Lenalidomide in hemato-oncology: immunomodulation gains power

M. Delforge

The immunomodulatory drugs are a class of orally bioavailable compounds that exert their antitumoral effects through several biological functions. Lenalidomide is a 4-amino thalidomide analogue with strong anti-inflammatory and immunomodulatory activities. Lenalidomide in combination with dexamethasone is currently licensed for the treatment of patients with multiple myeloma having received at least one prior line of treatment. In addition, lenalidomide can induce impressive erythropoietic responses in patients with myelodysplastic syndromes. Promising clinical results with lenalidomide arise in lymphoproliferative disorders, whereas it is too early to assess the future value of this drug for solid tumor treatment.
(Belg J Hematol 2010;1:22-27)

Introduction

The immunomodulatory drugs (IMiDs) are a class of orally bioavailable compounds that have been developed using the parent compound thalidomide (α-N-phtalimidoglutarimide), a synthetic glutamic acid derivative as chemical backbone.

In the late 1950s, thalidomide was marketed by the German pharmaceutical company Grünenthal in more than 40 countries as a sedative-hypnotic drug, and later as an anti-emetic for hyperemesis gravidarum. Because of the lack of toxicity in several animal models and healthy volunteers, thalidomide was initially promoted as a very safe alternative for barbiturates. However, in 1961 the extreme teratogenicity of thalidomide was recognized and the drug was immediately withdrawn from the market. But this could not prevent the birth of around 10,000 babies with severe developmental deformities, including phocomelia. By refusing thalidomide licensing, even though it was because of concerns for peripheral neuropathy, the Food and Drug Administration (FDA) could avoid an even larger tragedy. Nevertheless, in some countries thalidomide continued to be used as a sedative drug which resulted by chance in the discovery of its remarkable activity in erythema nodosum leprosum (ENL), a serious inflammatory complication of lepromatous leprosy. This observation further catalyzed the exploration of thalidomide use in several chronic inflammatory disorders (such as chronic graft-versus-host disease, HIV wasting syndrome) and autoimmune diseases (such as cutaneous lesions of lupus erythematosus, Behçet's disease), finally resulting in a FDA approval for treatment of ENL, more than 20 years after the initial refusal. This licensing combined with the discovery of the potent antitumoral effect of thalidomide in multiple myeloma (MM) launched

Author: M. Delforge, Department of Hematology, University Hospitals Leuven, Belgium.

Please send all correspondence to: M. Delforge, MD, PhD, Department of Hematology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium, tel: 0032 16 34 68 80, e-mail: michel.delforge@uzleuven.be

Conflict of interest: The author is a senior clinical investigator of the Flanders Fund for Scientific Research (FWO-Vlaanderen). The author is also a consultant for Celgene and has received speaker's honoraria.

Key words: IMiDs, immunomodulatory drugs, lenalidomide, multiple myeloma, myelodysplastic syndromes, non-Hodgkin's lymphoma, thalidomide

