

Review

Thalidomide

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Despite its history as a human teratogen, thalidomide is emerging as a treatment for cancer and inflammatory diseases. Although the evolution of its clinical application could not have been predicted from the tragedy associated with its misuse in the past, its history serves as a lesson in drug development that underscores the need to understand the molecular pharmacology of a compound's activity, including associated toxicities. Here, we summarise the applications for thalidomide with an emphasis on clinical trials published over the past 10 years, and consider our knowledge of the molecular pharmacology of the drug in the context of clinical trial data, attempting to provide a mechanism-guided understanding of its activity.

Thalidomide (figure 1) was synthesised in 1954 by the CIBA pharmaceutical company,¹ and prescribed as a sedative, tranquiliser, and antiemetic for morning sickness. Chemically similar to barbiturates, the drug became a popular sedative, marketed under at least 37 names worldwide,^{2,3} though it was never approved by the US Food and Drug Administration (FDA) due in part to concerns raised about potentially irreversible neuritis and the drug's safety.⁴ Initial reports of limb abnormalities—phocomelia, dysmelia, amelia, bone hypoplasticity—and other congenital defects—ear, heart, internal organs—were made by women who took as little as a single dose of thalidomide during gestation.^{2,5} The highest risk for teratogenicity arose when the drug was taken between weeks 3 and 8 after conception.^{5,6} About 10 000 children worldwide were born with malformations related to the use of thalidomide and, as a result, it was withdrawn from the European and Canadian markets in 1961 and 1962, respectively.⁶ The drug resurfaced in 1965 as an effective treatment for erythema nodosum leprosum lesions and, in 1998, the FDA approved it for this indication.³

In 1994, D'Amato and colleagues¹ postulated that thalidomide-associated malformations were the result of the drug's interference with vasculogenesis, and that a similar mechanism might prevent the growth of blood vessels recruited by solid tumours. The ability of thalidomide to inhibit angiogenesis was confirmed in a rabbit cornea micropocket assay.^{1,7} Establishment of thalidomide as an anti-inflammatory, immunomodulatory, and antiangiogenic compound inspired researchers to define its mechanism of action and clinical range. That a drug with antivasular side-effects that was originally prescribed as a sedative is now in clinical trials for vascular diseases with sedation considered to be the side-effect is ironic. Here, we review the basic science of thalidomide and summarise the mounting clinical trial data in inflammatory disorders and neoplasms.

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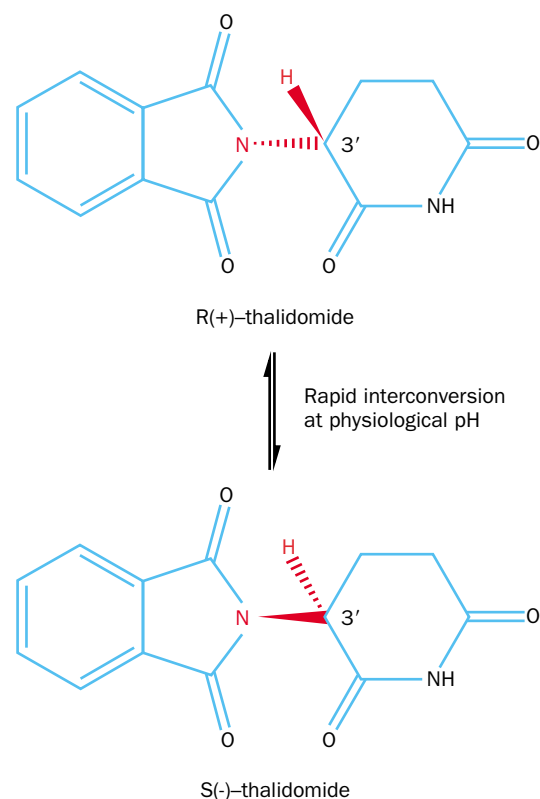


Figure 1: Structure of thalidomide enantiomers

Structure and bioactivity

The thalidomide molecule is a racemic glutamic acid analogue, consisting of S(–) and R(+) enantiomers that interconvert under physiological conditions (figures 1 and 2).⁷ The S(–) form potently inhibits release of tumour necrosis factor (TNF) α from peripheral

Search strategy

We searched MEDLINE and PubMed databases with the term thalidomide associated with the terms mechanism, pharmacology, analogues, and clinical trials. Historical information was taken from reviews. We restricted our search to English-language papers published between 1970 and 2003, and excluded clinical abstracts as a general rule. Articles were selected on the basis of their relevance in both basic science and clinical diseases.

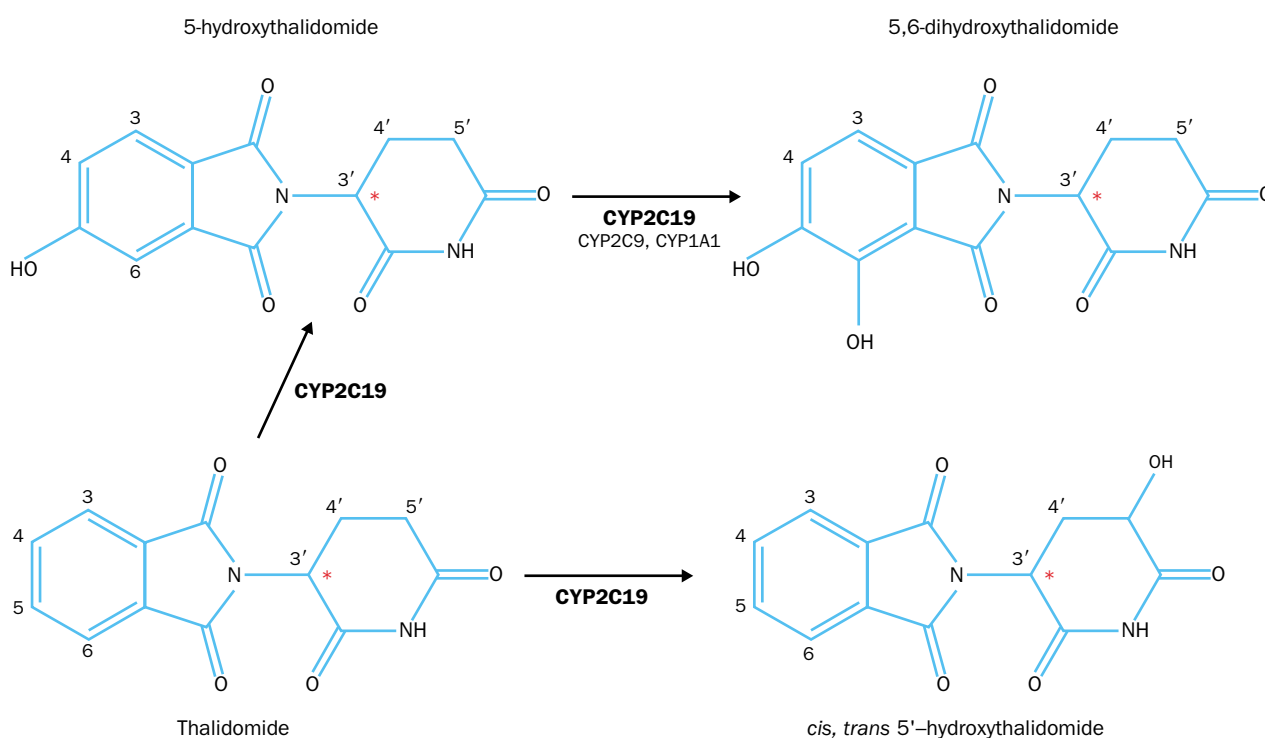


Figure 2: **Thalidomide metabolism by cytochrome P450 enzymes**
*3' chiral centre.

mononuclear blood cells,⁸ whereas the R(+) form seems to act as a sedative, probably mediated by sleep receptors in the forebrain.⁹

One of the unique chemical aspects of thalidomide is that the parent compound undergoes spontaneous hydrolysis in aqueous solution at pH 7.0. Thalidomide

degradation results in more than 20 products, and its activity—eg, inhibition of microvessel formation or reduction of aortic endothelial cell proliferation—seems to depend on its metabolism.¹⁰ The active metabolite seems to be generated by cytochrome P450 2C19 (CYP2C19) isozyme-mediated oxidation of thalidomide (figures 2 and 3).¹⁰ However, there are some preliminary data from a human placental arterial model, indicating antiangiogenic activity without the addition of microsomes (Stirling D, Celgene, personal communication). Whether the metabolism of thalidomide contributes specifically to its immunomodulatory activity, therefore, remains unclear.

Mechanism of action

The mechanisms that underlie the immunomodulatory, anti-inflammatory, and antiangiogenic properties of thalidomide are also unclear, although modulation of inflammatory cytokines such as TNF α , γ interferon, interleukin 10, interleukin 12, cyclooxygenase 2 (COX-2), and possibly the nuclear factor κ B (NF- κ B) transcription factor, are involved.

