available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.ejconline.com

Thalidomide and lenalidomide in the treatment of multiple myeloma

*Shaji Kumar, S. Vincent Rajkumar**

Division of Haematology, Department of Internal Medicine, Mayo Clinic and Foundation, Rochester, Minnesota, United States

ARTICLE INFO

Article history:
Received 4 November 2005
Accepted 20 April 2006
Available online 5 June 2006

Keywords:
Thalidomide
Lenalidomide
Multiple myeloma

ABSTRACT

Although multiple myeloma (MM) is incurable with currently available treatments, the introduction of thalidomide and the development of safer and more active thalidomide analogues represent a major advance in the therapy of this disease. Thalidomide, initially introduced for treatment of MM because of its anti-angiogenic properties, has shown remarkable activity alone and in combination with other drugs in patients across all stages of the disease. Given the potential for teratogenicity with thalidomide and the non-haematologic toxicities of the drug, several analogues referred to as "immunomodulatory drugs" (IMiDs) were developed with the intent of enhancing the immunomodulatory effect while minimizing the teratogenic risk. Lenalidomide (CC-5013) and Actimid (CC-4047) are the first such analogues to undergo clinical testing. Lenalidomide has shown impressive activity in relapsed refractory myeloma as well as newly diagnosed disease. The precise mechanism of anti-MM activity of thalidomide and the IMiDs is not clear, but studies suggest that several other mechanisms besides anti-angiogenic effects may play a role. In this paper we review the development, pharmacology, mechanism of action, pre-clinical and clinical efficacy, and the current status of thalidomide and the IMiDs in the treatment of MM.

1. Introduction

Multiple myeloma is the second most common haematological malignancy after non-Hodgkin's lymphoma, affecting over 16 000 individuals each year in the United States alone and contributing to nearly 12 000 cancer related deaths.[1] It is characterized pathologically by accumulation of clonal malignant plasma cells predominantly in the bone marrow and clinically by destructive bone lesions, anaemia, hypercalcemia and or renal insufficiency.[2] The median survival for patients with myeloma treated by conventional agents such as alkylating agents and steroids is 3–4 years with some survival improvement seen with high-dose therapy and stem cell rescue.[2–4] However the current therapeutic approaches remain non-curative and novel, effective therapies are needed for treating this disease. Thalidomide, a sedative hypnotic that had become infamous due to its teratogenic side effects, was first introduced for treating myeloma due to its potential anti-angiogenic activity and became the first effective drug to become available for this disease in over two decades.[5,6] Thalidomide alone or in combination with other drugs rapidly became an important part of the armamentarium for treating myeloma. However, given the continuing concern for the teratogenic potential, efforts had been underway early on to develop analogues that retained the anti-myeloma activity without the teratogenicity. Two of the immunomodulatory analogues (termed immunomodulatory drugs; IMiDs) of thalidomide, CC4047 (IMiD1; Actimid™, Celgene Corporation) and lenalidomide (CC5013; IMiD3; CDC-501; Revlimid™, Celgene Corporation) are currently undergoing clinical trials in multiple myeloma and the results so far point towards very promising activity either alone or in combination with other

* *Corresponding author:* Tel.: +1 507 284 2511; fax: +1 507 266 4972.
E-mail address: rajks@mayo.edu (S.V. Rajkumar).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2006.04.004

drugs, especially for lenalidomide.[7,8]. Other IMiDs are in various stages of pre-clinical development. In this paper, we provide a comprehensive review of the preclinical development and clinical evaluation of thalidomide and its analogues in the treatment of myeloma.

2. Historical background

Thalidomide was initially introduced in 1956 as a sedative hypnotic and was widely prescribed to pregnant women for morning sickness, for which it was found to be particularly effective. Nearly four years later, multiple birth defects including absence or hypoplasia of arms (phocomelia), absence of ears, deafness, defects of the femur and tibia as well as malformations of the heart and the bowel were observed and associated with use of thalidomide in early pregnancy leading to its withdrawal from the market. Soon after, the powerful growth inhibitory effect of thalidomide on growing fetal tissues prompted clinical trials of the drug in patients with cancer.[9–11] The Eastern Cooperative Oncology Group (ECOG) studied 21 patients with fourteen types of advanced cancer, including two with myeloma at doses ranging between 600–2000 mg/day.[11] Subjective palliation of symptoms was noted in a third of the patients. However, other than minimal slowing of tumour growth in 2 patients with rapidly progressive disease, no significant anti-tumour effects could be discerned. In another study, thalidomide was evaluated in 71 patients with a variety of cancers at doses ranging from 300 to 2000 mg/day.[10] Except for resolution of pulmonary metastasis in a patient with renal cell carcinoma, no other responses were seen. Following these initial unimpressive trials, there was little enthusiasm with thalidomide as an antineoplastic agent until the late 1990s when the anti-angiogenic activity of thalidomide was described.[12,13] This, together with better appreciation of the importance of the role of angiogenesis in cancer biology.[14,15] laid the ground for further evaluation of the drug. Based on the observation of increased bone marrow angiogenesis in myeloma, researchers at the University of Arkansas tested the role of thalidomide in 84 patients with relapsed and refractory myeloma.[5] They observed a 32% response rate, including two complete remissions, in this heavily pre-treated population. The dramatic effect seen in patients with myeloma resulted in a renewed interest in studying the role of thalidomide as an anti-cancer agent.

3. Pharmacology

Thalidomide (α-N-[phthalimido] glutarimide, $C_{13}H_{10}N_2O_4$), is a glutamic acid derivative and contains a glutarimide moiety with a single chiral center. It is formulated as a racemic mixture of the two optically active S (−) and R (+) enantiomers, which can rapidly interconvert at physiologic pH. The S enantiomer is primarily responsible for the teratogenic effects, and the R enantiomer for the sedative properties.[16] The poor water solubility of thalidomide and the lack of an intravenous formulation have hampered reliable pharmacokinetic studies of this agent. The time to peak concentration varies from 3 to 6 hours and significant variability is seen in the C_{max} indicating slow, poor absorption from the GI tract.[17–20] There is no significant drug binding by plasma proteins and it has a large apparent volume of distribution as noted in human and animal studies.[18,19] The majority of the drug appears to undergo spontaneous non-enzymatic hydrolytic cleavage in the blood circulation into several active metabolites. Though *in vitro* studies in rat suggest a role for the cytochrome P450 system in its metabolism, human studies have so far failed to demonstrate any significant hepatic metabolism.[21,22] However, in a SCID-Hu mouse myeloma model, thalidomide demonstrated efficacy only in the presence of implanted human liver tissue.[23] Differences have been noted in terms of the drug metabolism between mice and humans.[24] Elimination of thalidomide is mainly by spontaneous hydrolysis, with an apparent mean clearance of 10 L/h for the (R)- and 21 L/h for the (S)-enantiomer leading to higher blood concentrations of the (R)-enantiomer compared to those of the (S)-enantiomer.[25] The pharmacokinetics of thalidomide in individuals with hepatic and renal dysfunction remains poorly understood. No induction of its own metabolism has been noted with prolonged use.[26] Thalidomide and its metabolites are rapidly eliminated in the urine, with none of the parent compound detected in the urine 48 hours following a single dose.

