ELSEVIER

European Journal of Cancer 40 (2004) 2377–2382

European Journal of Cancer

www.ejconline.com

Review

Thalidomide in solid tumours: the resurrection of an old drug

Stefan Sleijfer *, Wim H.J. Kruit, Gerrit Stoter

Department of Medical Oncology, Daniel den Hoed Cancer Center, Erasmus University Medical Center, Groene Hilledijk 301, EA Rotterdam 3075, The Netherlands

Received 13 July 2004; accepted 20 July 2004
Available online 11 September 2004

Abstract

Following reports of its teratogenicity, thalidomide was banned from the market in the 1960s. Later, the elucidation that the inhibition of angiogenesis underlies this teratogenicity and the recognition of the importance of angiogenesis in malignancies has raised interest in thalidomide as an anti-tumour agent. Since then, numerous other mechanisms accounting for the anti-tumour effect of thalidomide have been revealed and many studies exploring the efficacy of thalidomide in tumours have been initiated. This Review focuses on the application of thalidomide and its derivatives in solid tumours, the mechanisms underlying their anti-tumour effects, and their potential to be applied in combination with other anti-tumour agents.

Keywords: Thalidomide; Solid tumours; Drug combinations; Efficacy

1. Introduction

Thalidomide is a derivative of glutamic acid and was introduced as a sedative and anti-emetic agent for pregnant women in the 1950s. Following reports revealing an association between limb growth defects in babies and maternal usage of thalidomide, this drug was withdrawn from the market in 1961. The exact underlying mechanism whereby thalidomide causes limb defects was unknown for many years, but was elucidated by the group of Folkman in 1994. Since development of the fetal limb was known to depend strongly on the formation of new blood vessels, this group examined the hypothesis that thalidomide affects this process. Using a rabbit cornea model in which angiogenesis was induced by the angiogenic protein, basic fibroblast growth factor (bFGF), it was demonstrated that thalidomide inhibits angiogenesis [1]. This feature and the recognition of the importance of angiogenesis in the pathogenesis of several disease conditions prompted investigators to assess the efficacy of thalidomide in malignancies. The first tumour entity in which the activity of thalidomide was tested was refractory multiple myeloma [2]. In a group of extensively pretreated patients, anti-tumour activity was observed in a substantial number of patients. The favourable outcomes of this study led to the initiation of trials aiming to establish the efficacy of thalidomide in several other tumour types. Simultaneously, investigators attempted to design analogues of thalidomide with improved activity and a more favourable toxicity profile.

This Review addresses the application of thalidomide in solid tumours. In particular, it will focus on the mechanisms by which thalidomide and its derivatives exert their anti-tumour activity and the rationale behind applying these drugs in combination with other anti-tumour agents.

* Corresponding author. Tel: +31 10 4391733; fax: +31 10 4391003.
E-mail address: s.sleijfer@erasmusmc.nl (S. Sleijfer).

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2004.07.023

2. Mechanisms of action of thalidomide and its analogues

Since angiogenic features, such as microvessel density, did not correlate with response to thalidomide in patients with multiple myeloma, other mechanisms involved in the anti-tumour activity of this drug were thought to exist. Since then, many differential mechanisms have been revealed and there are not many drugs used in oncology for which so many mechanisms of action have been identified. Besides the anti-angiogenic effect, these comprise direct cytotoxic effects on tumour cells, increasing tumour cell susceptibility to apoptotic triggers, stimulation of immune-mediated responses, reduction of growth stimulating factors, and attenuation of the metastatic potential (Table 1). This very wide range of activities may be explained to a great extent by its effects on Nuclear factor-κB (NF-κB) activity. NF-κB is involved in the transcription regulation of many genes including cytokines (e.g., tumour necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-12), proteins involved in apoptosis (e.g., cellular inhibitor of apoptosis protein 2 (c-IAP2), FLICE, Bcl-2 family members), and angiogenic factors (e.g., vascular endothelial growth factor (VEGF), TNF-α, IL-8). As a consequence, NF-κB plays a central role in the regulation of pivotal processes including proliferation, tumour growth, apoptosis, and immune responses [3]. Since thalidomide is able to suppress NF-κB activity [4,5], this drug has an impact on all of these processes.