TNF α regulates inflammatory cascades and represents a therapeutic target in inflammatory diseases, some of which have been associated with raised concentrations of the cytokine in patients' tissues.¹¹ Thalidomide inhibits production of TNF α in lipopolysaccharide-induced human monocytes and mouse macrophages by enhancing degradation of its mRNA.^{12,13} It also inhibits the production of tumour-

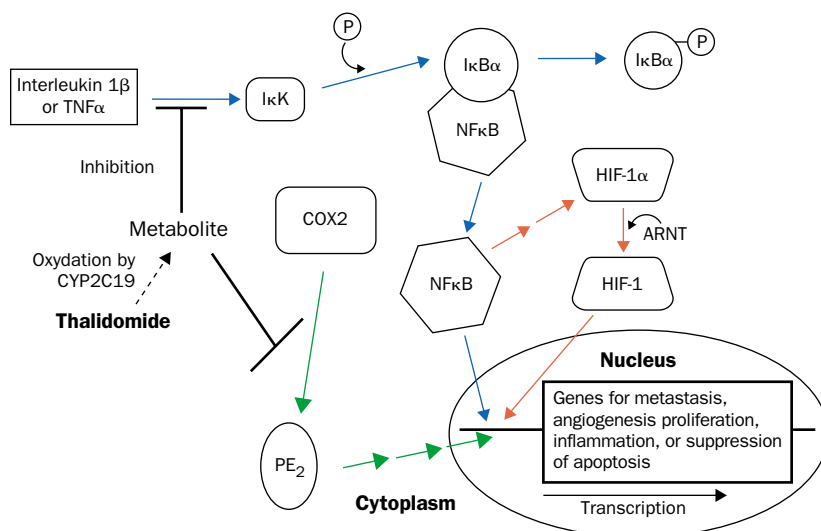


Figure 3: **Mechanisms by which thalidomide modulates immune responses and angiogenesis**

CYP2C19 oxidises thalidomide to active metabolite, which interferes with TNF α or interleukin 1 β -induced activation of I κ K. Inhibition of I κ K prevents dissociation of I κ B α from NF κ B, precluding its nuclear translocation and induction of genes that function in cellular proliferation, inflammation, angiogenesis, and protection from apoptosis. Inactivation of NF κ B also prevents induction of hypoxia inducible factor 1 α (HIF-1 α) accumulation, association with aryl hydrocarbon receptor nuclear translocator, nuclear translocation, and activation of inflammatory and angiogenic genes. Blue arrows=TNF α -mediated or interleukin 1 β -mediated induction of inflammatory and angiogenic genes via NF- κ B. Red arrows=TNF α -mediated or interleukin 1 β -mediated induction of HIF-1 via NF- κ B. Green arrows=COX2-mediated induction of prostaglandin E₂ (PE₂) biosynthesis and up-regulation of angiogenic growth factor production. Multiple arrows=poorly understood pathways. Dotted arrow=unclear whether thalidomide's immunomodulatory activity depends on its metabolism to an active compound.

| | Number of treated patients | Daily thalidomide dose (mg) | Response rate* | Reference |
|---|----------------------------|-------------------------------------|----------------|-----------|
| Refractory myeloma | | | | |
| Thalidomide monotherapy | 84 | 200–800 | 25% | 73 |
| | 169 | 200–800 | 30% | 74 |
| | 16 | 200–800 | 25% | 77 |
| | 20 | 200–800 | 43% | 78 |
| | 17 | 200–800 | 59% | 85 |
| | 17 | 100–400 | 29% | 79 |
| | 53 | 200–400 | 36% | 81 |
| | 60 | 100–800 | 28% | 82 |
| | 83 | 50–800 | 48% | 84 |
| | 75 | 200–800 | 28% | 86 |
| | 51 | 100–400 | 18% | 25 |
| | 23 | 200–800 | 13% | 87 |
| Thalidomide and steroids | 38 | 100+dexamethasone | 52% | 90 |
| | 47 | 200–800+dexamethasone | 47% | 92 |
| | 21 | Unknown+dexamethasone | 57% | 89 |
| | 37 | 100+dexamethasone | 51% | 91 |
| Thalidomide, steroids, and chemotherapy | 135 | 400+dexamethasone+PACE | 54% | 75 |
| | 38 | 400+DCEP | 36% | 75 |
| | 42 | 400+CED | 78% | 93 |
| | 24 | 50–200+clarithromycin+dexamethasone | 93% | 94 |
| | 4 | 50+VAD | 100%† | 95 |
| Newly diagnosed or untreated myeloma | | | | |
| Thalidomide monotherapy | 16 | 200–800 | 38% | 97 |
| | 28 | 200–600 | 36% | 98 |
| Thalidomide and steroids | 26 | 200–800+dexamethasone | 77% | 97 |
| | 16 | 200–600+dexamethasone | 72% | 98 |

PACE=cisplatin/doxorubicin/cyclophosphamide/etoposide. DCEP=dexamethasone/cyclophosphamide/etoposide/cisplatin. CED=cyclophosphamide/etoposide/dexamethasone. VAD=vincristine/doxorubicin/dexamethasone. *>50% reduction in urine or serum concentrations of paraprotein. Responses included ability to undergo peripheral blood stem cell transplant.

Table 1: Results of studies of thalidomide in refractory and newly diagnosed multiple myeloma

associated macrophages in rats with MAT-Lu tumours. The immunomodulatory and antiangiogenic effects of the drug probably produce an additive antitumour response. Thalidomide-mediated inhibition of immune responses and angiogenesis are probably interrelated because affected cytokines, such as TNF α , function in both processes. However, by contrast with the suppressive effect of thalidomide on TNF α production by monocytes and macrophages, interleukin-2-dependent superinduction of TNF α takes place in CD4 $^+$ and CD8 $^+$ T cells treated with thalidomide, indicating an elaborate pharmacology during an inflammatory response that is not yet understood.¹⁴

A dose-dependent inhibition of the cancer-associated growth factor interleukin 6 has been noted after treatment with thalidomide.¹⁵ Likewise, the drug inhibits production of interferon γ in mitogen-stimulated peripheral blood mononuclear cells¹⁶ and the stimulating effects of insulin-like growth factor 1 on chondrogenesis and limb-bud development;¹⁷ thalidomide might inhibit growth factor-mediated activation of $\alpha_v\beta_3$ -integrin genes,¹⁷ thus preventing stimulation of angiogenesis in developing limb buds. Interference with integrin and growth-factor gene expression may contribute to immunomodulatory responses via NF- κ B.¹⁸ A similar effect of thalidomide on cancer cells would result in decreased production of integrins needed for angiogenesis. Results of molecular studies have resulted in the identification of several mechanisms whereby thalidomide is active in multiple myeloma.¹⁹ These include: reduction of cell adhesion in multiple myelomas and related drug resistance;²⁰ induction of apoptosis;²¹ inhibition of angiogenesis in the bone marrow;¹ and augmentation of immunity of multiple myelomas through stimulation of natural killer cells (with subsequent increase of interleukin-2-mediated T-cell proliferation and γ -interferon production) and increase in cytotoxicity of natural killer cells.^{22,23}

TNF α (or interleukin 1 β) induces normoxic accumulation of the inflammatory and angiogenic factor hypoxia-inducible-factor 1 α in kidney cells by way of an unknown pathway via NF- κ B.²⁴ Maybe, thalidomide abrogates hypoxia-inducible-factor 1 α -mediated activity by way of its anti-TNF α activity (figure 3)? Our knowledge of the mechanism of action of thalidomide thus indicates a primary role for cytokine modulation. In one report,²⁵ however, no decrease in TNF α , vascular endothelial growth factor (VEGF), or interleukin 6 concentrations were noted in patients who responded to thalidomide, suggesting that other mechanisms could be responsible for the drug's clinical activity.

The anti-inflammatory and antiangiogenic functions of thalidomide are controlled in part through the transcription factor NF- κ B. This factor is located in the cytoplasm and is bound by inhibitory proteins—eg, I κ -B α or other I κ -B-like proteins. Once stimulated by inducers such as interleukin 1 β or TNF α , a phosphorylation cascade results in dissociation of the inhibitory proteins from NF- κ B, freeing it to activate the expression of genes involved in cell growth, suppression of apoptosis, metastasis, and immune and inflammatory responses.^{26–29} Thalidomide-mediated inactivation of NF- κ B takes place in various cells, including endothelial and epithelial cells, T cells, and myeloid cells (figure 3).^{26,30} A thalidomide metabolite, such as 5-hydroxythalidomide, could possibly induce its immunomodulatory effects as well as its antiangiogenic effects. We propose that a metabolite of thalidomide needed for activity in our angiogenesis assays also inactivates NF- κ B by interacting with a factor upstream of I κ B α phosphorylation (figure 3). Studies are needed to elucidate the elaborate molecular pharmacology of thalidomide with emphasis on endpoints upstream of NF- κ B, including the identification of a specific thalidomide-binding factor.

