Current role of thalidomide in cancer treatment

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Thalidomide (Thalidomid, Celgene, Warren, NJ) is a putative anti-angiogenesis and immunomodulatory agent that has demonstrated activity in various dermatologic and rheumatologic conditions in addition to Crohn's disease. The biologic effects of thalidomide and the clinical trials conducted in solid tumors, hematologic malignancies, chronic graft-versus-host disease (GVHD), and cancer-related cachexia are reviewed. A summary of the preliminary results of ongoing clinical trials is presented, and the future directions of thalidomide research in the oncology are discussed. Curr Opin Oncol 2000, 12:564–573

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Abbreviations:

bFGF	basic fibroblast growth factor
GM	glioblastoma multiforme
GVHD	graft-versus-host disease
IL	interleukin
TNF-α	tumor necrosis factor alpha
VEGF	vascular endothelial growth factor

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Historical perspective

Thalidomide was first introduced in 1953 by Chemie Grunenthal as an oral sedative-hypnotic [1]. It had no toxicity or addictive properties at therapeutic levels; however, peripheral neuritis was noted in some patients with long-term use. It was also used to ameliorate nausea and vomiting during pregnancy. In 1960, limb malformations and abnormalities of internal organs in newborns were associated with the maternal use of thalidomide. It was thus withdrawn from the market in 1961 due to its teratogenecity [2].

In 1965, the surprising activity of thalidomide in reactive lepromatous leprosy (seen during its use as a sedative-hypnotic) stimulated further study [3]. After a series of confirmatory placebo-controlled trials, thalidomide was approved by the Food and Drug Administration as treatment for the acute cutaneous manifestations of erythema nodosum leprosum and as maintenance therapy to prevent recurrence. Its immunomodulatory properties have been effective in other dermatologic diseases such as cutaneous lupus erythematosus, recurrent erythema multiforme, and recurrent aphthous ulcers (especially in AIDS patients) [3–7].

The first oncology studies of thalidomide were also reported in 1965. Grabstad and Golbey treated 71 patients with various malignancies with doses ranging from 300 mg to 2 g daily [8]. The one clinical responder had renal cell carcinoma metastatic to the lung and was treated after nephrectomy. Olson *et al.* [9] treated 21 patients with various solid tumors with doses ranging from 200 mg thrice daily up to 1400 mg daily. No tumor regressions were noted, but slowing of disease progression was observed in two patients, with palliation of symptoms in seven (33%). Because of the paucity of objective tumor responses, interest in thalidomide as an anti-cancer agent waned.

Recently, investigators discovered that the biologic effects of thalidomide include inhibition of angiogenesis and suppression of tumor necrosis factor alpha (TNF-α). Owing to these unique mechanisms of action and favorable side effect profile relative to chemotherapy (Table 1), the study of thalidomide as a potential anti-tumor agent has intensified.

Role for thalidomide in oncology: anti-angiogenesis

In 1971, Folkman [10] determined that angiogenesis was essential for tumor development. Progressive

Table 1. Rationale for thalidomide in oncology

Parameter	Chemotherapy	Thalidomide
Onset at effect	Rapid	Slower
Mechanism of action	Specific to agent	Inhibits bFGF- and VEGF-angiogenesis Inhibits TNF-α, IL-12, IL-6 Stimulates IL-2, IFN-γ Stimulates CD8+ T cells Alters adhesion molecules
Drug resistance	Commonly acquired	Less likely due to multiple targets without cross resistance
Toxicity		
Alopecia	Frequent	Rare
Gastrointestinal	Mucositis, nausea, diarrhea	Constipation
Myelosuppression	Frequent	Rare, more common in HIV, GVHD
Wound healing	Delayed	Delayed
Teratogenicity	Known with specific agents	Severe
Secondary	Risk with some agents (*eg*,etoposide)	No known mutagenicity, carcinogenicity
MDS/AML	Specific to agent (ara-C, ataxia; vincristine, peripheral neuropathy)	Somnolence; peripheral neuropathy with long-term use
Neurologic		
Clinical trial endpoint		
Phase I	Maximum tolerated dose	Maximum biologic effect
Phase II	Tumor reduction	Time to progression and survival
Combination	Overlapping toxicities, reduced doses required for drug combinations	Synergy with chemotherapy, XRT, other antiangiogenesis agents

AML, acute myelogenous leukemia; bFGF, basic fibroblast growth factor; GVHD, graft-versus-host disease; IFN-γ, interferon-γ; IL-6, interleukin-6; IL-12, interleukin-12; MDS, myelodysplasia; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor; XRT, radiation therapy.

recruitment of blood vessels to the tumor site resulted in proliferation and allowed cancer cells access to the vascular system for hematogenous spread. The degree of tumor vascularization is an independent prognostic factor for survival in carcinomas of the breast [11,12], lung [13], prostate [14,15], and esophagus [16]. The tumor vascular density also correlates with increased metastases, recurrences, or worse prognosis for carcinomas of the bladder [17,18], colon [19], and stomach [20], and for melanoma [21].

