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Review

Thalidomide as an anti-cancer agent

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Abstract

Thalidomide is a glutamic acid derivative initially introduced as a sedative hypnotic nearly forty years ago. It was withdrawn following numerous reports linking it to a characteristic pattern of congenital abnormalities in babies born to mothers who used the drug for morning sickness. It has gradually been re-introduced into clinical practice over the past two decades, albeit under strict regulation, since it was found to be useful in the management of erythema nodosum leprosum and HIV wasting syndrome. Recognition of its anti-angiogenic effect led to its evaluation in the treatment of various malignancies, where angiogenesis has been shown to play an important role. Numerous clinical trials done over the past four years have confirmed the significant anti-myeloma activity of this drug. It has also shown promise in preliminary trials in the treatment of a variety of different malignant diseases. The mechanisms of its antineoplastic effects continue to be the focus of ongoing research. It has become clear that even though its anti angiogenic effects play a significant role in the anti-tumor activity, there are other properties of this drug which are responsible as well. It also possesses anti-TNF alpha activity, which has led to its evaluation in several inflammatory states. In this concise review, we briefly describe the historical background and pharmacological aspects of this drug. We have concisely reviewed the current knowledge regarding mechanisms of its anti-neoplastic activity and the results of various clinical trials in oncology.

Keywords: Thalidomide - anti-neoplastic agent - angiogenesis - myeloma - TNF-alpha

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Historical background

Thalidomide was introduced into clinical practice in the late fifties in Germany as a non-barbiturate sedative-hypnotic. It was subsequently widely marketed in several countries in Europe, Asia and the Americas except the United States. It rapidly gained popularity as a sedative due its efficacy and an unusually low risk of fatal overdose unlike other sedatives of that time. A large number of pregnant women in these countries were prescribed this drug for morning sickness, for which it was found to be quite effective. It was not until the early sixties that reports linking thalidomide to certain birth defects began to appear in the medical literature [1]. Fetal malformations with thalidomide included absence of the ears, deafness, absence or hypoplasia of arms (phocomelia), preferentially affecting the radius and the thumb, defects of the femur and of the tibia and malformations of the heart, the bowel, the uterus, and the gallbladder. By the time the drug was withdrawn late 1961, nearly 10,000 children worldwide had been affected. The mechanism of thalidomide has been the subject of intense investigations during the last four decades and several hypotheses have been put forth. Animal studies have demonstrated abnormalities in the neural crest development [2] and others have shown changes in the mesonephros of the developing embryo which may lead to the limb abnormalities [3]. Its ability to inhibit angiogenesis may play a role in the developmental defects.

Ironically, the earliest clinical studies using thalidomide for other indications began soon after its withdrawal. Israeli physicians using thalidomide as a sedative in leprosy patients with erythema nodosum leprosum (ENL) observed striking improvement in the patients' symptoms. Based on the results of numerous studies done worldwide, FDA approved this drug in 1998 for the treatment of ENL. During the last decade many potential uses have been uncovered for this once shunned drug. It has been found to be effective in the treatment of HIV wasting syndrome, aphthous ulcers in patients with Behçet's disease and in the treatment of chronic graft versus host disease. The identification of its anti angiogenic properties led to its evaluation in therapy of neoplastic conditions, where the role of angiogenesis was being increasingly appreciated [4]. It hasn't been until the last few years that we have started understanding the mechanisms behind its therapeutic efficacy in different conditions.

Pharmacology

Thalidomide (α-N- [phthalimido] glutarimide, $C_{13}H_{10}N_2O_4$), a glutamic acid derivative, which exists in one of two optically active forms designated S-(-) or R-(+). These enantiomers are present in equal amounts and rapidly interconvert at physiologic pH. The *S* isomer may be responsible for its teratogenic effects, and the *R* isomer for its sedative properties.

Thalidomide is only available as an oral formulation due to its poor water solubility and this in turn has precluded an accurate estimation of its bioavailability. The time to peak concentration varies from 3 to 6 hours indicating a slow absorption [5]. No significant binding by plasma proteins have been described and it seems to have a large apparent volume of distribution [5, 6]. Most of the thalidomide appears to undergo spontaneous non-enzymatic hydrolytic cleavage in the circulation into several metabolites, many of which are active. Elimination of thalidomide is mainly by the spontaneous hydrolysis, which occurs in all body compartments [7]. The pharmacokinetics of thalidomide in individuals with hepatic and renal dysfunction remains poorly understood. No induction of its own metabolism has been noted with prolonged use. There is rapid elimination of thalidomide and its metabolites in the urine, with no thalidomide detected in the urine at 48 hours following a single dose. No effect of gender or age has been noted in the different studies.

Thalidomide is usually well tolerated at doses below 400mg/day and most of the side effects can be controlled by appropriate dose reduction. The reported side effects are shown in Table 1. The common adverse effects include sedation, fatigue, constipation, and skin rash. Prophylactic use of laxatives often prevents or minimizes