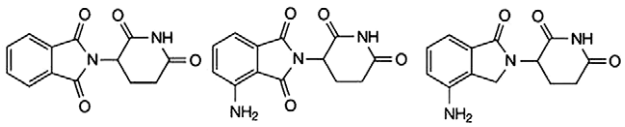

Fig. 1 – Chemical structure of thalidomide, CC-4047 and lenalidomide (CC-5013).

Lenalidomide and CC4047 are second generation analogues of thalidomide that share a similar chemical structure (Fig. 1). These drugs were found to be 50 000-fold more potent in inhibiting TNF-alpha *in vitro* compared to the parent compound. They have also demonstrated higher inhibitory effect than thalidomide in HUVEC (human umbilical vein endothelial cells) proliferation and tube formation assays. Lenalidomide appears not to be teratogenic in the New Zealand rabbit preclinical model, which is sensitive to the teratogenic effect of thalidomide.[27]

4. Preclinical activity and mechanism of action

In vitro studies of thalidomide examining its effect on the myeloma cells as well as the mechanisms of its cytotoxicity has been hampered by several of it properties. First, mechanistic studies with the drug are complicated by its enantiomeric inter-conversion and spontaneous cleavage to many metabolites in solutions at physiologic pH.[25] Second, thalidomide probably requires some form of metabolic activation since its activity in most of the *in vitro* assays is modest or negligible, compared to highly potent effects *in vivo*.[22,28] Finally, various effects in animal models appear to be highly dependent on species and route of administration, making correlations to humans complicated and unreliable.[13] In comparison, the IMiDs (lenalidomide and CC 4047) have been well

studied in the *in vitro* systems and there is a better understanding of their mechanisms in myeloma. In addition, correlative studies on tumour samples from patients undergoing therapy with these agents have enabled more precise understanding of the potential mechanisms.

Many different mechanisms have been suggested to explain the effectiveness of thalidomide in the treatment of cancer and multiple myeloma remains the best studied. Both thalidomide and its analogues have direct cytotoxic effects on myeloma cells and induce apoptosis or growth arrest of myeloma cell lines *in vitro* as well as patient derived primary myeloma cells.[29] The apoptotic signalling by IMiDs appear to be related to activation of related adhesion focal tyrosine kinase. The *in vitro* activity of the IMiDs appear to be several fold higher compared to thalidomide, which may be related to the need for thalidomide metabolism to active metabolites. Additionally, IMiDs have been shown to trigger activation of caspase-8, enhance MM cell sensitivity to Fas-induced apoptosis, and down-regulate nuclear factor (NF)-κB activity as well as expression of cellular inhibitor of apoptosis protein-2 and FLICE inhibitory protein.[30] In addition to its direct effect on the myeloma cell, these drugs appear to modulate the marrow microenvironment. The IMiDs are able to potentiate the effect of TRAIL, dexamethasone and the proteasome inhibitor PS341 on myeloma cells. These drugs can inhibit the up regulation of IL-6 and VEGF that is usually seen when myeloma cells come in contact with marrow stromal cells.[31]

D'Amato and colleagues showed that thalidomide is a potent anti-angiogenic agent based on studies using rabbit cornea micro pocket assay and a mouse cornea model of neovascularization, presumably by inhibition of bFGF and VEGF.[12,13] Animal studies support this hypothesis since thalidomide treatment can decrease vascular density in granulation tissue.[32] Studies suggest that one or more of the thalidomide metabolites may be responsible for its anti-angiogenic effects, and their generation may be species dependent.[28] For example, thalidomide inhibits microvessel formation in the rat aortic ring assay and slows human aortic endothelial cell proliferation in the presence of human or rabbit liver microsomes, but not in the presence of rat liver microsomes. In the absence of liver microsomes, thalidomide had no effect on either microvessel formation or cell proliferation.[28] The extent to which the anti-angiogenic properties of thalidomide play a role in its anti-myeloma activity is not clearly understood. The rapidity of response in some tumours such as myeloma has raised questions regarding this. However, we have seen dramatic changes in bone marrow microvessel density in patients with myeloma responding to thalidomide therapy,[33] which is different compared to our observations with conventional or high-dose cytotoxic chemotherapy regimens.[34,35] In a mouse model of myeloma, IMiDs were shown to have significant anti-angiogenic activity as demonstrated by decreased microvessel density in the tumours.[36]

The anti-inflammatory activity of thalidomide and the IMiDs may have significant role in its anti-myeloma effects. Based on the studies done in the context of erythema nodosum leprosum (ENL), thalidomide has been shown to have an anti-TNF-α action.[37] Thalidomide inhibits the production of TNF-α by enhancing the degradation of TNF-α mRNA.[37] It may also bind to and increase the effect of α1-acid glycoproteins, which possess intrinsic anti-TNF-α activity.[38,39] This mechanism is different from that of other drugs that inhibit TNF-α like pentoxifylline or glucocorticoids. TNF-alpha is believed to play an important role in the biology of myeloma. High pre-treatment TNF-α levels appear to predict progression-free survival after thalidomide in patients with myeloma.[40] In addition, DNA polymorphisms involving the TNF-α gene has been correlated with response to thalidomide in myeloma.[41]

The anti-tumour properties of thalidomide are also believed to be related to its immunomodulatory effects and effects on cellular adhesion molecules. Thalidomide has direct effects on the T-lymphocytes stimulating cytotoxic T cell proliferation, and induction of secretion of interferon γ and IL-2.[42] Thalidomide and IMiDs induce an increased proliferation of $CD3^+$ cells from healthy donors and patients with MM, when cultured either in the presence of anti-CD3 or dendritic cells and is accompanied by increased IFN-γ and IL-2 secretion.[43] Proliferation of CD4 and CD8 T cells were also observed with all three drugs. In healthy male volunteers given 200 mg/day for 4 days, thalidomide significantly decreased the circulating T-helper to T-suppressor cell ratio.[44] It also induced T helper cell type 2 (Th2) cytokine production in human peripheral blood mononuclear cell cultures, while concomitantly inhibiting T helper cell type 1 (Th1) cytokine production.[45] Some of the anti-tumour activity of thalidomide and IMiDs may be mediated by modulation of natural killer cell activity.[43] When PBMCs from patients with MM are treated with IL-2 and Thalidomide or IMiDs, there is increased killing of autologous MMcells, an effect that is decrease significantly when NK cells are depleted. Patients receiving therapy with thalidomide can be associated with increase in the absolute numbers of $CD56^+$ NK cells.[43]

Thalidomide can modulate the expression of cell surface adhesion molecules like TNF-α, ICAM-1 (CD54), VCAM-1 (CD106), E-selectin and L-selectin (CD62L) in endothelial cells and on leucocytes.[46] Its interference of leukocyte migration through modulation of cell adhesion molecules is also believed to play an important role in ENL.[47] Other suggested mechanisms for anti-tumour effects include inhibition of NFκB activity through suppression of IκB kinase activity and inhibition of the cyclooxygenase 1 and 2 enzymes.[48,49]

5. Clinical activity

Thalidomide and IMiDs have been studied the most in the setting of MM, where a number of clinical trials have demonstrated activity for this class of drugs, either alone or in combination with other agents. Unless otherwise specified, all response rates stated in this manuscript refer to proportion of patients achieving partial response or better (i.e., partial response plus complete response) defined by standard response criteria and excludes minor responses and stable disease.

