Thalidomide in Cancer

Potential Uses and Limitations

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Abstract

In addition to immunomodulatory and cytokine-modulatory properties, thalidomide has antiangiogenic activity. It has been investigated in a number of cancers including multiple myeloma, myelodysplastic syndromes, gliomas, Kaposi's sarcoma, renal cell carcinoma, advanced breast cancer, and colon cancer. Its role has been best explored in myeloma, where, at daily doses of 100 to 800mg, it is remarkably active, causing clinically meaningful responses in one-third of extensively pretreated patients and in over half of patients treated early in the course of the disease. It also acts synergistically with corticosteroids and chemotherapy in myeloma. Thalidomide produces improvement of cytopenias characteristic of myelodysplastic syndrome, resulting in the reduction or elimination of transfusion dependence in some patients. Responses have also been seen in one-third of patients with Kaposi's sarcoma, in a small proportion of patients with renal cell carcinoma and high grade glioma and, in combination with irinotecan, in some patients with colon cancer. Thalidomide is being investigated currently in a number of clinical trials for cancer. Drowsiness, constipation and fatigue are common adverse effects seen in 75% of patients. Symptoms of peripheral neuropathy and skin rash are seen in 30%. A minority of patients experience bradycardia and thrombotic phenomena. Despite the high frequency of adverse effects, those severe enough to necessitate cessation of therapy are seen in only 10 to 15% of patients. A therapeutic trial of thalidomide should be considered in all patients with myeloma who are unresponsive to or relapse after standard therapy. In other malignant diseases, the most appropriate way to use the drug is in the setting of well designed clinical trials. In the absence of access to such studies, thalidomide could be considered singly or in combination with standard therapy in patients with no meaningful therapeutic options.

Thalidomide, a synthetic glutamic acid derivative, was originally introduced as a sedative-hypnotic in Europe and Canada in the late 1950s. Belated recognition of severe teratogenic effects resulted in its withdrawal in the early 1960s.[1] Subsequently, the drug was found to possess diverse immunomodulatory and anti-inflammatory properties,[2-4] which are, at least in part, responsible for its activity in erythema nodosum leprosum[5] and graft-versus-host disease (GVHD).[6]

The limited early efforts exploring thalidomide in cancer were inconclusive.[7,8] The description of its powerful activity in patients with end-stage myeloma by Singhal et al.[9] has given rise to investigation of thalidomide in a number of malignant disorders. The purpose of this review is to summarise the limited data available on the use of thalidomide in cancer[10-39] and to provide some practical guidelines for its use based on our experience.

1. Mechanism of Action

While the exact mechanism of the antimalignancy action of thalidomide is not known, it is likely that angiogenesis inhibition, immunomodulation and cytokine modulation,[40-60] individually or in combination, underlie its antitumour activity. The rapid tempo of response in some myeloma patients[9] suggests that thalidomide may have some direct cytotoxic effect on plasma cells. Table I summarises some of the properties of the drug which may contribute to its activity in cancer.

Thalidomide inhibits the production of tumour necrosis factor (TNF)-α by monocytes as well as T cells.[40,41,51,55,56,58] Inhibition of TNFα production is not associated with inhibition of other cytokines such as interleukin (IL)-2. In fact, thalidomide enhances the production of IL-2,[46,48] which itself may possess antitumour activities or may modulate the immune system to induce anticancer activity. Data on its effects on interferon (IFN)-γ production have been variable[45,51,55,56] but more reports have shown it to increase IFN-γ production than to inhibit it. Thalidomide inhibits IL-6, IL-10 and IL-12 production[50,51,56] and enhances IL-4 and IL-5 production.[45] IL-6 is a potent growth factor for malignant plasma cells and its inhibition may be partly responsible for the action of thalidomide in myeloma. In addition to increasing total lymphocyte counts as well as CD4+ and CD8+ T cells,[48,60] thalidomide is a potent costimulator of T lymphocytes.[52]

Angiogenesis is important in tumour progression and correlates with prognosis in a number of malignant diseases.[61,62] D'Amato et al.[43] were the first to show the angiogenesis inhibitory activity of thalidomide in a rabbit model of corneal neovascularisation induced by basic fibroblast growth factor. These data have subsequently been confirmed in other studies,[49,53,54,57] and the combination of thalidomide and sulindac,[59] a nonsteroidal anti-inflammatory agent with antiangiogenic activity, has been shown to be synergistic in inhibiting angiogenesis.

