FEATURE ARTICLE

Lenalidomide: A New Agent for Patients With Relapsed or Refractory Multiple Myeloma

Joseph D. Tariman, RN, MN, APRN-BC, OCN®

Lenalidomide is a potent, novel thalidomide analog that has demonstrated promising clinical activity in patients with relapsed or refractory multiple myeloma (MM). It is a lead immunomodulatory drug currently approved by the U.S. Food and Drug Administration. Neutropenia, thrombocytopenia, and thromboembolic events are common adverse effects associated with lenalidomide therapy in patients with MM. Careful monitoring of those known serious adverse effects is essential to prevent life-threatening complications. This article discusses lenalidomide's mechanisms of action, clinical trial results, and the management of common adverse effects in patients with MM.

Multiple myeloma (MM) is a B-cell malignancy characterized by proliferation of monotypic plasma cells (PCs). It is the second most common hematologic malignancy and accounts for 1.16% of all cases of cancer. Approximately 19,900 cases of MM will be diagnosed in 2007, and approximately 10,790 deaths are expected (Jemal et al., 2007).

A hallmark of MM is the production of a homogeneous immunoglobulin fraction, detectable in the serum and/or urine, called myeloma protein (also known as paraprotein, M protein, or M spike) by malignant PCs (Lokhorst, 2002). Pathologic bone damage is the most characteristic feature of MM and is caused by the production of osteoclastic factors by malignant PCs. Bone pain is the predominant presenting symptom, but other symptoms such as anemia, hypercalcemia, renal insufficiency, neuropathy, and spinal cord compression may be present at the time of diagnosis. The classic triad of symptoms is plasmacytosis (> 30% PCs in the bone marrow), monoclonal protein either in the urine or blood, and lytic bone lesions (Lokhorst; Tariman & Estrella, 2005).

Immunomodulatory Drugs and Multiple Myeloma

In the late 1990s, thalidomide (Thalomid®, Celgene Corporation) was used empirically to treat MM based on its antiangiogenic activity and showed clinical activity in refractory or relapsed myeloma (Singhal et al., 1999). However, thalidomide has significant and dose-limiting side effects, including somnolence, constipation, and neuropathy (Tariman, 2003a). The dose-limiting toxicities of thalidomide prompted the search for more potent but less toxic thalidomide derivatives (Richardson et al., 2002).

At a Glance

- Lenalidomide, a lead immunomodulatory drug, is effective in relapsed or refractory multiple myeloma (MM) and positively affects multiple pathways of MM cell survival, leading to apoptosis.
- Neutropenia, thrombocytopenia, and thromboembolic events are common adverse effects associated with lenalidomide therapy.
- A drug-distribution program must be followed strictly to prevent the potential teratogenic effects of lenalidomide.

Thalidomide initially was approved by the U.S. Food and Drug Administration (FDA) for the treatment of erythema nodosum leprosum in 1997 (Celgene Corporation, 2006d). The Oncology Drug Products division of the FDA accepted the supplemental

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new drug application (sNDA) to market thalidomide for the treatment of MM in February 2004 (Celgene Corporation, 2006c) The FDA granted sNDA approval of thalidomide in combination with dexamethasone for the treatment of newly diagnosed MM in May 2006 (Celgene Corporation, 2006c).

Lenalidomide, formerly known as CC-5013 (Revlimid®, Celgene Corporation), is an immunomodulatory drug (IMiD) that is a potent thalidomide-derived immunomodulatory analog. It markedly stimulates T-cell proliferation, as well as interleukin-2 (IL-2) and interferon-γ (IFN-γ) production, but does not inhibit phosphodiesterase-4 (PDE4) (inhibition of PDE4 leads to immunosuppression), leading to induced host anti-MM immune response (Corral et al., 1999). Lenalidomide is 50–2,000 times more potent than thalidomide in stimulating T-cell proliferation triggered via the T-cell receptor and 50–100 times more potent than thalidomide in augmenting IL-2 and IFN-γ (Richardson et al., 2002). Additionally, lenalidomide, like thalidomide, activates apoptotic pathways through caspase-8–mediated cell death (Anderson, 2005).