5.1. *Relapsed/refractory MM*

5.1.1. *Thalidomide*

Singhal and colleagues studied thalidomide as a single agent in 84 patients with relapsed, refractory MM, many of whom

had relapsed after stem cell transplantation.[5] In this phase II study, thalidomide at doses of 200 to 800 mg/day resulted in a response rate of 25%. When minor responses (at least 25% reduction in paraprotein levels) are included the response rate was 32%. Responses included two complete remissions, which was remarkable for this heavily treated group of patients. Responses were apparent within two months in most of the responding patients. This study went on to enroll a total of 169 patients confirming the initial results.[50] Overall survival at 18 months was 55% and event free survival was 30%. Given these initial results, multiple clinical trials were initiated to study activity of thalidomide in patients earlier in their course of the disease. In another phase II study of 120 patients (62 male and 58 female, median age 65.3 yrs) with relapsed/refractory MM, including 40 patients who had failed previous stem cell transplantation, Grosbois reported a 32% overall response rate with thalidomide as a single agent.[51] Dose escalation beyond 400 mg/day did not yield additional responses in this study. Overall survival was 65.8% at 6 months and 50% at 1 year. In a phase II trial from Mayo Clinic that enrolled 32 patients with relapsed MM, a response was seen in 31% of patients. The median duration of response was 11.9 months (3.7–20.3 months), and the median progression-free and overall survival was 15.7 and 22 months respectively.[52] Several other groups have also demonstrated single agent activity of thalidomide in relapsed and refractory MM, with response rates of 25–69%.[7,51–64] (Table 1)

5.1.2. *Lenalidomide*

In a phase I dose-escalation study of lenalidomide, 27 patients with relapsed, refractory MM were treated at doses of 5–50 mg/d.[7] This group consisted of heavily treated patients having received 2–6 prior therapies, including autologous stem cell transplantation and thalidomide. Most of the responses were seen at the 25 mg/day and 50 mg/day doses. The dose limiting toxicity in this study was myelosuppression and a dose of 25 mg/day was suggested for subsequent clinical trials. Compared to thalidomide, no significant somnolence, constipation, or neuropathy was observed. A reduction of at least 25% reduction in paraprotein (minor response or better) was seen in 71% of the patients. Richardson have reported the preliminary results of a multi-center randomized phase II trial with two different schedules of lenalidomide in relapsed/refractory myeloma.[65] Of 83 evaluable patients, 24% achieved a response with at least a 50% or greater reduction in monoclonal protein levels.

5.1.3. *CC-4047*

In a phase I study, CC-4047 was administered to 24 patients with relapsed MM.[64] Responses were observed in 54% of patients. A greater than 25% reduction in paraprotein (minor response or better) was seen in two-thirds of the patients and four patients achieved complete remissions. Deep vein thrombosis (DVT) was noted in four patients. The maximum tolerated dose of CC-4047 was 2 mg/d. CC-4047 treatment was associated with increase in serum interleukin (IL)-2 receptor and IL-12 levels, consistent with activation of T cells, monocytes, and macrophages, and confirming the immunomodulatory properties *in vivo*.

5.1.4. *Combination therapy*

Thalidomide and the IMiDs have been studied in combination with other chemotherapeutic agents with known activity in myeloma in several clinical trials. *In vitro* studies have suggested synergy between these agents and dexamethasone. In a phase II study, Palumbo and co-workers treated

Table 1 – Thalidomide or IMiDs as single agents for therapy of relapsed/refractory multiple myeloma

Trial	Number of Evaluable Patients	Starting Dose (mg/day)	Maximum Dose (mg/day)	Response Rate[a]
Thalidomide				
Singhal 1999[5]	84	200	800	25%
Yakoub-Agha 2000[102]	27	400	400	33%
Alexanian 2000[54]	43	100–200	800	26%
Juliusson 2000[55]	23	200	800	43%
Barlogie 2001[56]	169	200	800	44%
Grosbois 2001[51]	120	200	800	15%
Hus 2001[57]	53	200	400	35%
Bladé 2001[58]	17	200	800	18%
Bertolini 2001[59]	17	100	400	29%
Tosi 2002[60]	60	100	800	47%
Schey 2003[61]	69	200	800	48%
Kumar 2003[52]	32	200	800	31%
Richardson 2004[62]	30	200	600	43% (includes minor response)
Wu 2005[63]	122	100	400	38%
Lenalidomide (CC-5013)				
Richardson 2002[7]	27	5	50	71% (includes minor response)
Actimid (CC-4047)				
Schey 2004[64]	24		2	54%

a Response rate represents proportion of patients achieving partial response or better unless otherwise specified.

77 patients with relapsed MM with 100 mg/day thalidomide continuously and dexamethasone 40 mg, days 1–4, every month. At 3 months, the response rate with this therapy was 41%, with paraprotein reductions of 75%–100%, 50–75%, 25–50%, and <25% or disease progression observed in 18%, 23%, 25% and 34% of patients respectively.[66] Thalidomide has also been studied in combination with multiple other drugs in myeloma; response rates in relapsed disease are about 50% with the combination of thalidomide and steroids, and over 65% with combinations of thalidomide, steroids and alkylators.[66–79] (Table 2)

Two phase III trials have evaluated the combination of lenalidomide plus dexamethasone (Rev-Dex) versus dexamethasone plus placebo. Preliminary results show significantly better response rates with the Rev-Dex regimen compared to dexamethasone plus placebo, 51% versus 30% (North American trial) and 48% versus 18% (Europe/Australian trial), respectively.[80] Time to progression was also significantly better with Rev-Dex, >14 months versus 5 months (North American trial) and 11 versus 5 months (Europe/Australian trial), respectively. The most common adverse effect with Rev-Dex was grade 3–4 neutropenia occurring in 17–24% of the patients treated. The incidence of thrombotic events appeared to be higher with Rev-Dex, and needs careful monitoring.

