REVIEW ARTICLE

Drugs 2007; 67 (13): 1869-1881
0012-6667/07/0013-1869/$49.95/0



# Lenalidomide in Myelodysplastic Syndrome and Multiple Myeloma

*Sachin R. Shah*[1] and *Thu M. Tran*[2]

1 Texas Tech University Health Sciences Center-School of Pharmacy/VA North Texas Health Care System, Dallas, Texas, USA
2 Huntsman Cancer Hospital, Salt Lake City, Utah, USA

## Contents



## Abstract

The use of thalidomide is limited by adverse effects of sedation, constipation, neuropathy and thromboembolism. In order to discover more potent and less toxic immunomodulators than thalidomide, its chemical structure was modified and lenalidomide was formed.

Lenalidomide is approved by the US FDA for the treatment of patients with low-risk myelodysplastic syndrome (MDS) with deletion 5q cytogenetic abnormality. Two studies and a case report have evaluated lenalidomide in these MDS patients and showed significantly higher cytogenetic responses and durable red blood cell transfusion independence. Lenalidomide should be the drug of choice for patients with low and intermediate-1 risk MDS (based on the International Prognostic Scoring System) with chromosome 5q31 deletion with or without other karyotype abnormalities.

Lenalidomide, in combination with dexamethasone, has been compared with dexamethasone alone in patients with relapsed or refractory multiple myeloma (MM) in two studies (MM-009 in North America and MM-010 in Europe, Israel and Australia). In these two phase III trials, lenalidomide demonstrated impressive (58–59%) response rates with dexamethasone. Lenalidomide has also been shown to overcome thalidomide resistance in MM patients. Therefore, the

lenalidomide plus dexamethasone regimen provides another treatment option, in addition to first line MM treatment regimens of bortezomib, thalidomide or high-dose dexamethasone, for the treatment of relapsed or refractory MM.

Lenalidomide does not produce significant sedation, constipation or neuropathy, but does lead to significant myelosuppression, unlike thalidomide. The prescribing information has a black box warning for risk of myelosuppression, deep vein thrombosis/pulmonary embolism and teratogenicity. Administration of lenalidomide is recommended at a starting dose of 10 mg/day orally for deletion 5q in MDS patients. Significant risk of myelosuppression may lead to dose reduction in the majority of these patients. Clinical trials of relapsed and refractory MM have shown that lenalidomide is clinically efficacious at a dosage of 25 mg/day when administered in combination with dexamethasone. Lenalidomide should be continued until disease progression in both MDS and MM patients.

Thalidomide was first marketed in 1954, making it the first immunomodulatory agent.[1] Initial animal studies showed that the agent was nontoxic and could be safely used as a sedative. Thalidomide was never approved in the US but was used in Germany, the UK, Canada and Australia.[2] Besides its therapeutic efficacy as a sedative, additional studies also showed that thalidomide could be used as an effective antiemetic.[3] Therefore, it was marketed for insomnia and motion sickness in pregnant women. After the approval of the drug in European markets and with its increased use, case reports of deformed babies due to fetal toxicities began to surface: birth defects included stunted limb development (phocomelia).[4] These teratogenic events led to the withdrawal of thalidomide from the market in 1962.[5]

After being withdrawn from European markets, further studies showed that thalidomide was effective in treating skin lesions associated with erythema nodosum leprosum in males. Thalidomide was then approved by the US FDA for the treatment of erythema nodosum leprosum in August 1998, but with a strict drug distribution programme because of the high risk of teratogenicity.[6,7] Continuing clinical trials have also shown that thalidomide has activity in haematological disorders such as myelodysplastic syndrome (MDS), multiple myeloma (MM), chronic lymphocytic leukaemia, myelofibrosis with myeloid metaplasia, Waldenstrom's macroglobulinaemia and other malignancies.[8-12] As a single agent, thalidomide has shown clinical efficacy in MM.[9] In May 2006, it received FDA approval for treatment of newly diagnosed MM in combination with dexamethasone.[13] The use of thalidomide is limited by its adverse effect profile, which includes sedation, constipation, neuropathy and thromboembolism, in addition to fetal abnormalities.[14] Another generation of immunomodulatory agents (lenalidomide [CC-5013] and CC-4047) are being evaluated as alternative options for thalidomide. The purpose of developing these two agents was to produce an immunomodulator with increased potency and an improved adverse effect profile.[3]

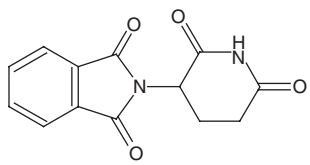
Lenalidomide was approved by the FDA in December 2005 for the treatment of patients with transfusion-dependent anaemia due to low or intermediate-1 risk MDS (based on the International Prognostic Scoring System [IPSS]) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.[15] In June 2006, it received FDA approval in combination with dexamethasone for the treatment of patients with MM who have received at least one prior therapy.[15] The purpose of this review article is to discuss the characteristics and role of lenalidomide in MDS and MM.

## 1. Pharmacology

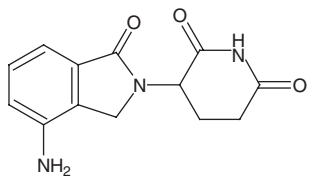
Thalidomide and its analogues have similar mechanisms of action. They not only act to inhibit angiogenesis but can also induce apoptosis and

growth arrest. Abnormal production of angiogenesis factors, cytokines and tumour necrosis factor (TNF)-α have been suggested as potential mediators of MDS and MM.[16-18] Pathological features of early stage MDS include accelerated apoptotic death of haematopoietic progenitors, including erythroid progenitor. The apoptotic death is due to overproduction of cytokines including TNF, interleukin (IL)-6 and IL-1 in bone marrow.[19] In addition, the bone marrow microenvironment has a direct correlation between measured microvascular density and myeloblast percentage, suggesting a role for angiogenesis in the pathogenesis and progression of MDS.[19] Thalidomide analogues block the increased production of vascular endothelial growth factor (VEGF), IL-6 and TNFα.[16-18] In MM, they work to block the adhesion of the myeloma cells to bone marrow stromal cells and protect against apoptosis. Immunomodulators increase natural killer cell and T cell numbers, and improve function of natural killer cells and T cells against MM cells.[17]