The discovery that thalidomide inhibits lipopoly-saccharide-mediated induction of COX-2 by destabilising

| | Number of participants | Therapy | Daily thalidomide dose (mg) | Objective response* | Reference |
|------------------|------------------------|--------------------------------------|-----------------------------|---------------------|-----------|
| Cancer | | | | | |
| Prostate | 63 | Thalidomide | 200, 1200 | 18%† | 113 |
| | 20 | Thalidomide | 100 | 15%† | 115 |
| | 75 | Thalidomide/docetaxel | 200 | 51%‡, 35%† | 116§ |
| Renal cell | 18 | Thalidomide | 100 | 17% | 121 |
| | 26 | Thalidomide | 200–800 | 0% | 122 |
| | 25 | Thalidomide | 600 | 9% | 123 |
| | 40 | Thalidomide | 400–1200 | 5% | 124 |
| | 19 | Thalidomide | 200–1200 | 10% | 125 |
| | 29 | Thalidomide | 400–1200 | 4% | 126 |
| | 21 | Thalidomide+fluorouracil+gemcitabine | 200–400 | 10% | 127 |
| Glioma | 39 | Thalidomide | 800–1200 | 6% | 129 |
| | 42 | Thalidomide | 100–500 | 5% | 131 |
| | 18 | Thalidomide | 100 | 6% | 130 |
| Colorectal | 18 | Thalidomide+irinotecan | 400 | 29% | 132 |
| Melanoma | 17 | Thalidomide | 100 | 0% | 121 |
| | 12 | Thalidomide+temozolamide | 100–400 | 50% | 135 |
| Breast | 12 | Thalidomide | 100 | 0% | 121 |
| | 28 | Thalidomide | 200–1200 | 0% | 140 |
| Ovarian | 19 | Thalidomide | 100 | 0% | 121 |
| Head and neck | 21 | Thalidomide | 200–1200 | 0% | 142 |
| Kaposi's sarcoma | 17 | Thalidomide | 100 | 35% | 62 |
| | 20 | Thalidomide | 200–1000 | 40% | 63 |

*Complete or partial response. †PSA reduction >50%. ‡Soft tissue response. §Includes data from Dahut WL, personal communication.

Table 2: Results of studies of thalidomide in non-haematological cancers

its mRNA and subsequent prostaglandin-E₂ biosynthesis might explain in part its antiangiogenic activity (figure 3).³¹ COX-2 is highly expressed in various human cancers and is needed for angiogenesis in a rat corneal model.^{32,33}

Clinical applications

Inflammatory and infectious conditions

Dermatological

Interest in thalidomide resurfaced in 1965 after, by chance discovery,³ it was found to be beneficial in erythema nodosum leprosum, a vasculitic complication of leprosy characterised by painful subcutaneous nodules, fever, and other constitutional symptoms. Short-term improvement was seen in 52% of patients who received 100 mg four times daily in a double-blind, randomised trial against aspirin.³⁴ Responses were seen in 70–80% of patients on thalidomide versus 25% in other placebo-controlled trials, and maintenance doses of 25–100 mg per day have proved equally efficacious after controlling initial symptoms.³ Results of a review of 15 years' experience and more than 4000 patients with the condition and treated with thalidomide showed that 99% of individuals responded to treatment with thalidomide within 24–48 h.³⁵ Thalidomide is first-line therapy for symptomatic, moderate-to-severe erythema nodosum leprosum, and can be used for the suppression and prevention of cutaneous disease.³

The granulomatous skin lesions of sarcoidosis, similar to those of erythema nodosum leprosum, were also effectively controlled with single-agent thalidomide in three small studies,^{36–38} and the best responses, either partial or complete, were noted in seven of ten patients.³⁸ Raised concentrations of angiotensin converting enzyme were reduced with thalidomide in another report.³⁶ Activity in the visceral manifestations of sarcoidosis is less clear.

In non-randomised studies, thalidomide was moderately effective for the treatment of refractory, cutaneous lesions of lupus. Overall, clinical response rates ranged from 84% to 100% at daily doses of 50–400 mg, with the possibility of subsequent maintenance therapy

after initial response, mostly in patients refractory to other therapies.^{39,40} In one study of thalidomide 300 mg daily,⁴¹ erythrocyte sedimentation rates and γ -globulin concentrations improved, and steroid use was reduced by more than 50%. Results of studies conflict with respect to thalidomide's effect on visceral and articular lupus.^{41,42} Thalidomide is considered second-line therapy in cutaneous lupus, based primarily on several reports of neurotoxicity and extent of relapse after discontinuation of therapy.^{39,40}

Oral and genital lesions of Behçet's disease improved after treatment with thalidomide (100 mg or 300 mg) versus placebo in a randomised, controlled trial in 96 patients,⁴³ with complete responses reported in seven of 63 participants. Typically, oral lesions healed in 3–4 weeks, but recurrences were common after cessation of therapy. Findings of additional small series support mucocutaneous improvement with thalidomide monotherapy,⁴⁴ although its effects on uveitis are inconsistent.⁴⁵

Graft-versus-host disease generally targets the skin, and can be quite debilitating after bone marrow transplantation. Results of a randomised, controlled study⁴⁶ of thalidomide 200 mg per day in 59 transplant patients, showed worsening of chronic graft-versus-host disease associated with reduced survival. Thalidomide prophylaxis is, therefore, not recommended. Overall response rates to the drug in high-risk or refractory, chronic graft-versus-host disease range from 20% to 88%, however, with acceptable toxicity.⁴⁷ In this setting, thalidomide seems useful as an adjunct to standard immunosuppressive therapy, rather than as first-line or single-agent treatment, where its role is limited at best.^{48,49}

Case reports indicate that thalidomide monotherapy might also be useful in the following dermatoses: pyoderma granulorum, prurigo nodularis, porphyria cutanea tarda, and lichen planus.⁵⁰ The dermatological manifestation toxic epidermal necrosis, mediated in part by TNF α ,⁵¹ was judged a good target for thalidomide. Unfortunately, in one study,⁵¹ the drug exacerbated the disease, with greater mortality noted in the thalidomide-

| | Proportion of patients affected | | |
|--------------------|--|--|---------|
| | Thalidomide 200 mg ^{73,90} | Thalidomide 800 mg ^{73,90} | Placebo |
| Side-effect | | | |
| Constipation | 2–35% | 59% | 0% |
| Fatigue | 0–29% | 48% | 0% |
| Somnolence | 34–38% | 43% | 11% |
| Neuropathy | 8–12% | 28% | 0% |
| Dizziness | 4–19% | 28% | 0% |
| Rash | 16–25% | 26% | 31% |
| Mood alterations | 5–22% | 22% | 3% |
| Oedema | 3–8% | 22% | 0% |
| Tremor | 0–10% | 22% | 0% |
| Nausea | 4–13% | 11% | 3% |
| Headache | 12–19% | 11% | 11% |
| Xerostomia | 0–9% | – | 6% |
| Leukopenia | 0–25% | – | 9% |
| Fever | 0–22% | – | 17% |

Table 3: Reported toxicity of thalidomide in selected trials and according to revised thalidomide package insert (July, 1998; Celgene)

treated group than in controls. Thalidomide is, therefore, contraindicated in patients with toxic epidermal necrosis.

Rheumatological

The effect of thalidomide is variable in joint pain associated with refractory rheumatoid arthritis, a disease mediated in part by TNF α . Durable responses (80% complete or partial response), with therapeutic reductions in rheumatoid factor, were described in one report.⁵² Combination treatment with thalidomide and methotrexate or pentoxifylline seems to have a beneficial effect.^{53,54} However, large, controlled trials are necessary to further define thalidomide's use in rheumatoid arthritis in view of the efficacy of other anti-TNF α therapies in the disease. Ankylosing spondylitis, Still's disease, systemic sclerosis, Sjögren's syndrome, and other rheumatological disorders have also been treated with thalidomide, but only in a limited number of patients.⁵⁵

Gastrointestinal

Crohn's disease, thought to be in part mediated by TNF α and interleukin 12, has been effectively controlled with thalidomide for short periods in steroid-dependent patients.^{56–58} Clinical improvement was shown in stool frequency,⁵⁷ fistulae,⁵⁸ and the Crohn's disease activity index. Additionally, steroid requirements were reduced by more than half in all thalidomide-treated patients in one study.⁵⁶ Overall, clinical response rates ranged from 50% to 72%. Serum marker responses to thalidomide in this setting are of questionable importance (erythrocyte sedimentation rate, interleukin 12, C-reactive protein, TNF α).^{57,59} Thalidomide might also be beneficial in patients refractory to infliximab,⁶⁰ or as a maintenance adjunct to this drug.⁶¹ Controlled, multicentre studies are underway to assess the drug's efficacy, since inflammatory bowel disease can have a variable clinical course.

HIV-1

Thalidomide has shown moderate activity in HIV-1-associated Kaposi's sarcoma. A phase II trial⁶² of 17 patients given thalidomide 100 mg daily resulted in a 35% partial response rate; serum titres of human herpesvirus 8 were reduced in all assessable responders. In another trial,⁶³ with doses ranging from 200 mg to 1000 mg, treatment with thalidomide resulted in partial responses and stable disease in 40% and 10% of individuals, respectively. Haematological complications were rare.

Results of randomised, placebo controlled trials^{64,65} of patients with painful oral aphthous ulcers associated with HIV-1 show overall response rates greater than 50%, and improvement in refractory, severe lesions with a 100–200 mg daily dose.⁶⁶ Responses to pain and burning sensations were prompt—usually less than 2 weeks—but relapses were frequent after discontinuation of therapy. Thalidomide is also effective for the treatment of gastrointestinal lesions.⁶⁷

Cachexia and weight loss are common in the late stages of HIV/AIDS. Results of several studies have shown improved weight gain with thalidomide over a short period.^{68,69} In this setting, treatment with thalidomide seems beneficial, and outweighs the unproven risk of immune-function compromise.^{64,70}

Congestive heart failure

Advanced congestive heart failure is characterised by raised inflammatory mediators, including TNF α . In a preclinical model,⁷¹ thalidomide and its analogues blocked cardiac myocyte synthesis of TNF α in response to lipopolysaccharide stimulation. Findings of a small study⁷² indicated improvement in clinical variables—eg, functional capacity, ejection fraction—with thalidomide therapy. We await validation of this use of thalidomide.

