Anti-Cancer Drugs 2000, **11,** pp. 787–791

Review paper

Thalidomide in the treatment of cancer

Julian Weldon Adlard[1]
[1]Yorkshire Centre for Clinical Oncology, Cookridge Hospital, Leeds LS16 6QB, UK.

Thalidomide caused severe malformations in babies born to mothers taking the drug for morning sickness in the late 1950s and early 1960s. It is now known that these teratogenic effects are due to potent anti-angiogenic and immunomodulatory actions. These properties have lead to the testing of thalidomide in a number of infective, inflammatory and malignant conditions. Promising activity has been reported in myeloma, AIDS-related Kaposi's sarcoma, renal cell carcinoma and glioblastoma multiforme. A review is presented of the history of thalidomide and its recent development with an emphasis on applications in malignant disease.

Key words: Angiogenesis, cancer, neoplasms, thalidomide, tumor necrosis factor.

Introduction

Thalidomide was synthesized in 1953 and produced by the German pharmaceutical company Chemie Grünenthal. From 1956 to 1961 thalidomide was used as a sedative and anti-emetic in pregnancy, particularly in Europe and Canada. In the US the drug was kept off the market by the Federal Drug Administration (FDA) because of concerns over drug-induced neuropathy. It was not until 1961 that the teratogenicity of thalidomide was recognized following separate observations by McBride[1] and Lenz.[2] Up to 12 000 babies were born worldwide with thalidomide-induced malformations. The most recognized abnormalities are the severe limb defects known as phocomelia from the Greek for 'sealed limb'. Other malformations include absence of the auricles and deafness, and defects of the eye, face and internal organs. About 40% of victims died before their first birthday.

Correspondence to JW Adlard, Cookridge Hospital, Hospital Lane, Leeds LS16 6QB, UK.
Tel: (+44) 113 2673411; Fax: (+44) 113 3924072;
E-mail: jwa@doctors.org.uk

More recently, thalidomide has shown activity in a number of diseases. In particular, it has been used in leprosy.[3,4] The FDA licensed thalidomide in July 1998 for treatment of erythema nodosum leprosum (ENL). Following early reports of use in malignant disease[5,6] and increased understanding of its pharmacology, thalidomide is now being tested as an anti-neoplastic agent.

Pharmacology

Thalidomide is also known as *N*-α-phthalimidoglutarimide, having a two-ring structure with a phthalimide ring and a glutarimide ring (Figure 1). There are equal mixtures two enantiomers. It is only sparingly soluble in water and ethanol. There is no available i.v. formulation. By the oral route the time to maximal concentration is about 4 h, with an elimination half-life of about 8 h for doses of 200 mg and about 18 h for 800 mg.[7,8] The major route of elimination is by non-enzymatic hydrolysis. Only 0.7% is excreted in the urine. The drug is usually given as a single daily dose in the evening. Typical doses used in clinical trials have been 100–1200 mg daily.

Mechanisms of action

Thalidomide is an inhibitor basic fibroblast growth factor (bFGF)-induced angiogenesis.[9] The hepatic production of the active anti-angiogenic metabolite is species dependent and may explain why initial testing of thalidomide in rodents did not reveal its teratogenicity.[10,11]

Thalidomide also acts as a partial inhibitor of tumor necrosis factor (TNF)-α.[12] TNF-α is a cytokine produced by peripheral blood mononuclear cells, and to a lesser extent by lymphocytes and natural killer cells. It is involved in the host immune response to infections and in autoimmune disorders. TNF-α also enhances

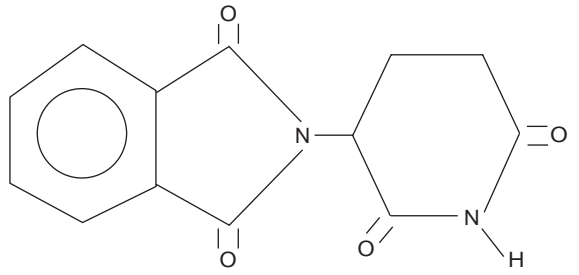

Figure 1. Structure of thalidomide.

angiogenesis by up-regulation of bFGF and vascular endothelial growth factor (VEGF). TNF-α and other cytokines are thought to be responsible for cachexia and fever of malignancy, and other abnormal immune responses such as septic shock syndrome, joint inflammation in rheumatoid arthritis and ENL. Thalidomide inhibits TNF-α by causing enhanced degradation of TNF-α messenger RNA. It also acts as a costimulatory factor for T cell activation and modulates production of other cytokines.[13] Other suggested mechanisms of action are via alteration of cell surface adhesion molecules and free-radical-mediated oxidative DNA damage.

Side effects and precautions

Teratogenicity is the most serious adverse effect of thalidomide. A single tablet taken during pregnancy can produce defects. The greatest risk is at 34–50 days after the last menstrual cycle. Dose-dependent somnolence and orthostatic hypotension are common, hence the drug is usually taken *nocte*. Constipation may necessitate a regular laxative. A pruritic erythematous macular rash and neutropenia have been reported, particularly in patients being treated for HIV and graft-versus-host disease. Peripheral neuropathy may be seen due to axonal degeneration without demyelination, usually in the toes and feet, and less often in the upper limbs. This side effect is age and dose dependent, and may be exacerbated by the concomitant use of other neurotoxic drugs such as cisplatin and vinca alkaloids. Peripheral neuropathy is reversible if the drug is stopped early. If continued the neuropathy may extend proximally and become permanent. Other side effects include brittle fingernails, decreased libido, endocrine effects, face and limb edema, mood changes, menstrual abnormalities, and weight gain.

In the US, thalidomide prescribing is monitored by the System for Thalidomide Education and Prescribing Safety (STEPS) program.[14] Registration is required of all participating prescribers, pharmacies and patients. Women who are post-hysterectomy or post-menopausal may be prescribed the drug. All potentially fertile women must undergo pregnancy testing within 24 h prior to starting treatment, weekly for 4 weeks and monthly thereafter (2 weekly in women with irregular menstrual cycles). Women are required to use two effective contraceptives, one highly effective (e.g. intrauterine device, oral contraceptive pill, partner's vasectomy) and one other (e.g. condom, diaphragm, cervical cap). Men taking thalidomide must use condoms during sex with women of childbearing age and women who are breast-feeding should not take the drug. Patients must sign an informed-consent form and individual prescriptions are given for no more than a 28-day period. Other countries have separate arrangements. For example, in the UK there is no licensed indication for thalidomide. However, the Committee on Safety of Medicines has published similar guidance.[15]

Cancer trials

Preclinical studies in animal models have supported an anti-neoplastic role for thalidomide.[16,17] Since 1997 there have been several reports of the use of thalidomide in advanced malignant disease. Most of these have been phase I/II studies in small numbers of heavily pretreated patients. These suggest small response rates in several tumor sites, with acceptable toxicities over a typical dose range of 100–1200 mg. There is no convincing evidence of a dose–response relationship and toxicities seem to be greater in the higher dose range. These studies are summarized in Table 1.[18–33]

Myeloma

A phase II trial enrolled 84 patients with myeloma who had been heavily pretreated (90% had received prior high-dose chemotherapy).[18] Oral thalidomide was given starting at 200 mg daily and increasing in 200 mg increments every 2 weeks to a maximum of 800 mg. Serum or urine paraprotein levels fell by at least 25% in 32% of patients including two complete responses. Paraprotein responses were usually associated with bone marrow responses. Median follow-up at the time of the report was short at just over a year. Of the responding patients, 44% were judged to have progressed at 12 months. Common side effects were constipation, fatigue and somnolence which were usually grade 1 or 2, but 11% of patients were unable to tolerate the drug; 47% reached the 800 mg dose level. These promising results have been supported by

Table 1. Single-agent phase I/II studies of thalidomide in malignant disease

Reference	Site	Evaluable Patients	Findings
Singhal[18]	myeloma	84	32% paraprotein fall by >25% in 32%
Barlogie[19]	myeloma	169	paraprotein fall by >25% in 36%
Kneller[20]	myeloma	17	paraprotein PR in 65%
Dimopolous[21]	Waldenstrom's	7	paraprotein PR in 43%
Fine[22]	high-grade glioma	36	6% PR, 6% MR, 33% SD
Marx[23]	glioblastoma	34	15% PR, 32% SD
Little[24]	AIDS-Kaposi's	17	47% PR, 12% SD
Politi[25]	AIDS-Kaposi's	12	17% PR, 58% SD
Ventura[26]	angiosarcoma	1	PR
Eisen[27]	renal	18	16% PR and 16% SD
Eisen[27]	ovary, melanoma, breast	48	No responses
Minor[28]	renal	12	8% PR, 8% MR
Patt[29]	hepatocellular	21	5% PR, 5% MR
Figg[30]	prostate	12	PSA improvement in 33%
Raza[31]	myelodysplasia	25	68% response
Baidas[32]	breast	28	No responses
Tseng[33]	head neck	17	No responses

PR, partial response; MR, minor response; SD, stable disease; PSA, prostate-specific antigen.

further reports in both myeloma and Waldenstrom's macroglobulinemia.[19–21]

Glioblastoma

The use of thalidomide for high-grade gliomas has been investigated in two small studies.[22,23] Single-agent response rates of 12–15% were found with disease stabilization in about a third of patients. Changes in serum bFGF were found to have possible prognostic implications,[23] but there was no correlation found with VEGF levels.[22] Ongoing trials are investigating combinations of thalidomide with radiotherapy and chemotherapy.

AIDS-related Kaposi's sarcoma

Vascular tumors such as Kaposi's sarcoma have been obvious targets for anti-angiogenic agents and thalidomide has shown promising levels of activity in this disease with response rates of up to 47%.[24,25] However, these studies were non-randomized and some of the responses may have been due to changes in anti-retroviral treatment or spontaneous regressions. There has also been a single case report of a response in angiosarcoma following failure of chemotherapy and radiotherapy.[26]

Others

Responses have also been reported in renal cell carcinoma[27,28] and hepatocellular carcinoma.[29] Reductions in prostate-specific antigen have been noted in patients with hormone-independent prostate cancer.[30] In the myelodysplastic syndromes thalidomide has shown evidence of good palliation with improvement in cytopenias and reduction in requirement for red cell transfusions.[31] Absence of responses have been noted in breast cancer,[27,32] squamous carcinomas of the head and neck,[33] and melanoma and ovary.[27]

Use in terminal care

A further suggested use of thalidomide is for the amelioration of symptoms of terminal cancer. TNF-α and other cytokines are thought to mediate symptoms such as anorexia, cachexia and night sweats. In addition to its anti-TNF-α properties, the sedative effects of thalidomide may be of benefit. The use of thalidomide at 100–200 mg daily in non-randomized open-label studies has been reported to improve symptoms of insomnia, nausea and poor appetite, and to enhance a feeling of general well-being in about half of the evaluable patients.[34–36]

Conclusions

Thalidomide has shown single-agent response rates in a number of cancers, most notably myeloma, AIDS-related Kaposi's sarcoma, glioblastoma multiforme and renal cell carcinoma. There are so far no reported phase III data and thalidomide remains unlicensed for use in malignant disease. There are side effects, but

generally these are tolerable, particularly in the lower dose range. The effects of appetite enhancement, suppression of night sweats and sedation can be of use in terminal care. There is understandable concern from some patients about taking the drug, and from thalidomide sufferers and others about its recent re-emergence. Prevention of pregnancy whilst on thalidomide remains of highest priority. New analogs of thalidomide are being developed which will hopefully have improved potency, and reduced teratogenic and side effect profiles.[37,38]