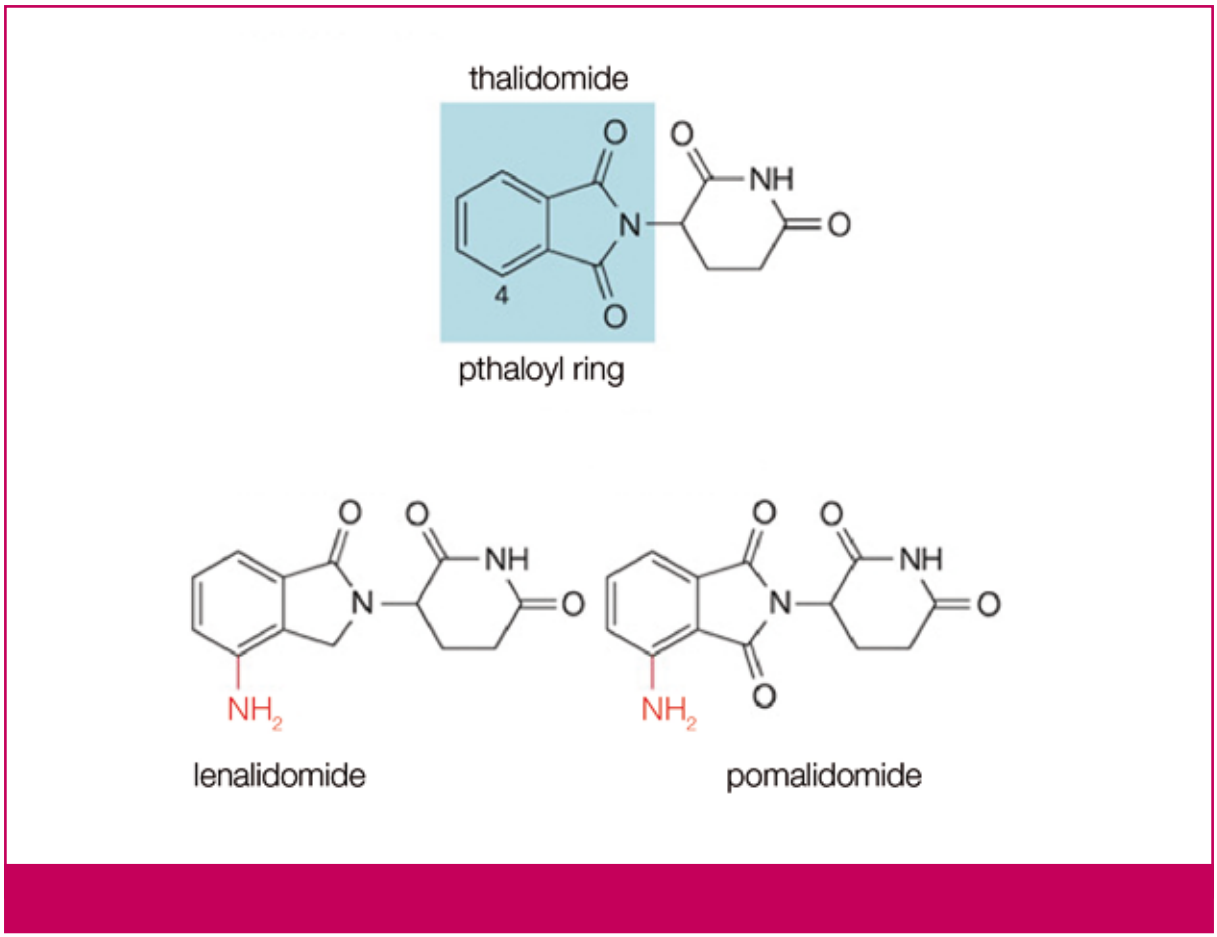

Figure 1. Chemical structure of thalidomide, lenalidomide, and pomalidomide.

the resurrection of thalidomide, and stimulated the search for new analogues with greater therapeutic efficacy and a better safety profile.[1,2] The initial goal was to design analogues with greater potency of tumor necrosis factor (TNF)-α inhibition, which was at that time believed to be the major mechanism of action of thalidomide. The 4-amino analogues, in which an amino group is added to the fourth carbon of the phtaloyl ring of thalidomide, were found to have the strongest anti-inflammatory and immunomodulating properties. These compounds are designated as IMiDs. Pharmacokinetic studies and preclinical testing identified CC-5013 (lenalidomide) and CC-4047 (pomalidomide) as the 2 most interesting IMiDs for further clinical development (*Figure 1*).[3]

Mechanisms of action

Building further on the clinical experience with thalidomide, several trials with lenalidomide in hematology were started, even before the full biological activities of this drug were fully unravelled. After all, IMiDs interfere with multiple pathways both at the cellular and extracellular level, therefore complicating a fast and complete understanding of the mechanism(s) of action in the different diseases where these compounds are explored. More precisely, lenalidomide targets malignant cells directly, but even more importantly also indirectly by alteration of the production of cytokines, downregulation of adhesion receptors, inhibition of angiogenesis, and last but not least by upregulation of the endogenous immune system.[2-4]