For hematologic malignancies, the pathologic correlate of tumor vascularization is bone marrow microvessel density. Studies in childhood acute lymphocytic leukemia [22], multiple myeloma [23–25], agnogenic myeloid metaplasia [26], and other acute and chronic leukemias [27] have shown increased marrow microvessel density to correlate with poor risk features. Promoters of angiogenesis such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and TNF-α are elevated in several hematopoietic malignancies [28,29].

In 1994, D'Amato *et al.* [30] showed that thalidomide inhibited bFGF-induced angiogenesis in a rabbit cornea micropocket assay. It also inhibited VEGF in a murine model of corneal vascularization [31]. In preclinical studies using a murine breast cancer model, thalidomide monotherapy did not reduce tumor size, but when combined with chemotherapy, prevention of distant lung and liver metastasis was observed compared with chemotherapy alone [32]. Other investigators have confirmed the anti-angiogenic effects of thalidomide after metabolic activation [33].

Cytokine modulation and other biologic effects of thalidomide

The level of TNF-α is elevated in various malignancies and other pathologic processes such as rheumatoid arthritis [34] and Crohn's disease [34]. It enhances neo-angiogenesis, interacts with other proliferative cytokines such as interleukin (IL)-6, and contributes to many of the systemic symptoms of advanced malignancy. TNF-α can induce endothelial production and secretion of collagenase, urokinase-type plasminogen activator, and plasminogen activator inhibitor (PAI)-1 to promote tumor expansion and metastasis. It induces bFGF mRNA (and collagenase and IL-6 mRNA) in human omental microvascular cells [35]. Soluble receptors for TNF-α are present in human ovarian and breast carcinomas [36,37].

Thalidomide inhibits TNF-α production by stimulated monocytes, macrophages, and neutrophils [38]. Proposed mechanisms include (1) decreased synthesis by accelerated degradation of TNF-α mRNA, (2) binding to α_1-acid glycoproteins with intrinsic anti-TNF-α activity, and (3) decreased binding activity of NFκB, which controls the activation of the TNF-α gene [38–41]. Thalidomide also inhibits monocyte IL-12 production, enhances synthesis of IL-2, and inhibits IL-6 [42–44].

Immunomodulatory effects on lymphocytes include (1) differential CD8+ T-cell stimulation resulting in decreased CD4/CD8 ratio, (2) shift from Th1 to Th2 T-cell responses, and (3) inhibition of T-cell proliferation in stimulated lymphocytes [45–48]. Thalidomide also inhibits neutrophil chemotaxis and modifies expression of surface adhesion molecules such as integrin receptors on leukocytes [49–51]. Direct anti-tumor effects of thalidomide include morphologic differentiation of the human leukemia cell line K562 in vitro [52].

Pharmacology and toxicity

Thalidomide is a racemate; the *S* and *R* isomer forms represent derivatives of *l*- and *d*-glutamic acid, respectively. The *S* isomer has been linked to teratogenicity, whereas the *R* isomer appears responsible for the sedative properties [53]. At physiologic pH, these isomers rapidly interconvert in vivo. The absolute bioavailability has not been characterized because of poor aqueous solubility. In studies of healthy volunteers and subjects with Hansen's disease, the mean time to peak plasma concentrations ranged from 2.9 to 5.7 hours, indicating that it is slowly absorbed from the gastrointestinal tract [54••]. The influence of food on the rate or extent of absorption has not been determined.

Side effects of thalidomide include somnolence, nausea, dry mouth and skin, skin rashes, constipation, increased appetite, headache, hypertension, bradycardia, dizziness and orthostatic hypotension, altered temperature sensitivity, irregularities in menstrual cycles, hypothyroidism, edema of lower extremities, teratogenicity, and peripheral neuropathy [54••]. Constipation can be controlled with an aggressive laxative regimen. Rash and leukopenia appear to be more common in AIDS patients and recipients of allogeneic bone marrow transplant. The immunomodulatory action of thalidomide has not been associated with an increased incidence of infections.

