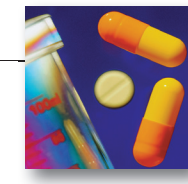

Lenalidomide (Revlimid)

A Thalidomide Analogue in Combination With Dexamethasone For the Treatment of All Patients With Multiple Myeloma

Martin Paspe Cruz, PharmD, CGP, BCPP, FASCP

INTRODUCTION

Multiple myeloma (MM) is characterized by proliferation of abnormal plasma cells in the bone marrow that interferes with the production of normal blood cells, resulting in leukopenia, anemia, and thrombocytopenia. The second most prevalent blood cancer after non-Hodgkin's lymphoma, it represents approximately 1% of all cancers and 2% of all cancer deaths.[1] In the United States, approximately 30,330 new cases of MM (17,900 in men and 12,430 in women) will be diagnosed in 2016; the lifetime risk of MM is one in 143 (0.7%). Approximately 12,650 deaths from MM (6,430 in men and 6,220 in women) are predicted in 2016.[2] Presentations of the disease vary from asymptomatic to severely symptomatic, with complications such as kidney failure, bone lesions, hypercalcemia, and spinal cord compression.[3,4] The relative five-year survival rate of MM, which is higher in younger than older populations, is approximately 46.6%.[5–7]

Lenalidomide (Revlimid, Celgene) is a thalidomide derivative introduced in 2004 as an immunomodulatory agent for the treatment of various cancers such as MM, myelodysplastic syndrome (MDS), and lymphoma. Lenalidomide, despite its known toxicities, has significantly improved the once-poor prognosis and survival rates of MM.[8] The Food and Drug Administration (FDA) expanded the existing indication for lenalidomide in combination with dexamethasone to include newly diagnosed MM in February 2015, based on safety and efficacy results from a phase 3 study of 1,623 newly diagnosed patients who were not stem-cell transplant candidates.[9] This study evaluated continuous lenalidomide in combination with dexamethasone until disease progression versus melphalan, prednisone, and thalidomide for 18 months as the primary analysis.[10] Although lenalidomide has other approved indications, this article focuses on MM.

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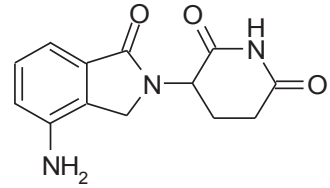
MECHANISM OF ACTION

Lenalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties that inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells, including MM, mantle cell lymphoma, and del (5q) MDS. It causes a delay in tumor growth in some nonclinical hematopoietic tumor models, including MM. Activation of T cells and natural killer T (NKT) cells, increased numbers of NKT cells, and inhibition of pro-inflammatory cytokines (e.g., tumor necrosis factor-alpha and interleukin-6) by monocytes are considered to be lenalidomide's immunomodulatory properties. In addition, lenalidomide inhibits tumor angiogenesis, tumor-secreted cytokines, and tumor proliferation through the induction of apoptosis. During clinical studies, the synergistic combination of lenalidomide and dexamethasone in MM cells inhibited cell proliferation and induced apoptosis.[10–13]

Figure 1 Chemical Structure of Lenalidomide[10]



Lenalidomide is an off-white to pale yellow powder with the chemical name 3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione, empirical formula of $C_{13}H_{13}N_3O_3$, and gram molecular weight of 259.3 (Figure 1). It is soluble in organic solvent, water mixtures, and buffered aqueous solvents; its solubility is significantly lower in less acidic buffers (ranging from 0.4–0.5 mg/mL). Lenalidomide is available in 2.5-mg, 5-mg, 10-mg, 15-mg, 20-mg, and 25-mg capsules for oral administration. Each capsule contains lenalidomide and inactive ingredients such as lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.[10]

PHARMACOKINETICS

Lenalidomide is absorbed rapidly following single and multiple oral administrations with maximum plasma concentrations (C_{max}) between 0.5 and six hours post-dose in patients with MM and MDS. It has a linear pharmacokinetic profile, with area under the curve (AUC) and C_{max} values increasing proportionally with single and multiple doses. Recommended multiple dosing did not result in accumulation of the drug during studies.