Several other mechanisms of action of lenalidomide that are similar to thalidomide have been reported (Richardson & Anderson, 2004). They include triggering of dose-dependent decreased secretion of tumor necrosis factor alpha, IL-1 beta (a cytokine with a broad range of activities, including stimulation of thymocyte proliferation by inducing IL-2 release, B-cell maturation and proliferation, and the ability to stimulate the release of prostaglandin and collagenase from synovial cells), and IL-6 (a growth factor for the proliferation of myeloma cells). All of the mechanisms could lead to MM cell growth arrest and apoptosis. Lenalidomide stimulates increased secretion of IL-10 (a cytokine with two major activities: inhibition of cytokine production by macrophages and inhibition of the accessory functions of macrophages during T-cell activation) (Richardson & Anderson). Moreover, lenalidomide inhibits MM cell proliferation by decreasing the binding of MM cells to bone marrow stromal cells through the blockage of intracellular adhesion molecule production by the myeloma cells. Lenalidomide also inhibits production in the bone marrow milieu of cytokines such as vascular endothelial growth factor and basic fibroblast growth factor, thus blocking angiogenesis (Davies et al., 2001; Gupta et al., 2001; Hideshima et al., 2000, 2001; Tariman, 2003b) (see Figure 1). Because lenalidomide is more potent than thalidomide, it has been shown to achieve clinical responses at lower doses (Anderson, 2005).

Lenalidomide was approved by the FDA in December 2005 for the treatment of patients with transfusion-dependent anemia caused by low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. On June 29, 2006, the FDA approved an sNDA of lenalidomide for the treatment of relapsed or refractory MM in combination with dexamethasone (Celgene Corporation, 2006a).

IMiDs are proprietary, innovative, small-molecule, orally available compounds. Another thalidomide analog, CC-4047 (Actimid™, Celgene Corporation), is the second IMiD to enter clinical trial. In in vitro models, it demonstrated approximately 15,000-fold greater inhibition of tumor necrosis factor alpha activity than thalidomide. It also inhibits IL-1 levels (a proinflammatory cytokine, IL-1 has a role in immune, degradative, and growth-promoting processes) and MM cell proliferation (Dredge et al., 2002). CC-4047 also has been shown to block osteoclast differentiation and may have promising clinical applications in tumors' osteoclastic activity (leading to osteolytic lesions) in patients with MM (Lentzsch et al., 2005). CC-4047 and lenalidomide have different activity profiles, and they currently are being tested in different malignancies. The two novel thalidomide analogs display antiangiogenic activity independent of their immunomodulatory effects (Dredge et al.). Phase I and II studies have been started in the United States and United Kingdom (Celgene Corporation, 2007; Streetly, Gyertson, Kazmi, Zeldis, & Schey, 2007).

- Decreases multiple myeloma cell binding to bone marrow stromal cells through inhibition of intracellular adhesion molecules
- Inhibits angiogenesis through vascular endothelial and basic fibroblast growth factor inhibition
- Blocks interleukin-6, interleukin-1 beta, and tumor necrosis factor alpha, which are myeloma cell growth factors
- Stimulates natural killer cell immunity through an increase of interleukin-2 and interferon gamma production
- Induces apoptosis

Figure 1. Lenalidomide's Mechanisms of Action

Note. Based on information from Davies et al., 2001; Gupta et al., 2001; Hideshima et al., 2000, 2001; Tariman, 2003b.