References

1. McBride WG. Thalidomide and congenital embryopathies. *Lancet* 1961; **ii**: 1358.
2. Lenz W. Thalidomide and congenital abnormalities. *Lancet* 1962; **i**: 45.
3. Sheskin J. The treatment of lepra reaction in lepromatous leprosy. Fifteen years' experience with thalidomide. *Int J Dermatol* 1980; **19**: 318–22.
4. Sampaio EP, Kaplan G, Miranda A, *et al*. The influence of thalidomide on the clinical and immunological manifestations of erythema nodosum leprosum. *J Infect Dis* 1993; **168**: 408–14.
5. Olson KB, Hall TC, Horton J, *et al*. Thalidomide (*N*-phthaloylglutamimide) in the treatment of advanced cancer. *Clin Pharmacol Ther* 1965; **6**: 292–7.
6. Grabstald H, Golbey R. Clinical experiences with thalidomide in patients with cancer. *Clin Pharmacol Ther* 1965; **6**: 298–302.
7. Chen TL, Vogelsang GB, Petty BG, *et al*. Plasma pharmacokinetics and urinary excretion of thalidomide after oral dosing in healthy male volunteers. *Drug Metab Disp* 1989; **17**: 402–5.
8. Figg WD, Raje S, Bauer KS, *et al*. Pharmacokinetics of thalidomide in an elderly prostate cancer population. *J Pharm Sci* 1999; **88**: 121–5.
9. D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide as an inhibitor of angiogenesis. *Proc Natl Acad Sci USA* 1994; **91**: 4082–5.
10. Bauer KS, Dixon SC, Figg WD. Inhibition of angiogenesis by thalidomide requires metabolic activation, which is species dependent. *Biochem Pharmacol* 1998; **55**: 1827–34.
11. Nguyen M, Tran C, Barsky JR, *et al*. Thalidomide and chemotherapy combination: preliminary results of preclinical and clinical studies. *Int J Oncol* 1997; **10**: 965–9.
12. Sampaio EP, Sarno EN, Galilly R, Cohn ZA, Kaplan G. Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes. *J Exp Med* 1991; **173**: 699–703.
13. Marriot JB, Muller G, Dalgleish AG. Thalidomide as an emerging immunotherapeutic agent. *Immunol Today* 1999; **20**: 538–40.
14. Lary JM, Daniel KL, Erickson JD, Roberts HE, Moore CA. The return of thalidomide: can birth defects be prevented? *Drug Saf* 1999; **21**: 161–9.
15. Anonymous. Guidance on Thalidomide. *Curr Prob Pharmacovigilance* 1994; **20**: 8.
16. Minchinton AI, Fryer KH, Wendt KR, Clow KA, Hayes MM. The effect of thalidomide on experimental tumours and metastases. *Anti-Cancer Drugs* 1996; **7**: 339–43.
17. Verheul HM, Panigrahy D, Yuan J, D'Amato RJ. Combination oral antiangiogenic therapy with thalidomide and sulindac inhibits tumour growth in rabbits. *Br J Cancer* 1999; **79**: 114–8.
18. Singhal S, Mehta J, Desikan R, *et al*. Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med* 1999; **341**: 1565–71.
19. Barlogie B. Thalidomide (T) in the management of multiple myeloma (MM): the arkansas experience in >300 patients (Pts) with single agent (SA) and combination chemotherapy (CT). *Proc Am Soc Clin Oncol* 2000; abstr 28.
20. Kneller A, Raanani P, Hardan I, *et al*. Therapy with thalidomide in refractory multiple myeloma patients—the revival of an old drug. *Br J Haematol* 2000; **108**: 391–3.
21. Dimopoulos M, Viniou N, Zomas A, *et al*. Activity of thalidomide in Waldenstrom's Macroglobulinemia. *Proc Am Soc Clin Oncol* 2000; abstr 99.