In a study comparing patients with renal impairment to healthy subjects, lenalidomide's half-life increased and drug clearance decreased linearly as creatinine clearance decreased from mild to severe impairment. Patients with moderate and severe renal impairment had a threefold increase in half-life and a 66% to 75% decrease in drug clearance compared with healthy subjects.

Although an approximate 20% decrease in AUC and 50% decrease in C_{max} were observed following administration of a single 25-mg dose with a high-fat meal in healthy subjects, lenalidomide may be administered without regard to meals.

A similar absorption rate was observed among mantle cell lymphoma patients.[10]

Lenalidomide is approximately 30% plasma protein-bound and is present in semen at two hours (1,379 ng/ejaculate) and 24 hours (35 ng/ejaculate) following oral administration of 25 mg daily. The drug is metabolized unchanged with 5-hydroxy-lenalidomide and N-acetyl-lenalidomide as metabolites, each constituting less than 5% of parent levels in circulation. Lenalidomide is primarily eliminated through the kidneys, with renal clearance exceeding the glomerular filtration rate. Approximately 82% of the radioactive dose (4.59% hydroxy-lenalidomide, 1.83% N-acetyl-lenalidomide) is excreted in the urine within 24 hours, and 90% in urine and 4% in feces within 10 days, following a single 25-mg lenalidomide oral administration. Lenalidomide has a mean half-life of three hours in healthy subjects and three to five hours in patients with MM, MDS, or mantle cell lymphoma.[10]

Lenalidomide does not prolong the QTc interval based on a study of 60 healthy male subjects in a randomized, thorough QT study (the two-sided 90% confidence interval [CI] for the mean differences between lenalidomide and placebo was less than 10 ms).[10]

PIVOTAL CLINICAL TRIALS

Newly Diagnosed Multiple Myeloma

A randomized, multicenter, open-label, three-arm trial (N = 1,623) showed the efficacy and safety of lenalidomide and low-dose dexamethasone (Rd) given for two different durations compared with that of melphalan, prednisone, and thalidomide (MPT) in newly diagnosed MM patients who were not stem-cell transplant candidates. The first arm (Rd continuous) of the study consisted of Rd given continuously until progressive disease; the second arm (Rd18) consisted of Rd given for up to 18 28-day cycles (72 weeks); and the third arm (MPT) consisted of melphalan, prednisone, and thalidomide given for a maximum of 12 42-day cycles (72 weeks). Patients in the first and second arms were treated with lenalidomide 25 mg once daily on days 1–21 and dexamethasone 40 mg once daily on days 1, 8, 15, and 22 of a 28-day cycle. The dexamethasone dose was reduced to 20 mg once daily for patients older than 75 years of age on days 1, 8, 15, and 22. Initial and maintenance dosages were adjusted according to age and renal function in the first and second arms. Aspirin was given to all patients as prophylactic anticoagulation. The primary efficacy endpoint, progression-free survival (PFS), was defined as the time from randomization to the first documentation of disease progression as determined by an independent response adjudication committee based on International Myeloma Working Group criteria or death due to any cause during the study.[10,14] An updated analysis released in June 2015 demonstrated median PFS of 26.0 months for patients in the Rd continuous group compared with 21.9 months for patients in the MPT group (hazard ratio [HR], 0.69; 95% CI, 0.59–0.80; $P = 0.00031$). The median PFS in the Rd18 arm was 21.0 months. Rd continuous treatment led to a 25% reduction in risk of death versus the MPT regimen (HR, 0.75; 95% CI, 0.62–0.90), with a median overall survival (OS) improvement of 10.4 months (from 48.5 months to 58.9 months). The median OS for Rd18 was 56.7 months. The median follow-up was 45.5 months.[15]

Previously Treated Multiple Myeloma

Two randomized, multicenter, multinational, double-blind, placebo-controlled studies demonstrated the efficacy and safety of combination lenalidomide and oral high-dose dexamethasone over dexamethasone alone in MM patients who had received at least one prior treatment.[10,16,17]