Table I. Potential mechanisms of action of thalidomide in cancer

Action	References
Inhibition of angiogenesis	43,49,53,54,57,59
Alteration of adhesion molecule expression	42,44,47
Selective inhibition of tumour necrosis factor-α production	40,41,51,55,56,58
Induction of T_h2 cytokine production (IL-4 and IL-5)	45
Variable effects of interferon-γ production	45,51,55,56
Increase in the synthesis of IL-2 by mononuclear cells	46
Increase in soluble IL-2 receptor levels	48
Inhibition of IL-6, IL-10 and IL-12 production	50,51,56
Increase in total lymphocyte and CD4+ and CD8+ T cell numbers	48,60
Costimulation of T lymphocytes	52

IL = interleukin; T_h = helper T lymphocyte.

2. Clinical Studies

2.1 Multiple Myeloma/Plasma Cell Disorders

Thalidomide was administered to patients with terminal myeloma[9] on the basis of observations that bone marrow angiogenesis was prominent in active myeloma[63] and thalidomide inhibited angiogenesis.[43] After treating 5 patients on a compassionate basis, Singhal et al.[9] treated 84 additional patients with thalidomide as a single agent for 2 to 465 days on a US Food and Drug Administration-approved protocol. Most patients had relapsed after a preceding autotransplant. The starting dose of 200mg daily was increased by 200mg every 2 weeks to a maximum of 800mg. 32% of the patients responded, with the serum or urine paraprotein levels declining by ≥90% in 8 patients (including 2 complete remissions), ≥75% in 6, ≥50% in 7, and ≥25% in 6. Paraprotein reduction was evident

within 2 months in 78% of the responders. Responses were associated with reduction in marrow plasmacytosis. The actuarial 1-year overall and event-free survival was 58% and 22%, respectively. Currently, after more than 2 years of follow-up, 60% of responding patients have relapsed.

These encouraging data have now been replicated by a number of other groups.[19-23,25,27,28,32,33] The response rates described have varied between 20 and 70%. It is clear that not all patients respond to thalidomide, and that a number of responding patients eventually relapse. The combination of thalidomide with dexamethasone[27,39] or chemotherapy[18,20,24] ('angiochemotherapy') has been found to be active under these circumstances. The 2 noteworthy combinations are DT-PACE (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide)[18] and BLT-D (clarithromycin, thalidomide, dexamethasone).[39] DT-PACE (2 cycles) resulted in ≥50% paraprotein decline in almost 70% of previously treated patients. However, the mortality was considerable, with 3 of 43 patients dying of toxicity.[18] BLT-D was tolerated well by 17 patients with myeloma (n = 14) or Waldenstrom's macroglobulinaemia (n = 3), with all 14 evaluable patients showing a response [including 3 complete responses (CR)].[39] The daily dose of thalidomide used in the DT-PACE regimen was 200 to 400mg, and that in the BLT-D regimen, 50 to 200mg.

How thalidomide is best used in a patient with relapsed myeloma depends on the tempo of disease progression and bone marrow reserves. For instance, if the disease is slowly progressive, thalidomide can be used as a single agent. Chemotherapy or corticosteroids can be added if there is no response. On the other hand, if the disease is rapidly progressive, a combination of agents may have to be used from the beginning.

We have used thalidomide as a single agent at the dose of 200 to 400mg to treat 12 previously untreated patients who refused standard therapy. Paraprotein declined by ≥50% in 8 patients, and this response has been sustained on continued therapy for over 8 months in 7 patients (unpublished observations). More data are required before the drug can be recommended as first-line therapy of myeloma outside the setting of a comparative clinical trial. However, in patients refusing standard therapy, thalidomide is a reasonable choice.

Thalidomide can be administered as maintenance therapy following autologous stem cell tranplantation as a means of prolonging remission duration. We use thalidomide for post-transplant maintenance in patients who cannot tolerate IFN-α or dexamethasone, have poor marrow function, or have disease that was unresponsive to dexamethasone or responsive to thalidomide before the transplant (table II).