As previously mentioned, inhibition of angiogenesis was the first mechanism identified by which thalidomide exerts its anti-tumour activity. Thalidomide inhibits the angiogenesis-stimulating property of angiogenic factors [1]. In addition, it reduces the levels of angiogenesis promoting factors, such as TNF-α, VEGF, and IL-6 [6,7]. Furthermore, a decrease of cyclooxygenase-2 [8] leading to a diminished prostaglandin synthesis may contribute as prostaglandins stimulate angiogenesis.

In preclinical models, growth inhibition of tumour cells has been reported against several tumour types. These effects of thalidomide are probably mainly due to an enhanced susceptibility to apoptosis. In recent years, it has become clear that there are two apoptotic signalling pathways, an intrinsic and extrinsic one. Following severe cellular stress such as DNA damage and cell cycle defects, the intrinsic pathway is activated, which involves activation of the pro-apoptotic members of the Bcl-2 family and subsequent release of apoptosis-inducing factors by the mitochondria. The extrinsic pathway involves members of the TNF-superfamily, such as Fas and TNF-related-apoptosis-inducing-ligand (TRAIL), and plays a role in apoptosis induced by chemotherapy and cellular immunity. Thalidomide affects both pathways; the intrinsic pathway by reducing levels of the anti-apoptotic members of the Bcl-2 family [9] and the extrinsic pathway by downregulating proteins conferring resistance against Fas- or TRAIL-mediated apoptosis [10]. Another mechanism leading to growth inhibition is reduction of growth stimulating factors, for example, IL-6 that stimulates growth of some solid tumour types [11].

Table 1
Mechanisms of action

Inhibition of angiogenesis	Attenuation of activity of angiogenic factors Reduction in the levels of angiogenic factors
Inhibition of tumour growth	Increased susceptibility to apoptosis Reduction of growth-stimulating factors
Stimulation immune responses	Stimulation of T-lymphocytes Stimulation of natural killer cells Increased susceptibility to cellular immunity
Attenuation of metastatic potential	Reduction of adhesion molecules

Thalidomide and its analogues have various effects on the immune system. By acting as a costimulator, thalidomide increases the response of T-lymphocytes to T-cell receptor-mediated stimulation, yielding increased proliferation and greater production of IL-2 and interferon-γ [12,13]. In addition, thalidomide increases the number of natural killer cells, while these cells exhibit augmented cytotoxic activity against tumour cells [12]. Furthermore, the increased sensitisation to Fas- and TRAIL-induced apoptosis after exposure to thalidomide [10] renders tumour cells more prone to immune responses since cellular immunity exerts anti-tumour effects partially through Fas and TRAIL.

An additional mechanism underlying the anti-tumour activity of thalidomide is attenuation of metastatic potential of tumour cells by reducing TNF-α-induced upregulation of adhesion molecules on endothelial cells such as intracellular adhesion molecule-1 (ICAM-1), vascular-cell adhesion molecule-1 (V-CAM-1), and E-selectins [14]. These molecules are involved in the pathogenesis of dissemination by facilitating the adherence of tumour cells to the endothelium, one of the first events required for the development of metastases.

Hence, numerous mechanisms accounting for anti-tumour efficacy have been found in recent years. However, it is unlikely that all of the mechanisms involved have been revealed. Increased knowledge of these mechanisms will improve the potential activity of thalidomide-based treatments.

2.1. Thalidomide as a single agent in solid tumours

The promising outcomes obtained in patients with multiple myeloma prompted investigators to assess the anti-tumour efficacy of thalidomide in several solid tumour types. Although no phase I trials assessing the

maximum tolerated dose (MTD) or optimal administration scheme have been performed, a dose-escalation design, starting at low doses (100 or 200 mg/day) and gradually increasing to 1000 to 1200 mg/day, depending on tolerability, is usually applied in most phase II studies. In general, the use of thalidomide is accompanied by a mild toxicity profile. Because of the teratogenic features, this drug is absolutely contraindicated in pregnant women. In addition, effective contraception should be used in women of childbearing potential. The most frequently encountered side-effects are fatigue, somnolence, which can be handled by administrations in the evening, skin toxicity, constipation, for which a vigorous laxative policy is indicated, and peripheral neurotoxicity. Less common untoward sequelae are dry mouth, liver enzyme disturbances, hypothyroidism, bradycardia and depression. One important advantageous feature of thalidomide over other drugs frequently used in cancer medicine is its lack of severe myelosuppression. Bone marrow depression occurs in only 5% of the patients, of which a substantial number has been heavily pretreated with chemotherapy.