In both studies, lenalidomide/dexamethasone patients were randomized to receive lenalidomide 25 mg once daily on days 1–21 and placebo once daily on days 22–28 of each 28-day cycle, while placebo/dexamethasone patients received one placebo on days 1–28 of each 28-day cycle. Dexamethasone 40 mg was given orally once daily to all patients on days 1–4, 9–12, and 17–20 of each 28-day cycle for the first four cycles of therapy. After the first four cycles, dexamethasone was reduced to 40 mg orally once daily on days 1–4 of each 28-day cycle. Treatment was continued until disease progression with lenalidomide dose reductions to 15 mg, 10 mg, or 5 mg once daily permitted based on patients' clinical conditions and laboratory test results. Patients included in the studies had absolute neutrophil counts (ANCs) of at least 1,000/mm^3, platelet counts of at least 75,000/mm^3, serum creatinine no higher than 2.5 mg/dL, serum aspartate aminotransferase or alanine aminotransferase no higher than three times the upper limit of normal (ULN), and serum direct bilirubin of 2 mg/dL or less. The time from randomization to the first occurrence of progressive disease, or time to progression (TTP), was the primary efficacy endpoint in both studies. Preplanned interim analyses in both studies showed that the combination of lenalidomide/dexamethasone was significantly superior to dexamethasone alone for TTP. The studies were unblinded to allow patients in the placebo/dexamethasone group to receive treatment with the lenalidomide/dexamethasone combination.[10,16,17] Selected results are shown in Table 1.[10]

For both studies, the extended follow-up survival data with crossovers were analyzed. In study 1, the median survival time was 39.4 months (95% CI, 32.9–47.4) in the lenalidomide/dexamethasone group and 31.6 months (95% CI, 24.1–40.9) in the placebo/dexamethasone group (HR, 0.79; 95% CI, 0.61–1.03). In study 2, the median survival time was 37.5 months (95% CI, 29.9–46.6) in the lenalidomide/dexamethasone group and 30.8 months (95% CI, 23.5–40.3) in the placebo/dexamethasone group (HR, 0.86; 95% CI, 0.65–1.14).[10]

SAFETY PROFILE

Adverse Events[10]

The most common adverse effects (20% or more) reported with lenalidomide during MM treatment included diarrhea, anemia, fatigue, constipation, peripheral edema, neutropenia, back pain, nausea, asthenia, insomnia, thrombocytopenia, rash, dyspnea, cough, pyrexia, muscle cramps/spasms, upper respiratory tract infections, decreased appetite, and tremor. Pneumonia, hypokalemia, cataract, lymphopenia, deep-vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), hyperglycemia, leukopenia, itching, tiredness, swelling of the limbs and skin, abdominal pain, vomiting, bone pain, atrial fibrillation, congestive heart failure, hirsutism, blindness, angina pectoris, mood swings, hallucination, loss of libido, and erectile dysfunction have also been reported. Post-marketing adverse drug effects reported globally include allergic conditions such as angioedema, Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), tumor lysis syndrome (TLS), tumor flare reaction (TFR), pneu-

Table 1 Selected Results From Two Trials of Lenalidomide and Dexamethasone Versus Placebo and Dexamethasone in Previously Treated Multiple Myeloma Patients[10]

	Study 1		Study 2	
	Lenalidomide/ Dexamethasone (n = 177)	Placebo/ Dexamethasone (n = 176)	Lenalidomide/ Dexamethasone (n = 176)	Placebo/ Dexamethasone (n = 175)
Time to progression (TTP)				
Events, n (%)	73 (41)	120 (68)	68 (39)	130 (74)
Median TTP in months (95% CI)	13.9 (9.5–18.5)	4.7 (3.7–4.9)	12.1 (9.5–NE)	4.7 (3.8–4.8)
Hazard ratio (95% CI)	0.285 (0.210–0.386)		0.324 (0.240–0.438)	
P value	*P* < 0.001		*P* < 0.001	
Response				
Complete response, n (%)	23 (13)	1 (1)	27 (15)	7 (4)
Partial response, n (%)	84 (48)	33 (19)	77 (44)	34 (19)
Overall response, n (%)	107 (61)	34 (19)	104 (59)	41 (23)
P value	*P* < 0.001		*P* < 0.001	
Odds ratio (95% CI)	6.38 (3.95–10.32)		4.72 (2.98–7.49)	

CI = confidence interval; NE = not estimable.

monitis, hepatic failure, toxic hepatitis, cytolytic and cholestatic hepatitis, transient abnormal liver laboratory tests, hypothyroidism, and hyperthyroidism.