5.2. *Newly diagnosed MM/smoldering MM*

5.2.1. *Thalidomide*

In a phase II trial, Rajkumar and colleagues reported a minor response or better in two thirds of patients with smoldering/indolent MM treated with single agent thalidomide (200 to 800 mg/day).[81] Similar results have also been reported by Weber and colleagues form the MD Anderson Cancer Center.[82]

Table 2 – Combination Regimens of Thalidomide for treatment of MM

Regimen	Evaluable Patients (Disease Stage)	Dosing	Response Rate*
Thal + Dex[70]	44 (refractory)	Thal 200–400 mg/day, Dexamethasone dose of 20 mg/m2 p.o. daily for four days on day 1–4, 9–12, 17–20, followed by monthly dexamethasone for four days	55%
Thal + Dex[66]	77 (relapsed/refractory)	Thalidomide 100 mg/day continuously and dexamethasone 40 mg, days 1–4, every month	41%
Thal + Dex[71]	40 (newly diagnosed)	Thalidomide maximum dose 400 mg; dexamethasone 20 mg/m(2) for 4 days beginning on days 1, 9, and 17	72%
Thal + Dex[72]	50 (newly diagnosed)	Thal 200 mg/d orally. Dex 40 mg/d orally on days 1 to 4, 9 to 12, and 17 to 20 (odd cycles) and 40 mg/d on days 1 to 4 (even cycles)	64%
Thal + Dex[73]	202 (newly diagnosed)	Thal 200 mg/day with Dex 40 mg PO days 1–4, 9–12, and 17–20	58%
Thal + cyclophosphamide + Dex (CDT)[74]	53 (relapsed)	Cyclophosphamide 150 mg/m(2) p.o. every 12 h days 1–5, thalidomide 400 mg p.o. days 1–5 and 14–18 and dexamethasone 20 mg/m(2) on days 1–5 and 14–18	60%
ThaCyDex[75]	71 (relapsed/ refractory)	Thalidomide 200–800 mg/day, cyclophosphamide 50 mg/day and dexamethasone 40 mg/day, 4 days every 3 wkss	2% CR 55%PR
Thal + Mel[76]	27 (relapsed)	Thalidomide 100 mg/day escalated up to 600 mg/day, 0.20 mg/kg/day melphalan day 1–4	59%
Thal + Mel + Dex[67]	43 (newly diagnosed)	Mel 8 mg/m^2 days 1–4, dex 12 mg/m^{2}p.o. days 1–4 and 14–18 and thal 300 mg p.o. days 1–4, 14–18.	72% PR 10% CR
Mel + Pred + Thal[69]	102 (newly diagnosed)	Mel 4 mg/m^2 PO and Pred 40 mg/m^2 for 7 days Thal 100 mg/day continuous	48% PR 26% CR 6% nCR
HyperCDT[68]	60 (relapsed refractory)	Cyclophosphamide (300 mg/m2 i.v. q 12 h, d 1–3); dexamethasone (20 mg/m2/d p.o., d 1–4, 9–12, 17–20) and daily 100–400 mg/d	4% CR 68%PR
TVAD-Doxil[77]	39 (newly diagnosed)	Vincristine 2 mg i.v., liposomal doxorubicin 40 mg/m(2) i.v. day 1, and dexamethasone 40 mg daily on days 1–4, and 15–18 of the first cycle of treatment. Thalidomide 200 mg daily	10%CR 64%PR
Vel + Thal[78]	79 (relapsed/ refractory)	Vel 1.0 mg/m^2 on days 1, 4, 8 and 11; Thal 50–200 mg/d	40% PR n-CR 20%
Vel + Thal + Dex[79]	25 (newly diagnosed)	Vel 1.0 to 1.9 mg/m^2 days 1, 4, 9, 11, Thal 100–200 mg, Dex 20 mg/m^2 days 1–4, 9–12, 17–20	84% PR

• Response rate represents proportion of patients achieving partial response or better unless otherwise specified.
• PR, partial response; CR, complete response.

However, more data on the durability of response is needed before recommending this strategy as standard clinical practice.

5.2.2. *Thalidomide-dexamethasone*

In a phase II study of thalidomide and dexamethasone (Thal-Dex) from Mayo Clinic, 50 patients with early MM were treated with thalidomide (200 mg/day) and dexamethasone (40 mg/day) on days 1–4, 9–12, 17–20 (odd cycles) and 40 mg/day days 1–4 (even cycles) repeated monthly. The response rate was 64% with frequent toxicities being venous thrombosis (10%), constipation (8%), and rash (6%).[83] Two other phase II studies showed similar efficacy with Thal-Dex in newly diagnosed myeloma.[82,84] Cavo in a case-control showed study showed that response rates were significantly higher with Thal-Dex compared to vincristine-doxorubicin-dexamethasone (VAD), 76% versus 52%, respectively.[85] The Thal-Dex combination has been compared to dexamethasone alone in a phase III randomized trial of induction therapy for newly diagnosed MM.[73] Results show that the response rate was significantly higher with Thal-Dex compared to dexamethasone alone, 63% *versus* 41%, respectively. Grade 3 or greater non-haematologic toxicities occurred within the first 4 cycles in 67% of pts on the Thal-Dex arm versus 43% with dexamethasone alone, highlighting the need to balance toxicity with response rates.[73] Importantly as in prior trials, there was a higher risk of deep vein thrombosis with Thal-Dex, 17% versus 3%, respectively. As a result, routine prophylactic anti-coagulation with either low molecular weight heparin (equivalent of enoxaparin 40 mg subcutaneously once daily) or warfarin (at therapeutic doses) is recommended for patients receiving Thal-Dex.

5.2.3. *Melphalan-prednisone-thalidomide*

Palumbo compared melphalan, prednisone, thalidomide (MPT) to the conventional melphalan and prednisone combination in a phase III randomized trial.[86] The MPT regimen included 6 monthly courses of oral melphalan 4 mg/m^2 and prednisone 40 mg/m^2 for 7 days every month plus thalidomide 100 mg/day continuously until any sign of progressive disease or relapse and the MP regimen was the same without thalidomide. At the interim analysis (102 pts), the proportion of patients in each response category in the MPT group compared to MP group were: 25.9% vs. 4.2% for immunofixation negative complete response (CR); 5.5% vs. 0% for immunofixation positive near CR (nCR); 48.2% vs. 43.6% for partial response (M-protein reduction 50–99%); 9.3% vs. 23% for stable disease (SD) (M-protein reduction 0–49%); and 11.1% vs. 29.2% for progressive disease (PD). At a median follow-up of 15 months, 38 patients relapsed: 11 (29%) after MPT and 27 (71%) after MP. The major toxicity with MPT compared to that with MP were deep-vein thrombosis (19.3% vs 1.9%), grade III–IV infections (12.9% vs 1.9%), and grade I–II neurotoxicity (35.5% vs 5.5%). The IFM 99–06 trial compared standard MP (12 courses at 6 weeks intervals) to MP-THAL (same MP, THAL at doses up to 400 mg/day) and a MEL100-based treatment (intermediate-dose MEL) in patients aged 65–75 years.[87] The first interim analysis suggested an advantage for the MP-Thal arm. The results from these studies point towards the MPT combination being an active regimen in elderly patients with myeloma and will likely become the standard of care in this population replacing the MP regimen.