Direct tumor cell killing by induction of apoptosis

IMiDs like lenalidomide have proven to exert direct antiproliferative activity against several types of cancer cells, by activating Fas-mediated pro-apoptotic signals resulting in upregulation of caspase-8, but not caspase-9. From a clinical perspective, this finding has catalyzed the use of

combinations between lenalidomide and caspase-9 inhibitors like dexamethasone and bortezomib. At the mitochondrial level, lenalidomide activates c-jun N-terminal kinase (c-JNK), increasing the permeability of the mitochondria and stimulating the release of pro-apoptotic proteins like cytochrome c and Smac.[4] In addition, nuclear factor-κB, a key transcription factor is also directly inhibited by lenalidomide.[2-4]

Cytokine inhibition

The anti-inflammatory effects of thalidomide are largely due to enhanced degradation of TNF-α mRNA in activated human monocytes, and by in vitro testing, lenalidomide is approximately a 2,000 fold more potent inhibitor of monocyte derived TNF-α secretion.[3] TNF-α is a cytokine that plays an important role in several malignant and non-malignant diseases and for long has been an interesting therapeutic target in many disease types. In addition to TNF-α inhibition, lenalidomide can suppress the production of other pro-inflammatory cytokines like transforming growth factor (TGF)-β, interleukin (IL)-1β, and IL-6, and upregulate the anti-inflammatory effects of IL-10.[2-4] The pro-erythropoietic effect of thalidomide and particularly lenalidomide in myelodysplastic syndromes (MDS) is believed to be primarily due to the inhibition of pro-apoptotic and pro-inflammatory cytokines, whereas in MM, downregulation of IL-6 and TNF-α abrogate the stimulating effect of these molecules on the growth and survival of myeloma cells.[4,5]

Modulation of adhesion receptors

IMiDs like lenalidomide can decrease the expression of critical cell surface receptors including integrins and other cell adhesion molecules (CAM) like intracellular adhesion molecule (ICAM)-1. These adhesion receptors not only anchor the tumor cells to the stromal niche, but they can also facilitate cytokine-mediated tumor growth and contribute to adhesion-mediated chemotherapy resistance.[4]

Antiangiogenesis

Using a rabbit cornea micropocket assay, it was shown already several decades ago that thalidomide can inhibit basic fibroblast growth factor (bFGF) induced angiogenesis.[6] Moreover, inhibition of angiogenesis was the primary hypothesis why thalidomide was given to patients with MM. Despite clinical efficacy in one third of refractory myeloma patients, no clear correlation between therapeutic efficacy and angiogenesis markers like microvessel density, could be found.[7] In vitro, lenalidomide exerts more potent inhibition of angiogenic growth factor mediated neovascularization, supposably by inhibition of proangiogenic cytokines like vascular endothelial growth factor (VEGF) and bFGF.[3,4] In addition, IMiDs can interfere with cytokine-stimulated endothelial cell migration and adhesion, although the precise mechanisms are not yet well characterized.

Immunological stimulation

In conjunction with the primary T cel receptor mediated signal, costimulation of T cells is crucial to generate an antigenspecific immunological response and to prevent the induction of immunological tolerance or anergy. IMiDs potentiate the costimulatory signal or mimic it when it is not present.[2-4] This costimulatory activity of the IMiDs is important to enhance an otherwise ineffective immune response.

Lenalidomide is much more potent than thalidomide at the costimulation of $CD4^+$ and $CD8^+$ T cells that are partially activated via their T cell receptor.[3] Consequences of the type 1 helper T cell (Th1) cellular immune response stimulation include increased production of IL-2 and interferon (IFN)-γ, which enforce clonal T cell proliferation and natural killer (NK) cell activity. Additionally, lenalidomide can also activate the innate immunological compartment directly by augmenting the cytotoxicity of NK cells and thereby enhancing tumor cell lysis. IMiD induced increased secretion of cytokines such as TNF-α and IL-12 from T cell activated antigen presenting cells can, at least partially, explain why the effect on the immune system can be variable depending upon the underlying disease and/or the status of the immune system of the individual patient being treated.[2-4]

Clinical results

Given its pleiotropic biological activities, clinical efficacy of lenalidomide has been pursued in various malignant and nonmalignant disorders resulting

in an increasing number of clinical trials. The rest of this paper will focus on the clinical results with lenalidomide in hemato-oncological disorders, with an emphasis on MM and MDS. Additionally, we briefly highlight the most recent clinical data with lenalidomide in chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), and solid tumors.

Multiple myeloma

MM is a malignant plasma cell disorder affecting around 5 per 100,000 persons each year, making this disease the second most common hematological malignancy. Until 2 decades ago, the overall prognosis of myeloma patients looked grim due to the limited therapeutic options. A first major step forward was the introduction of high dose melphalan in combination with hematopoietic stem cell support. A second wave of therapeutic improvement was heralded by the so-called 'new drugs' being thalidomide, the proteasome inhibitor bortezomib, and lenalidomide.[8] In phase I and II studies, lenalidomide showed clinical benefit as monotherapy in patients with relapsed or refractory myeloma, and 25 mg daily was defined as the maximum tolerated dose.[9]

In 2 prospective, randomized, double-blind, placebo-controlled phase III clinical trials (MM-009 and MM-010), it was demonstrated that lenalidomide combined with dexamethasone induced significantly higher rates of overall response, complete response, as well as longer time to progression and overall survival, compared with placebo plus dexamethasone in patients with relapsed or refractory MM.[10,11] Based on these studies, the combination lenalidomide + dexamethasone was licensed by the European Medicines Agency (EMEA) in June 2007 for the treatment of patients with MM after at least one prior line of treatment. Lenalidomide 25 mg/day is taken orally on days 1 to 21 of each 28-day cycle, with 40 mg/day of dexamethasone on days 1 to 4, 9 to 12 and 17 to 20 of each 28-day cycle for the first 4 cycles, with a reduction to 40 mg/day of dexamethasone on days 1 to 4 of each cycle thereafter. According to the label and the registration studies, lenalidomide is given until disease progression. Dose reductions need to be applied in case of renal insufficiency or poor bone marrow reserve.[12] Lenalidomide combined with weekly pulses (also called 'low dose') of 40 mg dexamethasone has been proven to be nearly as effective and less toxic, especially in elderly subjects or patients with comorbidities.[13] Treatment with lenalidomide should be continued until progressive disease, in contrast with thalidomide where peripheral neuropathy usually precludes treatment duration beyond 6 to 12 months.[14] Despite some degree of cross-resistance between thalidomide and lenalidomide, the majority of thalidomide exposed patients, and even 50% of thalidomide refractory patients, will respond to the combination of lenalidomide plus dexamethasone.[15] Encouraged by the results in relapsed MM, lenalidomide combinations are under investigation for first-line treatment in MM both in transplant- and non-transplant candidates, and as consolidation and maintenance treatment post autologous stem cell transplantation with very promising preliminary results on progression-free survival.[16-18]

Myelodysplastic syndromes

The first publications on the efficacy of lenalidomide treatment in hematology was not in MM, but in MDS, a clonal hematopoietic disorder characterized by progressive bone marrow failure and frequently complicated by transfusion dependent anemia. In MDS patients with a low-risk for leukemic transformation who do not respond to erythropoietin, single-agent lenalidomide was found to significantly reduce transfusion need.[19] Most impressively, in the subgroup of patients with the interstitial chromosome 5q deletion, rapid and sustained erythropoietic responses can be obtained in up to 75%, with two third of the patients even becoming transfusion independent.[20] Nevertheless, in contrast to the FDA granting fast-track approval for lenalidomide in MDS, EMEA approval is still pending. In contrast to MM, the maximum tolerated dose of lenalidomide in MDS is only 10 mg. For MDS patients without the chromosome 5q deletion, clinical trials with lenalidomide are ongoing.