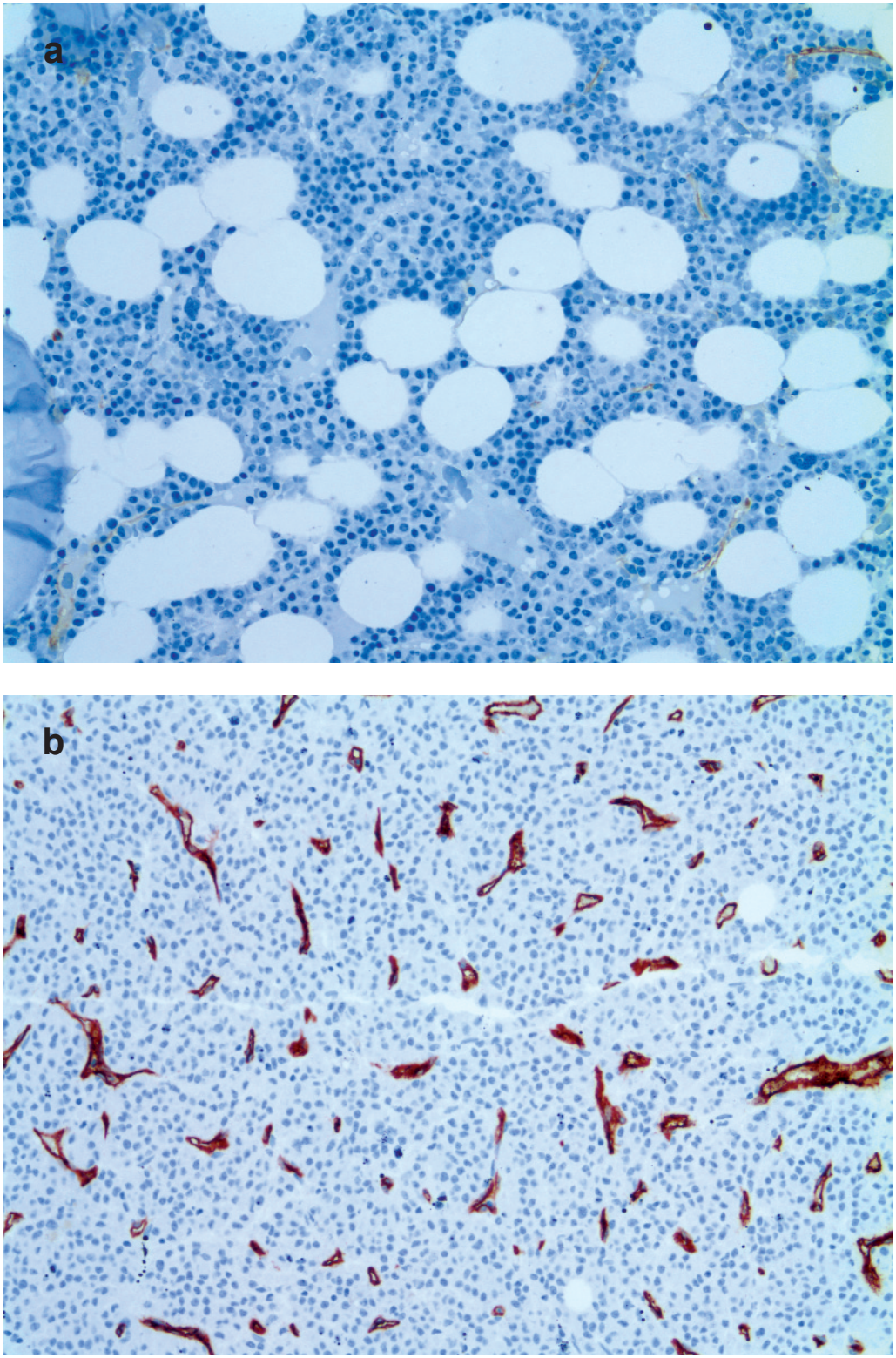

Fig. 1 Bone marrow biopsy specimens with immunohistochemical staining for CD34 at 200x magnification showing low grade angiogenesis in normal marrow (A), and high grade angiogenesis in newly diagnosed multiple myeloma (B). The increased angiogenesis seen in myeloma provided the rationale for initial trials of thaldiomide therapy in this disease.

constipation and is recommended. If a skin rash occurs, the drug should be discontinued, and restarted at a lower dose after the rash clears. Longer term use of thalidomide over months can cause peripheral neuropathy, though it has rarely been reported following short term use. Little is known about interactions between thalidomide and other medications. Due to the risk of severe teratogenicity, the use of thalidomide in pregnant women is absolutely contraindicated. Under the System for Thalidomide Education and Prescribing Safety (STEPS) program, instituted by the manufacturers of the drug, women in the childbearing age group must undergo pregnancy testing before starting therapy, and every 2-4 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 on treatment even if they have had a successful vasectomy. All patients must continue the above measures for at least one month following the last dose of the drug. Breast-feeding is contraindicated. In the United States all patients sign a consent that explains the risks and precautions prior to starting therapy.

The optimal dosing schedule for thalidomide as an anti-neoplastic agent is not clear. Doses between 200 and 800 mg/day, has been used in most of the cancer clinical trials. The best dose is probably the highest dose that patients can tolerate with the minimum of side effects, which in most patients is between 200 and 400 mg/day. As mentioned before, it is not clear if there is a dose response relationship, and if smaller doses can be equally effective with lesser side effects.

Table 1. Side effects of thalidomide therapy.

Common side effects:
Birth Defects
Drowsiness and Somnolence
Orthostatic hypotension and dizziness
Peripheral neuropathy
Constipation
Skin rash
Xerostomia
Neutropenia
Less common side effects
Steven-Johnson syndrome
Headache
Malaise
Asthenia
Impotence
Tremor
Peripheral Edema
Hepatitis (Elevated serum transaminases)
Hyper or hypoglycemia
Deep vein thrombosis
Confusion
Hair loss
Fever
Loss of libido
Nausea
Pruritus
Menstrual abnormalities
Hypothyroidism

Mechanism of action

Effect on angiogenesis

The mechanism(s) of action of thalidomide continue to be understood. It is pharmacologically classified as an immunomodulatory agent. Most of the initial work on the effects of thalidomide has been to understand the mechanisms behind its teratogenicity. D'Amato and colleagues while studying the mechanisms of teratogenicity discovered its anti angiogenic properties [4]. Based on their initial studies using rabbit cornea micro pocket assays, they hypothesized that these effects may be related to inhibition of bFGF and VEGF activity. Animal studies indicate that thalidomide treatment can decrease vascular density in granulation tissue. 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 [8]. 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 anti-angiogenic effects. In