Adverse effects such as somnolence, nausea, and skin rashes are dose-dependent and generally resolve with discontinuation of therapy. Tachyphylaxis has been observed to the somnolence and can be minimized by administration at bedtime. Thalidomide appears to enhance the sedative effects of barbiturates and alcohol and the catatonic effects of chlorpromazine and reserpine. Thalidomide-induced sedation can be antagonized with the central nervous system stimulants methylphenidate and methylamphetamine.

Thalidomide-associated neuropathy is generally characterized by painful symmetric paresthesias in the toes and feet, and electrophysiologic findings are often consistent with axonal degeneration without demyelination [55–57]. Other associated symptoms include muscle cramps or weakness, signs of pyramidal tract involvement, and carpal tunnel syndrome. Rapid improvement is usually observed with discontinuation of therapy; however, cases of irreversible or longstanding sensory loss have been reported. The incidence of neuropathy appears to be increased in older patients and after administration of high cumulative doses; there may be a relation between slow acetylation and development of neuropathy.

Thalidomide is teratogenic and should never be used by women who are pregnant or who could become pregnant while taking the drug. Major human fetal abnormalities have been documented: amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, abnormalities or absence of organs (kidney, spleen, gallbladder), external ear abnormalities, facial palsies, eye abnormalities, and congenital heart defects. The highest risk occurs when the thalidomide is ingested during days 35 to 50 of pregnancy; severe effects can occur even with a single 100-mg dose. Thus, the drug must not be used at any time during pregnancy, and recommended contraceptive methods must be used by both women and men of child-bearing potential. Females on rifampin, rifabutin, barbiturates, steroids, phenytoin or carbamazepine should not rely on hormonal contraception, since efficacy is reduced. Studies of the plasma pharmacokinetics of oral contraceptives given concomitantly with thalidomide do not indicate reduced efficacy [58]. The S.T.E.P.S. program has been instituted to reduce fetal exposure; access is controlled by registration of prescribing physicians, dispensing pharmacies, and patients [59•]. A comprehensive consent process with educational materials is mandatory.

Clinical trials in solid tumor malignancies

High-grade gliomas

Two early phase II studies have shown promising activity of thalidomide in patients with recurrent high-grade gliomas (highly vascular tumors with high microvessel density are an adverse prognostic factor) such as anaplastic mixed glioma, anaplastic astrocytoma, or glioblastoma multiforme (GBM). Fine *et al.* [60••] administered 800 mg to 1200 mg daily to patients previously treated with external radiation therapy with or without chemotherapy. Two of 36 patients (6%) had partial responses, two (6%) had minor responses, and 12 (33%) had stable disease. Median time to progression was only 10 weeks for the entire group, but it was 33 weeks for the responders, 15 for those with stable disease, and 8 weeks for the nonresponders. Median survivals were 74, 30, and 22 weeks, respectively. Increases in bFGF correlated with progression and shorter survival. Adverse events were grade 4 seizures in four patients with prior history of seizures or tumor progression. Somnolence and constipation were the main toxicities attributable to thalidomide.

In another single-agent trial, 37 patients with recurrent GBM were treated with doses ranging from 100 mg to 500 mg daily [61]. Of the 34 patients evaluable, 5 (15%) had a partial response, 11 (32%) had stable disease, and 18 (53%) had progressive disease. No correlation between VEGF levels and outcome was observed. In a combination trial, 46 patients with recurrent high-grade gliomas were treated with carboplatin (AUC 8) and thalidomide 300 mg/m^2 daily [62]. Five partial responses (12%) were observed and 28 (70%) patients had stable disease with a median response duration of 24 weeks and estimated survival of 40 weeks. Hematologic toxicity was prominent in patients receiving prior nitrosurea. Major nonhematologic toxicities attributable to thalidomide were constipation and drowsiness. Complete results of these two trials are not yet published.

Kaposi's sarcoma

Recent data indicate that thalidomide is active in AIDS-related Kaposi's sarcoma. Fife et al. [63] conducted a phase II study of 100 mg daily for 8 weeks in 17 patients with cutaneous AIDS-related Kaposi's sarcoma. Six of 17 patients achieved a partial response (35%), and 8 patients withdrew from therapy because of toxicity (n=6), progression (n=1), or noncompliance (n=1). Interestingly, human herpesvirus 8 DNA load became undetectable in three of the five assessable partial responders.