Malignant disease

Haematological cancers

Multiple myeloma is an incurable disease despite aggressive treatment with high-dose chemotherapy with stem-cell rescue. Novel therapies are needed. The rationale for the use of thalidomide therapy was based primarily on the observation of enhanced neovascularisation in the bone marrow of patients with progressive disease, and the potential antiangiogenic effects of the drug via TNF α , basic fibroblast growth factor, and VEGF in preclinical studies.^{1,13} The University of Arkansas group first reported on the efficacy and safety of single-agent thalidomide in refractory multiple myeloma;⁷³ in 84 evaluable patients given 200 mg of thalidomide, escalated to 800 mg, serum paraprotein concentrations were reduced by more than half in 25% of patients and by more than 90% in eight patients. Two complete responses were seen, which were durable, since median time to disease progression was not reached at 14 months' follow-up. Although more than three-quarters of those who responded had concordant reductions in marrow plasma cell infiltrates, microvascular density was not affected by therapy.⁷³ Findings of further follow-up of 169 patients by this group⁷⁴ showed 2-year event-free and overall survival rates of 20% and 48%, respectively. Moreover, higher doses of thalidomide were associated with improved survival in high-risk patients, lending support to a dose-dependent effect.⁷⁵ Response to thalidomide in patients with myeloma typically arises after 1–2 months of treatment with a 200–400 mg daily dose, and a dose of 50 mg per day can be an adequate maintenance dose for clinical response in selected cases.⁷⁶ Early single-agent clinical data have been supported by more robust results,^{77–88} and, based on early favourable results in refractory myeloma, thalidomide has been given orphan drug status, which provides for 7 years of protected research and development.

Since then, results of phase I and phase II studies of combination therapies of thalidomide with dexamethasone^{89–92} or cytotoxic chemotherapy^{75,93} have shown improved activity compared with thalidomide alone in patients with refractory myeloma. Combination therapy with thalidomide, steroids, and clarithromycin was also

effective in one study,⁹⁴ and thalidomide treatment in patients with chemotherapy-refractory multiple myeloma seems to permit subsequent stem-cell transplantation in the salvage setting.⁹⁵ Addition of dexamethasone to treatment of thalidomide-refractory patients is also useful, even with prior steroid failure.⁹⁶ Additionally, a phase II dose-escalation study of thalidomide 200–800 mg in newly diagnosed patients demonstrated a 2 year progression-free survival rate of 63%.⁹⁷ Clinical responses in individuals with newly diagnosed disease have also been reported by others,⁹⁸ but use of thalidomide in this setting to delay progression to symptomatic disease remains controversial.

CC-5013, an immunomodulatory derivative of thalidomide with a favourable side-effect profile, has shown promise in relapsed and refractory myeloma, with 71% of 24 patients treated showing a reduction of paraprotein concentrations of 25%. Responders included those who had received previous treatment with thalidomide. CC-5013 alone or in combination with other therapies is under further assessment.⁹⁹

Larger, prospective, randomised studies are underway, which will further define the role of thalidomide in the treatment of advanced, refractory multiple myeloma and its potential use in newly diagnosed myeloma or as a maintenance therapy. Table 1 shows results of trials published for thalidomide single-agent and combination strategies in multiple myeloma.

Thalidomide also seems to be effective in treatment of other haematological disorders. In a phase II study,¹⁰⁰ patients with refractory Waldenström's macroglobulinaemia had a 25% response rate to thalidomide given at a daily dose of 200–600 mg. Combination therapy with clarithromycin, steroids, and thalidomide has also been used with some success.^{101,102} Responses in myelofibrosis have been shown, with improvements in anaemia, thrombocytopenia, and hepatosplenomegaly described by more than half of patients.^{103–107} However, drug toxicity and extramedullary haemopoiesis have arisen after thalidomide therapy, and caution is indicated in this setting.^{103,105}

Results of a phase I study¹⁰⁸ of 51 patients with early myelodysplasia who received up to 400 mg thalidomide daily, showed a response rate of 31% in evaluable patients, although criteria for response was not clearly defined. Objective responses were noted in patients with advanced and refractory myelodysplasia.^{109,110} Thalidomide could have some adverse effect on leukaemic transformation in therapy-related myelodysplasia, which needs to be assessed further.¹¹¹

Prostate cancer

Over the past 8 years, clinical focus has shifted to prostate cancer, the most commonly diagnosed solid organ cancer in American men.¹¹² Findings of a phase II randomised trial,¹¹³ comparing low-dose (200 mg daily) and high-dose (up to 1200 mg daily) thalidomide in androgen-independent prostate cancer, showed sustainable reductions in prostate specific antigen of more than 50% in about a fifth of patients. However, dose escalation over 600 mg in this elderly cohort was rare. Improvements in measurable disease by bone scan and positron emission tomography¹¹⁴ were also noted in some responsive patients. In another study¹¹⁵ in men with androgen independent prostate cancer, thalidomide 100 mg per day resulted in a fall in prostate specific antigen in 15% of patients, with VEGF and basic fibroblast growth factor serum concentrations correlating with progression and favourable response, respectively.

Combination therapy with thalidomide and docetaxel has been used for androgen independent prostate cancer in a randomised phase II study.¹¹⁶ A reduction in serum prostate-specific antigen concentrations of greater than half was shown in 51% of the combined treatment group versus 37% in patients who took docetaxel alone. Although the study was not powered to detect a difference in median overall survival, the addition of thalidomide improved survival by a median 14 months (28.9 *vs* 14.7 months; William Dahut, NCI, personal communication). The survival reported with docetaxel monotherapy was in line with other reports (12–20 months), which further substantiates this finding.^{117–119}

Thalidomide has a therapeutic role in advanced prostate cancer, either alone or in combination with other drugs, and several trials are underway to more fully define this role. In conjunction with a cytotoxic agent, thalidomide could further act to stabilise prostate cancer growth when tumour burden is lowest, prolonging disease control with potentially reduced toxicity.

Renal-cell carcinoma

Renal-cell cancers secrete VEGF and TNF α , forming the basis for the use of thalidomide in this disease. Notably, the first oncology report of use of thalidomide was published in 1965,¹²⁰ and the lone clinical responder was a patient with metastatic renal cell carcinoma after nephrectomy. More recently, Eisen and colleagues¹²¹ treated 18 patients with 100 mg of thalidomide with some success; three partial responders (17%), and three others with short duration stable disease. Unfortunately, partial radiographic responses were rare in several other phase II trials^{122–126} in which higher doses (200–1200 mg) were given. Overall, an objective response rate of 0–10% with some effect on disease stability (26–32%) was shown with thalidomide monotherapy^{121,122–126} or with combination regimens, including gemcitabine, fluorouracil, and thalidomide.¹²⁷ Some preliminary data,¹²⁸ however, suggest combination therapy with thalidomide and interleukin 2 might be clinically useful, and the progression-free and overall survival benefit of thalidomide in combination with other biological response modifiers or chemotherapy is being assessed.

Glioma

High-grade gliomas often have enhanced vascularity and microvessel density, and some have postulated that thalidomide could provide some benefit in this poor-prognosis group that includes anaplastic mixed glioma, anaplastic astrocytoma, and glioblastoma multiforme. In a phase II, non-randomised trial¹²⁹ of thalidomide 200–1200 mg in 36 patients, two partial radiographic responses were noted, with disease stability in 33%. A criticism of this report was that tumour histology was not identified at the time of treatment and, given the variable prognosis of glioma subtypes, the responses are questionable.⁴⁷ Partial responses to thalidomide monotherapy were rare in other studies (5–6% partial response).^{130,131} Combination regimens are under investigation.

Colorectal cancer

Thalidomide nightly (400 mg), in combination with irinotecan, showed clinical utility in four of 14 (29%) evaluable patients (one complete response, three partial response) in a phase II study¹³² in metastatic, chemotherapy-refractory colon cancer. A response rate of 12–21% was noted with irinotecan alone. Stable disease was also noted in 38% of patients after short-term follow-

up. Importantly, the dose-limiting gastrointestinal side-effects of irinotecan were also minimised with thalidomide treatment—nearly all patients completed therapy.¹³³ Preliminary data from this group¹³⁴ also indicate improved survival in the group treated with irinotecan and thalidomide when compared with historical data. Phase III studies of this complementary combination are in accrual, and a double-blind, placebo controlled trial of thalidomide after resection of stage IV colon cancer metastases is underway at the US National Cancer Institute, USA.

Melanoma

Although single-agent thalidomide is ineffective in metastatic melanoma at 100 mg,¹²¹ results of a phase I trial¹³⁵ in 12 patients with thalidomide (up to 400 mg) and temozolamide showed some antitumour activity in six of 12 patients (one complete response, five partial responses). Previous work showed great responses in patients with melanoma brain metastases.¹³⁶ Combination therapy seems to be well tolerated, and phase II and phase III trials are in progress.