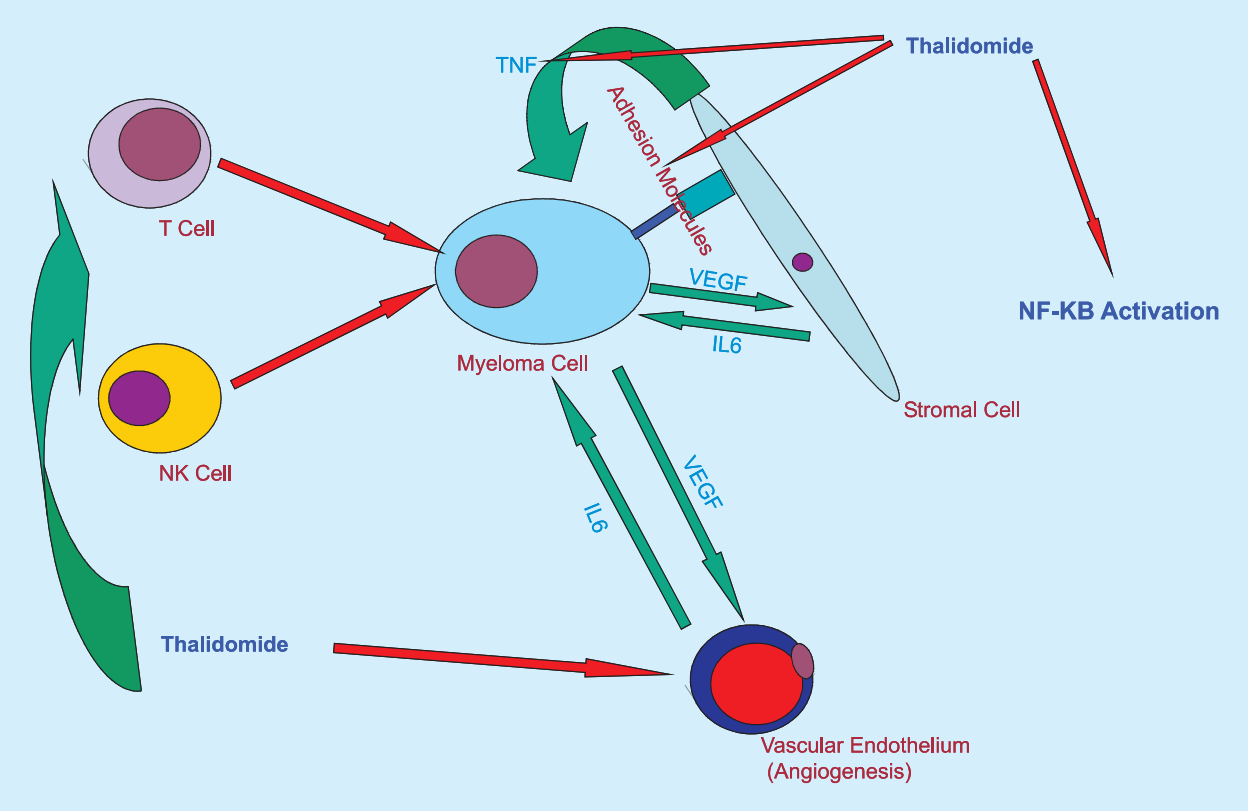

Fig. 2 Schematic depiction of the possible mechanisms of action of thalidomide. Green arrows denote a stimulatory effect and red arrows an inhibitory effect.

studies on murine Lewis lung tumors, thalidomide reduced the development of metastases, and increased sensitivity to chemoradiotherapy [9].

The critical role of angiogenesis in the pathology and progression of malignancies has been the subject of intense investigation since the initial observations by Folkman and colleagues in the early seventies [10]. Angiogenesis or new blood vessel formation from existing blood vessels (in contrast to vasculogenesis or de novo formation of blood vessels) occurs physiologically during normal growth, tissue healing and regeneration. The role of abnormal, increased angiogenesis in the development and spread of tumors is being increasingly recognized [11]. Increasing levels of tumor angiogenesis has been correlated with poor prognosis for a variety of solid tumors in humans [12-14]. As in solid tumors, new vessel formation (occurring in the bone marrow) seem to play an integral role in the pathophysiology of hematological malignancies like leukemias, myeloma [15] and in myelofibrosis with myeloid metaplasia. Increased bone marrow angiogenesis has been shown in these studies to be a poor prognostic indicator in acute leukemia as well as in multiple myeloma. In the case of multiple myeloma, the malignant cells are known to secrete a variety of different angiogenic cytokines including vascular endothelial growth factor (VEGF) [16], basic fibroblast growth factor (bFGF) [17] and hepatocyte growth factor (HGF) [18]. Vascular endothelial growth factor (VEGF) plays an important role in angiogenesis by acting as a potent inducer of vascular permeability as well as serving as a specific endothelial cell mitogen [16]. Stimulation of human microvascular endothelial cells and bone marrow stromal cells with recombinant human VEGF have been shown to induce a significant increase in interleukin-6

(IL-6) secretion, which is a potent growth factor for myeloma cells and an inhibitor of plasma cell apoptosis. Conversely, rhIL-6 was shown to stimulate VEGF expression and secretion in myeloma cell lines and to a variable degree in plasma cells purified from the marrow of patients with multiple myeloma [19]. Successful therapy of myeloma have been associated with decrease in the serum levels of VEGF, bFGF and HGF [20]. It was initially thought to express its anti-neoplastic effect mainly through its inhibition of angiogenesis. In studies involving its use in multiple myeloma, one of the first cancers to show benefit of therapy, there was no statistically significant difference between pre and post treatment microvessel density (MVD) [21]. We have also demonstrated that pre-treatment MVD is not been a predictor of response. However, MVD is only a measure of the distance between vessels and may not necessarily decrease following any form of therapy, including transplantation. The lack of a consistent decrease in bone marrow MVD following therapy does not necessarily exclude an anti-angiogenic mechanism of action. However, recent studies suggest that the anti angiogenic properties of thalidomide are modest at best and it probably affect tumors through a variety of other mechanisms as well.

Effect on tumor necrosis factor alpha (TNF-α)

Based on the studies done in the context of ENL, it has been shown to have an anti-TNF-α action. It can inhibit the production of TNFα by enhancing the degradation of TNF-α mRNA [22] and may also bind to and increase the effect of α1-acid glycoproteins, which possess intrinsic anti-TNFα activity [23]. This mechanism is different from that of other drugs that inhibit TNF like pentoxifylline or glucocorticoids. The demonstration of the anti TNF-α also led to exploration of its use in various other disease states known to be mediated by TNF-α like mycobacterial infections, endotoxic shock, graft versus host disease and various autoimmune disorders.

Effect on T lymphocytes

Thalidomide is a potent co-stimulator of primary human T cells in vitro, synergizing with stimulation via the T cell receptor complex to increase interleukin 2-mediated T cell proliferation and interferon gamma production. The co stimulatory effect is greater on the CD8+ than the CD4+ T cell subset [24]. The drug also increases the primary CD8+ cytotoxic T cell response induced by allogeneic dendritic cells in the absence of CD4+ T cells. In healthy male volunteers given 200 mg/day for 4 days, it significantly decreased the circulating T-helper to T-suppressor cell ratio [25]. It also 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. [26].

Other actions

Thalidomide can modulate the expression of cell surface adhesion molecules like TNF-α, ICAM-1 (CD54), VCAM-1 (CD106), E-selectin and L-selectin (CD62L) [27]. Its interference of leukocyte migration through modulation of cell adhesion molecules is believed to play an important role in ENL. Thalidomide has been reported to inhibit NFκB activity through suppression of IκB kinase activity and this may play a role in its anti inflammatory and anti neoplastic activity [28]. Thalidomide and some of its more potent analogues have been shown to induce apoptosis in myeloma cell lines that are refractory to conventional agents [29]. This mechanism may play a role in the other tumors as well. In addition thalidomide has been shown to be capable of inhibiting the cyclooxygenase 1 and 2 enzymes [30]. It is not clear if this contributes any to its antineoplastic activity. Some of the anti myeloma activity of thalidomide and its derivatives may be mediated by modulation of natural killer cell activity [31]. The effects of thalidomide on tumor microenvironment, VEGF, plasma cell apoptosis, and angiogenesis are all being actively investigated. A significant advantage of this drug is the lack of any myelosuppression or mutagenic effect.