Lymphoproliferative disorders

Inspired by the success of lenalidomide in MM, the drug is currently under investigation in several other lymphoproliferative diseases with the most promising data in mantle cell lymphoma (MCL), and CLL. Phase II data with lenalidomide monotherapy in MCL, a subtype of NHL with a very dismal

Key messages for clinical practice

1. Lenalidomide and thalidomide are members of the family of immunomodulatory drugs.
2. Antitumoral activity of lenalidomide occurs through several mechanisms including direct tumor cell killing, interference with the micro-environment, and modulation of the immune system.
3. Lenalidomide is currently registered for the treatment of patients with relapsed or refractory multiple myeloma after at least one prior line of treatment where the drug is given in combination with dexamethasone.
4. Lenalidomide is under investigation in myelodysplastic syndromes, chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and some solid tumors.
5. The toxicity of lenalidomide is manageable. Most common side effects include hematological toxicity and fatigue.

prognosis, have shown clinically relevant response rates in more than 50% of relapsing patients, with some patients achieving a complete remission.[21] Similarly, encouraging results with lenalidomide are obtained in the treatment of patients with CLL.[22] Interestingly, in this disease standard doses of 25 mg lenalidomide can induce life threatening tumor flare reactions characterized by painful enlargement of the lymph nodes and/or spleen, requiring treatment with non-steroidal anti-inflammatory agents or even prednisone.[23] Rapid upregulation of B-cell activation and co-stimulatory markers are believed to provoke tumor flare. Consequently, lenalidomide is initiated at lower doses in ongoing CLL trials.

Solid tumors

A recently published international, multicenter, randomized, double-blind study in refractory stage IV metastatic malignant melanoma did not show significant differences in response, time to progression or overall survival between lenalidomide and placebo.[24] Trials assessing the safety and efficacy of lenalidomide in refractory solid tumors including prostate cancer, renal cell carcinoma, ovarian and colon cancer are currently being conducted.[25,26]

Side effect profile

Overall, the toxicity of lenalidomide is manageable. The principal side effect of lenalidomide is hematological toxicity, and more precisely leukopenia, neutropenia, and thrombocytopenia. Grade 4 hematological toxicity is rare if appropriate starting doses are used and the dose modification guidelines are followed. When lenalidomide is used in combination with other immunosuppressive drugs like dexamethasone, additional caution for infections like pneumonia is warranted. The most frequently reported nonhematological adverse events include fatigue, muscle cramps, and more occasionally constipation, diarrhea or skin eruptions.[12] In contrast to thalidomide, lenalidomide does not cause excess neurotoxicity. Importantly, as has been documented in MM, the combination of IMiDs with dexamethasone and/or chemotherapy significantly increases the risk for venous thromboembolism, necessitating appropriate thromboprophylaxis.[27] This can include low molecular weight heparins, low dose aspirin or treatment with coumarins depending on the disease status and patient related risk factors for venous thrombosis. Based on the structural and pharmacological similarity to thalidomide and foetal alterations observed in rabbits, lenalidomide has to be contraindicated during pregnancy, and precautions should be taken for women of childbearing potential.

Conclusions

The revival of thalidomide has heralded a new

era for the treatment of MM. Lenalidomide is a more powerful IMiD than thalidomide in the management of MM, and is also explored for the treatment of other hematological malignancies including MDS, CLL, NHL, and some solid tumors. Given its pleiade of biological functions, lenalidomide use has boosted continued research into the biology of IMiDs. Lenalidomide has a favorable toxicity profile, even after prolonged use. However, given its high price, every physician prescribing this drug has the clinical and ethical duty to pursue its optimal use.

References

1. Rajkumar SV. Thalidomide: tragic past and promising future. Mayo Clin Proc 2004;79:899-903.

2. Bartlett JB, Dredge K, Dalgleish AG. The evolution of thalidomide and itis IMiD derivatives as anticancer agents. Nat Rev Cancer 2004;4:314-22.

3. Quach H, Ritchie D, Stewart AK, Neeson P, Harrison H, Smith MJ, Prince HM. Mechanisms of action of immunomodulatory drugs (IMiDS) in multiple myeloma. Leukemia 2010;24:22-32.

4. Anderson KC. Lenalidomide and thalidomide: mechanisms of action-similarities and differences. Semin Hematol 2005;42:S3-8.