Cancer supportive care

Anorexia and cachexia are common in late stage cancers, probably associated with a TNF α mediated effect. Great improvement in sleep, nausea, and appetite in 72 cachectic cancer patients has been reported with thalidomide 400 mg nightly.¹³⁷ Other groups confirm the short-term palliative benefits of thalidomide in this setting.^{137–139}

Other cancers

Thalidomide monotherapy has been fairly ineffective in breast, ovarian, head and neck, and various solid-organ cancers,^{121,140–142} although trials of combination regimens are planned and in progress (http://www.nci.nih.gov/search/clinical_trials; <http://www.cancer.gov>; <http://www.clinicaltrials.gov>; <http://www.controlled-trials.com>). Table 2 shows results of trials published for thalidomide treatment in non-haematological cancers.

Adverse effects

Aside from its well documented teratogenicity, sedation is the most frequently reported thalidomide-associated toxicity,³ followed by peripheral neuropathy.^{143,144} Calculation of a total neuropathy score helps to ascertain proper dosing so as to prevent permanent nerve damage.¹⁴⁴ Other frequent thalidomide-associated adverse effects include rash, dizziness, constipation, tremor, mood changes, and headache.⁷³ In what seems to be synergistic enhancement of toxicity, combination of thalidomide and some chemotherapies raises the risk of deep vein thrombosis.^{145–147} Rash is also potentiated when thalidomide and steroids are combined,⁹⁸ and docetaxel and thalidomide use in patients with prostate cancer is associated with additional pulmonary toxicity.¹⁴⁸ Rare complications with combination treatments have also been reported, such as toxic epidermal necrosis,^{149,150} severe hepatic toxicity,^{151,152} hypothyroidism, bradycardia, and poor CD34+ cell mobilisation with stem-cell procurement.¹⁵³

The frequency of side-effects with thalidomide monotherapy is summarised in table 3. The drug should be administered in combination with chemotherapy only in the setting of clinical trials, wherein adverse effects are closely monitored.¹⁴⁵ The STEPS program (System for Thalidomide Education and Prescribing Safety) was initiated by the manufacturer of thalidomide (Celgene,

Warren, NJ, USA) to reduce the risk of teratogenicity and, in the USA, thalidomide cannot be prescribed without first registering a patient with the programme. Included in STEPS are strategies that control drug access, provide education to patients, doctors, and pharmacists, and guide compliance.¹⁵⁴

Dosing and pharmacogenetics

Clinical responses have been shown at many doses (50–1200 mg), and because of its history and development, no formal systematic dose-escalation studies have been done. Off-protocol dosing should be started at 100–200 mg daily, typically given in the evening as a single dose. Split-dosing has no additional benefit with respect to toxicity profile. The target dose varies for individual patients for various reasons, including age, co-administration with other drugs, and genetic polymorphisms in genes that alter thalidomide metabolism. For example, the polymorphic hepatic enzyme CYP2C19, involved in the conversion of thalidomide to the 5-hydroxythalidomide metabolite, could contribute to thalidomide's clinical activity, although metabolism of drugs other than thalidomide might be also affected.¹⁵⁵ Identification of patients with specific genetic polymorphisms in this gene could help to stratify the likelihood of clinical response to thalidomide. We are investigating this notion of individualised cancer therapy.^{156,157}

Cancer summary

Thalidomide has shown single-agent activity. However, in almost all cases of haematological and solid malignant diseases, combination strategies seem more beneficial. Efficacy is unproven, since few phase III trials have been undertaken but its usefulness in refractory multiple myeloma is impressive and thalidomide's use in plasma cell dyscrasias has been summarised.¹⁵⁸ Future studies will yield optimum dosing and combination strategies for multiple myeloma and other cancers. Toxicity, which is variable, has occasionally limited the length and durability of responses. Thalidomide is a candidate drug for novel trial designs being considered by the National Cancer Institute and other agencies that use compounds where traditional endpoints are less appropriate—ie, angiogenesis inhibitors.

Thalidomide analogue development

Our laboratory has developed 118 novel thalidomide analogues. Preclinical assessment of some of these analogues has revealed their potent antiangiogenic activity in ex-vivo aortic ring, and in in-vitro endothelial cell proliferation and tube formation assays.¹⁵⁹ Furthermore, certain analogues have shown significant antitumour activity in prostate cancer xenograft preclinical models. Clinical assessment of promising lead compounds will result in the development of thalidomide-like drugs that could have an improved clinical profile relative to the parent compound. Molecular pharmacological studies are now underway to elucidate the mechanisms of action for these analogues and other products, including the immunomodulatory derivatives, two of which (CC-5013 and CC-4047) are in phase I trials, and selective cytokine inhibitory drugs. Such studies should lead to the identification of specific molecular targets of thalidomide and its analogues, structural determination of these targets, and rational design of specific small-molecule inhibitors (other than thalidomide and its analogues) with better pharmacological profiles.

Conflict of interest statement

None declared.