Role in cancer therapy

The initial hope that the inhibitory effect of thalidomide on growing tissues can be used against cancer led to some early trials in the 60s. No significant benefit was observed and the drug was forgotten by the oncologists. The resurgence of interest in this drug as an antineoplastic agent in the nineties coincided with the appreciation of the role of angiogenesis in cancer biology [11] and the discovery of the anti angiogenic properties of thalidomide [4]. Angiogenesis or the formation of new blood vessels is critical for the proliferation and metastases of most malignant neoplasms and in its absence, tumors cannot grow beyond 1-2 mm in size. Increased angiogenesis has been uniformly shown to be an adverse prognostic factor in solid tumors as well as hematologic malignancies such as myeloma.

Multiple myeloma and other hematological malignancies

Myeloma was the first disease in which thalidomide resulted in a dramatic response rate and it remains the most studied. A number of clinical trials have been conducted looking at the use of thalidomide alone or in combination with other agents known to have anti-myeloma activity, in different patient groups with myeloma.

The first clinical trial of thalidomide for multiple myeloma was conducted at the University of Arkansas, and included 84 patients with relapsed, refractory myeloma [32], most of who had previous stem cell transplantation. There was a 32% response rate with reduction of paraprotein levels in serum or urine were by at least 90 percent in eight patients including two complete remissions and by at least 50 percent in seven patients. Common side effects observed were mild or moderate constipation, weakness or fatigue, or somnolence. The best predictor of a response was a low plasma cell labeling index. Considering the refractory nature of the disease in the patients in this study, these impressive results firmly placed thalidomide among the armamentarium for myeloma therapy. An update to this study confirms the activity of thalidomide in 169 patients with relapsed myeloma. [33] Overall survival at 18 months was 55% and event free survival was 30%.

Table 2. Phase II trials evaluating single agent thalidomide for relapsed/refractory multiple myeloma.

Trial	Number of evaluable patients	Starting dose (mg/day)	Maximum dose (mg/day)	Response rate (complete or partial response)
Tosi *et al.*, 2002[43]	60	100	800	47%
Schey *et al.*, 2002[44]	69	200	800	48%
Barlogie *et al.*, 2001 [36]	169	200	800	44%
Grosbois *et al.*, 2001 [38]	120	200	800	15%
Hus *et al.*, 2001[39]	53	200	400	35%
Durie *et al.*, 2001[40]	36	50	400	25%
Rajkumar *et al.*, 2001 [35]	32	200	800	31%
Bertolini *et al.*, 2001[41]	17	100	400	29%
Alexanian *et al.*, 2000 [45]	43	100-200	800	26%
Raza *et al.*, 2000 [42]	26	200	800	47%
Juliusson *et al.*, 2000 [37]	23	200	800	43%
Rajkumar *et al.*, 2000 [34]	16	200	800	25%

Several other groups have also demonstrated the single agent activity of thalidomide in relapsed and refractory myeloma [34-45]. Table 2 summarizes the results of clinical trials evaluating single agent thalidomide in relapsed/refractory myeloma. Response rates have ranged 25-69%. It is clear from these multiple studies that thalidomide is an active agent in patients with relapsed myeloma.

The efficacy of thalidomide in combination with other chemotherapeutic agents has been evaluated in a few small phase I/II studies. It has also been shown to be an effective agent when used upfront for newly diagnosed myeloma. In a phase II study of thalidomide and dexamethasone, conducted at the Mayo Clinic, 50 patients active myeloma were enrolled. Patients were treated with thalidomide at a fixed dose of 200 mg/day and dexamethasone was given orally at a dose of 40 mg/day orally on days 1-4, 9-12, 17-20 (odd cycles) and 40 mg/day days 1-4 (even cycles) repeated monthly. The overall response rate was 64%. In a smaller trial, patients with smoldering/indolent myeloma were treated with single agent thalidomide (200 to 800 mg/ day); we observed responses in 69% patients including six patients with more than 50% reduction in M protein. The Eastern Cooperative Oncology Group is currently planning a phase III randomized trial comparing the combination of thalidomide with dexamethasone against dexamethasone alone.

Thalidomide has been evaluated for the therapy of other plasma cell proliferative disorders like Waldenström's Macroglobulinemia (WM) [46] and Systemic amyloidosis [47] (Table 3). It has also been evaluated in the therapy of acute myelogenous leukemia (AML) [48] where the authors also observed a significant decrease in the microvessel densities in the responding patients treated with thalidomide, which was accompanied by declining plasma levels of bFGF. It has shown some degree of efficacy in the treatment of myelodysplastic syndrome, where it

Table 3. Clinical trials of thalidomide in hematological malignancies

Disease		Evaluable patients	Thalidomide starting dose (mg/day)	Thalidomide maximum dose (mg/day)	Response rate (complete or partial response)
Waldenstrom's macro-globulinemia [46]	Phase II	20	200	600	20%
Systemic amyloidosis [47]	Phase I/II	12	200	600	41%
Acute myelogenous leukemia [48]	Phase I/II	20	200	400	20%
Myelodysplastic syndrome [49]	Phase I/II	83	200	400	31%
Myelodysplastic syndrome [50]	Phase I/II	30	100	400	30%
Non-hodgkin lymphoma [52]	Phase II	12	200	800	8% CR, 25% SD
Myelofibrosis [61]	Phase II	15	200	400	80% (platelet count improved)
Myelofibrosis [51]	Phase II	13	100	400	43% (improved anemia)

CR = complete response; SD = stable disease.

Table 4. Clinical trials of thalidomide in solid tumors.

Disease	Trial type	Number of patients	Regimen	Thalidomide dose (mg/day)	Response rate (complete or partial response)
Prostate Cancer					
Figg *et al.* [53]	Phase II randomized	63	Thal	200-1200	27%
Figg *et al.* [54]	Phase II	36	Thal + Docetaxel	200	53%
Breast					
Baidas *et al.* [55]	Phase II	28	Thal	200-800 or 1200	No true PR or CR
Eisen *et al.* [62]	Phase II	12	Thal	100	No response
Kaposi's Sarcoma					
Fife *et al.* [56]	Phase II	17	Thal	100	35%
Little *et al.* [63]	Phase II	20	Thal	200-1000	47%
Renal					
Stebbing *et al.* [64]	Phase II	25	Thal	600	9%
Motzer *et al.* [65]	Phase II	26	Thal	200-800	62% (SD only)
Brain					
Fine *et al.* [57]	Phase II	36	Thal	800-1200	12% (33% SD)
Short *et al.* [66]	Phase II	18	Thal	100	6%
Marx *et al.* [67]	Phase II	42	Thal	100-500	5% (42% SD)
Melanoma					
Hwu *et al.* [58]	Phase II	38	Thal + Temozolomide	100-250	10%