Contraindications[10]

Lenalidomide use in pregnancy is contraindicated due to birth defects and abnormalities seen in animal studies as well as the medication's structural similarities to the known human teratogen thalidomide. It is also contraindicated in patients who have known hypersensitivity to lenalidomide, such as angioedema, SJS, or TEN.

Warnings and Precautions[10]

The label for lenalidomide has three boxed warnings: for embryo-fetal toxicity, for hematological toxicity (significant neutropenia and thrombocytopenia), and for venous and arterial thromboembolism.

Embryo-Fetal Toxicity

Lenalidomide is contraindicated during pregnancy and available only through the Revlimid Risk Evaluation and Mitigation Strategy (REMS) program. Prescribers must be certified by enrolling and complying with the REMS requirements; patients must sign a patient-physician agreement form and comply with the REMS requirements; female patients of reproductive potential who are not pregnant must comply with pregnancy testing and contraception requirements; and males must comply with contraception requirements. Pharmacies must be certified with the Revlimid REMS program, must only dispense to patients who are authorized to receive Revlimid, and must comply with REMS requirements. Information about the Revlimid REMS program is available at www.celgeneriskmanagement.com or 1-888-423-5436.

Lenalidomide resulted in birth defects similar to those observed with thalidomide during pregnancy in animal embryo-fetal development studies. Pregnancy should be avoided at least four weeks prior to lenalidomide treatment, during treatment, during dose adjustments, and at least four weeks after treatment ends. Two negative pregnancy tests—one within 10 to 14 days and one within 24 hours—are required before starting lenalidomide. Pregnancy tests should be continued weekly for one month, then monthly or every two weeks in women with regular and irregular menstrual cycles, respectively. Men receiving lenalidomide must not donate sperm and should use condoms during sexual intercourse because the drug is present in the semen up to 28 days after discontinuing the drug, even after a vasectomy.

Hematological Toxicity

Due to potential significant drug-induced neutropenia and thrombocytopenia, complete blood counts should be evaluated weekly for the first two cycles, on days 1 and 15 of cycle 3, and every 28 days thereafter in patients receiving lenalidomide and dexamethasone combination treatment for MM. In clinical trials of lenalidomide plus dexamethasone in MM patients, reported thrombocytopenia of any grade ranged from 19% to 22% and neutropenia of any grade ranged from 33% to 42%. If a patient's platelets fall below 30,000/mcL or if absolute neutrophil counts fall below 1,000/mcL, treatment should be interrupted, monitored, and resumed as described in Table 2.

Thromboembolism

Among MM trial patients treated with lenalidomide and dexamethasone, DVT and PE were reported more frequently (7.4% and 3.7%, respectively) compared to patients treated with placebo and dexamethasone (3.1% and 0.9%, respectively). DVT and PE were also reported among newly diagnosed MM patients who received antithrombotic prophylaxis in the lenalidomide and low-dose dexamethasone group (3.6% and 3.8%, respectively); the group that received lenalidomide and low-dose dexamethasone for up to 18 28-day cycles (2.0% and 2.8%); and the group that received melphalan, prednisone, and thalidomide (1.7% and 3.7%). MI (1.7%) and stroke (2.3%) increased in MM patients exposed to lenalidomide and dexamethasone combination therapy compared to patients treated with placebo and dexamethasone (0.6% and 0.9%, respectively).