Preliminary results of two additional studies have been reported. Politi *et al.* [64] treated 12 patients with doses ranging from 200 to 600 mg daily. Two of 12 patients (17%) responded at doses of 200 and 400 mg per day, respectively; 7 patients (58%) had stable disease. The partial responses lasted for 3+ and 8 months. The median time to disease progression was 4 months. Dose-dependent somnolence was observed, requiring cessation of therapy in two of three patients treated at 600 mg per day. Rash, headache, and paresthesias were observed. Yarchoan *et al.* [65] treated 13 patients with AIDS-related Kaposi's sarcoma in an escalating fashion beginning with 200 mg up to 1000 mg as tolerated. Four of 11 evaluable patients (36%) achieved a partial response. Two maintained their response at 30+ and 50+ weeks, whereas two progressed at 16 and 49 weeks. Five patients (45%) had stable disease ranging from 12 to 52 weeks. Rash, neutropenia, depression, and sedation were reported.

Renal cell carcinoma

In a large phase II study, Eisen *et al.* [66•] treated 66 advanced cancer (ovarian, melanoma, renal, breast) patients with thalidomide 100 mg daily. Three of 18 patients (17%) with renal cell carcinoma had partial responses, and 3 had stable disease for 3 months or longer. Two of the responders had failed bioimmunochemotherapy; tumor shrinkage was observed within 2 weeks of starting thalidomide. No other objective responses were observed, but patients had reduced insomnia and stabilization of weight loss. Toxicities included grade 2 lethargy (n=8), grade 2 neuropathy (n=2), and skin rashes. Progression correlated with increasing serum and urine levels of VEGF. Preliminary results of another phase II study in 15 patients with renal cell carcinoma used higher doses ranging from 400 mg to 1200 mg daily [67]. Of the 12 patients evaluable for response (at least 4 weeks of therapy), 1 had a partial response for 11+ months after failing IL-2, 1 had a minor response for 3+ months, 3 had stable disease, and 7 patients had progressive disease. Full results of this trial are not yet available.

Prostate cancer

Figg *et al.* [68] reported preliminary data of thalidomide in 63 patients with metastatic prostate cancer who had failed combined androgen blockade as well as antiandrogen withdrawal. The drug was administered at either a low dose (n=50, 200 mg daily) or high dose (n=13, titration to 1200 mg). Declines in prostate-specific antigen were observed in 58% and 68% of patients on the low-dose and high-dose arms, respectively. Eighteen percent treated with low-dose thalidomide had greater than 50% reductions in prostate-specific antigen, the longest maintained for 1.5 years. No objective tumor reductions were observed, but two patients had both symptomatic and radiographic improvement of bone scan lesions. Reduced bFGF levels were seen in responders. The most prevalent complaints were constipation, dizziness, edema, fatigue, xerostomia, and neurocortical symptoms. Peripheral neuropathy was observed with long-term use (> 9 months). Thalidomide upregulates prostate-specific antigen secretion in the human prostate cell line LNCaP [69], indicating that additional end points may be required to determine response in future trials.

Hepatocellular carcinoma

Patt *et al.* [70] studied patients with nonresectable hepatocellular carcinoma beginning at 400 mg daily with escalation to 1000 mg by week 5 (one-third dose was administered in the afternoon and two-thirds at bedtime). Twenty-seven patients were treated; 21 were evaluable for response. Preliminary results included one partial response and one minor response; 10 patients (48%) had stable disease for at least 2 months. Somnolence was observed in all patients, and grade 3–4 skin reactions were observed in 20%. One patient developed an exfoliative dermatitis. Combination trials with chemotherapeutic agents such as capecitabine are planned.

Melanoma

Reported thalidomide experience is limited in melanoma. Eisen *et al.* [66•] treated 17 patients with

advanced melanoma with low-dose thalidomide (100 mg daily). No objective responses were observed, but 4 patients (24%) had stable disease for up to 5 months. One patient was noted to have significant symptom control of his leg deposits.

Breast and ovarian cancer

Eisen *et al.* [66•] treated 12 patients with advanced breast cancer and 19 with ovarian carcinoma with low-dose thalidomide (100 mg daily); no objective responses were observed in these groups. Nguyen *et al.* [32] treated advanced breast cancer patients (n=7) with thalidomide (100 to 300 mg daily) in combination with cyclophosphamide, doxorubicin, and fluorouracil (CAF). Three patients had partial response, one had stable disease, two had progressive disease, and one was lost to follow-up.