OR = overall response; CR = complete response; PR = partial response.

has mostly helped stabilize the disease. In a study of 83 patients with MDS, Raza *et al.* noted hematologic improvement among 31% of evaluable patients including transfusion independence in nine patients who were previously transfusion dependant [49]. In another study thirty patients with MDS were treated with 100-400 mg/day of thalidomide resulting in hematological improvement in a third of the patients [50]. In both these studies, patients with higher platelet count and lower blast percentage at initiation of therapy were likely to respond. Barosi et al studied the role of thalidomide in 13 patients with myeloid metaplasia and noted improvement in anemia in three out of seven (43%), improvement in thrombocytopenia in two out of three (66.6%) and reduction in splenomegaly in four (30.8%) [51] . Doses as low

as 50 mg/day appeared to be effective in these patients. The role of angiogenesis is increasingly recognized in the pathogenesis of lymphoid malignancies and elevated serum levels of VEGF and bFGF have been correlated with poor prognosis in patients with NHL. In a phase II study by Pro et al one (8%) patient with refractory MALT lymphoma of the stomach achieved CR, 3(25%) had stable disease and 7 (63%) developed progressive of disease [52].

Role in solid tumors

Thalidomide has been evaluated in the treatment of a variety of solid tumors including prostate cancer, breast cancer, renal cancer and Kaposi's sarcoma in HIV positive and negative patients The results of various trials have been summarized in Table 4.

Figg et al conducted a phase II study evaluating two dosing regimens of thalidomide (200 mg/d vs 1200 mg/d) in androgen-independent prostate cancer (AIPC) [53]. Sixty three patients who had failed combined androgen deprivation were enrolled, 50 at the lower dose and 13 at the higher level. Serum prostate-specific antigen (PSA) decline of at least 50% was noted in 18% of patients on the low-dose arm and in none of the patients on the high-dose arm. Four patients were maintained for > 150 days. Ongoing trials are evaluating combinations of cytotoxic agents with thalidomide, initial studies of which appear promising [54].

Tumor angiogenesis has prognostic value in invasive breast cancer and has been shown to be correlated with metastatic potential. It was only logical that anti-angiogenic agents would be tried in its therapy. In a phase II randomized study, Baidas et al treated twenty-eight patients with progressive metastatic breast cancer either daily 200 mg of thalidomide or 800 mg to be escalated to 1,200 mg [55]. Each cycle consisted of 8 weeks of treatment. No patient had a true partial or complete response in this study at either of the dose levels. Evaluation of circulating angiogenic factors and pharmacokinetic studies failed to provide insight into the reason for the lack of efficacy.

The observation of Kaposi's sarcoma lesions improving in some individuals who were receiving thalidomide therapy for oral ulcers, combined with the highly vascular nature of this tumor formed the rationale for evaluating thalidomide in the treatment of KS. In a phase II study seventeen male HIV-seropositive patients with histopathologically diagnosed KS were treated with thalidomide 100mg orally once nightly for 8 weeks [56]. Six of 17 patients achieved a partial response associated with reduction in HHV8 DNA load to undetectable levels in 3 of the responders.

Stebbing et al evaluated the use of high-dose oral thalidomide (600 mg daily) in 25 patients with advanced renal carcinoma, who had either progressed on or were not suitable for immunotherapy. Of the 22 evaluable patients two showed partial responses (9%), seven (32%) had stable disease for more than 6 months and a further five (23%) had stable disease for between 3 and 6 months. In patients with SD > or = 3 months or an objective response, a significant decrease in serum TNF-alpha levels was seen. Ongoing clinical trials are examining the value of combining biological disease modifiers like interferon and interleukin 2 with thalidomide.

Fine et al reported a phase II clinical trial of thalidomide in patients with anaplastic mixed glioma, anaplastic astrocytoma, or glioblastoma multiforme who had tumor progression after radiotherapy with or without chemotherapy [57]. Patients were treated with escalating doses of thalidomide starting at 800 mg/d with increases in dose by 200 mg/d every 2 weeks to a final daily dose of 1,200 mg. Among the 39 patients who were accrued, there were two objective radiographic partial responses (6%), two minor responses (6%), and 12 patients with stable disease (33%). Eight patients were alive more than 1 year after starting thalidomide, although almost all with tumor progression. Again, thalidomide has been combined with other chemotherapy agents in the treatment of brain tumors.

Thalidomide has been used in combination with DTIC or temozolomide in the treatment of metastatic melanoma. Hwu et al studied thalidomide in combination with temozolomide in patients with unresectable stage III or stage IV melanoma without brain metastases [58]. TMZ 75 mg/m2/day for 6 weeks was followed by a 2-week break, and thalidomide at 200-400 mg/day. Of the

38 pts treated, 10 pts (26%) showed partial response, 4 pts showed minor response, 3 mixed response, 8 stable disease, and 13 had progressive disease. Frequent side-effects included rash, constipation, vomiting, dizziness, dyspnea, fatigue, headache, drowsiness, hyperglycemia and ALT/AST elevation.

Thalidomide has been studied in combination with irinotecan in metastatic colorectal cancer with some responses. Interestingly thalidomide ameliorated the common side effect of irinotecan, namely diarrhea, enabling a larger number of patients to complete planned therapy [59]. Responses have been observed in patients with unresectable hepatocellular carcinoma, with thalidomide alone or in combination with Cox-2 inhibitors. Phase II studies with thalidomide have been conducted in malignant mesothelioma, small cell lung cancer and metastatic neuroendocrine tumors.

Role in cancer supportive care

Cancer related anorexia and cachexia can be quite disabling and contributes to poor quality of life in patients with advanced cancer. Many pharmacological agents including progestogens and cannabis derivatives have been studied in this setting with variable benefits. Inflammatory cytokines like TNF-alpha are thought to play a key role in the etiology of this condition. Thalidomide has already been shown to be effective in the HIV wasting syndrome. Ongoing studies indicate that thalidomide may have a role in the treatment of cancer related anorexia and cachexia. In addition, preliminary studies have suggested that thalidomide may be effective in other syndromes related to advanced cancer, such as chronic nausea, insomnia, profuse sweating and pain.

Future directions

Enormous amount of work has been done in the past few years in trying to understand this once shunned drug. A large number of clinical trials currently underway are evaluating the role of this drug in a variety of different conditions from cancer to autoimmune disorders. Eventually as the evidence of efficacy accumulates, it is likely to get approval for many of these indications. However, the fear associated with this drug and the images of children with out limbs remain etched in the minds of many people. In spite of the very strict prescribing guidelines in place, there is always the danger of accidental exposure of pregnant women to this drug, and the risk will continue to increase with wider availability of the drug and expanding indications. This has lent a sense of urgency to understand the basis of its anti neoplastic activity as well as the teratogenicity. This information will allow us to develop derivatives or new drugs without the teratogenic effect. Thalidomide now belongs to a new class of immunomodulatory drugs known as IMiDs. A large number of these drugs are in various stages of development, including a few in phase I trials like the oral CC5013, an immunomodulatory thalidomide derivative which has been studied in patients with relapsed/refractory multiple myeloma [60].