The observation that in studies in which a dose-escalation is applied, not all patients tolerate the maximum dose suggests that a dose-toxicity relationship exists [15–17]. In studies assigning patients to receive either low-dose or high-dose thalidomide, the occurrence and severity of somnolence and constipation, in particular, were greater in patients allocated to the high-dose arm [18,19].

Since the anti-tumour activity of thalidomide was initially thought to be mainly through the inhibition of angiogenesis and stimulation of immune responses, its efficacy has been predominantly explored in tumour types in which these two factors are considered important. In terms of the response rates achieved, thalidomide exhibits no or little activity in metastatic colorectal cancer [20], renal cell carcinoma [16,21], breast cancer [19], hormone-refractory prostate cancer [18,22], high grade glioma [23], hepatocellular carcinoma [24,25], melanoma [26] and squamous head and neck cancer [15]. However, it is questionable whether response rate is an appropriate parameter for the evaluation of anti-tumour efficacy with regard to the mechanisms of action of thalidomide. Progression-free survival is probably a more accurate endpoint, and in a small proportion of patients with renal cell carcinoma and hepatocellular carcinoma, durable progression-free survival has been reported suggesting some activity in these tumour entities. Another tumour type in which anti-tumour activity has been demonstrated is hormone-refractory prostate cancer, with significant reductions in prostate-specific antigen (PSA) being observed in approximately 30–40% of patients [18,22]. The most favourable outcomes obtained in a solid tumour type were seen in acquired-immuno deficiency syndrome(AIDS)-related Kaposi's sarcoma with 8 of 17 evaluable patients achieving a partial response and a progression-free survival rate of 7.3 months [17]. These outcomes are comparable to those achieved with chemotherapy. However, to rate this study at its true value is rather difficult since most patients concurrently received anti-retroviral treatment as well.

Based on these results, randomised controlled trials with thalidomide as a single agent treatment have been initiated in patients with disseminated renal cell carcinoma and hormone-refractory prostate carcinoma.

3. Predictive factors

Numerous efforts have been made to identify factors associated with response. One of these is the total dose administered. In multiple myeloma, there are indications that patients receiving a higher total dose of thalidomide have a more favourable outcome than those administered lower doses [27]. However, in solid tumours no such relationship has been established, either with the total doses administered or with the plasma levels achieved [17,18].

Since the effects on angiogenesis may partially account for the efficacy of thalidomide, research has focused on the factors involved in this process. At initiation of treatment, a highly elevated bFGF [28], low level of soluble TNF-receptor 1 [29], or the presence of a particular polymorphism of the TNF-α promotor gene resulting in higher TNF-α levels [30], are all predictors of response in patients with multiple myeloma. However, such associations have not yet been demonstrated in solid tumour types. Decrements in circulating bFGF and TNF-α levels during thalidomide treatment are correlated with responses in patients with high-grade gliomas [23] and renal cell carcinoma [21], respectively. This may suggest thalidomide-mediated downregulation of angiogenic factors subsequently resulting in anti-tumour activity, but may also simply reflect a decrease in proliferative tumour activity. Taken together, in solid tumours, proper determinants affecting efficacy have not yet been elucidated. Identification of such predictive factors is warranted as this may allow patient-tailored treatment, thereby avoiding under- or overtreatment.

4. Thalidomide-containing combination treatments

When combining drugs, each one should preferably exert single agent activity, different mechanisms of action, non-overlapping toxicity profiles, and synergistic interactions. Thalidomide has a mild toxicity profile and multiple mechanisms of action, both differing from those commonly associated with chemo- and immunotherapy. In particular, the observation that thalidomide

makes tumour cells increasingly prone to apoptotic triggers, which is illustrated by synergistic interactions in preclinical studies, renders this drug very attractive to explore in combination with other anti-tumour agents.