Second Primary Malignancies

A risk of new malignancies such as acute myelogenous leukemia (AML) and MDS was reported in MM patients who received lenalidomide. The increase was seen mainly in newly diagnosed MM patients treated with lenalidomide and oral melphalan (5.3%) and in patients given high doses of intravenous mel-

Table 2 Lenalidomide Dose Adjustments for Hematological Toxicities in Multiple Myeloma[10]

Thrombocytopenia	
When platelet counts ...	***The recommended course is ...***
Fall to < 30,000/mcL	Interrupt lenalidomide treatment; follow CBC weekly.
Return to ≥ 30,000/mcL	Resume lenalidomide at next lower dose. Do not dose below 2.5 mg daily.
For each subsequent drop < 30,000/mcL	Interrupt lenalidomide treatment.
Return to ≥ 30,000/mcL	Resume lenalidomide at next lower dose. Do not dose below 2.5 mg daily.
Neutropenia	
When absolute neutrophil counts ...	***The recommended course is ...***
Fall to < 1,000/mcL	Interrupt lenalidomide treatment; follow CBC weekly.
Return to ≥ 1,000/mcL and neutropenia is the only toxicity	Resume lenalidomide at 25 mg daily or initial starting dose.
Return to ≥ 1,000/mcL and another toxicity exists	Resume lenalidomide at next lower dose. Do not dose below 2.5 mg daily.
For each subsequent drop < 1,000/mcL	Interrupt lenalidomide treatment.
Return to ≥ 1,000/mcL	Resume lenalidomide at next lower dose. Do not dose below 2.5 mg daily.

CBC = complete blood count.

phalan and autologous stem cell transplantation (ASCT) (frequency of up to 5.2%). Lenalidomide and dexamethasone treatment groups also reported AML and MDS (about 0.4%) during clinical trials.

Hepatotoxicity

Lenalidomide should be discontinued upon liver-enzyme elevation based on reported life-threatening hepatic failure in patients who received the lenalidomide and dexamethasone combination in studies. Other reported cases during lenalidomide studies in MM patients included angioedema, SJS, TEN, TLS, TFR, and impaired stem cell mobilization, such as a decrease in CD34+ cell count.

Use in Specific Populations[10]

Pregnancy and Lactation

Based on animal studies of embryocidal effects, lenalidomide is FDA pregnancy category X and contraindicated during pregnancy. No data from controlled studies in human pregnancy are available, but the structural similarity of lenalidomide to thalidomide suggests a potential risk to the developing fetus. Thalidomide can cause severe, life-threatening birth defects, including the absence of limbs, short limbs, hypoplasticity or absence of bone, external ear and eye abnormalities, facial palsy, congenital heart disease, and genitourinary tract malformations that cause mortality in approximately 40% of infants during or shortly after birth. If pregnancy occurs during treatment, immediately discontinue the drug and refer the patient to an obstetrician/gynecologist experienced in reproductive toxicity for evaluation and counseling. Any suspected fetal exposure to Revlimid must be reported to the FDA MedWatch program at 1-800-FDA-1088 and to Celgene Corporation at 1-888-423-5436.

Lenalidomide has not been studied for excretion in human milk. Celgene recommends weighing the risks versus the benefits prior to initiation of therapy.

Geriatric and Pediatric Use

Renal function should be monitored closely in the geriatric population due to potential decreased renal function. The safety and efficacy of lenalidomide in patients younger than the age of 18 years have not been evaluated.

Renal and Hepatic Impairment

The starting dose of lenalidomide should be adjusted in patients with renal impairment and in patients requiring dialysis treatments because lenalidomide primarily undergoes renal excretion. The recommended doses in MM patients with moderate (CrCl of 30–50 mL/min) and severe (CrCl below 30 mL/min not requiring dialysis) renal impairment are 10 mg orally every 24 hours and 15 mg orally every 48 hours, respectively. The recommended dose in patients on dialysis is 5 mg orally every 24 hours and should be taken after treatment on dialysis days. For patients with moderate renal impairment who tolerate once-daily 10-mg lenalidomide after two cycles, the dose can be increased to 15 mg once daily. Subsequent dose adjustments should be based on individual treatment response and tolerability.

Lenalidomide has not been evaluated in patients with hepatic impairment.