Thalidomide has been effective as a single agent 400mg daily in previously treated patients with Waldenstrom's macroglobulinaemia (A. Zomas, personal communication). The BLT-D combination regimen has also been reported to be effective in this indication.[39] We have used thalidomide in a patient with Castleman's disease with excellent response. The disease activity declined on thalidomide despite the reduction of prednisone from 100mg daily to 5mg daily and was accompanied by normalisation of a grossly elevated IL-6 level. There are no reports on the use of thalidomide in amyloidosis or POEMS (Polyneuropathy, Organomegaly, Endocrine abnormalities, Monoclonal protein, Skin changes) syndrome.

Table II. Our criteria for selection of patients for thalidomide maintenance after autotransplantation (based on unpublished observations)

Clinical situation	Patient selection
Already autografted	1. History of response to thalidomide in the past
	2. Intolerance of dexamethasone and interferon
	3. No response to dexamethasone in the past (alternative to interferon)
	4. Poor marrow function (alternative to dexamethasone)
Not autografted yet	Pretransplant therapeutic trial of thalidomide for 6 weeks: responders can receive thalidomide after transplant, whereas nonresponders should receive dexamethasone and/or interferon

2.2 Myelodysplastic Syndromes

Intramedullary apoptosis of bone marrow cells, probably mediated by TNFα,[64] is responsible for the cytopenias that characterise myelodysplastic syndromes (MDS). In an attempt to exploit the selective TNFα-inhibitory effect of thalidomide, Raza et al.[38] treated 61 patients with MDS with thalidomide 100 to 400mg for 12 weeks. 22 patients had refractory anaemia (RA), 13 had RA with ringed sideroblasts, 19 had RA with excess blasts (RAEB), 4 had RAEB in transformation, and 3 had chronic myelomonocytic leukaemia. At the time of the report, 11 had stopped therapy, 25 had not received the drug long enough, and 17 of the remaining 25 evaluable patients had shown improvement in cytopenia (3 trilineage, 4 bilineage, 10 single lineage). The best responses were seen in the erythroid series, with a number of patients becoming transfusion-independent. Longer follow-up is required to see how long these responses are sustained.

Thalidomide-containing angiochemotherapy combinations may be active in RAEB, RAEB in transformation and secondary acute myeloid leukaemia. These combinations (liposomal anthracycline with topotecan or cytarabine; with or without thalidomide) are being studied currently.[29]

2.3 Kaposi's Sarcoma

Soler et al.[13] described a 14-year-old girl with HIV infection and subcutaneous Kaposi's sarcoma (KS) who received thalidomide for aphthous ulcers. This resulted in regression of KS lesions, disappearance of KS-associated herpesvirus (KSHV) DNA from blood, and reduced viral load in tumour tissue. Fife et al.[15] administered 100mg thalidomide daily for 8 weeks to 17 patients with AIDS-related KS. Six patients achieved a partial response, and viral DNA load decreased to undetectable levels in 3 of the 5 responders assessed virologically.

Little et al.[36] treated 20 HIV-positive patients who had progressive KS with 200mg thalidomide in a phase II study. The dose was escalated to 1000mg for up to a year. Eight patients had partial response and 2 had stabilisation of progressive disease. The median drug dose at the time of response was 500mg. The median duration of therapy was 6.3 months, and the median time to progression 7.3 months. KSHV DNA titres were not studied. The disappearance of viral DNA in responding patients is of interest in the context of the activity of thalidomide in myeloma and the fact that some groups have isolated KSHV DNA in patients with myeloma.[65]

2.4 Breast Cancer

Eisen et al.[30] studied 12 patients with breast cancer as part of a group of 66 patients with various cancers who received 100mg thalidomide daily. No objective response was seen in any of these 12 patients. Baidas et al.[37] studied the efficacy of thalidomide in 28 women with heavily pretreated, progressive metastatic breast cancer who were randomised to receive either 200 or 800mg thalidomide daily. No response was seen in any patient. 13 of 14 patients receiving 800mg thalidomide experienced progressive disease within 8 weeks, compared with 12 of 14 in the 200mg arm. Two patients in the 200mg arm had stable disease at 8 weeks.