The chemical structure of thalidomide was modified to discover more potent and less toxic immunomodulators. Lenalidomide was formed by the addition of an amino group at position 4 of the phthaloyl and the removal of a carbonyl on the ring of thalidomide (figure 1).[2,3] This process made lenalidomide up to 50 000 times more potent as an inhibitor of TNFα than thalidomide.[16,17] Lenalidomide may inhibit the secretion of pro-inflammatory cytokines and increase the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells.[15] It may enhance cell-mediated immunity by the production of IL-2 and interferon-γ, and increase the responses of cytolytic T cells and natural killer cells.[19] Lenalidomide has also shown varying effectiveness on the cell lines with or without chromosome 5q deletions. An *in vitro* study suggests that lenalidomide may selectively inhibit cyclooxygenase (COX)-2 expression.[15] Compared with thalidomide, lenalidomide is more potent at suppressing COX-2 expression, inhibiting trophic responses to VEGF and potentiating T-cell immune response.[19]




Thalidomide




Lenalidomide

**Fig. 1.** Structural formulae of thalidomide and lenalidomide.

### 1.1 Pharmacokinetics

Lenalidomide reaches maximum concentration 0.625–1.5 hours after oral administration in healthy volunteers. Food does not affect the extent of absorption of lenalidomide but can slow absorption and thus reduce the maximum plasma concentration ($C_{max}$) by 36%.[15] Lenalidomide follows linear kinetics, where an increase in dose results in an increase in $C_{max}$ and area under the concentration-time curve (AUC) values. The AUC is 57% higher in MM patients than in healthy volunteers.[15] Approximately 30% of lenalidomide binds to plasma protein and steady-state plasma concentration is reached within 4 days. Multiple dose administration of lenalidomide does not result in drug accumulation or affect the pharmacokinetic profile.[3,15]

The metabolism of lenalidomide has not been studied in humans.[15] *In vitro* and animal studies have shown no effect on the cytochrome P-450 system. In healthy volunteers and MDS patients, ≈67% of the drug is excreted unchanged in urine within 24 hours.[3,20] Renal clearance of lenalidomide exceeds the glomerular filtration rate.[15] After reaching $C_{max}$, the plasma concentration of lenalidomide declines in a monophasic manner, with the elimination phase starting 1–8 hours after administration.[16] The approximate half-life of lenalidomide is 3 hours. The pharmacokinetics of

lenalidomide in moderate to severe renal impairment has not been studied.[15]

## 2. Clinical Use in Myelodysplastic Syndrome

### 2.1 Myelodysplastic Syndrome Overview

Myelodysplastic syndrome occurs in five per 100 000 people. However, in individuals older than 70 years, the incidence increases to 22–45 per 100 000.[21] MDS is characterised by the ineffective haematopoiesis of clonal haematopoietic stem cells. Allogenic haematopoietic stem cell transplantation (HSCT) is the only curative treatment for MDS. Because of the increased morbidity and mortality associated with HSCT in the elderly, treatment in this patient group usually consists of best supportive care, growth factors, azacitidine, decitabine, thalidomide, antithymocyte globulin (ATG) or ciclosporin (cyclosporine).[21] Best supportive care may consist of red blood cell (RBC) or platelet transfusion, antibacterials for bacterial infections, or iron chelation to counteract the effects of excessive RBC transfusion.

### 2.2 Clinical Trials

Lenalidomide was evaluated in a phase II open-label, single-centre, clinical trial in patients with MDS who were transfusion-dependent or symptomatically anaemic (table I).[22] In all patients, recombinant erythropoietin therapy had failed or endogenous erythropoietin levels were high. Three dose administration regimens were evaluated in this clinical trial: 25 or 10 mg/day or 10 mg/day for 21 days of a 28-day cycle, with responses measured at 16 weeks. Sequential dose reduction was allowed all the way down to lenalidomide 5mg every other day. Of the 43 patients enrolled, the median age was 72 years (range 28–85 years). On the basis of French, American and British (FAB) class, 47% had refractory anaemia, 30% refractory anaemia with ring sideroblast (RARS), 19% refractory anaemia with excess blasts (RAEB) and 2% refractory anaemia with excess blasts in transformation (RAEB-t). Median duration of disease prior to lenalidomide treatment was 29 months. Eighty-eight percent of the enrolled patients had low or intermediate-1 MDS risk stratification, according to the IPSS. Seventy-four percent of the patients were transfusion dependent, with baseline median haemoglobin levels of 8 g/dL (range 6.7–8.6 g/dL). Of the 20 patients with karyotypic abnormalities, 12 (60%) patients exhibited deletion of chromosome 5q31.1. Thirteen of the

**Table I.** Published studies of lenalidomide in myelodysplastic syndrome (MDS)

| Parameter | Study 1[22] (n = 43) | Study 2 (MDS-003)[23] (n = 148) |
|---|---|---|
| Median age, years (range) | 72 (28–85) | 71 (37–95) |
| FAB class (%) | | |
| RA | 20 (47) | 77 (52) |
| RARS | 13 (30) | 18 (12) |
| RAEB | 8 (19) | 30 (20) |
| RAEB-t | 1 (2) | |
| IPSS risk category (%) | | |
| low | 22 (51) | 55 (37) |
| intermediate-1 | 16 (37) | 65 (44) |
| intermediate-2 | 4 (9) | 6 (4) |
| high | 1 (2) | 2 (1) |
| Transfusion dependence (%) | 32 (74) | 146 (99) |
| Median duration of disease (months) | 29 | 30 |
| Cytogenetics (%) | | |
| deletion 5q | 12 (28) | 148 (100) |
| other | 8 (19) | 37 (25) |
| normal | 23 (53) | |
| **Results (%)** | | |
| Erythroid response | 24 (56) | 99 (67) |
| Cytogenetic response | | |
| deletion 5q | 10 (83) | 62 (73)[a] |
| other (non-5q deletion) | 1 (12) | |
| normal | 13 (57) | |
| Severe adverse effect[b] (%) | | |
| thrombocytopenia | 23 (53) | 65 (44) |
| neutropenia | 28 (65) | 81 (55) |

a n = 85 evaluable patients who had at least 20 cells in metaphase at baseline and at week 24.

b Grade 3 or 4.