5.2.4. *Lenalidomide-dexamethasone*

Lenalidomide appears to have a more favourable safety profile compared to thalidomide, based on initial studies, and this together with its promising single agent activity and the *in vitro* data pointing towards synergy with dexamethasone,[29] provided the basis for a phase II trial combining lenalidomide with dexamethasone in newly diagnosed patients.[88] Lenalidomide was given orally 25 mg daily on days 1–21 of a 28-day cycle. Dexamethasone was given orally 40 mg daily on days 1–4, 9–12, 17–20 of each cycle. Thirty-one of 34 (91%) of the enrolled patients achieved an objective response including 2 (6%) complete responses (CR), and 11 (32%) with near complete responses. Forty-seven percent of patients experienced grade 3 or higher non-haematologic toxicity, most commonly fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (6%) and rash (6%). Two phase III trials in the Untied States are currently evaluating Rev-Dex in newly diagnosed MM.

5.3. *Maintenance/consolidation therapy*

Stewart and colleagues recently presented the results of a randomized multicenter phase II dose-seeking trial of thalidomide and prednisone maintenance therapy for patients undergoing high-dose therapy.[89] Following transplant, patients were randomized to receive thalidomide 200 mg or 400 mg daily along with 50 mg prednisone on alternate days. The dose level of 200 mg was better tolerated, with an improvement in initial response seen in 53% of evaluable patients; 38% patients achieved a complete or near complete remission at one year. Progression-free survival from initiation of therapy was 42.2 months, with one year overall survival of 91%. In a French trial, patients were randomized to receive maintenance treatment with thalidomide plus pamidronate, pamidronate alone, or no maintenance following tandem transplant.[90] Progression-free survival (PFS) was superior in the thalidomide arm; PFS at 40-months post-diagnosis was 70% (thalidomide plus pamidronate) versus 53% (no maintenance) 52% (pamidronate alone). Overall survival improvements have not been noted yet.

Alexanian and colleagues evaluated thalidomide as consolidation therapy in 23 patients following autologous stem cell transplant, in an attempt to convert partial to complete remission.[91] Thalidomide (100 to 300 mg/day) given with dexamethasone (20 mg/m^2 days 1–4, 9–12, 17–21) led to further reduction of paraprotein more than 75% from control level in 18 patients (78%), including 3 complete remissions.

Clearly more data are needed for the use of thalidomide and lenalidomide in the above settings. Three phase III studies are currently ongoing in the Untied States evaluating thalidomide, Thal-Dex, and lenalidomide, respectively as maintenance therapy.

6. Adverse effects

Teratogenicity is the most feared adverse event, and occurs when taken between days 27 and 40 of gestation.[92,93] Fetal

abnormalities include malformed and markedly shortened extremities (phocomelia) and deformities of the ears, eyes, and the gastrointestinal tract. In the United States, thalidomide is marketed under the STEPS program to prevent teratogenic complications. Under this program, women in the childbearing age group must undergo pregnancy testing before starting therapy, and every 2–4 weeks during treatment. They must abstain from sexual intercourse, or use two highly effective contraceptive methods, during treatment. Males must abstain from sexual intercourse or use a condom while on treatment even if they have had a successful vasectomy. All patients must continue the above measures for at least one month following the last dose of the drug. Breast-feeding is contraindicated while on the drug.

In addition to its teratogenic potential, thalidomide therapy is associated with many other potential side effects (Table 3). The frequency, management, and prevention of these adverse events has been recently reviewed.[94] In general, thalidomide is well tolerated at doses below 400 mg/day. Majority of the side effects are mild or moderate in severity, and can be controlled by appropriate dose modification. Sedation, fatigue, skin rash and constipation are among the most commonly encountered side effects. Minor to moderate skin eruptions were noted in nearly half of patients taking thalidomide alone or with dexamethasone in one review.[95] Severe constipation is a common problem and use of prophylactic laxatives is recommended. These included morbilliform, seborrheic, maculopapular, or nonspecific dermatitis. Thalidomide should be discontinued if symptomatic skin rash appears and restarted at a lower dose after it clears. Rarely, severe dermatologic reactions like Stevens Johnson syndrome, erythema multiforme, or toxic epidermal necrolysis occur and preclude any further use of the drug.[96] Longer-term use of thalidomide (usually over 6 months) can cause peripheral neuropathy. Less common side effects include bradycardia, impotence neutropenia, menstrual irregularities, edema, increased liver enzymes, deep vein thrombosis (DVT), hyper or hypoglycemia, and hypothyroidism. Thromboembolic events appear to be higher when used along with other chemotherapy agents or dexamethasone.[97–100] Hyperkalemia has been reported in patients with myeloma and renal failure.[101]

Lenalidomide has a more favourable safety profile with the most common side effects being neutropenia and thrombocytopenia; constipation, neuropathy and sedation unlike thalid-

Table 3 – Adverse effects of thalidomide and IMiDs

Common side effects	Less common side effects
Thalidomide	
Birth Defects	Myocardial infarction, stroke, sudden death
Drowsiness and Somnolence	Cardiac arrhythmias
Dry mouth	Headache
Constipation	Confusion
Peripheral neuropathy	Tremor
Skin rash	Malaise
Deep vein thrombosis and pulmonary embolism	Hearing loss
(when used in combination with corticosteroids or chemotherapy)	
Orthostatic hypotension and dizziness	Hyper or hypoglycemia
Neutropenia	Pruritus
	Peripheral edema
	Elevated serum transaminases
	Hypothyroidism
	Steven-Johnson syndrome
	Impotence
	Nausea
	Diverticulits, bowel perforation
Lenalidomide (CC5013)	
Neutropenia	Myocardial infarction, stroke, sudden death
Thrombocytopenia	Cardiac arrhythmias
Deep vein thrombosis and pulmonary embolism	Warm auto-antibody hemolytic anaemia
(when used in combination with corticosteroids or chemotherapy)	
	Pulmonary hypertension
	Diverticulitis, bowel perforation
	Skin Rash
	Fatigue
	Light headedness
	Leg cramps
CC4047	
Neutropenia	Constipation
Deep vein thrombosis	Skin rash
Thrombocytopenia	Pedal edema
	Neuropathy
	Nausea
	Hypertension

omide are uncommon (Table 3). Other side effects include skin rash, neuropathy and thrombotic events. More data are needed to assess the nature and frequency of adverse events associated with CC-4047.

7. Future directions

Thalidomide and lenalidomide are being explored in combination with other drugs across different stages of MM. RevDex in particular appears to be an attractive oral regimen for initial therapy. Studies are also evaluating the potential benefit combining thalidomide or lenalidomide with bortezomib to develop more active combination regimens. The role of new agents in comparison to stem cell transplantation and their impact on the timing of transplantation (upfront versus at relapse) needs further study. A better understanding of the mechanism of action of these drugs will likely provide additional targets and insights into other potentially useful new agents. We also need to determine predictors of response to these agents based on pharmacogenomics and such studies are ongoing. Finally, therapy with thalidomide and lenalidomide although effective is not curative, and clearly more active agents are needed.

