a dose reduction.

Responses Seen in Brain Metastases

The prognosis of patients with cerebral metastases remains poor, and the median survival from diagnosis of central nervous system involvement is no more than 4 months, as reported in many series.[8] Chemotherapy is generally ineffective for brain metastases from melanoma, partly because most chemotherapeutic agents do not penetrate the blood-brain barrier.

Recently, at Memorial Sloan-Kettering Cancer Center, we used the combination of temozolomide (Temodar) and thalidomide to treat melanoma that has metastasized to the brain. When thalidomide was administered 30 to 60 minutes before temozolomide, it eliminated nausea and vomiting but also
increased constipation. Although either drug alone shows limited activity against metastatic melanoma in the brain, 6 of the 16 treated patients responded to the combination.

All patients who achieved systemic responses also had cerebral responses. Furthermore, responses were seen in patients who received prior therapy with temozolomide or dacarbazine (DTIC-Dome), an intravenous analog of temozolomide. At a median follow-up of 8 months, the median survival of the 16 patients is 9 months; 9 patients are alive and 2 show no evidence of metastatic disease. These preliminary results strongly support the hypothesis that the combination of cytotoxic and antiangiogenic agents provides more effective treatment for chemoresistant tumors.

Investigators from the University of Pittsburgh have reported that in animal models, the combination of an antiangiogenic compound and immunotherapy has a more potent antitumor effect than either modality alone.[8] In addition, the angiogenesis inhibitors had a stronger impact on immunogenic tumors than on nonimmunogenic tumors. This may provide the scientific basis for the encouraging preliminary results of the combination of thalidomide and interferon-alpha in metastatic renal cell carcinoma.[T.G. Eisen, personal communication, 2000.]

Conclusions

Dr. Rajkumar summarizes the clinical trials that established thalidomide as an effective antitumor agent in the treatment of myeloma. Preliminary results have suggested promising activity in other hematologic malignancies. However, except for Kaposi’s sarcoma, brain tumors, and renal cancer, thalidomide has little anticancer activity as a single agent in solid tumors. Many studies have demonstrated that thalidomide can be administered with standard antitumor agents. Both experimental and clinical data confirm the synergistic activity of thalidomide when combined with other antitumor agents. The combined use of thalidomide with standard anticancer therapy, such as chemotherapy, hormonal therapy, or immunotherapy, holds promise for more effective treatment of chemoresistant tumors.

References: