Current Status of Thalidomide in the Treatment of Cancer

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Tumor angiogenesis is a critical factor in the growth and metastasis of most malignant neoplasms. Thalidomide (Thalomid), banned from clinical use in the 1960s because of severe teratogenicity, has been shown to possess

Introduction

Thalidomide (Thalomid) has made a big comeback into clinical practice. It is actively being investigated for the treatment of a wide variety of malignant and nonmalignant conditions in the United States and around the world. Although the US Food and Drug Administration (FDA) has licensed thalidomide only for use in erythema nodosum leprosum (a type of immune reaction seen in leprosy), most prescriptions written today are for the treatment of various cancers, particularly multiple myeloma. Over the last 2 to 3 years, there has been a substantial increase in the number of studies of this agent for the treatment of cancer, and the results are being reported ongoingly. This article reviews the history, pharmacology, and current status of thalidomide in the treatment of cancer. Other related uses, including its role in the treatment of cancer cachexia, insomnia, and graft-vs-host disease, are beyond the scope of this review and are not discussed.

Brief Historical Background

Thalidomide was first introduced into clinical practice as a sedative. Beginning in the late 1950s, it was marketed in more than 40 countries. In the United States, the FDA was concerned about nerve damage and did not approve thalidomide for clinical use. In countries in which it was available, thalidomide became popular because of its association with good sleep quality and an unusually low risk of fatal overdose (unlike other sedatives marketed at the time).

Subsequently, thalidomide was found to be effective in the treatment of pregnancy-related morning sickness. Unfortunately, many women took thalidomide before its severe teratogenic potential was realized in 1961. As a result, almost 10,000 children worldwide were born with birth defects. The fetal malformations associated with thalidomide involved the extremities (phocomelia), ears, eyes, and the gastrointestinal tract.[1,2] Thalidomide was withdrawn from the market in 1962.

Pregnant women are vulnerable to its teratogenic effects between days 27 and 40 of gestation. The mechanism of its teratogenicity is unclear, but may be related to its antiangiogenic properties or inhibition of tumor necrosis factor-alpha (TNF-alpha) production.[3] Free-radical-mediated oxidative damage to DNA has also been postulated as a mechanism of its teratogenic effects.[4] A single pill (50 mg) may be sufficient to cause the teratogenic effects.

Despite its tragic past, thalidomide has reentered clinical practice due to its immunomodulatory and antiangiogenic properties. It was reported to be effective in the treatment of erythema nodosum leprosum in the mid-1960s.[5] Over the past 10 years, studies of thalidomide have confirmed its efficacy in the treatment of AIDS-related cachexia and aphthous ulcers. It has also been effective in the treatment of aphthous ulcers in patients with Behçet’s disease and in the treatment of chronic graft-vs-host disease. In 1998, the FDA approved thalidomide for use in erythema nodosum leprosum, with substantial precautions.

Early Clinical Trials of Thalidomide in Cancer

Thalidomide began to be studied as an anticancer agent within months of the discovery that it caused teratogenicity. In 1962, only 4 months after the initial reports of its severe teratogenicity,
Rogerson questioned whether a drug with such remarkable inhibitory powers on growing tissues can be used as an anticancer agent.[6] Within a week, Woodyatt responded that he had used thalidomide to treat a woman with a malignant mixed mesodermal tumor of the uterus, and was waiting to see if it demonstrated any activity.[7]

Over the next few years, interest in studying the drug as an anticancer agent persisted, and led to the initiation of at least two trials in the early 1960s. The Eastern Cooperative Oncology Group (ECOG) administered thalidomide to 21 patients with 14 types of advanced cancer, at doses ranging from 600 to 2,000 mg/d.[8] Included in the ECOG study were two patients with multiple myeloma. Although no tumor responses were noted, significant subjective palliation of symptoms was seen in seven patients (33%). The researchers also noted that there probably was a slowing of tumor growth in two patients with rapidly progressive disease. They concluded that further study was warranted.

Grabstad and Golbey reported on 71 patients who received treatment with thalidomide for a variety of cancers.[9] Doses ranged from 300 to 2,000 mg/d. One patient with renal cell carcinoma achieved resolution of pulmonary metastases. No other responses were seen. In addition to these two published studies, there was at least one other investigation conducted in more than 100 patients with advanced cancer, which failed to show any response to thalidomide therapy.[8]

It is not clear whether the lack of response seen in these trials was due to the advanced stage of the disease in the patients receiving treatment or whether it was just a reflection of the inadequate imaging methods used to measure response. In any case, following the completion of these initial trials, interest in thalidomide as an anticancer agent diminished greatly.

Tumor Angiogenesis

Angiogenesis—the formation of new blood vessels—occurs physiologically during embryonal growth, wound healing, and in the female genital system during the menstrual cycle. Angiogenesis is critical for the proliferation and metastases of most malignant neoplasms.[10] In the absence of angiogenesis, tumors cannot grow beyond 1 to 2 mm in size.[10] Increased angiogenesis is an adverse prognostic factor in several tumors, including hematologic malignancies such as myeloma.[11-15]

Over the past few years, there has been a marked interest in tumor angiogenesis, especially after the discovery of angiostatin and endostatin, two potent antiangiogenic compounds.[16,17] Enthusiasm for studying thalidomide as an anticancer agent has paralleled the increased interest in tumor angiogenesis due to reports suggesting that the drug possessed potent antiangiogenic properties.[18]

Thalidomide Therapy in Multiple Myeloma

Single-Agent Therapy in Relapsed Myeloma

Singhal and colleagues at the University of Arkansas conducted the first trial investigating the activity of thalidomide in relapsed myeloma.[19] Most patients in this study had failed stem cell transplantation. Treatment consisted of oral doses of thalidomide at 200 mg/d initially for 2 weeks, then increased by 200 mg/d every 2 weeks, up to a maximum daily dose of 800 mg/d, depending on toxicity. The overall response rate was 32%. Median time to response was 1 month. Approximately 10% of patients achieved ≥ 90% reduction in paraprotein levels. Paraprotein responses were accompanied by improvements in anemia and other symptoms.

Among the 48 patients who underwent repeat bone marrow analysis after thalidomide therapy, 81% had confirmation of paraprotein responses. The best predictor of response was a plasma cell labeling index < 0.2. Median duration of response had not been reached after 14.5 months of follow-up. Considering that 90% of patients in this study had failed transplantation, these results are impressive. An update to this study confirmed the activity of thalidomide in 169 patients with relapsed myeloma.[20,21] Overall survival at 18 months was 55%, and event-free survival was 30%.
We reported on 16 patients with relapsed myeloma treated at the Mayo Clinic on a similar schedule of thalidomide.[22,23] Of these patients, 25% had failed prior stem cell transplantation; 88% had received two or more chemotherapy regimens prior to beginning thalidomide therapy, including 25% who had failed four or more regimens. Four patients (25%) achieved a partial response to therapy, thus confirming the initial results obtained at the University of Arkansas. A larger Mayo Clinic phase II study of thalidomide in relapsed myeloma reconfirmed these findings.[24]

Several other groups have also demonstrated the single-agent activity of thalidomide in relapsed and refractory myeloma.[21, 23-34] Table 1 summarizes the results of the major trials of single-agent thalidomide in relapsed myeloma.[21,23-34] Response rates ranged from 25% to 75%. Based on the evidence thus far, thalidomide can clearly be recommended for the treatment of relapsed myeloma, although the FDA has not yet approved it for this indication.

Combination Therapy in Relapsed Myeloma

Ongoing studies are assessing the efficacy of thalidomide in combination with other effective agents for myeloma (Table 2).[33,35,36] In one investigation conducted by Weber and colleagues, 24 of 47 patients (52%) with resistant myeloma responded to the combination of thalidomide and dexamethasone.[35] Single-agent therapy with dexamethasone and thalidomide had previously failed in many (46%) of these patients, suggesting a synergistic effect with this combination.

Barlogie and colleagues have used thalidomide in a combination chemotherapy regimen known as DT-PACE (dexamethasone, thalidomide, cisplatin [Platinol], doxorubicin [Adriamycin], cyclophosphamide [Cytoxan, Neosar], etoposide) for patients with aggressive myeloma and plasma cell leukemia.[37] Responses were observed in four of five patients, including three who achieved a complete response. Updated results reported for 43 patients indicate a 40% response rate after two cycles of therapy, and no unfavorable effects on subsequent stem cell harvest.[38]

Coleman and colleagues are studying the combination of thalidomide, low-dose dexamethasone, and clarithromycin (Biaxin). Preliminary results show significant activity.[36] More data are needed, however, and the role of clarithromycin in the combination needs to be clarified. Kropff and colleagues are evaluating a combination of hyperfractionated cyclophosphamide, pulsed dexamethasone, and thalidomide.[39]

Previously Untreated Myeloma

Given the activity of thalidomide in relapsed myeloma, studies are now evaluating the effect of this agent as first-line therapy in previously untreated patients with myeloma (Table 1). Preliminary results from an ongoing Mayo Clinic study showed that the combination of thalidomide and dexamethasone is very active in this setting, with a response rate of 77%.[33] The initial protocol called for escalation of the dose of thalidomide up to 800 mg/d. However, among the first seven patients treated, two developed grade 3/4 skin toxicity including one patient with toxic epidermal necrolysis.[40] The protocol was then amended to stop dose escalation of thalidomide, and keep the dose constant at 200 mg for the subsequent 19 patients studied.

Major grade 3/4 toxicities included the development of a rash in three patients, and syncope, sedation, constipation, arrhythmia, and myalgia in one patient each. This regimen may be an appropriate oral alternative to infusional chemotherapy with VAD (vincristine, doxorubicin [Adriamycin], dexamethasone) as initial treatment of myeloma in preparation for stem cell transplantation. However, these results are preliminary and require further confirmation.

ECOG is developing a randomized trial of thalidomide plus dexamethasone vs dexamethasone alone in newly diagnosed symptomatic myeloma. This study will help confirm the activity of combination therapy with thalidomide plus dexamethasone in previously untreated myeloma and determine if there is any significant excess toxicity associated with this regimen. An ongoing randomized study at the University of Arkansas is investigating whether the addition of thalidomide to a chemotherapy regimen has a role in the management of newly diagnosed myeloma, and whether thalidomide has a role in posttransplant maintenance.
Thalidomide is also being studied as a single agent in patients with previously untreated asymptomatic myeloma. Initial reports show a response rate of approximately 35%. [33,34] However, because the main goal of therapy in patients with smoldering and indolent myeloma is to delay the need for chemotherapy, more data on the durability of response are needed before this strategy can be recommended for standard clinical practice. Moreover, the effect of prolonged thalidomide therapy on stem cell harvest is unknown.

**Summary of Thalidomide Therapy in Myeloma**

It is clear from the data discussed above that thalidomide is effective in the treatment of relapsed and refractory myeloma. In patients who are refractory to thalidomide, the addition of dexamethasone may induce a response, even if patients have previously failed steroid therapy. Studies are ongoing to define the role of thalidomide alone or in combination with other chemotherapeutic agents or dexamethasone in previously untreated myeloma. In light of toxicity concerns, previously untreated patients should receive thalidomide therapy primarily in the context of carefully conducted clinical trials. Further studies are needed to determine whether thalidomide has a role in maintenance therapy following transplantation.

**Thalidomide Therapy in Other Hematologic Malignancies**

Given its striking activity in myeloma, there is considerable interest in studying the role of thalidomide therapy in a wide spectrum of hematologic malignancies. Since these studies have only recently been initiated, most results described below are preliminary and need further confirmation. In addition to the hematologic malignancies discussed below, trials of thalidomide are being developed in chronic myeloid leukemia, chronic lymphocytic leukemia, and lymphomas.

**Waldenström’s Macroglobulinemia**

Dimopoulos and colleagues have studied thalidomide therapy in 20 patients with Waldenström’s macroglobulinemia. [41] More than a 50% reduction in paraprotein levels was seen in five patients (25%). Activity was also observed in previously untreated patients and in patients whose disease had relapsed. The median daily dose delivered was 200 mg/d. These results are encouraging and consistent with the responses observed in multiple myeloma.

**Acute Leukemia and Myelodysplastic Syndrome**

Raza and colleagues treated 51 patients with myelodysplastic syndrome with single-agent thalidomide therapy. [42] A partial response was seen in 21 (41%) of 51 patients. The most striking result was that eight patients who were previously transfusion dependent became completely independent of transfusions. Hematologic responses were noted in all three lineages, but in many cases, there was no decrease in bone marrow myeloblasts.

Thomas reported two responses among 15 evaluable patients with relapsed acute myeloid leukemia or high-risk myelodysplastic syndrome treated at the M. D. Anderson Cancer Center. [43] However, a recent study at the same institution has shown no benefit for the addition of thalidomide to induction therapy with liposomal daunorubicin (DaunoXome) and cytarabine in 74 previously untreated patients with poor-prognosis acute myeloid leukemia and myelodysplastic syndrome. [44]

**Myelofibrosis With Myeloid Metaplasia**

Early reports indicate that thalidomide is effective in myelofibrosis with myeloid metaplasia. [45,46] However, there are some concerns as to whether the drug may lead to serious myeloproliferative reactions including severe thrombocytosis. [47] Further studies continue in an attempt to clarify the nature of these unexpected reactions.

**Thalidomide in the Treatment of Solid Tumors**

Given the activity observed in relapsed myeloma, there is renewed interest in studying thalidomide
in advanced solid tumors. In 1997 and 1998, the FDA issued 575 single-patient investigational new drug (IND) applications for the use of thalidomide in advanced malignancies, including glioblastoma, melanoma, breast, colon, prostate, pancreatic, and renal cancers. The FDA recently reported the results of a survey of the practitioners requesting these INDs.[48] They received responses from 359 practitioners, with data on 480 patients.

Most patients were treated at doses of 200 to 400 mg/d. The most common adverse effects were sedation, constipation, rash, fatigue, and mental status changes. Responses were observed in 36 patients (8%). However, only 10 responders were not receiving other chemotherapy agents in combination with thalidomide, and the criteria for response were not defined. This report underscores the serious interest in studying thalidomide as an anticancer agent.

Several clinical trials of thalidomide in a variety of solid tumors are currently underway.[49-57] Table 3 summarizes the early results from these trials. In general, the role of thalidomide in solid tumors remains unknown.[49-57] The results discussed below are preliminary and need confirmation.

Kaposi’s Sarcoma

Little and colleagues recently investigated thalidomide in AIDS-related Kaposi’s sarcoma.[50] The rationale for studying thalidomide in this setting was based on the highly vascular nature of Kaposi’s sarcoma and the antiangiogenic properties of thalidomide. Twenty patients who had not previously received systemic therapy for Kaposi’s sarcoma were treated. The investigators observed eight responses on intent-to-treat analysis, yielding a response rate of 40%. The median tolerated dose was 600 mg/d, but the optimum dose needed to achieve a response remains to be determined. Because most patients also received concurrent antiretroviral therapy, the researchers recommended caution in interpreting results and called for additional studies.

Brain Tumors

Fine et al reported on 39 patients with recurrent glioma who were treated with thalidomide at doses ranging from 800 to 1,200 mg/d.[51] A partial response was seen in two patients (6%), and minor responses were seen in two others. The major toxicities were somnolence and constipation. Four patients had seizures, although all had a history of prior seizures or evidence of tumor progression at the time of the seizures. Changes in serum levels of basic fibroblast growth factor (bFGF) correlated with time to progression and survival. Another trial conducted by Marx and colleagues also suggests that thalidomide may have activity (15%) in recurrent glioma,[52] but larger studies are needed to confirm these observations.

Prostate Cancer

A randomized phase II trial from the National Cancer Institute reported by Figg et al used thalidomide at 400 and 1,200 mg/d in patients with hormone-refractory prostate cancer. Of 12 patients, 4 (30%) responded.[57] Toxicities were mainly of grade 1/2 severity. Patients receiving thalidomide for more than 6 months were at increased risk of developing peripheral neuropathy. It must be emphasized that the responses observed mainly represent an improvement in prostate-specific antigen (PSA) levels, and it is unclear whether this will translate into meaningful clinical benefit.

Renal Cancer

Eisen et al have reported the results of a clinical trial of low-dose thalidomide in 66 patients with an advanced malignancy.[53] Patients enrolled in the trial had metastatic melanoma or renal, ovarian, or breast cancer. The dose of thalidomide administered was 100 mg/d. Of 18 patients, 3 (17%) with renal cancer responded to therapy. Again, further confirmatory studies are needed, especially in light of the fact that spontaneous improvement is sometimes seen in patients with renal cancer.

Colorectal Cancer
Thalidomide is being studied in combination with irinotecan (Camptosar) in the treatment of advanced colorectal carcinoma at the University of Arkansas for Medical Sciences.[58] An interim analysis of the first nine patients treated in a pilot trial showed a marked decrease in gastrointestinal side effects that are the hallmark of irinotecan therapy. Vomiting and diarrhea were absent in eight patients; one patient had grade 1/2 diarrhea. One complete response and two partial responses were observed. The authors concluded that the combination effectively eliminated the major dose-limiting side effect of irinotecan, and they are planning a larger phase II trial.

**Pharmacology of Thalidomide**

Thalidomide (alpha-N-[phthalimido] glutarimide) is formulated as a racemic mixture, as the optically active S- and R-isomers [59]. The S-isomer may be responsible for its teratogenic effects, and the R-isomer for its sedative properties. The pharmacokinetic properties of thalidomide are not well known. The agent is only available as an oral formulation, and appears to be well absorbed. In a study of 34 patients with high-grade glioma, the maximum serum concentration following a single oral dose of 800 mg was achieved at a median of 4.7 hours.[51] The median maximum serum concentration was 4.09 mg/mL. The oral clearance, volume of distribution, and elimination half-life were 13.83 ± 7.79 L/h, 146.19 ± 92.63 L, and 8.28 ± 6.00 hours, respectively.

Upon absorption, thalidomide undergoes spontaneous nonenzymatic cleavage to over 20 metabolites.[59] The role or fate of these metabolites is not well known. Most appear to be excreted in the urine. Although a hepatic metabolite is felt to be involved in its antiangiogenic effect, most of the drug is not metabolized by the hepatic cytochrome P450 system.

**Mechanism of Action of Thalidomide in Cancer**

The major reason for the reemergence of thalidomide as an anticancer agent is related to the pioneering observations made by D’Amato and colleagues, who noted that the agent had potent antiangiogenic properties.[18] Indeed, laboratory studies using the rabbit cornea micropocket assay have shown that thalidomide has potent antiangiogenic properties, probably by blocking the action of angiogenic factors such as bFGF and vascular endothelial growth factor (VEGF).[18,60] Animal studies indicate that treatment with thalidomide can decrease vascular density in granulation tissue.[61] In studies of murine Lewis lung tumors, thalidomide reduced the development of metastases, and increased sensitivity to chemoradiotherapy.[62]

Thalidomide inhibits microvessel formation in the rat aortic ring assay and slows human aortic endothelial cell proliferation in the presence of human or rabbit microsomes, but not in the presence of rat microsomes.[63] In the absence of microsomes, thalidomide has no effect on either microvessel formation or cell proliferation. These studies suggest that a metabolite of thalidomide may be responsible for its antiangiogenic effects.

Although thalidomide was first studied in myeloma because of its antiangiogenic properties, its mechanism of action in cancer remains unclear. In the Arkansas myeloma study, there were no statistically significant differences in posttreatment microvessel density between responders and nonresponders.[19] We have confirmed these findings, and in our studies, pretreatment microvessel density has not been a predictor of response.[24,33] However, microvessel density is only a measure of the distance between vessels and may not necessarily decrease following any form of therapy, including transplantation.[64,65] Thus, the lack of a consistent decrease in bone marrow microvessel density following thalidomide therapy does not exclude an antiangiogenic mechanism of action for this agent, but does raise questions as to whether other mechanisms are involved.