Conflict of interest statement

Dr. Rajkumar and Dr. Kumar have received research support for the conduct of clinical trials from Celgene Corporation.

Acknowledgement

Supported in part by Grants CA85818, CA93842, CA100080, and CA62242 from the National Cancer Institute, Bethesda, MD.

REFERENCES

1. Jemal A, Murray T, Ward E, et al. Cancer statistics. *CA Cancer J Clin.* 2005;**55**:10–30.
2. Kyle RA, Rajkumar SV. Multiple myeloma. *N Engl J Med* 2004;**351**:1860–73.
3. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc* 2003;**78**:21–33.
4. Kumar SK, Therneau TM, Gertz MA, et al. Clinical course of patients with relapsed multiple myeloma. *Mayo Clin Proc* 2004;**79**:867–74.
5. Singhal S, Mehta J, Desikan R, et al. Anti-tumour activity of thalidomide in refractory multiple myeloma. *New England Journal of Medicine* 1999;**341**:1565–71.
6. Rajkumar SV. Thalidomide: tragic past and promising future. *Mayo Clin Proc* 2004;**79**:899–903.
7. 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**:3063–7.
8. Schey SA, Fields P, Bartlett JB, et al. Phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma. *J Clin Oncol* 2004;**22**:3269–76.
9. Rogerson G. Thalidomide and congenital abnormalities. *Lancet* 1962;**1**:691.
10. Grabstad H, Golbey R. Clinical experience with thalidomide in patients with cancer. *Clin Pharmacol Therap* 1965;**6**:298–302.
11. Olson KB, Hall TC, Horton J, Khung CL, Hosley HF. Thalidomide (N-phthaloylglutamimide) in the treatment of advanced cancer. *Clin Pharmacol Ther* 1965;**6**:292–7.
12. D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. *Proceedings of the National Academy of Sciences of the United States of America* 1994;**91**:4082–5.
13. Kenyon BM, Browne F, D'Amato RJ. Effects of thalidomide and related metabolites in a mouse corneal model of neovascularization. *Experimental Eye Research* 1997;**64**:971–8.
14. Folkman J. Tumour angiogenesis: therapeutic implications. *N Engl J Med* 1971;**285**:1182–6.
15. Folkman J. Seminars in Medicine of the Beth Israel Hospital, Boston. Clinical applications of research on angiogenesis. *New England Journal of Medicine* 1995;**333**:1757–63.
16. Eriksson T, Bjorkman S, Roth B, Hoglund P. Intravenous formulations of the enantiomers of thalidomide: pharmacokinetic and initial pharmacodynamic characterization in man. *Journal of Pharmacy & Pharmacology* 2000;**52**:807–17.
17. Chen TL, Vogelsang GB, Petty BG, et al. Plasma pharmacokinetics and urinary excretion of thalidomide after oral dosing in healthy male volunteers. *Drug Metab Dispos* 1989;**17**:402–5.
18. Figg WD, Raje S, Bauer KS, et al. Pharmacokinetics of thalidomide in an elderly prostate cancer population. *J Pharm Sci* 1999;**88**:121–5.
19. Piscitelli SC, Figg WD, Hahn B, Kelly G, Thomas S, Walker RE. Single-dose pharmacokinetics of thalidomide in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother.* 1997;**41**:2797–9.
20. Teo SK, Scheffler MR, Kook KA, et al. Thalidomide dose proportionality assessment following single doses to healthy subjects. *J Clin Pharmacol* 2001;**41**:662–7.
21. Tsambaos D, Bolsen K, Georgiou S, Monastirli A, Goerz G. Effects of oral thalidomide on rat liver and skin microsomal P450 isozyme activities and on urinary porphyrin excretion: interaction with oral hexachlorobenzene. *Arch Dermatol Res* 1994;**286**:347–9.
22. Stirling DI. Pharmacology of thalidomide. *Semin Hematol* 2000;**37**:5–14.
23. Yaccoby S, Johnson CL, Mahaffey SC, Wezeman MJ, Barlogie J, Epstein J. Antimyeloma efficacy of thalidomide in the SCID-hu model. *Blood* 2002;**100**:4162–8.
24. Lu J, Palmer BD, Kestell P, et al. Thalidomide metabolites in mice and patients with multiple myeloma. *Clin Cancer Res* 2003;**9**:1680–8.
25. Eriksson T, Bjorkman S, Hoglund P. Clinical pharmacology of thalidomide. *Eur J Clin Pharmacol* 2001;**57**:365–76.
26. Aweeka F, Trapnell C, Chernoff M, et al. Pharmacokinetics and pharmacodynamics of thalidomide in HIV patients treated for oral aphthous ulcers: ACTG protocol 251. AIDS Clinical Trials Group. *J Clin Pharmacol.* 2001;**41**:1091–7.
27. Bartlett JB, Dredge K, Dalgleish AG. The evolution of thalidomide and its IMiD derivatives as anticancer agents. *Nat Rev Cancer* 2004;**4**:314–22.
28. Bauer KS, Dixon SC, Figg WD. Inhibition of angiogenesis by thalidomide requires metabolic activation, which is species-dependent. *Biochemical Pharmacology* 1998;**55**:1827–34.
29. 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.
30. Mitsiades N, Mitsiades CS, Poulaki V, et al. Apoptotic signalling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications. *Blood* 2002;**99**:4525–30.
31. Gupta D, Treon SP, Shima Y, et al. Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications. *Leukemia* 2001;**15**:1950–61.
32. Adeoti AG, Vega KJ, Dajani EZ, Trotman BW, Kloser PC. Idiopathic esophageal ulceration in acquired immunodeficiency syndrome: successful treatment with misoprostol and viscous lidocaine. *Am J Gastroenterol* 1998;**93**:2069–74.
33. Kumar S, Witzig TE, Wellik L, Greipp PR, Rajkumar SV. Effect of Thalidomide Therapy on Bone marrow Angiogenesis in Multiple Myeloma. *Blood* 2003;**102**:A5274.
34. Kumar S, Fonseca R, Dispenzieri A, et al. Bone marrow angiogenesis in multiple myeloma: Effect of therapy. *Br J Haematol* 2002;**119**:665–71.
35. Rajkumar SV, Fonseca R, Witzig TE, Gertz MA, Greipp PR. Bone marrow angiogenesis in patients achieving complete response after stem cell transplantation for multiple myeloma. *Leukemia* 1999;**13**:469–72.