Several phase II studies with thalidomide-containing multidrug treatments have been conducted in renal cell carcinoma [31,32], high-grade gliomas [33,34], melanoma [35,36], and hormone-refractory prostate cancer [37]. The combinations tested proved to be well-tolerated and feasible, with the exception of an unexpectedly high rate of thromboembolic events. This adverse event was encountered in patients concurrently treated with agents such as gemcitabine and 5-fluorouracil [31] or docetaxel [37]. This is in line with observations in multiple myeloma patients of which approximately 15% encounter this particular side-effect during multidrug treatment, in contrast to 5% of patients receiving either thalidomide or chemotherapy alone [38]. Currently, it is not clear whether prophylactic anticoagulation prevents this detrimental effect.

Concerning efficacy, combining thalidomide with carmustine [34] or temozolomide [33] yields favourable outcomes compared with historical controls in recurrent high-grade gliomas and glioblastoma multiforme, respectively. In addition, the combinations of thalidomide with either interferon-α in patients with renal cell carcinoma [32] or temozolomide in melanoma patients [35] are active. In patients with disseminated renal cell carcinoma showing progression during IL-2, thalidomide seems to overcome resistance against IL-2 as responses are reported following the addition of thalidomide [7]. Several phase II trials in a randomised setting have been carried out. Danson and colleagues described a comparison between temozolomide alone, the combination of temozolomide and interferon-α, and the combination of temozolomide with thalidomide in 181 patients with metastatic melanoma. With regard to efficacy, there were no obvious differences between the three regimens, but in view of the more favourable toxicity profile of the thalidomide/temozolomide arm, this regimen was regarded as the most promising [36]. Another phase II study randomly assigned patients with hormone-refractory prostate cancer to receive treatment with either thalidomide and docetaxel or docetaxel alone. In 71 evaluable patients, a decrease in PSA levels of more than 50% was achieved by 9/24 and 25/47 patients receiving docetaxel and the combination, respectively [37].

Regarding the feasibility of thalidomide to be concurrently administered with other anti-tumour agents and the promising efficacy of such regimens, several phase III in diverse tumour types have been initiated.

Table 2
Activity of thalidomide in solid tumour types

Single-agent	
No activity	Colorectal cancer
	Breast cancer
	Melanoma
	Head and neck cancer
Some activity	Renal cell cancer
	Hepatocelullar carcinoma
	Prostate cancer
	High grade glioma
	Kaposi's sarcoma
In combination treatment	
Promising activity	Renal cell cancer
	Prostate cancer
	High grade glioma
	Melanoma

4.1. Thalidomide analogues

The intriguing activity of thalidomide prompted investigators to design novel compounds derived from thalidomide with enhanced activity, while lacking some of the side-effects of the parent drug. Until now, two classes of thalidomide analogues have been developed called Immunomodulatory drugs (IMiDs) and Selective cytokine inhibitory drugs (SelCIDs). In preclinical models, both classes inhibit tumour growth and angiogenesis more potently than thalidomide. IMiDs and SelCID differ predominantly from each other in their T-cell costimulatory effects which SelCIDs lack.

Clinical studies, mainly performed in patients with multiple myeloma, revealed that these drugs are safe and possess anti-tumour efficacy. In addition, in patients with solid tumours, CC-5013, an IMiD, was well-tolerated while indications for anti-tumour effects were seen [39]. Meanwhile, several other phase I and II trials with these compounds are in progress.

5. Conclusions

After being removed from the market in the 1960's, thalidomide has risen 'phoenix-like' from the ashes and is currently a valuable compound in the treatment of multiple myeloma patients. In solid tumours, thalidomide and its analogues are also potentially active drugs (Table 2). Applied as a single agent, thalidomide exhibits efficacy in a small group of patients with solid tumour entities, such as Kaposi's sarcoma, renal cell carcinoma, hormone-refractory prostate cancer and hepatocellular carcinoma. It can be envisaged that, especially in combination with other anti-tumour agents, thalidomide and its compounds may form a valuable contribution to the armamentarium against cancer, as these drugs sensitise tumour cells to apoptotic triggers. Accordingly, phase II studies with thalidomide-containing combinations have yielded promising results. However, it should

be emphasised that outcomes of randomised phase III studies assessing thalidomide and its analogues, either as a single agent or in combination, are not yet available. Until then, the relative contribution of thalidomide in the treatment of patients with solid tumour types remains to be defined.