**FAB** = French, American and British; **IPPS** = International Prognostic Scoring System; **RA** = refractory anaemia; **RAEB** = refractory anaemia with excess blasts; **RAEB-t** = refractory anaemia with excess blasts in transformation; **RARS** = refractory anaemia with ring sideroblast.

total 43 patients had previously received thalidomide therapy.

Twenty-one patients (49%) had a major erythroid response, defined as freedom from RBC transfusion or an increase in haemoglobin level of >2 g/dL in transfusion-independent patients. Twenty of 32 (63%) RBC transfusion-dependent patients achieved transfusion independence. A minor erythroid response was reported in 7% of the patients, defined as ≥50% reduction in transfusion or a sustained elevation of haemoglobin levels of 1–2 g/dL. The median time to response was 9 weeks in the 25 mg/day group, compared with 11.5 weeks in the 10 mg/day for 21 of 28 days group. The median duration of major response was not reached at 81 weeks. Erythroid response was very impressive, at 83% (10 of 12) in patients with deletion of 5q31.1. Of these ten patients with response, nine had complete cytogenetic responses and one had a minor cytogenetic response. A minor cytogenetic response was defined as a ≥50% reduction in the number of abnormal cells. Fifty-seven percent of the patients with normal karyotype and 12% with other karyotype abnormalities had an erythroid response. The median time to erythroid response was significantly earlier, at 8 weeks in patients with deletion of 5q31.1, compared with 11.2 weeks in other patients. In addition, 46% (6/13) of patients who had previously received thalidomide responded to lenalidomide.[22]

A case report has also been published on a patient who was identified with a complex karyotype, including deletion of 5q31.1, and was prescribed lenalidomide 10 mg/day orally on a compassionate use basis. After 5 months of treatment, the dose was reduced to 5 mg/day because of itching, nausea and vomiting. The patient achieved a complete cytogenetic, haematological and morphological response after 6 months of treatment. At 9 months follow-up, the patient still maintained a complete response.[24]

The MDS-003 registration trial evaluated the efficacy of lenalidomide in patients with transfusion-dependent anaemia in low to intermediate-1 risk MDS with isolated 5q31 cytogenetic deletion or accompanied additional cytogenetic abnormalities (table I).[23] This was a phase II, open-label, single arm, multicentre study. Transfusion-dependent anaemia was defined as having received ≥2 units of RBC transfusion within 8 weeks of enrolment in the study. Patients were excluded from the study if they had an absolute neutrophil count (ANC) of <500 cells/mm$^3$ and a platelet count of <50 000/mm$^3$. Initially, patients were scheduled to receive lenalidomide 10mg once daily for 21 out of 28 days. Later, the treatment schedule was amended to 10mg given every day. Forty-six patients received the 21-day dosage. Dose reduction was allowed to 5 mg/day and 5mg every other day. Granulocyte colony stimulating factors were allowed if the patient developed neutropenia or febrile neutropenia. The study evaluated the overall RBC transfusion requirement after 24 weeks of treatment.

Overall, 148 patients were evaluated in the study. The median age of the patients was 71 years (range 37–95 years) and the median time with MDS diagnosis prior to receiving lenalidomide was 2.5 years. The median number of RBC transfusion units within the 8-week period before study enrolment was 6. Seventy-one percent of the patients required >2 units of RBC transfusion per month at the time of enrolment. Seventy-three percent of patients had received prior erythropoietin treatment and 39% had received prior cytotoxic chemotherapy; 25% of the patients had other cytogenetic abnormalities, in addition to deletion 5q. On the basis of FAB criteria, 64% of the patients had either refractory anaemia or RARS.

Overall, 67% (99/148) of the patients became transfusion-independent with lenalidomide treatment by week 24. Transfusion independence was defined as the absence of RBC transfusion during any consecutive 8 weeks. The median time to RBC transfusion independence was 4.6 weeks, and duration of RBC transfusion independence at 104 weeks of follow-up was not reached in 53 responders.[15] Thrombocytopenia (platelet counts of <100 000/μL; odds ratio [OR] 4.53; p = 0.003) and high transfusion requirement (OR 3.59; p = 0.01) adversely affected haematological response on multivariate analysis. At week 24, of 85 evaluable patients, 38

(45%; 95% CI 34, 56) had complete cytogenetic remission and 24 patients (28%; 95% CI 19, 39) had a partial cytogenetic response. There was no statistically significant association between karyotype complexity and the frequency of a cytogenetic response. Thrombocytopenia (OR 4.78; p = 0.02) and age ≤60 years (OR 2.99; p = 0.07) were associated with lower cytogenetic response on multivariate analysis. A significant proportion of patients required dose adjustment in this study. Of all the patients enrolled, 84% required lenalidomide dose reduction or interruption, which was seen most frequently on day 22.[23]

Lenalidomide has shown activity in non-deletion 5q patients. A combined analysis of MDS-002 (non-deletion 5q patients) and MDS-003 (deletion 5q patients) showed that 26% (56/215) of the non-deletion 5q patients achieved RBC transfusion independence.[25] Of 215 patients, 77% of the patients had normal karyotype. No difference in RBC transfusion independence was noted between normal and abnormal karyotype. Duration of response was 52 weeks in 10% (22/215) of the responders. Lenalidomide had lower efficacy and durability of response in non-deletion 5q patients compared with deletion 5q patients. The same combined analysis in deletion 5q patients showed 68% (66/97) of the patients achieving RBC transfusion independence. The duration of response was at least 52 weeks in 53% (52/97) of the patients.[25]

### 2.3 Summary

Lower-risk MDS patients (IPSS low or intermediate-1) with anaemia have limited treatment options. In addition to best supportive care, the choice of an appropriate first-line agent should be based on a number of factors. Anaemic patients with serum erythropoietin levels <500 mU/mL should be offered recombinant erythropoietin with or without granulocyte colony stimulating factor.[21] If the patient has serum erythropoietin >500 mU/mL, ATG with or without ciclosporin, decitabine and azacitidine are reasonable treatment options.[21,26-29] Patients with severe thrombocytopenia and/or neutropenia should be considered for azacitidine or decitabine treatment.[21,26,27] Lenalidomide has produced significantly higher cytogenetic responses and durable RBC transfusion independence in deletion 5q31, especially deletion 5q31.1 patients. It should be the drug of choice for low and intermediate-1 risk MDS patients with chromosome 5q31 deletion with or without other karyotype abnormalities. A subgroup of patients with baseline thrombocytopenia may have significantly reduced probability of good haematological and cytogenetic response. Lower response rates in this group could be attributed to significantly (p = 0.004)[23] low numbers of consecutive days of drug treatment due to repeated treatment interruptions. Therefore, all lenalidomide recipients, particularly patients with baseline thrombocytopenia (platelet counts of <100 000/μL) should be monitored closely for the need for dose reduction and possible prevention of dose interruption due to myelosuppression. Although lenalidomide has a lower frequency and shorter duration of response compared with deletion 5q patients, overall it has shown promising activity in non-deletion 5q MDS. Further studies are warranted to investigate pathogenic differences among various karyotypes. At the same time, lenalidomide is yet to be evaluated in a phase III MDS trial.

## 3. Clinical Use in Multiple Myeloma

### 3.1 Overview of Multiple Myeloma

The American Cancer Society estimated 19 900 new diagnoses of MM and 10 790 deaths due to MM in 2006.[30] From 2002 to 2003, the median age of diagnosis was 70 years.[31] MM is a plasma cell disorder, characterised by abnormal production of monoclonal antibodies and/or light chains, and is not a curable disease. Advanced MM is commonly treated with conventional dose chemotherapy, followed by auto- or allogenic HSCT, based on patients' eligibility to receive HSCT. HSCT after conventional-dose therapy provides better survival of ≈4.5 years compared with 3.5 years with conventional chemotherapy alone.[32] In contrast, recent studies show conventional-dose therapy provides similar to superior overall survival compared with

HSCT.[33,34] Primary conventional therapy may consist of melphalan plus prednisone (MP), vincristine plus doxorubicin plus dexamethasone (VAD), pulse dexamethasone, thalidomide plus dexamethasone or MP plus thalidomide (MP-T).[35,36] Bortezomib, thalidomide or high-dose dexamethasone alone are some of the common agents used as salvage therapy in patients in whom primary treatment has failed.[9,37,38] Thalidomide has shown encouraging results in the treatment of MM. Initially, it demonstrated efficacy in advanced relapsed and refractory MM,[9] now it has been established as an effective agent with dexamethasone in first line MM treatment.[13,14,39,40]

### 3.2 Clinical Trials

Lenalidomide, in combination with dexamethasone or as a single agent, has been evaluated in patients with relapsed or refractory MM. The first combination study (MM-010) was completed in Europe, Israel and Australia, with 351 patients enrolled (table II).[41] It was a phase III, multicentre, randomised, double-blind trial, where all patients received dexamethasone 40mg on days 1–4, 9–12 and 17–20 every 28 days. Patients were randomised to receive lenalidomide 25mg or placebo daily for 21 of 28 days. A pre-planned interim analysis was performed, with a median study duration of 18 months. The median time to progression was 13.3 versus 5.1 months in the combination group compared with single-agent dexamethasone ($p < 0.000001$). There was a significant difference in overall response rates between dexamethasone plus lenalidomide (58%) and dexamethasone alone (22%). There was a significantly greater incidence of grade 3 or 4 neutropenia (16.5% vs 1.2%) and thromboembolic events were higher (8.5% vs 4.5%) with combination treatment.

The second combination study (MM-009) was conducted in North America and evaluated 354 patients with relapsed or refractory MM (table II).[42] The doses and frequency of lenalidomide and dexamethasone administrations were the same as the MM-010 study, except that beginning with the fifth cycle, the frequency of dexamethasone administration was reduced to days 1–4 only, every 28 days. The median time to progression was significantly better with the combination arm, at 11.1 months, compared with 4.7 months with dexamethasone alone, and the overall response rate was significantly better, at 59% compared with 21%, respectively. Complete response was achieved in 12.9% of the patients receiving lenalidomide plus dexamethasone compared with 0.6% of placebo plus dexamethasone recipients. The median overall survival was not reached for the combination regimen at 24 months. Combination treatment had a significantly greater incidence of grade 3 or 4 neutropenia (24% vs 3.5%), and a higher rate of thromboembolic events (15% vs 3.5%).

**Table II.** Phase III trials of lenalidomide in refractory/relapsed multiple myeloma (MM)

| Parameter | Study MM-010[41] (n = 351) | Study MM-009[42] (n = 354) |
|---|---|---|
| **Results** | | |
| Overall response rate (%) | | |
| lenalidomide + dexamethasone | 58 | 59.4 |
| placebo + dexamethasone | 22 | 21.1 |
| Time to progression (mo) | | |
| lenalidomide + dexamethasone | 13.3 | 11.1 |
| placebo + dexamethasone | 5.1 | 4.7 |
| **Adverse effect (%)** | | |
| Neutropenia[a] | | |
| lenalidomide + dexamethasone | 16.5 | 24 |
| placebo + dexamethasone | 1.2 | 3.5 |
| Thromboembolism | | |
| lenalidomide + dexamethasone | 8.5 | 15 |
| placebo + dexamethasone | 4.5 | 3.5 |

a Grade 3 or 4.

Another study evaluated two dose administration regimens of lenalidomide in patients with relapsed and refractory MM.[43] In this multicentre, single-arm, open-label, phase II study, the first cohort of 70 patients was randomised to receive either 30mg once daily or 15mg twice daily for 21 of every 28

days. Dexamethasone was added to the treatment if the patient had progressive or stable disease after two cycles of lenalidomide alone. As a result of an increased incidence of severe myelosuppression with the twice daily regimen, an additional 32 patients in cohort 2 were treated with lenalidomide 30mg once daily. Fifty-six percent of patients had received at least three previous treatments, including thalidomide (76%), HSCT (61%) and bortezomib (18%). The overall response rate was 24% with once-daily and 29% with twice-daily lenalidomide. Median progression-free survival was 7.7 months with once-daily and 3.9 months with twice-daily regimen.

In addition, a dose-finding phase I study in patients with relapsed MM, with a median of three prior chemotherapy regimens, has shown at least a 25% reduction in paraprotein in 71% (17/24) of the patients.[16] Eleven of the 17 patients who responded had received previous thalidomide treatment. Combined subgroup analyses of the MM-009 and MM-010 studies further support lenalidomide efficacy in patients with thalidomide-refractory MM.[44] Pooled data from 692 patients showed a 60% response with lenalidomide plus dexamethasone, compared with 23% with dexamethasone alone. Median time to progression was longer with the combination arm, at 48 weeks, compared with 20 weeks with dexamethasone. Prior use of thalidomide may affect response to the lenalidomide combination significantly, since time to tumour progression was 59 weeks in patients who had received no prior thalidomide, compared with 37 weeks in patients who had previously received thalidomide. The overall response rate was higher, at 63% in patients with no thalidomide, compared with 53% in thalidomide recipients.

Lenalidomide has also been evaluated for the treatment of newly diagnosed MM. A phase II clinical trial evaluated the efficacy of lenalidomide plus dexamethasone in patients with newly diagnosed MM who had not received treatment.[45] The treatment regimen consisted of lenalidomide 25 mg/day for 21 days of a 28-day cycle, with dexamethasone 40mg administered on days 1–4, 9–12 and 17–20. The primary endpoint was response rate, defined as a >50% reduction in serum monoclonal (M) protein and reduction in 24-hour urinary M-protein level by at least 90%. Thirty-four patients had median age of 64 years (range 32–78 years). Objective response was achieved in 91%, with median time of 1 month, and 6% achieved a complete response. An additional study has evaluated lenalidomide plus dexamethasone with clarithromycin ('BiRD' regimen) in patients with newly diagnosed MM.[46] Dexamethasone was given once weekly and clarithromycin 500mg twice daily. Efficacy endpoints were evaluated at a median 9 months' follow-up in 58 patients. The regimen yielded a 95% overall response, with 38% of the patients achieving complete or near complete response. There are multiple early phase studies evaluating lenalidomide in various combinations, which will provide additional efficacy and safety in MM. There is a study of lenalidomide in combination with the MP regimen in newly diagnosed (not HSCT candidate) MM patients.[47] Lenalidomide is also being evaluated in combination with bortezomib and doxorubicin plus dexamethasone in relapsed or refractory MM.[48,49]

### 3.3 Summary

These studies show lenalidomide has significant activity in MM patients. The efficacy of lenalidomide in newly diagnosed MM patients needs to be further evaluated in a phase III clinical trial. MP, VAD, thalidomide plus dexamethasone, and melphalan plus prednisone plus thalidomide are still regimens of choice for newly diagnosed MM patients.[31] An appropriate regimen should be chosen based on patient and disease characteristics in this population. Lenalidomide with dexamethasone has shown impressive response rates (58–59%) in patients with relapsed or refractory MM. Lenalidomide also has been shown to overcome drug resistance, including thalidomide resistance. Therefore, lenalidomide plus dexamethasone is another option, in addition to first line MM treatment regimens of bortezomib, thalidomide or high-dose dexamethasone, for the treatment of relapsed or refractory

**Table III.** Ongoing phase III clinical trials with lenalidomide[45,50-53]

| Study design | Patient population | Drug regimen |
|---|---|---|
| Randomised, double-blind, placebo-controlled | Previously untreated MM (S0232) | Lenalidomide + dexamethasone vs placebo + dexamethasone |
| Randomised, double-blind[a,b] | Previously untreated MM (E4A03) | Lenalidomide + high-dose dexamethasone vs lenalidomide + low-dose dexamethasone |
| Randomised, double-blind, placebo-controlled | Maintenance after autologous HSCT for MM | Lenalidomide vs placebo |
| Randomised, double-blind, crossover | Previously untreated MM | Lenalidomide + dexamethasone × 3 cycles then maintenance dexamethasone vs dexamethasone alone |
| Randomised, double-blind, placebo-controlled | MDS with deletion 5q abnormality | Lenalidomide vs placebo |

a High-dose dexamethasone: 40mg orally daily, days 1–4, 9–13 and 17–20 of each cycle and low-dose dexamethasone: 40mg orally daily, days 1–4 of each cycle.

b Study is currently suspended.

**MDS** = myelodysplastic syndrome; **MM** = multiple myeloma; **HSCT** = haematopoietic stem cell transplant.

MM. There are multiple other ongoing studies evaluating the role of lenalidomide in newly diagnosed MM as well as maintenance of MM patients (table III).[40,50-53] These studies may further support existing information or open the door for new indications of lenalidomide in MM.

## 4. Adverse Effects

Thalidomide analogues, such as lenalidomide, have an altered structure with a different toxicity profile. Lenalidomide does not cause significant sedation, constipation or neuropathy, but does lead to significant myelosuppression, unlike thalidomide.[15,23] The lenalidomide prescribing information has a black box warning for risk of myelosuppression, deep vein thrombosis/pulmonary embolism (DVT/PE) and teratogenicity. In addition, data from the MDS and MM studies indicate that MM patients are able to tolerate higher dosages of lenalidomide without reaching significant toxicity.[23,41,42]

Lenalidomide alone or in combination with dexamethasone has a 28–59% incidence of neutropenia and a 17–62% incidence of thrombocytopenia.[15] Grade 3 or 4 neutropenia was reported in 17–55% and thrombocytopenia in 10–50% of patients. Myelosuppression as a severe dose-limiting toxicity is significantly more common in patients with MDS compared with MM.[15,23,41,42] Seventy-seven percent of MDS patients receiving 25 mg/day and 62% receiving 10 mg/day required treatment interruption. In the phase I MM study, all 13 patients receiving 50 mg/day had to have the dosage reduced to 25 mg/day because of grade 3 myelosuppression after 28 days of treatment.[16] In addition to higher doses, frequent daily therapy can also significantly increase the risk of severe myelosuppression compared with once daily. A study by Richardson and colleagues[43] showed that lenalidomide 15mg twice daily had a significantly higher incidence of grade 3 or 4 myelosuppression than 30mg once daily (41% versus 13%; $p = 0.03$). The time to clinically significant myelosuppression was shorter with 15mg twice daily (1.8 vs 5.5 months; $p = 0.05$). Phase III MM studies have reported a marked incidence of myelosuppression at ≈17–24%.[41,42]

Thromboembolic events are another troubling adverse event of thalidomide and its analogues, with an incidence of 1–4% in MM patients receiving thalidomide as a single agent.[9,14,39] The incidence of DVT/PE increases significantly when thalidomide is combined with dexamethasone to as high as 20–25%.[14,39] Because of this risk, therapeutic warfarin anticoagulation or prophylactic low molecular weight heparin is routinely recommended for patients receiving combination thalidomide therapy.[14,39] As a single agent in MDS, lenalidomide has shown a 3% incidence of pulmonary embolism.[23] When lenalidomide is used in combination

with dexamethasone in MM patients, the reported incidence of thromboembolism is anywhere from 8.5% to 15%.[41,42] It appears that high-dose dexamethasone (40 mg/day on days 1–4, 9–12 and 17–20) with lenalidomide may result in an increased incidence (18.4%) compared with low-dose dexamethasone (40 mg/day on days 1, 8, 15 and 22; 5.4%).[54] The addition of erythropoietic agents to lenalidomide and dexamethasone combination therapy has increased incidence reports up to 23%.[55] Multivariate analysis suggests that concomitant erythropoietin use can increase the risk of thrombosis by 3-fold in MM patients.[56] Early clinical trial data suggest that aspirin, already shown to be effective in arterial thrombosis prevention, may be an effective venous thromboprophylaxis in patients receiving lenalidomide as combination therapy.[51,55,57]

Skin rash is common with both thalidomide and lenalidomide, at 31–36%. Severe skin rash is reported in 4–7% of the patients.[14,15] Sedation, constipation and neuropathy are common toxicities of thalidomide, reported to occur in approximately 48%, 55% and 54% of recipients, respectively. These toxicities may worsen with increases in dose or prolonged treatment. Grade 3 and 4 sedation, constipation and neuropathy occur in approximately 10%, 8% and 4% of patients, respectively.[13,14] At times, these are the dose-limiting toxicities. Lenalidomide-induced sedation, constipation and neuropathy are reported at 21%, 24% and 21% of patients, respectively. No lenalidomide-induced severe (grade 3 or 4) sedation, constipation or neuropathy was reported in the MDS trials.[22,23]

Lenalidomide 50 mg/kg has shown embryocidal activity in rabbits but 500 mg/kg has shown no teratogenic activity in rats. These doses are equivalent to 120 and 600 times the human dose of 10mg based on body surface area, respectively.[15] There are no case reports or well controlled studies of lenalidomide in pregnant women. Since lenalidomide is structurally similar to thalidomide, its prescribing information has a black box warning regarding the risk of teratogenicity. Lenalidomide is contraindicated in pregnant women and is assigned category X.[15] Like the S.T.E.P.S® (System for Thalidomide Education and Prescribing Safety) dispensing system of thalidomide, lenalidomide dispensing is regulated by the RevAssist® programme.[14,15]

**Table IV.** Recommended dose adjustment for myelodysplastic syndrome (MDS) patients on lenalidomide treatment[15]

| | | |
|---|---|---|
| **Thrombocytopenia** | | |
| Within 4 weeks of starting lenalidomide | | |
| If baseline platelet count (per μL) | Treatment interruption at platelet count (per μL) | Resume treatment at platelet count (per μL)[a] |
| ≥100 000 | <50 000 | ≥50 000 |
| <100 000 to ≥60 000 | fall to 50% of the baseline | ≥50 000 |
| <60 000 | fall to 50% of the baseline | ≥30 000 |
| After 4 weeks of starting lenalidomide | | |
| NA | <30 000 | ≥30 000[b] |
| **Neutropenia** | | |
| Within 4 weeks of starting lenalidomide | | |
| If baseline ANC (per μL) | Treatment interruption at ANC (per μL) | Resume treatment at ANC (per μL)[a] |
| ≥1000 | <750 | ≥1000 |
| <1000 | <500 | ≥500 |
| After 4 weeks of starting lenalidomide | | |
| NA | <500 for ≥7 days | ≥500[b] |
| | <500 with fever ≥38.5°C | ≥500[b] |

a Resume lenalidomide dose: 5 mg/day if starting dose 10 mg/day.

b Resume lenalidomide dose: 5mg every other day if starting dose 5 mg/day.

**ANC** = absolute neutrophil count; **NA** = not applicable.

**Table V.** Recommended dose adjustment for multiple myeloma (MM) patients on lenalidomide treatment[15]

| | | |
|---|---|---|
| **Thrombocytopenia** | | |
| Treatment interruption at platelet count (per μL) | Resume treatment at platelet count (per μL)[a] | Resume at lenalidomide dosage[a] |
| <30 000 | ≥30 000 | 15 mg/day |
| each subsequent <30 000 | ≥30 000 | 5mg <previous dose |
| **Neutropenia** | | |
| Treatment interruption at ANC (per μL) | Resume treatment at ANC (per μL)[a] | Resume at lenalidomide dosage[a] |
| <1000 and no other toxicity | ≥1000 | 25 mg/day |
| <1000 and other toxicity | ≥1000 | 15 mg/day |
| each subsequent <1000 | ≥1000 | 5mg <previous dose |

a Do not give lenalidomide below 5 mg/day in MM patients.

**ANC** = absolute neutrophil count.

Other common adverse effects associated with lenalidomide include diarrhoea, pruritus and fatigue. Rarely, patients may develop pneumonia, hypothyroidism or hypogonadal dysfunction.[15,23,40]

## 5. Dosage and Administration

Lenalidomide is available orally in capsule formulations of 5, 10 and 25mg.[15] It is recommended at a dosage of 10 mg/day orally with water for the FDA-approved indication of MDS with deletion 5q.[22,23] Clinical trials in patients with MM show that lenalidomide is clinically efficacious at a dosage of 25 mg/day from days 1–21 of a 28-day cycle, in combination with dexamethasone.[15,41,42] It is recommended that patients receiving lenalidomide have a complete blood count weekly during the first 8 weeks of initial treatment and then monthly. Dose adjustments for haematological toxicities during lenalidomide treatment are provided in table IV and table V.[15] No specific dose adjustments are recommended for renal or hepatic impairment. No fully published trials of lenalidomide have included patients with serum creatinine >2.5 mg/dL.[43,45]

A combined subgroup analysis of the MM-009 and MM-010 studies of patients with renal impairment has been performed.[58] The analysis identified a significantly higher incidence of moderate to severe thrombocytopenia in patients with a creatinine clearance ($CL_{CR}$) <50 mL/min (13.8%) and <30 mL/min (18.8%). No statistically significant difference was identified in the incidence of neutropenia. The efficacy of lenalidomide was lowered in refractory or relapsed MM patients with a $CL_{CR}$ <30 mL/min as a result of dose interruptions. Another study of the BiRD regimen in newly diagnosed MM patients confirmed the increased risk of myelosuppression in renal impairment. It identified that baseline serum creatinine >1.4 mg/dL or $CL_{CR}$ ≤40 mL/min was significantly associated with increased risk of myelosuppression.[46]

## 6. Conclusion

Lenalidomide is a thalidomide analogue with a potent anti-tumour activity. It lacks common adverse effects associated with thalidomide. It is also active in patients with thalidomide-resistant disease. It should be the drug of choice in low and intermediate-1 risk MDS patients with deletion 5q31 with or without other karyotype abnormalities. Lenalidomide has shown very promising results in the treatment of newly diagnosed or relapsed and refractory MM. Lenalidomide in combination with dexamethasone is an option in the treatment of relapsed or refractory MM, and its efficacy in newly diagnosed MM needs to be further evaluated in a phase III trial. Significant myelosuppression is a concern, especially in MDS patients, which may lead to a lowering of starting dose or dose interruption in the majority of patients. There is increased incidence of thromboembolic events when lenalidomide is combined with high-dose dexamethasone, which could be reduced with effective thromboprophylaxis. More phase III trials are underway, which should

further help delineate the efficacy and toxicity of lenalidomide in MDS and MM.

## Acknowledgements

We would like to thank Brad Stanford and Melissa Lockman for their help in the preparation of this manuscript. None of the authors have received any funding for the preparation of the paper. The authors have declared that they have no conflicts of interest that are directly relevant to the content of this review. Dr Tran was a haematology/oncology specialty pharmacy resident at Texas Tech University Health Sciences Center-School of Pharmacy/VA North Texas Health Care System during the preparation of this manuscript.

## References

1. Argiles JM, Carbo N, Lopez-Soriano FJ. Was tumour necrosis factor-alpha responsible for the fetal malformations associated with thalidomide in the early 1960s? Med Hypotheses 1998; 50: 313-8
2. Teo SK. Properties of thalidomide and its analogues: implications for anticancer therapy. AAPS J 2005; 7: E14-9
3. Knight R. IMiDs: a novel class of immunomodulators. Semin Oncol 2005; 32 Suppl. 5: S24-30
4. Lenz W. Perthes-like changes in thalidomide children. Lancet 1967; II: 562
5. Rajkumar SV. Current status of thalidomide in the treatment of cancer. Oncology 2001; 15: 867-74
6. Teo SK, Resztak KE, Scheffler MA, et al. Thalidomide in the treatment of leprosy. Microbes Infect 2002; 4: 1193-202
7. Sheskin J. Thalidomide in the treatment of lepra reactions. Clin Pharmacol Ther 1965; 6: 303-6
8. Raza A, Meyer P, Dutt D, et al. Thalidomide produces transfusion independence in long-standing refractory anemias of patients with myelodysplastic syndromes. Blood 2001; 98: 958-65
9. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 1999; 341: 1565-71
10. Furman RR, Leonard JP, Allen SL, et al. Thalidomide alone or in combination with fludarabine are effective treatments for patients with fludarabine-relapsed and refractory CLL [abstract]. Proc Am Soc Clin Oncol 2005; 23: 6640
11. Mesa RA, Elliott MA, Schroeder G, et al. Durable responses to thalidomide-based drug therapy for myelofibrosis with myeloid metaplasia. Mayo Clin Proc 2004; 79: 883-9
12. Dimopoulos MA, Tsatalas C, Zomas A, et al. Treatment of Waldenstrom's macroglobulinemia with single-agent thalidomide or with the combination of clarithromycin, thalidomide and dexamethasone. Semin Oncol 2003; 30: 265-9
13. Rajkumar SV, Blood E, Vesole D, et al. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2006; 24: 431-6
14. Celgene Corporation. Thalidomid® (thalidomide) package insert. Warren (NJ): Celgene Corporation, 2006
15. Celgene Corporation. Revlimid® (lenalidomide) package insert. Summit (NJ): Celgene Corporation, 2006
16. 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
17. Richardson P, Anderson K. Immunomodulatory analogs of thalidomide: an emerging new therapy in myeloma. J Clin Oncol 2004; 22: 3212-4
18. Hellstrom-Lindberg E. Update on supportive care and new therapies: immunomodulatory drugs, growth factors and epigenetic-acting agents. Hematology (Am Soc Hematol Educ Program) 2005; 2005 (1): 161-6
19. List AF. Emerging data on IMiDs in the treatment of myelodysplastic syndromes (MDS). Semin Oncol 2005; 32 Suppl. 5: S31-5
20. Wu A, List A, Lush R, et al. A pharmacokinetic and pharmacodynamic study of oral lenalidomide in patients with low or intermediate-risk myelodysplastic syndromes [abstract]. Blood 2006; 108: 4854
21. National Comprehensive Cancer Network. NCCN guidelines v.4.2006: myelodysplastic syndrome [online]. Available from URL: http://www.nccn.org [Accessed 2006 Sep 13]
22. List A, Kurtin S, Roe DJ, et al. Efficacy of lenalidomide in myelodysplastic syndromes. N Eng J Med 2005; 352: 549-57
23. List AF, Dewald G, Bennett A, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med 2006; 355: 1456-65
24. Giagounidis AA, Germing U, Strupp C, et al. Prognosis of patients with del(5q) MDS and complex karyotype and the possible role of lenalidomide in this patient subgroup. Ann Hematol 2005; 84: 569-71
25. List A, Dewald G, Bennett J, et al. Clinical benefit from 2 phase II trials evaluating lenalidomide (Revlimid) in lower-risk myelodysplastic syndrome patients with or without del 5q cytogenetic abnormalities [abstract]. European Hematology Association 11th Congress Proceedings; 2006 Jun 15-18; Amsterdam, 1032
26. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the CALGB. J Clin Oncol 2002; 20: 2429-40
27. Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. Cancer 2006; 106: 1794-803
28. Jonasova A, Neuwirtova R, Cermak J, et al. Cyclosporin A therapy in hypoplastic MDS patients and certain refractory anaemias without hypoplastic bone marrow. Br J Haematol 1998; 100: 304-9
29. Molldrem J, Caples M, Mavroudis D, et al. Antithymocyte globulin for patients with myelodysplastic syndromes. Br J Haematol 1997; 99: 699-705
30. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. CA Cancer J Clin 2007; 57: 43-66
31. National Cancer Institute. Cancer topics: multiple myeloma [online]. Available from URL: http://www.cancer.gov/cancertopics/pdq/treatment/myeloma/healthprofessional [Accessed 2006 Jun 8]
32. Child JA, Morgan GJ, Davies FE. Medical Research Council Adult Leukemia Working Party. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Eng J Med 2003; 348: 1875
33. Facon T, Mary J, Harousseau J, et al. Superiority of melphalan-prednisone (MP) + thalidomide (THAL) over MP and autologous stem cell transplantation in the treatment of newly diag-