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References

1. **McBride W.G.,** Thalidomide and congenital abnormalities, *Lancet*, **2**: 1358, 1961
2. **McCredie J.,** Neural crest defects. A neuroanatomic basis for classification of multiple malformations related to phocomelia, *J. Neurol. Sci.*, **28**: 373, 1976
3. **Lash J.W., Saxen L.,** Human teratogenesis: invitro studies on thalidomide-inhibited chondrogenesis, *Dev. Biol.*, **28**: 61, 1972
4. **D'Amato R.J., Loughnan M.S., Flynn E., Folkman J.,** Thalidomide is an inhibitor of angiogenesis, *Proceedings of the National Academy of Sciences of the United States of America*, **91**: 4082, 1994

5. **Figg W.D., Raje S., Bauer K.S., Tompkins A., Venzon D., Bergan R., Chen A., Hamilton M., Pluda J., Reed E.,** Pharmacokinetics of thalidomide in an elderly prostate cancer population, *J. Pharm. Sci.*, **88**: 121, 1999
6. **Piscitelli S.C., Figg W.D., Hahn B., Kelly G., Thomas S., Walker R.E.,** Single-dose pharmacokinetics of thalidomide in human immunodeficiency virus-infected patients, *Antimicrob. Agents Chemother*, **41**: 2797, 1997
7. **Eriksson T., Bjorkman S., Hoglund P.,** Clinical pharmacology of thalidomide, *Eur. J. Clin. Pharmacol.*, **57**: 365, 2001
8. **Bauer K.S., Dixon S.C., Figg W.D.,** Inhibition of angiogenesis by thalidomide requires metabolic activation, which is species-dependent, *Biochemical Pharmacology*, **55**: 1827, 1998
9. **Minchinton A.I., Fryer K.H., Wendt K.R., Clow K.A., Hayes M.M.,** The effect of thalidomide on experimental tumors and metastases, *Anti Cancer Drugs*, **7**: 339, 1996
10. **Folkman J.,** Tumor angiogenesis: therapeutic implications, *N. Engl. J. Med.*, **285**: 1182, 1971
11. **Folkman J.,** Seminars in Medicine of the Beth Israel Hospital, Boston. Clinical applications of research on angiogenesis, *New England Journal of Medicine*, **333**: 1757, 1995
12. **Vermeulen P.B., Verhoeven D., Fierens H., Hubens G., Goovaerts G., Van Marck E., De Bruijn E.A., Van Oosterom A.T., Dirix L.Y.,** Microvessel quantification in primary colorectal carcinoma: an immunohistochemical study, *Br. J. Cancer*, **71**: 340, 1995
13. **Weidner N., Folkman J., Pozza F., Bevilacqua P., Allred E.N., Moore D.H., Meli S., Gasparini G.,** Tumor angiogenesis: a new significant and independent prognostic indicator in early-stage breast carcinoma, *J. Natl. Cancer Inst.*, **84**: 1875, 1992
14. **Dickinson A.J., Fox S.B., Persad R.A., Hollyer J., Sibley G.N., Harris A.L.,** Quantification of angiogenesis as an independent predictor of prognosis in invasive bladder carcinomas, *British Journal of Urology*, **74**: 762, 1994
15. **Rajkumar S.V., Leong T., Fonseca R., Dispenzieri A., Lacy M.Q., Witzig T.E., Lust J.A., Gertz M. A., Kyle R.A., Greipp P.R.,** Bone marrow angiogenesis has prognostic value in multiple myeloma. An Eastern Cooperative Oncology Group Study, *Proc Am Soc Clin Oncol*, **18**: 19a, 1999
16. **Bellamy W.T., Richter L., Frutiger Y., Grogan T. M.,** Expression of vascular endothelial growth factor and its receptors in hematopoietic malignancies, *Cancer Research*, **59**: 728, 1999
17. **Rajkumar S. V., Yoon S. Y., Li C. Y., Roche P. C., Fonseca R., Dispenzieri A., Lacy M.Q., Lust J.A., Gertz M.A., Kyle R.A., Greipp P.R., Witzig T.E.,** Angiogenesis in myeloma: expression of basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF) and their receptors by neoplastic plasma cells, *Blood*, **94**: 303b, 1999
18. **Di Raimondo F., Azzaro M.P., Palumbo G., Bagnato S., Giustolisi G., Floridia P., Sortino G., Giustolisi R.,** Angiogenic factors in multiple myeloma: higher levels in bone marrow than in peripheral blood, *Haematologica*, **85**: 800, 2000
19. **Dankbar B., Padro T., Leo R., Feldmann B., Kropff M., Mesters R.M., Serve H., Berdel W. E., Kienast J.,** Vascular endothelial growth factor and interleukin-6 in paracrine tumor-stromal cell interactions in multiple myeloma, *Blood*, **95**: 2630, 2000
20. **Sezer O.,** Serum levels of the angiogenic cytokines basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) in multiple myeloma, *European Journal of Haematology*, **66**: 83, 2001
21. **Kumar S., Fonseca R., Dispenzieri A., Lacy M.Q., Lust J.A., Witzig T.E., Gertz M.A., Kyle R.A., Greipp P.R., Rajkumar S.V.,** Bone marrow (BM) angiogenesis in multiple myeloma (MM): effect of therapy and prognostic value, *Blood*, **96**: 363a, 2000
22. **Moreira A.L., Sampaio E.P., Zmuidzinas A., Frindt P., Smith K.A., Kaplan G.,** Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation, *Journal of Experimental Medicine*, **177**: 1675, 1993
23. **Niwayama S., Turk B. E., Liu J.O.,** Potent inhibition of tumor necrosis factor-alpha production by tetrafluorothalidomide and tetrafluorophthalimides, *J. Med. Chem.*, **39**: 3044, 1996
24. **Haslett P.A., Corral L.G., Albert M., Kaplan G.,** Thalidomide costimulates primary human T lymphocytes, preferentially inducing proliferation, cytokine production, and cytotoxic responses in the CD8+ subset, *Journal of Experimental Medicine*, **187**: 1885, 1998
25. **Gad S.M., Shannon E.J., Krotoski W.A., Hastings R.C.,** Thalidomide induces imbalances in T-lymphocyte sub-populations in the circulating blood of healthy males, *Lepr. Rev.*, **56**: 35, 1985
26. **McHugh S.M., Rifkin I.R., Deighton J., Wilson A. B., Lachmann P.J., Lockwood C.M., Ewan P.W.,** The immunosuppressive drug thalidomide induces T helper cell type 2 (Th2) and

concomitantly inhibits Th1 cytokine production in mitogen- and antigen-stimulated human peripheral blood mononuclear cell cultures, *Clinical & Experimental Immunology*, **99**: 160, 1995