22. Fine HA, Figg WD, Jaeckle K, *et al*. Phase II trial of the antiangiogenic agent thalidomide in patients with recurrent high-grade gliomas. *J Clin Oncol* 2000; **18**: 708–15.
23. Marx GM, McCowatt S, Boyle F, *et al*. Phase II study of thalidomide as an anti-angiogenic agent in the treatment of recurrent glioblastoma multiforme (GBM). *Proc Am Soc Clin Oncol* 2000; abstr 613.
24. Little RF, Wyvill KM, Pluda JM, *et al*. Activity of thalidomide in AIDS-related kaposi's sarcoma. *J Clin Oncol* 2000; **18**: 2593–602.
25. Politi P, Reboredo G, Losso M, Vujacich C, Schwartsmann G, Lewi D. Phase I trial of thalidomide (T) in AIDS-related Kaposi sarcoma (KS). *Proc Am Soc Clin Oncol* 1998; abstr 161.
26. Ventura GJ, Roberts SC. Response of metastatic angiosarcoma to thalidomide; possible synergism with radiation therapy. *Proc Am Soc Clin Oncol* 2000; abstr 2268.
27. Eisen T, Boshoff C, Mak I, *et al*. Continuous low dose thalidomide: a phase II study in advanced melanoma, renal cell, ovarian and breast cancer. *Br J Cancer* 2000; **82**: 812–7.
28. Minor D, Elias L. Thalidomide treatment of metastatic renal cell carcinoma. *Proc Am Soc Clin Oncol* 2000; abstr 1384.
29. Patt YZ, Hassan MM, Lozano RD, *et al*. Phase II trial of thalomid (thalidomide) for treatment of non-resectable hepatocellular carcinoma (HCC). *Proc Am Soc Clin Oncol* 2000; abstr 1035.
30. Figg WD, Bergan R, Brawley O, *et al*. Randomized phase II study of thalidomide in androgen-independent prostate cancer (AIPC). *Proc Am Soc Clin Oncol* 1997; abstr 1189.
31. Raza A, Lisak L, Anderews C, *et al*. Encouraging improvement in cytopenias of patients with Myelodysplastic Syndromes (MDS) with thalidomide. *Proc Am Soc Clin Oncol* 2000; abstr 111.
32. Baidas S, Isaacs C, Crawford J, *et al*. A phase II evaluation evaluation of thalidomide in patients with metastatic breast cancer. *J Clin Oncol* 2000; **18**: 2710–7.
33. Tseng JE, Glisson BS, Khuri FR, *et al*. Phase II trial of thalidomide in the treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCHN). *Proc Am Soc Clin Oncol* 2000; abstr 1645.

34. Bruera E, Neumann E, Pituskin E, *et al*. Thalidomide in patients with cachexia due to terminal cancer: preliminary report. *Ann Oncol* 1999; **10**: 857–9.
35. Watanabe S, Pituskin E, Calder K, *et al*. Thalidomide (T) in the symptomatic treatment of cachexia in patients (pts) with terminal cancer. *Proc Am Soc Clin Oncol* 1999; abstr 180.
36. Boasberg PD, O'Day SJ, Weisberg M, Deck G, Frost J, Ye W. Thalidomide induced cessation of weight loss and improved sleep in advanced cancer patients with cachexia. *Proc Am Soc Clin Oncol* 2000; abstr 2396.
37. Corral LG, Kaplan G. Immunomodulation by thalidomide and thalidomide analogues. *Ann Rheum Dis* 1999; **58**(suppl 1): 1107–13.
38. Marriott JB, Westby M, Cookson S, *et al*. CC-3052: a water-soluble analog of thalidomide and potent inhibitor of activation-induced TNF-alpha production. *J Immunol* 1998; **161**: 4236–43.

(Received 25 August 2000; accepted 12 September 2000)