36. Lentzsch S, LeBlanc R, Podar K, et al. Immunomodulatory analogs of thalidomide inhibit growth of Hs Sultan cells and angiogenesis in vivo. *Leukemia* 2003;**17**:41–4.
37. Moreira AL, Sampaio EP, Zmuidzinas A, Frindt P, Smith KA, Kaplan G. Thalidomide exerts its inhibitory action on tumour necrosis factor alpha by enhancing mRNA degradation. *Journal of Experimental Medicine* 1993;**177**:1675–80.
38. Hideshima T, Chauhan D, Shima Y, et al. Thalidomide and its analogs overcome drug resistance of multiple myeloma cells to conventional therapy. *Blood* 2000;**96**:2943–50.
39. Niwayama S, Turk BE, Liu JO. Potent inhibition of tumour necrosis factor-alpha production by tetrafluorothalidomide and tetrafluorophthalimides. *J Med Chem* 1996;**39**:3044–5.
40. Thompson MA, Witzig T, Kumar S, et al. Plasma Levels Of Tumour Necrosis Factor Alpha And Interleukin-6 Predict Progression-free Survival Following Thalidomide Therapy In Patients With Previously Untreated Multiple Myeloma. *Br J Haematol* 2003;In Press.
41. Neben K, Mytilineos J, Moehler TM, et al. Polymorphisms of the tumour necrosis factor-alpha gene promoter predict for outcome after thalidomide therapy in relapsed and refractory multiple myeloma. *Blood* 2002;**100**:2263–5.
42. Haslett PA. Anticytokine approaches to the treatment of anorexia and cachexia. *Semin Oncol* 1998;**25**:53–7.
43. Davies FE, Raje N, Hideshima T, et al. Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. *Blood* 2001;**98**:210–6.
44. Gad SM, Shannon EJ, Krotoski WA, Hastings RC. Thalidomide induces imbalances in T-lymphocyte sub-populations in the circulating blood of healthy males. *Lepr Rev* 1985;**56**:35–9.
45. McHugh SM, Rifkin IR, Deighton J, et al. The immunosuppressive drug thalidomide induces T helper cell type 2 (Th2) and concomitantly inhibits Th1 cytokine production in mitogen- and antigen-stimulated human peripheral blood mononuclear cell cultures. *Clinical & Experimental Immunology* 1995;**99**:160–7.
46. Geitz H, Handt S, Zwingenberger K. Thalidomide selectively modulates the density of cell surface molecules involved in the adhesion cascade. *Immunopharmacology* 1996;**31**:213–21.
47. Sampaio EP, Kaplan G, Miranda A, et al. The influence of thalidomide on the clinical and immunologic manifestation of erythema nodosum leprosum. *J Infect Dis* 1993;**168**:408–14.
48. Keifer JA, Guttridge DC, Ashburner BP, Baldwin Jr AS. Inhibition of NF-kappa B activity by thalidomide through suppression of IkappaB kinase activity. *J Biol Chem* 2001;**276**:22382–7.
49. Noguchi T, Shimazawa R, Nagasawa K, Hashimoto Y. Thalidomide and its analogues as cyclooxygenase inhibitors. *Bioorg Med Chem Lett* 2002;**12**:1043–6.
50. Barlogie B, Spencer T, Tricot G, et al. Long term follow-up of 169 patients receiving a phase II trial of single agent thalidomide for advanced and refractory multiple myeloma (MM). *Blood* 2000;**96**:514a. (A2213).
51. Grosbois B, Bellissant E, Moreau P, Attal M, Zerbib R. Thalidomide (Thal) in the treatment of advanced multiple myeloma (MM) A prospective study of 120 patients. *Blood* 2001;**98**.. Abstract 689.
52. Kumar S, Gertz MA, Dispenzieri A, et al. Response rate, durability of response, and survival after thalidomide therapy for relapsed multiple myeloma. *Mayo Clin Proc* 2003;**78**:34–9.
53. Yakoub-Agha I, Facon T, Moreau P, et al. Thalidomide in patients with advanced multiple myeloma. *Haematology Journal* 2000;**1**:186–9.
54. Alexanian R, Weber D. Thalidomide for resistant and relapsing myeloma. *Seminars in Haematology* 2000;**37**:22–5.
55. Juliusson G, Malm C, Celsing F, Turesson I, Lenhoff S, Adriansson M. Frequent good partial remissions from thalidomide including best response ever in patients with advanced refractory and relapsed myeloma. *British Journal of Haematology* 2000;**109**:89–96.
56. 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 see comment. *Blood* 2001;**98**:492–4.
57. Hus M, Dmoszynska A, Soroka-Wojtaszko M, et al. Thalidomide treatment of resistant or relapsed multiple myeloma patients. *Haematologica* 2001;**86**:404–8.
58. Bladé J, Esteve J, Rosiñol L, et al. Thalidomide in refractory and relapsing multiple myeloma. *Seminars in Oncology* 2001;**28**:588–92.
59. 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. *Annals of Oncology* 2001;**12**:987–90.
60. 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.
61. Schey SA, Cavenagh J, Johnson R, Child JA, Oakervee H, Jones RW. An UK myeloma forum phase II study of thalidomide; long term follow-up and recommendations for treatment. *Leuk Res* 2003;**27**:909–14.
62. Richardson P, Schlossman R, Jagannath S, et al. Thalidomide for patients with relapsed multiple myeloma after high-dose chemotherapy and stem cell transplantation: results of an open-label multicenter phase 2 study of efficacy, toxicity, and biological activity. *Mayo Clinic Proceedings* 2004;**79**:875–82.
63. Wu KL, Helgason HH, van der Holt B, et al. Analysis of efficacy and toxicity of thalidomide in 122 patients with multiple myeloma: response of soft-tissue plasmacytomas. *Leukemia* 2005;**19**:143–5.
64. Schey SA, Fields P, Bartlett JB, et al. Phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma. *Journal of Clinical Oncology* 2004;**22**:3269–76.
65. Richardson PG, Jagannath S, Schlossman R, et al. A Multi-Center, Randomized, Phase 2 Study To Evaluate the Efficacy and Safety of 2 CDC-5013 Dose Regimens When Used Alone or in Combination with Dexamethasone (Dex)