Lenalidomide in Clinical Studies

A phase I study of lenalidomide (protocol #CC5013-MM-001) has shown that it overcomes drug resistance to conventional chemotherapy and is well tolerated in patients with relapsed MM (Richardson et al., 2002). More importantly, the study reported no significant somnolence, constipation, or neuropathy among four cohorts of patients who received doses of 5, 10, 25, or 50 mg per day. In 24 evaluable patients, no dose-limiting toxicities were observed at any dose level within the first 28 days; however, grade 3 myelosuppression developed after day 28 in all 13 patients treated with 50 mg per day. Twelve patients had a dose reduction to 25 mg, which was well tolerated and therefore considered the maximum tolerated dose. Best responses of at least 25% reduction in M protein occurred in 17 (71%) of 24 patients, including 11 (46%) who had received prior thalidomide. Stable disease (less than 25% reduction in M protein) was observed in an additional 2 patients (8%). Overall, 17 (71%) of 24 patients demonstrated benefit from lenalidomide treatment. The study provided the basis of further evaluation of lenalidomide, either alone or in combination with other anti-MM cell agents (Richardson et al., 2002).

A similar phase I study of 15 patients (all with chemorefractory disease that relapsed after at least one high-dose chemotherapy regimen with a median of 10 prior cycles of chemotherapy) reported that 3 patients (20%) showed a > 50% M protein reduction with a concomitant marrow response (Zangari et al., 2001). However, responses were observed only at the 25 and 50 mg doses. The study also reported the same significant myelosuppression found by Richardson et al. (2002), even in patients with adequate platelet counts and marrow cellularity. Furthermore, the study suggested that lenalidomide has the

potential to cause cardiovascular problems; two patients had thromboembolism, and one experienced syncope (Tariman, 2003b; Zangari et al.).

The phase II study of lenalidomide enrolled 101 patients. Results showed that lenalidomide had clinical activity in 83 patients evaluable for response. Patients were randomized to either 15 mg per day or 30 mg per day by mouth for three weeks with a one-week break (28-day cycle). Dexamethasone was added at a dose of 40 mg per day by mouth on days 1–4 every two weeks in patients with progressive disease at four weeks, at eight weeks in patients with stable disease. Preliminary results have shown the following response rates to lenalidomide alone.

- 6% complete response (100% reduction of M protein)
- 18% partial response (50%–99% reduction of M protein)
- 14% minimal response (25%–49% reduction of M protein)

The overall response rate to lenalidomide alone was 38%. Stable disease (< 25% reduction) was seen in 47%, and only 14% of the patients showed disease progression. Dexamethasone was added for 30 of 83 patients; 10 patients (33%) achieved at least partial response with the combination of lenalidomide and dexamethasone (Richardson et al., 2003). Significant neutropenia in 26 patients (28%) and thrombocytopenia in 17 patients (18%) were the common adverse events requiring dose reduction and cytokine support. No significant somnolence, constipation, or neuropathy was reported (Richardson et al., 2003).

Another phase II study enrolled 222 patients (protocol #CC-5013-MM-014) receiving lenalidomide 30 mg per day on days 1–21 with a one-week break (an increased incidence of cytopenia with an unknown explanation was noted in a previous phase 2 study in the 15 mg twice a day group, prompting investigators to use daily dosing of 30 mg) (Richardson et al., 2003). Partial response (50% reduction of M protein) or better was observed in 25% (53) of the patients enrolled (excluding 10 patients who were not evaluable). The researchers found that 71% (152) of the patients had stable disease or better. Median time to progression was 22.4 weeks (six months). Median survival had not been reached by the time a follow-up was published (Richardson et al., 2005).

The most common treatment-related adverse events were upper respiratory tract infection, neutropenia, and thrombocytopenia (all reported in > 10% of patients overall). Adverse events that most frequently led to dose reduction or interruption by percentage of cases were neutropenia (40%), thrombocytopenia (23%), fatigue (5%), and anemia (5%) (Richardson et al., 2005).