References

- 1 D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci USA* 1994; **91**: 4082–85.
- 2 Mellin GW, Katzenstein M. The saga of thalidomide: neuropathy to embryopathy, with case reports of congenital anomalies. *N Engl J Med* 1962; **267**: 1184–92.
- 3 Teo SK, Resztak KE, Scheffler MA, et al. Thalidomide in the treatment of leprosy. *Microbes Infect* 2002; **4**: 1193–202.
- 4 Kelsey FO. Thalidomide update: regulatory aspects. *Teratology* 1988; **38**: 221–26.
- 5 Mellin GW, Katzenstein M. The saga of thalidomide: neuropathy to embryopathy, with case reports of congenital anomalies. *N Engl J Med* 1962; **267**: 1238–44.
- 6 Lenz W. A short history of thalidomide embryopathy. *Teratology* 1988; **38**: 203–15.
- 7 Kenyon BM, Browne F, D'Amato RJ. Effects of thalidomide and related metabolites in a mouse corneal model of neovascularization. *Exp Eye Res* 1997; **64**: 971–78.
- 8 Wnendt S, Finkam M, Winter W, Ossig J, Raabe G, Zwingenberger K. Enantioselective inhibition of TNF- α release by thalidomide and thalidomide-analogues. *Chirality* 1996; **8**: 390–96.
- 9 Frederickson RC, Slater IH, Dusenberry WE, Hewes CR, Jones GT, Moore RA. A comparison of thalidomide and pentobarbital: new methods for identifying novel hypnotic drugs. *J Pharmacol Exp Ther* 1977; **203**: 240–51.
- 10 Bauer KS, Dixon SC, Figg WD. Inhibition of angiogenesis by thalidomide requires metabolic activation, which is species-dependent. *Biochem Pharmacol* 1998; **55**: 1827–34.
- 11 Marriott JB, Westby M, Dalgleish AG. Therapeutic potential of TNF- α inhibitors old and new. *Drug Discovery Today* 1997; **2**: 273–82.
- 12 Moreira AL, Sampaio EP, Zmuidzinis A, Frindt P, Smith KA, Kaplan G. Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation. *J Exp Med* 1993; **177**: 1675–80.
- 13 Sampaio EP, Sarno EN, Galilly R, Cohn ZA, Kaplan G. Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes. *J Exp Med* 1991; **173**: 699–703.
- 14 Marriott JB, Clarke IA, Dredge K, Muller G, Stirling D, Dalgleish AG. Thalidomide and its analogues have distinct and opposing effects on TNF- α and TNFR2 during co-stimulation of both CD4(+) and CD8(+) T cells. *Clin Exp Immunol* 2002; **130**: 75–84.
- 15 Singhal S, Mehta J. Thalidomide in cancer: potential uses and limitations. *BioDrugs* 2001; **15**: 163–72.
- 16 Rowland TL, McHugh SM, Deighton J, Dearman RJ, Ewan PW, Kimber I. Differential regulation by thalidomide and dexamethasone of cytokine expression in human peripheral blood mononuclear cells. *Immunopharmacology* 1998; **40**: 11–20.
- 17 Stephens TD, Bunde CJ, Fillmore BJ. Mechanism of action in thalidomide teratogenesis. *Biochem Pharmacol* 2000; **59**: 1489–99.
- 18 Meierhofer C, Dünzendorfer S, Wiedermann CJ. Theoretical basis for the activity of thalidomide. *BioDrugs* 2001; **15**: 681–703.
- 19 Hayashi T, Hideshima T, Anderson KC. Novel therapies for multiple myeloma. *Br J Haematol* 2003; **120**: 10–17.
- 20 Damiano JS, Cress AE, Hazlehurst LA, Shtil AA, Dalton WS. Cell adhesion mediated drug resistance (CAM-DR): role of integrins and resistance to apoptosis in human myeloma cell lines. *Blood* 1999; **93**: 1658–67.
- 21 Hideshima T, Chauhan D, Shima Y, et al. Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. *Blood* 2000; **96**: 2943–50.
- 22 Haslett PA, Corral LG, Albert M, Kaplan G. Thalidomide costimulates primary human T lymphocytes, preferentially inducing proliferation, cytokine production, and cytotoxic responses in the CD8+ subset. *J Exp Med* 1998; **187**: 1885–92.
- 23 Davies FE, Raje N, Hideshima T, et al. Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. *Blood* 2001; **98**: 210–16.
- 24 Zhou J, Schmid T, Brune B. Tumor necrosis factor- α causes accumulation of a ubiquitinated form of hypoxia inducible factor-1 α through a nuclear factor- κ B-dependent pathway. *Mol Biol Cell* 2003; **14**: 2216–25.
- 25 Neben K, Moehler T, Kraemer A, et al. Response to thalidomide in progressive multiple myeloma is not mediated by inhibition of angiogenic cytokine secretion. *Br J Haematol* 2001; **115**: 605–08.
- 26 Keifer JA, Guttridge DC, Ashburner BP, Baldwin AS Jr. Inhibition of NF- κ B activity by thalidomide through suppression of I κ B kinase activity. *J Biol Chem* 2001; **276**: 22382–87.
- 27 Wang CY, Guttridge DC, Mayo MW, Baldwin AS Jr. NF- κ B induces expression of the Bcl-2 homologue A1/Bfl-1 to preferentially suppress chemotherapy-induced apoptosis. *Mol Cell Biol* 1999; **19**: 5923–29.
- 28 Guttridge DC, Albanese C, Reuther JY, Pestell RG, Baldwin AS Jr. NF- κ B controls cell growth and differentiation through transcriptional regulation of cyclin D1. *Mol Cell Biol* 1999; **19**: 5785–99.
- 29 Mayo MW, Baldwin AS. The transcription factor NF- κ B: control of oncogenesis and cancer therapy resistance. *Biochim Biophys Acta* 2000; **1470**: M55–62.
- 30 Majumdar S, Lamothe B, Aggarwal BB. Thalidomide suppresses NF- κ B activation induced by TNF and H₂O₂, but not that activated by ceramide, lipopolysaccharides, or phorbol ester. *J Immunol* 2002; **168**: 2644–51.
- 31 Fujita J, Mestre JR, Zeldis JB, Subbaramaiah K, Dannenberg AJ. Thalidomide and its analogues inhibit lipopolysaccharide-mediated induction of cyclooxygenase-2. *Clin Cancer Res* 2001; **7**: 3349–55.
- 32 Yamada M, Kawai M, Kawai Y, Mashima Y. The effect of selective cyclooxygenase-2 inhibitor on corneal angiogenesis in the rat. *Curr Eye Res* 1999; **19**: 300–04.
- 33 Daniel TO, Liu H, Morrow JD, Crews BC, Marnett LJ. Thromboxane A₂ is a mediator of cyclooxygenase-2-dependent endothelial migration and angiogenesis. *Cancer Res* 1999; **59**: 4574–77.
- 34 Iyer CG, Languillon J, Ramanujam K, et al. WHO co-ordinated short-term double-blind trial with thalidomide in the treatment of acute lepra reactions in male lepromatous patients. *Bull World Health Organ* 1971; **45**: 719–32.
- 35 Sheskin J. The treatment of lepra reaction in lepromatous leprosy: fifteen years' experience with thalidomide. *Int J Dermatol* 1980; **19**: 318–22.
- 36 Carlesimo M, Giustini S, Rossi A, Bonaccorsi P, Calvieri S. Treatment of cutaneous and pulmonary sarcoidosis with thalidomide. *J Am Acad Dermatol* 1995; **32**: 866–69.
- 37 Baughman RP, Judson MA, Teirstein AS, Moller DR, Lower EE. Thalidomide for chronic sarcoidosis. *Chest* 2002; **122**: 227–32.
- 38 Estines O, Revuz J, Wolkenstein P, Bressieux JM, Roujeau JC, Cosnes A. Sarcoidosis: thalidomide treatment in ten patients. *Ann Dermatol Venerol* 2001; **128**: 611–13.
- 39 Knop J, Bonsmann G, Happle R, et al. Thalidomide in the treatment of sixty cases of chronic discoid lupus erythematosus. *Br J Dermatol* 1983; **108**: 461–66.
- 40 Karim MY, Ruiz-Irastorza G, Khamashta MA, Hughes GR. Update on therapy: thalidomide in the treatment of lupus. *Lupus* 2001; **10**: 188–92.
- 41 Atra E, Sato EI. Treatment of the cutaneous lesions of systemic lupus erythematosus with thalidomide. *Clin Exp Rheumatol* 1993; **11**: 487–93.
- 42 Bessis D, Guillot B, Monpoint S, Dandurand M, Guilhou JJ. Thalidomide for systemic lupus erythematosus. *Lancet* 1992; **339**: 549–50.
- 43 Hamuryudan V, Mat C, Saip S, et al. Thalidomide in the treatment of the mucocutaneous lesions of the Behçet syndrome: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1998; **128**: 443–50.
- 44 Shek LP, Lim DL. Thalidomide in Behçet's disease. *Biomed Pharmacother* 2002; **56**: 31–35.
- 45 Hamza MH. Treatment of Behçet's disease with thalidomide. *Clin Rheumatol* 1986; **5**: 365–71.
- 46 Chao NJ, Parker PM, Niland JC, et al. Paradoxical effect of thalidomide prophylaxis on chronic graft-vs-host disease. *Biol Blood Marrow Transplant* 1996; **2**: 86–92.
- 47 Richardson P, Hideshima T, Anderson K. Thalidomide: emerging role in cancer medicine. *Annu Rev Med* 2002; **53**: 629–57.
- 48 Koc S, Leisenring W, Flowers ME, et al. Thalidomide for treatment of patients with chronic graft-versus-host disease. *Blood* 2000; **96**: 3995–96.
- 49 Arora M, Wagner JE, Davies SM, et al. Randomized clinical trial of thalidomide, cyclosporine, and prednisone versus cyclosporine and prednisone as initial therapy for chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2001; **7**: 265–73.
- 50 Wines NY, Cooper AJ, Wines MP. Thalidomide in dermatology. *Australas J Dermatol* 2002; **43**: 229–38.
- 51 Wolkenstein P, Latarjet J, Roujeau JC, et al. Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. *Lancet* 1998; **352**: 1586–89.
- 52 Gutierrez-Rodriguez O, Starusta-Bacal P, Gutierrez-Montes O. Treatment of refractory rheumatoid arthritis—the thalidomide experience. *J Rheumatol* 1989; **16**: 158–63.
- 53 Huizinga TW, Dijkman BA, van der Velde EA,