Conflict of interest statement

None declared.

References

1. D'Amato RJ, Loughan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci USA* 1994, **91**, 4082–4085.
2. Singhal S, Mehta J, Desikan R, *et al.* Antitumor activity of thalidomide in refractory multiple myeloma. *New Engl J Med* 1999, **341**, 1565–1571.
3. Kucharczak J, Simmons MJ, Fan Y, Gélinas C. To be, or not to be: NF-κB is the answer – role of Rel/ NF-κB in the regulation of apoptosis. *Oncogene* 2003, **22**, 8961–8982.
4. Keifer JA, Guttridge DC, Ashburner BP, Baldwin AS. Inhibition of NF-κB activity by thalidomide through suppression of IκB kinase activity. *J Biol Chem* 2001, **276**, 22382–22387.
5. Majumbar S, Lamothe B, Aggarwal BB. Thalidomide suppresses NF-κB activation induced by TNF and H_2O_2, but not that activated by ceramide, lipopolysaccharides, or phorbol ester. *J Immunol* 2002, **168**, 2644–2651.
6. Sampaio EP, Sarno EN, Gallily R, Cohn ZA, Kaplan G. Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes. *J Exp Med* 1991, **173**, 699–703.
7. Kedar I, Mermershtain W, Ivgi H. Thalidomide reduces serum c-reactive protein and interleukin-6 and induces response to IL-2 in a fraction of metastatic renal cell cancer patients who failed IL-2-based therapy. *Int J Cancer* 2004, **110**, 260–265.
8. Fujita J, Mestre JR, Zeldis JB, *et al.* Thalidomide and its analogues inhibit lipopolysaccharide-mediated induction of cyclo-oxygenase-2. *Clin Cancer Res* 2001, **7**, 3349–3355.
9. Marriott JB, Clarke IA, Czajka A, *et al.* A novel subclass of thalidomide analogues with anti-solid tumor activity in which caspase-dependent apoptosis is associated with altered expression of bcl-2 family proteins. *Cancer Res* 2003, **63**, 593–599.
10. Mitsiades N, Mitsiades CS, Poulaki V, *et al.* Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications. *Cancer Res* 2002, **99**, 4525–4530.
11. Goswami S, Gupta A, Sharma SK. Interleukin-6-mediated autocrine growth promotion in human glioblastoma multiforme cell line U87MG. *J Neurochem* 1998, **71**, 1837–1845.
12. Davies FE, Raje N, Hideshima T, *et al.* Thalidomide and immunomodulatory derivates augment natural killer cell cytotoxicity in multiple myeloma. *Blood* 2001, **98**, 210–216.
13. Haslett PAJ, 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**, 1885–1892.
14. Geitz H, Handt S, Zwingenberger K. Thalidomide selectively modulates the density of cell surface molecules involved in the adhesion cascade. *Immunopharmacology* 1996, **31**, 213–221.
15. Tseng JE, Glisson BS, Khuri FR, *et al.* Phase II study of the angiogenesis agent thalidomide in recurrent or metastatic squamous cell carcinoma of the head and neck. *Cancer* 2001, **92**, 2364–2373.
16. Motzer RJ, Berg W, Ginsberg M, *et al.* Phase II trial of thalidomide for patients with advanced renal cell carcinoma. *J Clin Oncol* 2001, **20**, 302–306.
17. Little RF, Wyvill KM, Pluda JM, *et al.* Activity of thalidomide in AIDS-related Kaposi's sarcoma. *J Clin Oncol* 2000, **18**, 2593–2602.
18. Figg WD, Dahut W, Duray P, *et al.* A randomized trial of thalidomide, an angiogenesis inhibitor, in patients with androgen-independent prostate cancer. *Clin Cancer Res* 2001, **7**, 1888–1893.
19. Baidas SM, Winer EP, Fleming GF, *et al.* Phase II evaluation of thalidomide in patients with metastatic breast cancer. *J Clin Oncol* 2000, **18**, 2710–2717.