27. **Geitz H., Handt S., Zwingenberger K.,** Thalidomide selectively modulates the density of cell surface molecules involved in the adhesion cascade, *Immunopharmacology*, **31**: 213, 1996
28. **Keifer J.A., Guttridge D.C., Ashburner B.P., Baldwin A.S., Jr.,** Inhibition of NF-kappa B activity by thalidomide through suppression of Ikappa B kinase activity, *J.Biol. Chem.*, **276**: 22382, 2001
29. **Hideshima T., Chauhan D., Shima Y., Raje N., Davies F.E., Tai Y.T., Treon S.P., Lin B., Schlossman R.L., Richardson P., Muller G., Stirling D.I., Anderson K.C.,** Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy, *Blood*, **96**: 2943, 2000
30. **Noguchi T., Shimazawa R., Nagasawa K., Hashimoto Y.,** Thalidomide and its analogues as cyclooxygenase inhibitors, *Bioorg. Med. Chem. Lett.*, **12**: 1043, 2002
31. **Davies F.E., Raje N., Hideshima T., Lentzsch S., Young G., Tai Y.T., Lin B., Podar K., Gupta D., Chauhan D., Treon S.P., Richardson P.G., Schlossman R.L., Morgan G.J., Muller G.W., Stirling D.I., Anderson K.C.,** Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma, *Blood*, **98**: 210, 2001
32. **Singhal S., Mehta J., Desikan R., Ayers D., Roberson P., Eddlemon P., Munshi N., Anaissie E., Wilson C., Dhodapkar M., Zeddis J., Barlogie B.,** Antitumor activity of thalidomide in refractory multiple myeloma, *New England Journal of Medicine*, **341**: 1565, 1999
33. **Barlogie B., Spencer T., Tricot G., Zeldis J., Munshi N., Zangari M., Badros A., Toor A., Shaughnessy J., Morris C., Desikan R.,** Long term follow up of 169 patients receiving a phase II trial of single agent thalidomide for advanced and refractory multiple myeloma (MM), *Blood*, **96**: 514a, 2000
34. **Rajkumar S. V., Fonseca R., Dispenzieri A., Lacy M.Q., Lust J.A., Witzig T.E., Kyle R.A., Gertz M. A., Greipp P.R.,** Thalidomide in the treatment of relapsed multiple myeloma, *Mayo Clin. Proc.*, **75**: 897, 2000
35. **Rajkumar S.V., Dispenzieri A., Lacy M.Q., Geyer S., Itturia N., Fonseca R., Hayman S.R., Lust J. A., Kyle R.A., Greipp P.R., Gertz M.A., Witzig T. E.,** Response Rate and Durablity of Response with Thalidomide Therapy for Relapsed Multiple Myeloma (MM), *Blood*, **98**: 162a, 2001
36. **Barlogie B., Desikan R., Eddlemon P., Spencer T., Zeldis J., Munshi N., Badros A., Zangari M., Anaissie E., Epstein J., Shaughnessy J., Ayers D., Spoon D., Tricot G.,** Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: identification of prognostic factors in a phase 2 study of 169 patients, *Blood*, **98**: 492, 2001
37. **Juliusson G., Celsing F., Turesson I., Lenhoff S., Adriansson M., Malm C.,** Frequent good partial remissions from thalidomide including best response ever in patients with advanced refractory and relapsed myeloma, *Br. J. Haematol.*, **109**: 89, 2000
38. **Grosbois B., Bellissant E., Moreau P., Attal M., Zerbib R.,** Thalidomide (Thal) in the Treatment of Advanced Multiple Myeloma (MM). A Prospective Study of 120 Patients, *Blood*, **98**: Abstract 689, 2001
39. **Hus M., Dmoszynska A., Soroka-Wojtaszko M., Jawniak D., Legiec W., Ciepnuch H., Hellmann A., Wolska-Smolen T., Skotnicki A., Manko J.,** Thalidomide treatment of resistant or relapsed multiple myeloma patients, *Haematologica*, **86**: 404, 2001
40. **Durie B., Stepan D.E.,** Low Dose Thalidomide Alone and in Combination: Long Term Follow-Up, *Blood*, **98**: 163a, 2001
41. **Bertolini F., Mingrone W., Alietti A., Ferrucci P. F., Cocorocchio E., Peccatori F., Cinieri S., Mancuso P., Corsini C., Burlini A., Zucca E., Martinelli G., Cineri S.,** Thalidomide in multiple myeloma, myelodysplastic syndromes and histiocytosis. Analysis of clinical results and of surrogate angiogenesis markers, *Ann. Oncol.*, **12**: 987, 2001
42. **Raza S. N., Veksler Y., Sabir T., Li Z., Anderson L., Jagannath S.,** Durable response to thalidomide in relapsed/refractory multiple myeloma (MM), *Blood*, **96**: 168a, 2000
43. **Tosi P., Zamagni E., Cellini C., Ronconi S., Patriarca F., Ballerini F., Musto P., Di Raimondo F., Ledda A., Lauria F., Masini L., Gobbi M., Vacca A., Ria R., Cangini D., Tura S., Baccarani M., Cavo M.,** Salvage therapy with thalidomide in patients with advanced relapsed/refractory multiple myeloma, *Haematologica*, **87**: 408, 2002
44. **Schey S., Jones R. W., Cavenagh J., Johnson R.,** Thalidomide (T) in relapsed/refractory multiple myeloma (MM): a UK Myeloma Forum study: 6, 9, and 12-month results, *Proc. ASCO*: Abstract 1102, 2002
45. **Alexanian R., Weber D., Giralt S., Delasalle K.,** Consolidation Therapy of Multiple Myeloma with

Thalidomide-Dexamethasone after Intensive Chemotherapy, *Blood*, **98**: Abstract 686, 2001