- van de Pouw Kraan TC, Verweij CL, Breedveld FC. An open study of pentoxifylline and thalidomide as adjuvant therapy in the treatment of rheumatoid arthritis. *Ann Rheum Dis* 1996; **55**: 833–36.
- 54 Scoville CD. Pilot study using the combination of methotrexate and thalidomide in the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2001; **19**: 360–61.
- 55 Ossandon A, Cassara EA, Priori R, Valesini G. Thalidomide: focus on its employment in rheumatologic diseases. *Clin Exp Rheumatol* 2002; **20**: 709–18.
- 56 Vasiliauskas EA, Kam LY, Abreu-Martin MT, et al. An open-label pilot study of low-dose thalidomide in chronically active, steroid-dependent Crohn's disease. *Gastroenterology* 1999; **117**: 1278–87.
- 57 Bariol C, Meagher AP, Vickers CR, et al. Early studies on the safety and efficacy of thalidomide for symptomatic inflammatory bowel disease. *J Gastroenterol Hepatol* 2002; **17**: 135–39.
- 58 Ehrenpreis ED, Kane SV, Cohen LB, Cohen RD, Hanauer SB. Thalidomide therapy for patients with refractory Crohn's disease: an open-label trial. *Gastroenterology* 1999; **117**: 1271–77.
- 59 Bauditz J, Wedel S, Lochs H. Thalidomide reduces tumour necrosis factor alpha and interleukin 12 production in patients with chronic active Crohn's disease. *Gut* 2002; **50**: 196–200.
- 60 Kane S, Stone LJ, Ehrenpreis E. Thalidomide as "salvage" therapy for patients with delayed hypersensitivity response to infliximab: a case series. *J Clin Gastroenterol* 2002; **35**: 149–50.
- 61 Sabate JM, Villarejo J, Lemann M, Bonnet J, Allez M, Modigliani R. An open-label study of thalidomide for maintenance therapy in responders to infliximab in chronically active and fistulizing refractory Crohn's disease. *Aliment Pharmacol Ther* 2002; **16**: 1117–24.
- 62 Fife K, Howard MR, Gracie F, Phillips RH, Bower M. Activity of thalidomide in AIDS-related Kaposi's sarcoma and correlation with HHV8 titre. *Int J STD AIDS* 1998; **9**: 751–55.
- 63 Little RF, Wyvill KM, Pluda JM, et al. Activity of thalidomide in AIDS-related Kaposi's sarcoma. *J Clin Oncol* 2000; **18**: 2593–602.
- 64 Jacobson JM, Greenspan JS, Spritzler J, et al. Thalidomide for the treatment of oral aphthous ulcers in patients with human immunodeficiency virus infection. *N Engl J Med* 1997; **336**: 1487–93.
- 65 Ramirez-Amador VA, Esquivel-Pedraza L, Ponce-de-Leon S, Reyes-Teran G, Gonzalez-Guevara M, Sierra-Madero JG. Thalidomide as therapy for human immunodeficiency virus-related oral ulcers: a double-blind placebo-controlled clinical trial. *Clin Infect Dis* 1999; **28**: 892–94.
- 66 Revuz J, Guillaume JC, Janier M, et al. Crossover study of thalidomide vs placebo in severe recurrent aphthous stomatitis. *Arch Dermatol* 1990; **126**: 923–27.
- 67 Paterson DL, Georgioudis PR, Allworth AM, Kemp RJ. Thalidomide as treatment of refractory aphthous ulceration related to human immunodeficiency virus infection. *Clin Infect Dis* 1995; **20**: 250–54.
- 68 Peuckmann V, Fisch M, Bruera E. Potential novel uses of thalidomide: focus on palliative care. *Drugs* 2000; **60**: 273–92.
- 69 Kaplan G, Thomas S, Fierer DS, et al. Thalidomide for the treatment of AIDS-associated wasting. *AIDS Res Hum Retroviruses* 2000; **16**: 1345–55.
- 70 Gunzler V. Thalidomide in human immunodeficiency virus (HIV) patients: a review of safety considerations. *Drug Saf* 1992; **7**: 116–34.
- 71 Davey PP, Ashrafian H. New therapies for heart failure: is thalidomide the answer? *QJM* 2000; **93**: 305–11.
- 72 Agoston I, Dibbs ZI, Wang F, et al. Preclinical and clinical assessment of the safety and potential efficacy of thalidomide in heart failure. *J Card Fail* 2002; **8**: 306–14.
- 73 Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med* 1999; **341**: 1565–71.
- 74 Barlogie B, Desikan R, Eddlemon P, et al. 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* 2001; **98**: 492–94.
- 75 Barlogie B, Tricot G, Anaissie E. Thalidomide in the management of multiple myeloma. *Semin Oncol* 2001; **28**: 577–82.
- 76 Leleu X, Magro L, Fawaz A, Bauters F, Facon T, Yakoub-Agha I. Efficacy of a low dose of thalidomide in advanced multiple myeloma. *Blood* 2002; **100**: 1519–20.
- 77 Rajkumar SV, Fonseca R, Dispenzieri A, et al. Thalidomide in the treatment of relapsed multiple myeloma. *Mayo Clin Proc* 2000; **75**: 897–901.
- 78 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* 2000; **109**: 89–96.
- 79 Bertolini F, Mingrone W, Alietti A, et al. Thalidomide in multiple myeloma, myelodysplastic syndromes and histiocytosis: analysis of clinical results and of surrogate angiogenesis markers. *Ann Oncol* 2001; **12**: 987–90.
- 80 Rajkumar SV. Current status of thalidomide in the treatment of cancer. *Oncology (Huntingt)* 2001; **15**: 867–74.
- 81 Hus M, Dmoszynska A, Soroka-Wojtaszko M, et al. Thalidomide treatment of resistant or relapsed multiple myeloma patients. *Haematologica* 2001; **86**: 404–08.
- 82 Tosi P, Zamagni E, Cellini C, et al. Salvage therapy with thalidomide in patients with advanced relapsed/refractory multiple myeloma. *Haematologica* 2002; **87**: 408–14.
- 83 Yakoub-Agha I, Moreau P, Leyvraz S, et al. Thalidomide in patients with advanced multiple myeloma. *Hematol J* 2000; **1**: 186–89.
- 84 Yakoub-Agha I, Attal M, Dumontet C, et al. Thalidomide in patients with advanced multiple myeloma: a study of 83 patients—report of the Intergroupe Francophone du Myelome (IFM). *Hematol J* 2002; **3**: 185–92.
- 85 Kneller A, Raanani P, Hardan I, et al. Therapy with thalidomide in refractory multiple myeloma patients - the revival of an old drug. *Br J Haematol* 2000; **108**: 391–93.
- 86 Mileschkin LR, Biagi JJ, Mitchell P, et al. Multicenter phase 2 trial of thalidomide in relapsed/refractory multiple myeloma: adverse prognostic impact of advanced age. *Blood* 2003; **102**: 69–77.
- 87 Blade J, Esteve J, Rosinol L, et al. Thalidomide in refractory and relapsing multiple myeloma. *Semin Oncol* 2001; **28**: 588–92.
- 88 Neben K, Moehler T, Egerer G, et al. High plasma basic fibroblast growth factor concentration is associated with response to thalidomide in progressive multiple myeloma. *Clin Cancer Res* 2001; **7**: 2675–81.
- 89 Alexanian R, Weber D, Giral S, Delasalle K. Consolidation therapy of multiple myeloma with thalidomide-dexamethasone after intensive chemotherapy. *Ann Oncol* 2002; **13**: 1116–19.
- 90 Dimopoulos MA, Zervas K, Kouvatsos G, et al. Thalidomide and dexamethasone combination for refractory multiple myeloma. *Ann Oncol* 2001; **12**: 991–95.
- 91 Palumbo A, Giaccone L, Bertola A, et al. Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma. *Haematologica* 2001; **86**: 399–403.
- 92 Anagnostopoulos A, Weber D, Rankin K, Delasalle K, Alexanian R. Thalidomide and dexamethasone for resistant multiple myeloma. *Br J Haematol* 2003; **121**: 768–77.
- 93 Moehler TM, Neben K, Benner A, et al. Salvage therapy for multiple myeloma with thalidomide and CED chemotherapy. *Blood* 2001; **98**: 3846–48.
- 94 Coleman M, Leonard J, Lyons L, et al. BLT-D (clarithromycin [Biaxin], low-dose thalidomide, and dexamethasone) for the treatment of myeloma and Waldenström's macroglobulinemia. *Leuk Lymphoma* 2002; **43**: 1777–82.
- 95 Ahmad I, Islam T, Chanan-Khan A, et al. Thalidomide as salvage therapy for VAD-refractory multiple myeloma prior to autologous PBSC. *Bone Marrow Transplant* 2002; **29**: 577–80.
- 96 Rajkumar SV. Thalidomide in the treatment of multiple myeloma. *Expert Rev Anticancer Ther* 2001; **1**: 20–28.
- 97 Rajkumar SV, Gertz MA, Lacy MQ, et al. Thalidomide as initial therapy for early-stage myeloma. *Leukemia* 2003; **17**: 775–79.
- 98 Weber D, Rankin K, Gavino M, Delasalle K, Alexanian R. Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. *J Clin Oncol* 2003; **21**: 16–19.
- 99 Richardson PG, Schlossman RL, Weller E, et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. *Blood* 2002; **100**: 3063–67.
- 100 Dimopoulos MA, Zomas A, Viniou NA, et al. Treatment of Waldenström's macroglobulinemia with thalidomide. *J Clin Oncol* 2001; **19**: 3596–601.
- 101 Dimopoulos MA, Tsatalas C, Zomas A, et al. Treatment of Waldenström's macroglobulinemia with single-agent thalidomide or with the combination of clarithromycin, thalidomide and dexamethasone. *Semin Oncol* 2003; **30**: 265–69.
- 102 Coleman M, Leonard J, Lyons L, Szelenyi H, Niesvizky R. Treatment of Waldenström's macroglobulinemia with clarithromycin, low-dose thalidomide, and dexamethasone. *Semin Oncol* 2003; **30**: 270–74.
- 103 Barosi G, Grossi A, Comotti B, Musto P, Gamba G, Marchetti M. Safety and efficacy of thalidomide in patients with myelofibrosis with myeloid metaplasia. *Br J Haematol* 2001; **114**: 78–83.
- 104 Canepa L, Ballerini F, Varaldo R, et al. Thalidomide in agnogenic and secondary myelofibrosis. *Br J Haematol* 2001; **115**: 313–15.
- 105 Elliott MA, Mesa RA, Li CY, et al. Thalidomide treatment in myelofibrosis with myeloid metaplasia. *Br J Haematol* 2002; **117**: 288–96.
- 106 Piccaluga PP, Visani G, Pileri SA, et al. Clinical efficacy and antiangiogenic activity of thalidomide in myelofibrosis with myeloid metaplasia: a pilot study. *Leukemia* 2002; **16**: 1609–14.