20. Dal Lago L, Richter MF, Cancela AI, *et al.* Phase II trial and pharmacokinetic study of thalidomide in patients with metastatic colorectal cancer. *Invest N Drugs* 2003, **21**, 359–366.
21. Stebbing J, Benson C, Eisen T, *et al.* The treatment of advanced renal cell cancer with high-dose of thalidomide. *Br J Cancer* 2001, **85**, 953–958.
22. Drake MJ, Robson W, Mehta P, *et al.* An open-label phase II study of low-dose thalidomide in androgen-independent prostate cancer. *Br J Cancer* 2003, **88**, 822–827.
23. 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**, 708–715.
24. Hsu C, Chen C-N, Chen L-T, *et al.* Low-dose thalidomide treatment for advanced hepatocellular carcinoma. *Oncology* 2003, **65**, 242–249.
25. Wang T-E, Kao C-R, Lin S-C, *et al.* Salvage therapy for hepatocellular carcinoma with thalidomide. *World J Gastroenterol* 2004, **10**, 649–653.
26. Pawlak WZ, Legha SS. Phase II study of thalidomide in patients with metastatic melanoma. *Melanoma Res* 2004, **14**, 57–62.
27. Barlogie B, Desikan R, Eddelmon P, *et al.* Extended survival in advanced and refractory multiple myeloma after single-dose thalidomide: identification of prognostic factors in a phase 2 study of 169 patients. *Blood* 2001, **98**, 492–494.
28. 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. *Cancer Res* 2001, **7**, 2675–2681.
29. Brenne AT, Romstad LH, Gimsing P, *et al.* A low serum of soluble tumor necrosis factor receptor p55 predicts response to thalidomide in advanced multiple myeloma. *Haematologica* 2004, **89**, 552–556.
30. Neben K, Mytilineos J, Moehler TM, *et al.* Polymorphisms of the tumor necrosis factor-α gene promotor predict for outcome after thalidomide therapy in relapsed and refractory multiple myeloma. *Cancer Res* 2002, **100**, 2263–2265.
31. 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**, 1629–1636.
32. Hernberg M, Virkkunen P, Bono P, Ahtinen H, Mäenpää H, Joensuu H. Interferon alfa-2b three times daily and thalidomide in the treatment of metastatic renal cell carcinoma. *J Clin Oncol* 2003, **21**, 3770–3776.
33. Baumann F, Bjeljac M, Kollias S, *et al.* Combined thalidomide and temozolomide treatment in patients with glioblastoma multiforme. *J Neuro Oncol* 2004, **67**, 191–200.
34. Fine HA, Wen PY, Maher EA, *et al.* Phase II trial of thalidomide and carmustine for patients with recurrent high-grade gliomas. *J Clin Oncol* 2003, **21**, 2299–2304.
35. Hwu W-J, Krown SE, Menell JH, *et al.* Phase II study of temozolomide plus thalidomide for the treatment of metastatic melanoma. *J Clin Oncol* 2003, **21**, 3351–3356.

36. Danson S, Lorigan P, Arance A, *et al*. Randomized phase II study of temozolomide given every 8 hours or daily with either interferon alfa-2b or thalidomide in metastatic malignant melanoma. *J Clin Oncol* 2003, **21**, 2551–2557.
37. Dahut WL, Gulley JL, Arlen PM, *et al*. Randomized phase II trial of docetaxel plus thalidomide in androgen-independent prostate cancer. *J Clin Oncol* 2004, **22**, 2532–2539.
38. Bennett CL, Schumock GT, Desai AA, *et al*. Thalidomide-associated deep vein thrombosis and pulmonary embolism. *Am J Med* 2002, **113**, 603–606.
39. Bartlett JB, Michael A, Clarke IA, *et al*. Phase I study to determine the safety, tolerability and immunostimulatory activity of thalidomide analogue CC-5013 in patients with metastatic malignant melanoma and other advanced cancers. *Br J Cancer* 2004, **90**, 955–961.