In addition to its antiangiogenic effects, thalidomide has several immunomodulatory properties.[15] It inhibits the production of TNF-alpha by enhancing the degradation of TNF-alpha mRNA.[66] It may also bind to and increase the effect of alpha-1-acid glycoproteins, which possess intrinsic anti-TNF-alpha activity.[59,67] Its effect on TNF-alpha appears to be responsible for its efficacy in erythema nodosum leprosum and AIDS-related cachexia.[59]

Thalidomide stimulates cytotoxic T-cell proliferation, and induces the secretion of interferon-gamma
and interleukin 2 (IL-2) by these cells.[68] Similarly, it induces T-helper cell type 2 (TH2) cytokine production in human peripheral blood mononuclear cell cultures, while concomitantly inhibiting T-helper cell type 1 (TH1) cytokine production.[69] Thalidomide also modulates the expression of cell-surface adhesion molecules.[70] The effects of thalidomide on tumor microenvironment, VEGF, plasma cell apoptosis, and angiogenesis are all being actively investigated.[71]

**Dosage**

The optimal dosing schedule for thalidomide in cancer therapy has not been well studied. Most studies in myeloma and other cancers have used doses ranging from 200 to 800 mg/d, administered orally as a single dose at bedtime. The usual starting dose in myeloma is 200 mg/d, increased by 200 mg every 2 weeks to a maximum of 800 mg/d. The dose is then adjusted based on toxicity.[15] At present, the best dose is probably the highest dose that the patient can tolerate with a minimum of side effects. For most patients, this translates to a dose of 200 to 400 mg/d. Dose ranges in the presence of hepatic and renal dysfunction have not been established.

It is unclear whether there is a dose-response relationship, or whether smaller doses can be equally effective with lesser side effects. Durie and Stepan have observed responses in myeloma with doses as low as 50 mg/d.[28] However, some patients with myeloma who progress with lower doses of thalidomide (£ 400 mg/d) can respond to dose escalation (600 to 800 mg/d).

**Toxicity and Precautions**

Due to the risk of severe teratogenicity, the use of thalidomide in pregnant women is absolutely contraindicated. Both the prescribing physician and the dispensing pharmacy are required to register with the System for Thalidomide Education and Prescribing Safety (STEPS) program. Under this program, women in the childbearing age group must undergo pregnancy testing before beginning therapy, and every 2 to 4 weeks during treatment. They must abstain from sexual intercourse, or use two highly effective contraceptive methods during treatment. Males must abstain from sexual intercourse or use a condom while receiving treatment, even if they have had a successful vasectomy. All patients must continue the above measures for at least 1 month following the last dose of the drug. Breast-feeding is contraindicated. In the United States, all patients sign a consent form that explains the risks and precautions prior to starting therapy.

Thalidomide is generally well tolerated at doses below 400 mg/d. Most side effects are mild or moderate in severity, and can be controlled by appropriate dose reduction. The most common side effects are sedation, fatigue, constipation, and skin rash. Since severe constipation is a common problem, laxatives are recommended prophylactically. If a skin rash develops, the drug should be discontinued, and restarted at a lower dose after the rash clears. If severe exfoliation, Stevens-Johnson syndrome, or toxic epidermal necrolysis occur, use of the drug should cease, and it should not be used again. Thalidomide is also known to cause peripheral neuropathy, which generally develops following chronic use of the agent over a period of months. However, neuropathy can occur after relatively short-term use as well.

Less common but important side effects include edema, bradycardia, neutropenia, increased liver enzymes, deep-vein thrombosis, menstrual irregularities, impotence, hyper- or hypoglycemia, and hypothyroidism. Of these, the risk of deep-vein thrombosis (and possibly other thrombotic events) needs to be carefully studied, because patients with cancer are already at increased risk for thrombosis.

**Conclusions**

Thalidomide has emerged as an effective agent in the treatment of myeloma. Further studies in myeloma are ongoing to determine whether the agent can be used early in the treatment of this disease, and to understand its mechanism of action. The best dosing schedule, duration of therapy, and role in maintenance therapy also need to be determined. Its use in the treatment of other cancers remains strictly investigational. Preliminary data suggest promising activity in
Waldenström’s macroglobulinemia, myelodysplastic syndrome, myelofibrosis, and renal cell cancer. On the other hand, thalidomide appears to be ineffective in the treatment of breast, ovarian, and head and neck carcinomas.

Due its tragic past and increasing use in a variety of neoplastic and nonneoplastic conditions, patients and physicians must continue to exercise great caution when using or prescribing thalidomide. Safer thalidomide analogs are being developed,[71] to minimize the toxicities while preserving the drug’s beneficial effects.

**References:**