- 107 Piccaluga PP, Visani G, Finelli C, Grafone T, Baccarani M, Tura S. Efficacy of thalidomide in the treatment of myelodysplastic syndromes. *Haematologica* 2002; **87**: ELT18.
- 108 Raza A, Meyer P, Dutt D, et al. Thalidomide produces transfusion independence in long-standing refractory anemias of patients with myelodysplastic syndromes. *Blood* 2001; **98**: 958–65.
- 109 Thomas DA, Kantarjian HM. Current role of thalidomide in cancer treatment. *Curr Opin Oncol* 2000; **12**: 564–73.
- 110 Zorat F, Shetty V, Dutt D, et al. The clinical and biological effects of thalidomide in patients with myelodysplastic syndromes. *Br J Haematol* 2001; **115**: 881–94.
- 111 Badros A, Morris C, Zangari M, Barlogie B, Tricot G. Thalidomide paradoxical effect on concomitant multiple myeloma and myelodysplasia. *Leuk Lymphoma* 2002; **43**: 1267–71.
- 112 Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics, 2003. *CA Cancer J Clin* 2003; **53**: 5–26.
- 113 Figg WD, Dahut W, Duray P, et al. A randomized phase II trial of thalidomide, an angiogenesis inhibitor, in patients with androgen-independent prostate cancer. *Clin Cancer Res* 2001; **7**: 1888–93.
- 114 Kurdziel K, Bacharach S, Carrasquillo J, et al. 8:45-9:00 Using PET 18F-FDG, 11CO, and 15O-water for monitoring prostate cancer during a phase II anti-angiogenic drug trial with thalidomide. *Clin Positron Imaging* 2000; **3**: 144.
- 115 Drake MJ, Robson W, Mehta P, Schofield I, Neal DE, Leung HY. An open-label phase II study of low-dose thalidomide in androgen-independent prostate cancer. *Br J Cancer* 2003; **88**: 822–27.
- 116 Figg WD, Arlen P, Gulley J, et al. A randomized phase II trial of docetaxel (taxotere) plus thalidomide in androgen-independent prostate cancer. *Semin Oncol* 2001; **28** (suppl): 62–66.
- 117 Petrylak DP, MacArthur R, O'Connor J, et al. Phase I/II studies of docetaxel (Taxotere) combined with estramustine in men with hormone-refractory prostate cancer. *Semin Oncol* 1999; **26** (suppl): 28–33.
- 118 Sinibaldi VJ, Carducci MA, Moore-Cooper S, Laufer M, Zahurak M, Eisenberger MA. Phase II evaluation of docetaxel plus one-day oral estramustine phosphate in the treatment of patients with androgen independent prostate carcinoma. *Cancer* 2002; **94**: 1457–65.
- 119 Savarese DM, Halabi S, Hars V, et al. Phase II study of docetaxel, estramustine, and low-dose hydrocortisone in men with hormone-refractory prostate cancer: a final report of CALGB 9780. *J Clin Oncol* 2001; **19**: 2509–16.
- 120 Grabstald H, Golbey R. Clinical experiences with thalidomide in patients with cancer. *Clin Pharmacol Ther* 1965; **40**: 298–302.
- 121 Eisen T, Boshoff C, Mak I, et al. Continuous low dose thalidomide: a phase II study in advanced melanoma, renal cell, ovarian and breast cancer. *Br J Cancer* 2000; **82**: 812–17.
- 122 Motzer RJ, Berg W, Ginsberg M, et al. Phase II trial of thalidomide for patients with advanced renal cell carcinoma. *J Clin Oncol* 2002; **20**: 302–06.
- 123 Stebbing J, Benson C, Eisen T, et al. The treatment of advanced renal cell cancer with high-dose oral thalidomide. *Br J Cancer* 2001; **85**: 953–58.
- 124 Escudier B, Lassau N, Couanet D, et al. Phase II trial of thalidomide in renal-cell carcinoma. *Ann Oncol* 2002; **13**: 1029–35.
- 125 Daliani DD, Papandreou CN, Thall PF, et al. A pilot study of thalidomide in patients with progressive metastatic renal cell carcinoma. *Cancer* 2002; **95**: 758–65.
- 126 Minor DR, Monroe D, Damico LA, Meng G, Suryadevara U, Elias L. A phase II study of thalidomide in advanced metastatic renal cell carcinoma. *Invest New Drugs* 2002; **20**: 389–93.
- 127 Desai AA, Vogelzang NJ, Rini BI, Ansari R, Krauss S, Stadler WM. A high rate of venous thromboembolism in a multi-institutional phase II trial of weekly intravenous gemcitabine with continuous infusion fluorouracil and daily thalidomide in patients with metastatic renal cell carcinoma. *Cancer* 2002; **95**: 1629–36.
- 128 Amato RJ. Thalidomide therapy for renal cell carcinoma. *Crit Rev Oncol Hematol* 2003; **46** (suppl): 59–65.
- 129 Fine HA, Figg WD, Jaeckle K, et al. Phase II trial of the antiangiogenic agent thalidomide in patients with recurrent high-grade gliomas. *J Clin Oncol* 2000; **18**: 708–15.
- 130 Short SC, Traish D, Dowe A, Hines F, Gore M, Brada M. Thalidomide as an anti-angiogenic agent in relapsed gliomas. *J Neurooncol* 2001; **51**: 41–45.
- 131 Marx GM, Pavlakis N, McCowatt S, et al. Phase II study of thalidomide in the treatment of recurrent glioblastoma multiforme. *J Neurooncol* 2001; **54**: 31–38.
- 132 Govindarajan R. Irinotecan/thalidomide in metastatic colorectal cancer. *Oncology (Huntingt)* 2002; **16** (suppl): 23–26.
- 133 Govindarajan R, Heaton KM, Broadwater R, Zeitlin A, Lang NP, Hauer-Jensen M. Effect of thalidomide on gastrointestinal toxic effects of irinotecan. *Lancet* 2000; **356**: 566–67.
- 134 Govindarajan RSA, Maddox AM, Hutchins LF, McClellan JL. Irinotecan and thalidomide prolong disease free and overall survival in 5FU refractory metastatic colorectal cancer. *Proc Am Soc Clin Oncol* 2003; **22**: 249 abstr 997. <http://www.asco.org>.
- 135 Hwu WJ, Krown SE, Panageas KS, et al. Temozolomide plus thalidomide in patients with advanced melanoma: results of a dose-finding trial. *J Clin Oncol* 2002; **20**: 2610–15.
- 136 Hwu WJ, Raizer J, Panageas KS, Lis E. Treatment of metastatic melanoma in the brain with temozolomide and thalidomide. *Lancet Oncol* 2001; **2**: 634–35.
- 137 Bruera E, Neumann CM, Pituskin E, Calder K, Ball G, Hanson J. Thalidomide in patients with cachexia due to terminal cancer: preliminary report. *Ann Oncol* 1999; **10**: 857–59.
- 138 Deaner P. Thalidomide for distressing night sweats in advanced malignant disease. *Palliat Med* 1998; **12**: 208–09.
- 139 Eisen TG. Thalidomide in solid tumors: the London experience. *Oncology (Huntingt)* 2000; **14** (suppl): 17–20.
- 140 Baidas SM, Winer EP, Fleming GF, et al. Phase II evaluation of thalidomide in patients with metastatic breast cancer. *J Clin Oncol* 2000; **18**: 2710–17.
- 141 Gutheil J, Finucane D. Thalidomide therapy in refractory solid tumour patients. *Br J Haematol* 2000; **110**: 754.
- 142 Tseng JE, Glisson BS, Khuri FR, et al. Phase II study of the antiangiogenesis agent thalidomide in recurrent or metastatic squamous cell carcinoma of the head and neck. *Cancer* 2001; **92**: 2364–73.
- 143 Chaudhry V, Cornblath DR, Corse A, Freimer M, Simmons-O'Brien E, Vogelsang G. Thalidomide-induced neuropathy. *Neurology* 2002; **59**: 1872–75.
- 144 Molloy FM, Floeter MK, Syed NA, et al. Thalidomide neuropathy in patients treated for metastatic prostate cancer. *Muscle Nerve* 2001; **24**: 1050–57.
- 145 Zangari M, Siegel E, Barlogie B, et al. Thrombotic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy. *Blood* 2002; **100**: 1168–71.
- 146 Cavo M, Zamagni E, Cellini C, et al. Deep-vein thrombosis in patients with multiple myeloma receiving first-line thalidomide-dexamethasone therapy. *Blood* 2002; **100**: 2272–73.
- 147 Horne MK 3rd, Figg WD, Arlen P, et al. Increased frequency of venous thromboembolism with the combination of docetaxel and thalidomide in patients with metastatic androgen-independent prostate cancer. *Pharmacotherapy* 2003; **23**: 315–18.
- 148 Behrens RJ, Gulley JL, Dahut WL. Pulmonary toxicity during prostate cancer treatment with docetaxel and thalidomide. *Am J Ther* 2003; **10**: 228–32.
- 149 Rajkumar SV, Gertz MA, Witzig TE. Life-threatening toxic epidermal necrolysis with thalidomide therapy for myeloma. *N Engl J Med* 2000; **343**: 972–73.
- 150 Horowitz SB, Stirling AL. Thalidomide-induced toxic epidermal necrolysis. *Pharmacotherapy* 1999; **19**: 1177–80.
- 151 Trojan A, Chasse E, Gay B, Pichert G, Taverna C. Severe hepatic toxicity due to thalidomide in relapsed multiple myeloma. *Ann Oncol* 2003; **14**: 501–02.
- 152 Fowler R, Imrie K. Thalidomide-associated hepatitis: a case report. *Am J Hematol* 2001; **66**: 300–02.
- 153 Strasser K, Ludwig H. Thalidomide treatment in multiple myeloma. *Blood Rev* 2002; **16**: 207–15.
- 154 Zeldis JB, Williams BA, Thomas SD, Elsayed ME. S.T.E.P.S.: a comprehensive program for controlling and monitoring access to thalidomide. *Clin Ther* 1999; **21**: 319–30.
- 155 Ando Y, Fuse E, Figg WD. Thalidomide metabolism by the CYP2C subfamily. *Clin Cancer Res* 2002; **8**: 1964–73.
- 156 Price DK, Ando Y, Kruger EA, Weiss M, Figg WD. 5'-OH-thalidomide, a metabolite of thalidomide, inhibits angiogenesis. *Ther Drug Monit* 2002; **24**: 104–10.
- 157 Ando Y, Price DK, Dahut WL, Cox MC, Reed E, Figg WD. Pharmacogenetic Associations of CYP2C19 Genotype with In Vivo Metabolisms and Pharmacological Effects of Thalidomide. *Cancer Biol Ther* 2002; **1**: 669–73.
- 158 Dimopoulos MA, Anagnostopoulos A, Weber D. Treatment of plasma cell dyscrasias with thalidomide and its derivatives. *J Clin Oncol* 2003; **21**: 4444–54.
- 159 Ng SS, Gutschow M, Weiss M, et al. Antiangiogenic activity of N-substituted and tetrafluorinated thalidomide analogues. *Cancer Res* 2003; **63**: 3189–94.