nosed elderly patients with multiple myeloma [abstract]. Proc Am Soc Clin Oncol 2006; 24: 1

34. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. J Clin Oncol 2006; 24: 929-36
35. National Comprehensive Cancer Network. NCCN guidelines v.1.2006: multiple myeloma [online]. Available from URL: http://www.nccn.org [Accessed 2006 May 1]
36. Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet 2006; 367: 825-31
37. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005; 352: 2487-98
38. Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003; 358: 2609-17
39. Weber D, Rankin K, Gavino M, et al. Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. J Clin Oncol 2003; 21: 16-9
40. 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
41. Dimopoulos MA, Spencer A, Attal M, et al. Study of lenalidomide plus dexamethasone versus dexamethasone alone in relapsed or refractory multiple myeloma: results of a phase 3 study (MM-010) [abstract]. Am Soc of Hem 2005; 106: 6
42. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus high-dose dexamethasone provides improved overall survival compared to high-dose dexamethasone alone for relapsed or refractory multiple myeloma (MM): results of a North American phase III study (MM-009) [abstract]. Proc Am Soc Clin Oncol 2006; 24: 7521
43. Richardson PG, Blood E, Mitsiades CS, et al. A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. Blood 2006; 108: 3458-64
44. Wang M, Knight R, Dimopoulos M. Comparison of lenalidomide in combination with dexamethasone to dexamethasone alone in patients who have received prior thalidomide in relapsed or refractory multiple myeloma [abstract]. Proc Am Soc Clin Oncol 2006; 24: 7522
45. Rajkumar SV, Hayman SR, Lacy MQ, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. Blood 2005; 106: 4050-3
46. Nievsvizky R, Jayablan DS, Zafar F, et al. Lenalidomide induced myelosuppression is potentially associated with renal dysfunction in treatment naíve myeloma (MM) patients receiving BiRD (Biaxin/Revlimid/Dexamethasone) combination therapy (Rx) [abstract no. 3549]. American Society of Hematology Annual Meeting Proceedings; 2006 Dec 9-12; Orlando (FL)
47. Roy V, Leif BP, Jacob A, et al. Melphalan (M), prednisone (P), and lenalidomide (R) combination (MPR) for newly diagnosed multiple myeloma patients who are not candidates for stem cell transplantation [abstract no. 3558]. American Society of Hematology Annual Meeting Proceedings; 2006 Dec 9-12; Orlando (FL)
48. Richardson PG, Jagannath S, Avigan DE, et al. Lenalidomide plus bortezomib (Rev-Vel) in relapsed and/or refractory multiple myeloma: final results of multicenter phase 1 trial [abstract no. 405]. American Society of Hematology Annual Meeting Proceedings; 2006 Dec 9-12; Orlando (FL)
49. Knop S, Gerecke C, Topp MS, et al. Lenalidomide (Revlimid), adriamycin and dexamethasone chemotherapy (RAD) is safe and effective in treatment of relapsed multiple myeloma: first results of German Multicenter phase I/II trial [abstract]. Blood 2006; 108: 408
50. Southwest Oncology Group. Clinical trials: open protocols [online]. Available from URL: http://www.swog.org [Accessed 2006 Jun 2]
51. Rajkumar SV, Blood E. Lenalidomide and venous thromboembolism in multiple myeloma. N Engl J Med 2006; 354: 2080
52. Eastern Cooperative Oncology Group. General information: clinical trial [online]. Available from URL: http://www.ecog.org [Accessed 2006 Jun 2]
53. Clinical Trials. Lenalidomide [online]. Available from URL: http://www.clinicaltrials.gov [Accessed 2006 Jun 2]
54. Rajkumar SV, Jacobus S, Callander N, et al. A randomized phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group [abstract]. Blood 2006; 108: 799
55. Knight R, DeLap RJ, Zeldis JB. Lenalidomide and venous thromboembolism in multiple myeloma. N Engl J Med 2006; 354: 2079-80
56. Niesvizky R, Spencer A, Wang M, et al. Increased risk of thrombosis with lenalidomide in combination with dexamethasone and erythropoietin [abstract]. Proc Am Soc of Clin Oncol 2006; 24: 7506
57. Zonder JA, Barlogie B, Durie BG, et al. Thrombotic complications in patients with newly diagnosed multiple myeloma treated with lenalidomide and dexamethasone: benefit of aspirin prophylaxis. Blood 2006; 108: 403
58. Weber D, Wang M, Chen C, et al. Lenalidomide plus high-dose dexamethasone provides improved overall survival compared to high-dose dexamethasone alone for relapsed or refractory multiple myeloma(mm): results of 2 phase III studies (MM-009, MM-010) and subgroup analysis of patients with impaired renal function [abstract no. 3547]. American Society of Hematology Annual Meeting Proceedings; 2006 Dec 9-12; Orlando (FL)

Correspondence: Dr *Sachin R. Shah*, Texas Tech University Health Sciences Center-School of Pharmacy/VA North Texas Health Care System, 4500 South Lancaster, Bldg 7, R# 119A, Dallas, TX 75216, USA.
E-mail: sachin.shah@ttuhsc.edu