5. List AF. Lenalidomide in myelodysplastic syndromes. Clin Adv Hematol Oncol 2008;6:271-2.

6. D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci USA 1994;91:4082-5.

7. Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 1999;341:1565-71.

8. Kyle RA, Rajkumar SV. Multiple myeloma. Blood 2008;111:2962-72.

9. Richardson P, Jagannath S, Hussein M, Berenson J, Singhal S, Irwin D, et al. Safety and efficacy of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma. Blood 2009;114:772-8.

10. Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007;357:2123-32.

11. Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357:2133-42.

12. European Public Assessment Report for Revlimid. European Medicines Agency, 2008. Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/revlimid/H-717-en6.pdf

13. Rajkumar SV, Jacobus S, Callander NS, Fonseca R, Vesole DH, Williams ME, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 2010;11:29-37

14. Spencer A, Prince HM, Roberts AW, Prosser IW, Bradstock KF, Coyle L, et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. J Clin Oncol 2009;27:1788-93.

15. Wang M, Dimopoulos MA, Chen C, Cibeira MT, Attal M, Spencer A, et al. Lenalidomide plus dexamethasone is more effective than dexamethasone alone in patients with relpased or refractory multiple myeloma regardless of prior thalidomide exposure. Blood 2008;112:4445-51.

16. Palumbo A, Dimopoulos M, Delforge M, Hajek R, Kropff M, Petrucci MT, et al. A phase III study to determine the efficacy and safety of lenalidomide combined with melphalan and prednisone in patients ≥ 65 years with newly diagnosed multiple myeloma. EHA 2010, abstract 0566.

17. McCarthy PL, Owzar K, Anderson KC, HofmeisterCC, Hassoun H, Hurd DD, et al. Phase III intergroup study of lenalidoimde versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): CALGB 100104. ASCO 2010, abstract 8017.

18. Attal M, Cristine C, Marit G, Caillot D, Facon T, Hulin C, et al. Lenalidomide maintenance treatment after transplantation for myeloma. ASCO 2010, abstract 8018.

19. List A, Kurtin S, Roe, Buresh A, Mahadevan D, Fuchs D, et al. Efficacy of lenalidomide in myelodysplastic syndromes. N Eng J Med 2005;352:549-57.

20. List A, Dewald G, Bennett J, Giagounidis A, Raza A, Feldman E, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med 2006;355:1456-65.

21. Habermann TM, Lossos IS, Justice G, Vose JM, Wiernik PH, McBride K, et al. Lenalidomide oral monotherpay produces a high response rate in patients with relapsed or refractory mantle cell lymphoma. Br J Haematol 2009;145:344-9.

22. Ferrajoli A, Bang-Ning L, Schlette EJ, O'Brien SM, Gao H, Wen S, et al. Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. Blood 2008;11:5291-87.

23. Andritsos LA, Johnson AJ, Lozanski G, Blum W, Kefauver C, Awan F, et al. Higher doses of lenalidomide are associated with unacceptable toxicity including life-threatening tumor flare in patients with chronic lymphocytic leukemia. J Clin Oncol 2008;26:2519-25.

24. Eisen T, Trefzer U, Hamilton A, Hersey P, Millward M, Knight RD, et al. Results of a multicenter, randomized, double-blind phase 2/3 study of lenalidomide in the treatment of pretreated relapsed or refractory metastatic malignant melanoma. Cancer 2009;116:146-54.

25. Dahut WL, Aragon-Ching JB, Woo S, Tohnya TM, Gulley JL, Arlen PM, et al. Phase I study of oral lenalidomide in patients with refractory metastatic cancer. Clin Pharmacol 2009;49:650-60.

26. Amato RJ, Hernandez-McClain J, Saxena S, Khan M. Lenalidomide therapy for metastatic renal cell carcinoma. Am J Clin Oncol 2008;31:244-9.

27. Knight R, DeLap RJ, Zeldis JB. Lenalidomide and venous thrombosis in multiple myeloma. N Engl J Med 2006; 354: 2079-80.