Drug–Drug Interactions[10]

In vitro studies indicate that lenalidomide is not metabolized via cytochrome P450 pathways. However, digoxin serum levels should be monitored in patients receiving lenalidomide because studies showed that digoxin C_{max} and $AUC_{0-\infty}$ were increased by 14% when administered with multiple doses of lenalidomide 10 mg per day. Use caution with concomitant treatment of lenalidomide and other drugs that potentially induce thrombosis, such as erythropoietic or estrogen-containing drugs. The manufacturer recommends strict monitoring of prothrombin time and international normalized ratio in patients receiving both warfarin and lenalidomide, although no effects were observed with coadministration of these drugs during pharmacokinetics studies.

DOSAGE AND ADMINISTRATION[10]

For adults with MM, the recommended dose of lenalidomide is 25 mg orally once daily at the same time each day, with or without food, on days 1–21 of repeated 28-day cycles in combination with oral dexamethasone (40 mg once daily on days 1, 8, 15, and 22 of each 28-day cycle). The starting dose of dexamethasone may be decreased (20 mg orally once daily on days 1, 8, 15, and 22) in patients older than 75 years of age. Continue lenalidomide and dexamethasone combination therapy until disease progression or the occurrence of unacceptable or toxic adverse effects in patients who are not eligible

for ASCT. Among patients who are eligible for ASCT, hematopoietic stem cell mobilization occurs within four cycles of therapy. Lenalidomide dosage adjustments during MM treatments are recommended in patients who develop grade 3 or 4 neutropenia or thrombocytopenia as well as grade 3 or 4 lenalidomide-related toxicities (Table 2). As noted earlier, the starting dose of lenalidomide should be adjusted in patients with renal impairment and in patients requiring dialysis and may require adjustment based on clinical or laboratory findings.

Lenalidomide capsules are swallowed whole with water and should not be opened, crushed, or chewed.

COST

The average wholesale price (AWP) of a Revlimid tablet of any strength is $644, making the cost of a 28-day cycle of treatment $13,529. Generic dexamethasone costs as little as $234 per cycle, AWP, bringing the total price to $13,763 for a 28-day cycle ($178,913 for a full year).[18]

P&T COMMITTEE CONSIDERATIONS

Lenalidomide has significantly improved the prognosis and survival of MM patients despite its toxicities.[8] The combination of lenalidomide and dexamethasone for the treatment of newly diagnosed MM is not new but has been used for many years. However, that combination has now secured FDA approval, joining the regimen's earlier indication for treatment of MM patients who have received at least one prior therapy (in addition to its approved indications for other diseases). Data showing that lenalidomide and dexamethasone should be continued until progression of the disease also help make lenalidomide worthy of formulary consideration.

The National Comprehensive Cancer Network (NCCN) lists lenalidomide plus dexamethasone among its category 1 preferred regimens as primary therapy for ASCT candidates and as therapy for previously treated MM. Lenalidomide is also a category 1 option for non-ASCT candidates when coupled with low-dose dexamethasone or with melphalan and prednisone. In addition, the NCCN lists lenalidomide as a category 1 preferred regimen for maintenance therapy.[19]

Prescribers, pharmacies, and patients must enroll in a REMS program to use lenalidomide due to its potential teratogenic adverse effects (one of its three boxed warnings, along with hematological toxicity and venous and arterial thromboembolism). The most frequently reported adverse events during the study that led to approval of lenalidomide and dexamethasone for newly diagnosed patients included diarrhea, anemia, neutropenia, fatigue, back pain, insomnia, asthenia, rash, decreased appetite, cough, pyrexia, muscle spasms, and abdominal pain.

CONCLUSION

The safety and efficacy of the thalidomide analogue lenalidomide, in combination with dexamethasone, for patients with newly diagnosed MM were demonstrated in a randomized, open-label, three-arm trial with the primary endpoint of progression-free survival. The combination of lenalidomide and dexamethasone showed longer PFS (25.5 months) than the combination of melphalan, prednisone, and thalidomide (21.2 months; HR, 0.72; $P = 0.0001$). Patients who received lenalidomide and dexamethasone had a 25% reduction in the risk of death compared with patients who received melphalan, prednisone, and thalidomide. While the FDA has approved a new indication for use of the combination in treatment-naïve patients, additional studies, including those of longer duration, are needed to enhance lenalidomide's safety and efficacy profile.

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