Nguyen et al.[14] administered 100 to 300mg thalidomide daily for 4 weeks in addition to standard chemotherapy in 7 women with breast cancer. With a follow-up of 1 to 6 months, patients with stage 4 disease had either a partial response or stabilisation of disease. However, the disease eventually progressed in the 2 patients with the longest follow-up (5 and 6 months).

These studies included patients with advanced disease and used the drug as a single agent or for a limited duration. More benefit might be seen if thalidomide is combined with chemotherapy and then continued as maintenance therapy for an extended period, although such an approach requires systematic investigation.

2.5 Glioma

Because malignant gliomas are vascular tumours, angiogenesis inhibition may be therapeutically beneficial. Fine et al.[31] administered thalid-

omide to 39 patients with anaplastic mixed glioma, anaplastic astrocytoma or glioblastoma multiforme who had radiological evidence of progression after external-beam radiation with or without chemotherapy. The drug was started at the daily dose of 800mg and increased by 200mg every 2 weeks to 1200mg. Among the 36 evaluable patients, there were 2 radiologically evident partial responses (6%), 2 minor responses (6%) and 12 patients (33%) with stable disease. Eight patients were alive over a year after starting therapy, most with progressive disease. Once again, it is likely that thalidomide will have to be used as part of a multimodality treatment plan if it is to be of any benefit in this setting.

2.6 Colon Cancer

Govindarajan et al.[35] treated 9 colon cancer patients with irinotecan (325 to 350 mg/m^2 every 3 weeks) and 400mg thalidomide daily as second-line therapy. None of the patients had been treated with irinotecan in the past. Thalidomide was found to eliminate the dose-limiting gastrointestinal side effects of irinotecan, especially nausea and diarrhoea, almost completely, permitting 8 of 9 patients to complete therapy. Of the 7 patients evaluable for response, 1 attained complete remission and 2 partial remission. These data have important implications for the tolerability as well as efficacy of angiochemotherapy in colon cancer.

2.7 Renal Cell Carcinoma

Among 18 patients with renal cell carcinoma which was progressive despite biochemotherapy, 3 partial responses were noted with thalidomide monotherapy. One lasted 5 months, and the other two were ongoing at 5 and 11 months at the time of the report. 13 of the remaining 16 patients experienced disease stabilisation for 1 to 3 months (10) or >3 months (3).[30]

2.8 Other Cancers

Responses to thalidomide as a single agent at the dose of 200 to 400mg daily have been seen in Hodgkin's disease relapsing after autotransplantation (unpublished observations), Langerhans cell histiocytosis,[10-12,16] hepatocellular carcinoma,[34] and chronic myeloproliferative disorders.[29] No responses were seen in ovarian cancer and advanced melanoma.[30]

2.9 Graft-versus-Host Disease

Thalidomide is immunomodulatory rather than immunosuppressive in its action. In fact, thalidomide increases total lymphocyte counts as well as CD4+ and CD8+ lymphocytes. It is likely that its beneficial effect in treating established chronic GVHD[6] is a result of TNFα inhibition. Thalidomide has little effect on acute GVHD,[66] and prophylactic use of the drug, paradoxically, has been shown to result in increased chronic GVHD.[67] This may be because of some immunostimulatory effects.

GVHD and graft-versus-tumour effects are often closely linked. Thus, when GVHD resolves with successful immunosuppression, the underlying malignant disease often recurs. It was anecdotally observed in a small series that the patients whose GVHD resolved with thalidomide treatment did not relapse.[66] If this interesting observation is confirmed, it could mean that the immunomodulatory and/or antiangiogenesis effects of thalidomide may allow separation of GVHD and graft-versus-tumour effects in patients with established chronic GVHD.

2.10 Cancer Cachexia

High levels of TNFα have been linked with cancer cachexia and malaise. Because of its effects on TNFα, thalidomide was explored in 72 terminal cancer patients who were not receiving any cytotoxic therapy at the dose of 100mg at night for 10 days. Among the 37 evaluable patients, 44 to 69% reported significant improvement in insomnia, nausea, appetite and sensation of well-being.

3. Dosage and Administration

No systematic dose escalation studies of thalidomide have been performed in any disease. The

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