for the Treatment of Relapsed or Refractory Multiple Myeloma (MM). *Blood* 2003;**102**:235a.
66. 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.
67. Dimopoulos MA, Repoussis P, Terpos E, et al. Primary treatment with pulsed melphalan, dexamethasone, thalidomide (MDT) for symptomatic patients with multiple myeloma = 75 Years of age. *Blood* 2004;**104**. Abstract 1482.
68. Kropff MH, Bisping G, Dominé N, et al. Hyperfractionated cyclophosphamide in combination with pulsed dexamethasone and thalidomide (HyperCDT) in primary refractory or relapsed multiple myeloma. *British Journal of Haematology* 2003;**122**:607–16.
69. Palumbo A, Bertola A, Musto P, et al. A prospective randomized trial of oral melphalan, prednisone, thalidomide (MPT) vs oral melphalan, prednisone (MP): An interim analysis. *Blood* 2004;**104**. Abstract 207.
70. Dimopoulos MA, Zervas K, Kouvatseas G, et al. Thalidomide and dexamethasone combination for refractory multiple myeloma. *Annals of Oncology* 2001;**12**:991–5.
71. Weber D, Rankin K, Gavino M, Delasalle K, Alexanian R. Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. *Journal of Clinical Oncology* 2003;**21**:16–9.
72. Rajkumar SV, Hayman S, Gertz MA, et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. *Journal of Clinical Oncology* 2002;**20**:4319–23.
73. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR. Phase III Clinical Trial of Thalidomide Plus Dexamethasone compared with Dexamethasone Alone in Newly Diagnosed Multiplem Myeloma: A Clinical Trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol* 2006;**24**:431–6.
74. Dimopoulos MA, Hamilos G, Zomas A, et al. Pulsed cyclophosphamide, thalidomide and dexamethasone: an oral regimen for previously treated patients with multiple myeloma. *Haematology Journal* 2004;**5**:112–7.
75. Garcia-Sanz R, Gonzalez-Porras JR, Hernandez JM, et al. The oral combination of thalidomide, cyclophosphamide and dexamethasone (ThaCyDex) is effective in relapsed/refractory multiple myeloma. *Leukemia* 2004;**18**:856–63.
76. Offidani M, Corvatta L, Marconi M, et al. Thalidomide plus oral melphalan compared with thalidomide alone for advanced multiple myeloma. *Haematology Journal* 2004;**5**:312–7.
77. Zervas K, Dimopoulos MA, Hatzicharissi E, et al. Primary treatment of multiple myeloma with thalidomide, vincristine, liposomal doxorubicin and dexamethasone (T-VAD doxil): a phase II multicenter study. *Annals of Oncology* 2004;**15**:134–8.
78. Zangari M, Barlogie B, Hollmig K, et al. Marked Activity of Velcade Plus Thalidomide (V+T) in Advanced and Refractory Multiple Myeloma (MM). *Blood* 2004;**104**. Abstract 1480.
79. Alexanian R, Wang L, Weber D, Delasalle K. VTD (Velcade, Thalidomide, Dexamethasone) as Primary Therapy for Newly-Diagnosed Multiple Myeloma. *Blood* 2004;**104**. Abstract 210.
80. Dimopoulos MA, Weber D, Chen C, et al. Evaluating Oral Lenalidomide (Revlimid-) And Dexamethasone Versus Placebo And Dexamethasone In Patients With Relapsed Or Refractory Multiple Myeloma. *Haematologica* 2005;**90**:160.
81. Rajkumar SV, Gertz MA, Lacy MQ, et al. Thalidomide as initial therapy for early-stage myeloma. *Leukemia* 2003;**17**:775–9.
82. 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**:16–9.
83. Rajkumar SV, Hayman S, Gertz MA, et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. *J Clin Oncol* 2002;**20**:4319–23.
84. Cavo M, Zamagni E, Tosi P, et al. First-line therapy with thalidomide and dexamethasone in preparation for autologous stem cell transplantation for multiple myeloma. *Haematologica* 2004;**89**:826–31.
85. Cavo M, Zamagni E, Tosi P, et al. Superiority of thalidomide and dexamethasone over vincristine-doxorubicin-dexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. *Blood* 2005;**106**:35–9.
86. Palumbo A, Bertola A, Musto P, et al. A Prospective Randomized Trial of Oral Melphalan, Prednisone, Thalidomide (MPT) vs Oral Melphalan, Prednisone (MP): An Interim Analysis. *ASH Annual Meeting Abstracts*. 2004;**104**:207.
87. Facon T, Mary JY, Hulin C, et al. Randomized Clinical Trial Comparing Melphalan-Prednisone (MP), MP-Thalidomide (MP-THAL) and High-Dose Therapy Using Melphalan 100 MG/M2 (MEL100) for Newly Diagnosed Myeloma Patients Aged 65–75 Years. Interim Analysis of the IFM 99-06 Trial on 350 Patients. *ASH Annual Meeting Abstracts*. 2004;**104**:206.
88. Rajkumar SV, Hayman SR, Lacy MQ. Combination therapy with lenalidomide plus dexamethasone (REV/DEX) for newly diagnosed myeloma. *Blood* 2005;**106**:4050–3.
89. Stewart KA, Chen C, Howson-Jan K, et al. Results of a Multi-Center Randomized Phase II Trial of Thalidomide and Prednisone Maintenance Therapy for Multiple Myeloma Following Autologous Stem Cell Transplant. *Blood* 2004;**104**. Abstract 335.
90. Attal M, Harousseau JL, Leyvraz S, et al. Maintenance Treatment with Thalidomide after Autologous Transplantation for Myeloma: First Analysis of a Prospective Randomized Study of the Intergroupe Francophone du Myelome (IFM 99 02). *Blood* 2004;**104**. Abstract 535.
91. Alexanian R, Weber D, Anagnostopoulos A, Delasalle K, Wang M, Rankin K. Thalidomide with or without dexamethasone for refractory or relapsing multiple myeloma. *Semin Hematol* 2003;**40**:3–7.
92. Lenz W. A short history of thalidomide embryopathy. *Teratology* 1988;**38**:203–15.
93. Lenz W. A personal perspective on the thalidomide tragedy. *Teratology* 1992;**46**:417–8.
94. Ghobrial IM, Rajkumar SV. Management of thalidomide toxicity. *J Support Oncol* 2003;**1**:194–205.
95. Hall VC, El-Azhary RA, Bouwhuis S, Rajkumar SV. Dermatologic side effects of thalidomide in patients with multiple myeloma. *J Am Acad Dermatol* 2003;**48**:548–52.
96. Rajkumar SV, Gertz MA, Witzig TE. Life-threatening toxic epidermal necrolysis with thalidomide therapy for myeloma. *N Engl J Med* 2000;**343**:972–3.
97. Osman K, Comenzo R, Rajkumar SV. Deep vein thrombosis and thalidomide therapy for multiple myeloma. *N Engl J Med* 2001;**344**:1951–2.
98. Zangari M, Anaissie E, Barlogie B, et al. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. *Blood* 2001;**98**:1614–5.
99. Zangari M, Siegel E, Barlogie B, et al. Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy. *Blood* 2002;**100**:1168–71.
100. Zangari M, Saghafifar F, Anaissie E, et al. Activated protein C resistance in the absence of factor V Leiden mutation is a

common finding in multiple myeloma and is associated with an increased risk of thrombotic complications. *Blood Coagulation & Fibrinolysis* 2002;**13**:187–92.
101. Harris E, Behrens J, Samson D, Rahemtulla A, Russell NH, Byrne JL. Use of thalidomide in patients with myeloma and renal failure may be associated with unexplained hyperkalaemia. *Br J Haematol* 2003;**122**:160–1.
102. Yakoub-Agha I, Moreau P, Leyvraz S, et al. Thalidomide in patients with advanced multiple myeloma. *Haematology Journal* 2000;**1**:186–9.