46. **Dimopoulos M.A., Zomas A., Viniou N.A., Grigoraki V., Galani E., Matsouka C., Economou O., Anagnostopoulos N., Panayiotidis P.,** Treatment of Waldenstrom's macroglobulinemia with thalidomide, *J. Clin. Oncol.*, **19**: 3596, 2001
47. **Seldin D.C., Choufani E., Skinner M., Wright D.G., Dember L., Weisman J., Fennessey S., Finn K., Sanchorwala V.,** A phase I/II trial of thalidomide for patients with AL amyloidosis, *Blood*, **98**: Abstract 691, 2001
48. **Steins M.B., Padro T., Bieker R., Ruiz S., Kropff M., Kienast J., Kessler T., Buechner T., Berdel W.E., Mesters R.M.,** Efficacy and safety of thalidomide in patients with acute myeloid leukemia, *Blood*, **99**: 834, 2002
49. **Raza A., Meyer P., Dutt D., Zorat F., Lisak L., Nascimben F., du Randt M., Kaspar C., Goldberg C., Loew J., Dar S., Gezer S., Venugopal P., Zeldis J.,** Thalidomide produces transfusion independence in long-standing refractory anemias of patients with myelodysplastic syndromes, *Blood*, **98**: 958, 2001
50. **Zorat F., Shetty V., Dutt D., Lisak L., Nascimben F., Allampallam K., Dar S., York A., Gezer S., Venugopal P., Raza A.,** The clinical and biological effects of thalidomide in patients with myelodysplastic syndromes, *Br. J. Haematol.*, **115**: 881, 2001
51. **Barosi G., Grossi A., Comotti B., Marchetti M.,** Thalidomide in patients with myelofibrosis with myeloid metaplasia, *Blood*, **96**: 746a, 2000
52. **Pro B., Younes A., Albitar M., Hagemeister F. B., Rodriguez M.A., McLaughlin P., Clemons M., Samaniego F., Cabanillas F.,** Phase II study of thalidomide in patients with recurrent Hodgkin's disease (HD) and non-Hodgkin's lymphomas (NHL), *Blood*, **98**: Abstract 4712, 2001
53. **Figg W. D., Dahut W., Duray P., Hamilton M., Tompkins A., Steinberg S.M., Jones E., Premkumar A., Linehan W.M., Floeter M.K., Chen C.C., Dixon S., Kohler D.R., Kruger E.A., Gubish E., Pluda J.M., Reed E.,** A randomized phase II trial of thalidomide, an angiogenesis inhibitor, in patients with androgen-independent prostate cancer, *Clin. Cancer Res.*, **7**: 1888, 2001
54. **Figg W.D., Arlen P., Gulley J., Fernandez P., Noone M., Fedenko K., Hamilton M., Parker C., Kruger E.A., Pluda J., Dahut W.L.,** A randomized phase II trial of docetaxel (taxotere) plus thalidomide in androgen-independent prostate cancer, *Semin. Oncol.*, **28**: 62, 2001
55. **Baidas S.M., Winer E.P., Fleming G.F., Harris L., Pluda J.M., Crawford J.G., Yamauchi H., Isaacs C., Hanfelt J., Tefft M., Flockhart D., Johnson M.D., Hawkins M.J., Lippman M.E., Hayes D.F.,** Phase II evaluation of thalidomide in patients with metastatic breast cancer, *J. Clin. Oncol.*, **18**: 2710, 2000
56. **Fife K., Howard M.R., Gracie F., Phillips R.H., Bower M.,** Activity of thalidomide in AIDS-related Kaposi's sarcoma and correlation with HHV8 titre, *Int. J. STD. AIDS*, **9**: 751, 1998
57. **Fine H.A., Figg W.D., Jaeckle K., Wen P.Y., Kyritsis A.P., Loeffler J.S., Levin V.A., Black P. M., Kaplan R., Pluda J.M., Yung W.K.,** Phase II trial of the antiangiogenic agent thalidomide in patients with recurrent high-grade gliomas, *J. Clin. Oncol.*, **18**: 708, 2000
58. **Hwu W.J., Krown S.E., Menell J.H., Panageas K.S., Merrell J., Quinn C.J., Chapman P.B., Livingston P.O., Wolchok J.D., Williams L.J., Houghton A.N.,** Temozolomide (TMZ) plus thalidomide in patients with advanced melanoma: a phase II trial, *Proc. ASCO*: Abstract 1372, 2002
59. **Govindarajan R.,** Irinotecan and thalidomide in metastatic colorectal cancer, *Oncology (Huntingt)*, **14**: 29, 2000
60. **Richardson P.G., Schlossman R.L., Hideshima T., Davies F., LeBlanc R., Catley L., Doss D., Kelly K.A., McKenney M., Mechlowicz J., Freeman A., Deocampo R., Rich R., Ryoo J., Chauhan D., Munshi N., Weller E., Thomas S., Zeldis J., Anderson K.C.,** A phase 1 study of oral CC5013, an immunomodulatory thalidomide (Thal) derivative, in patients with relapsed and refractory multiple myeloma (MM). *Blood*, **98**: 775a, 2001
61. **Elliott M. A., Mesa R. A., Li C. Y., Hook C. C., Ansell S. M., Levitt R. M., Geyer S. M., Tefferi A.,** Thalidomide treatment in myelofibrosis with myeloid metaplasia, *Br. J. Haematol.*, **117**: 288, 2002
62. **Eisen T., Boshoff C., Mak I., Sapunar F., Vaughan M.M., Pyle L., Johnston S.R., Ahern R., Smith I.E., Gore M.E.,** Continuous low dose thalidomide: a phase II study in advanced melanoma, renal cell, ovarian and breast cancer, *Br. J. Cancer*, **82**: 812, 2000
63. **Little R.F., Wyvill K.M., Pluda J.M., Welles L., Marshall V., Figg W.D., Newcomb F.M., Tosato G., Feigal E., Steinberg S.M., Whitby D., Goedert J.J., Yarchoan R.,** Activity of thalidomide in AIDS-related Kaposi's sarcoma, *J. Clin. Oncol.*, **18**: 2593, 2000
64. **Stebbing J., Benson C., Eisen T., Pyle L., Smalley K., Bridle H., Mak I., Sapunar F., Ahern R., Gore M. E.,** The treatment of advanced renal cell cancer with high-dose oral thalidomide, *Br. J. Cancer*, **85**: 953, 2001

65. **Motzer R.J., Berg W., Ginsberg M., Russo P., Vuky J., Yu R., Bacik J., Mazumdar M.,** Phase II trial of thalidomide for patients with advanced renal cell carcinoma, *J. Clin. Oncol.*, **20**: 302, 2002
66. **Short S.C., Traish D., Dowe A., Hines F., Gore M., Brada M.,** Thalidomide as an anti-angiogenic agent in relapsed gliomas, *J. Neurooncol.*, **51**: 41, 2001
67. **Marx G.M., Pavlakis N., McCowatt S., Boyle F. M., Levi J.A., Bell D.R., Cook R., Biggs M., Little N., Wheeler H.R.,** Phase II study of thalidomide in the treatment of recurrent glioblastoma multiforme, *J. Neurooncol.*, **54**: 31, 2001