Long *et al.* [71] treated seven patients with breast cancer after intensive chemotherapy and autologous stem cell transplant with thalidomide 400 mg orally daily beginning at hematologic recovery until day 180. Fatigue and mild somnolence were observed at the time of the report. Modulation of VEGF was noted. Full results of this study were not available; accrual was ongoing.

Squamous cell carcinoma of the head and neck and non-small cell lung cancer

Preliminary results of a phase II trial of escalating thalidomide (200 to 1200 mg) in 17 heavily pretreated patients with recurrent or metastatic squamous cell carcinoma of the head and neck was recently reported [72]. No objective tumor responses were observed, with 94% of the patients discontinuing thalidomide due to progressive disease. The median survival of 5.4 months was similar to that of historical control subjects.

A pilot study of thalidomide in combination with paclitaxel 225 mg/m^2 over 3 hours with carboplatin (AUC 6) was conducted in patients with advanced non-small cell lung cancer (unresectable stage IIIA, IIIB, or stage IV) [73]. Thalidomide was given 200 mg daily and escalated to 1000 mg as tolerated. Patients with stage III disease without pleural effusion received two cycles of combination therapy followed by external radiation therapy plus thalidomide; those with a pleural effusion or stage IV disease received six cycles of combination therapy without external radiation therapy. Preliminary results in nine patients showed no objective responses; all six patients receiving two cycles of chemotherapy had stable disease. One stage IIIB patient with a pleural effusion had progressive disease. The regimen was well tolerated, with fatigue, myalgias, constipation, and grade I neuropathy the most common complaints. The mean tolerated dose of thalidomide was 711 mg. Accrual was ongoing at the time of the report.

Miscellaneous solid tumor malignancies

The Food and Drug Administration summarized the results of a physician survey regarding 575 single-patient Investigative New Drug applications issued for thalidomide in 1997 and 1998 [74]. Of the 544 practitioners surveyed, 359 (66%) responded to yield data on 480 patients whose age ranged from 11 to 90 years (median 52 years). The most common malignancies treated were those of the breast, central nervous system (GBM), prostate, skin (melanoma), colon, pancreas, and kidneys (renal cell carcinoma). Thalidomide was given in doses up to 2400 mg daily, with 400 mg the most common dose (33%), followed by 200 mg (26%), 800 mg (18%), and 1200 mg (15%). Fifty-eight patients (31%) were prescribed thalidomide in combination with chemotherapy. Responses were observed in 36 patients (7.5%), 10 of those with combination therapy. Most patients (53%) discontinued therapy for progressive disease, whereas only 10% ceased thalidomide because of toxicity. The most common side effects reported were somnolence, constipation, rash, fatigue, and mental status changes. Overall it appeared that thalidomide was well tolerated with no increased toxicities attributable to combination therapy.

Clinical trials in hematologic malignancies

Multiple myeloma, plasma cell leukemia, Waldenstrom's macroglobulinemia

The remarkable efficacy of single-agent thalidomide in 84 patients with refractory or relapsed multiple myeloma (90% relapsed after high-dose chemotherapy) was reported recently by Singhal *et al.* [75••]. The initial dose was 200 mg daily with escalation by 200 mg every 2 weeks to a maximum dose of 800 mg. The maximum tolerable dose was then continued until progressive disease. Median duration of therapy was 52 days (range, 2 to 465) with 80% receiving at least 4 weeks of therapy.

Reduction in paraprotein levels (for at least 6 weeks) was observed in 32% of the patients. Two patients achieved a complete response. Responses in paraprotein correlated with reduction in plasma cells and improvements in hemoglobin levels and were apparent within 2 months in 78% of the patients. Mild to moderate constipation, weakness, fatigue, or somnolence occurred in one third of the patients; 11% discontinued therapy due to intolerance. Neurologic side effects included somnolence, dizziness, confusion, tremors, incoordination, tingling, and numbness. Decreases in marrow marrow microvessel density were observed; no direct correlation with response could be demonstrated. An update by Barlogie summarizing the Arkansas experience with thalidomide in multiple myeloma in over 300 patients (single-agent and combination therapy) confirmed the activity of thalidomide monotherapy in an additional 85 patients (total 169 patients) [76]. Eighty-four percent of the

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