A phase III, multicenter, randomized, double-blind trial enrolled 351 patients with relapsed or refractory MM in Europe, Israel, and Australia (protocol #CC-MM-5013-010). All patients received dexamethasone 40 mg daily by mouth on days 1–4, 9–12, and 17–20 every 28 days and were randomized to receive either lenalidomide 25 mg daily by mouth on days 1–21 with a one-week break (28-day cycle) or placebo. At the beginning of cycle 5, the dexamethasone dose was reduced to 40 mg daily by mouth on days 1–4 only every 28 days. The median TTP at 18 months for patients treated with the combination of dexamethasone and lenalidomide was 13.3 months compared to 5.1 months for patients who were randomized to the placebo arm ($p < 0.000001$). The partial response rate (reduction of M protein greater than 50%) also was greater in the nonplacebo arm at 58% versus 22% ($p < 0.001$). The difference in TTP between the two arms surpassed the prespecified O'Brien-Fleming boundary for superior efficacy ($p < 0.0015$), and the monitoring committee recommended that the data be released to all study participants (Dimopoulos et al., 2005).

Grade 3 or 4 neutropenia was reported more frequently in patients who received the combination therapy of dexamethasone and lenalidomide (16.5% versus 1.2%). However, grade 3 and 4 infections were similar between the treatment groups. Thromboembolic events occurred in 8.5% of patients in the nonplacebo arm and in 4.5% of patients in the placebo arm. The study investigators recommended the use of prophylactic antithrombotic therapy for patients undergoing therapy with dexamethasone and lenalidomide (Dimopoulos et al., 2005).

A similar phase III, multicenter, randomized, double-blind trial has been completed in the United States (protocol #CC-5013-MM-009). The overall response rate was greater with lenalidomide and dexamethasone than with dexamethasone and placebo. The median TTP for patients treated with lenalidomide and dexamethasone was 11.1 months compared with 4.7 months for patients treated with dexamethasone and placebo ($p < 0.000001$). The median overall survival also was higher with lenalidomide and dexamethasone, which was not reached at the time of analysis, compared to dexamethasone and placebo (24 months) (Weber et al., 2006). Grade 3 and 4 neutropenia was more frequent with lenalidomide and dexamethasone than with dexamethasone and placebo (24% versus 3.5%), and thromboembolic events occurred in 15% of patients treated with lenalidomide and dexamethasone compared with 3.5% of patients treated with dexamethasone and placebo. The use of prophylactic antithrombotic therapy should be considered for patients treated with combination lenalidomide and dexamethasone (Weber et al.).

Most recently, lenalidomide and dexamethasone were studied as initial therapy for MM. Lenalidomide was given orally 25 mg daily on days 1–21 of a 28-day cycle with dexamethasone 40 mg orally on days 1–4, 9–12, and 17–20 of the same 28-day cycle. Thirty-one of 34 patients with an overall response rate of 91% achieved an objective response, including a 6% rate of complete response and a 32% rate of very good partial response. The most common adverse events reported by patients were fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (6%), and rash (6%). The study revealed that lenalidomide with dexamethasone is a highly active regimen with manageable side effects in the treatment of patients with newly diagnosed MM (Rajkumar et al., 2005).

Nursing Management

Table 1 outlines common adverse events associated with lenalidomide. Myelosuppression, particularly neutropenia and thrombocytopenia, are the most predominant toxicities associated with lenalidomide. They are dose dependent; therefore, withholding lenalidomide and reducing doses in a timely manner are important considerations. Monitoring blood counts biweekly during the first three cycles of therapy and then monthly thereafter is essential to prevent fatal complications such as neutropenic fever and sepsis (Celgene Corporation, 2006b). Blood-product transfusions (red blood cells or platelets) and

Table 1. Lenalidomide's Profile of Adverse Events Grade 1–4

MOST COMMON ADVERSE EVENTS	LENALIDOMIDE/ DEXAMETHASONE (N = 346)		PLACEBO/ DEXAMETHASONE (N = 345)	
	n	%	n	%
Hematologic				
Neutropenia	96	27.7	16	4.6
Anemia (non–organ specific)	84	24.3	60	17.4
Thrombocytopenia	59	17.1	34	9.9
Nonhematologic				
Constipation	134	38.7	64	18.6
Diarrhea	101	29.2	85	24.6
Muscle cramps	104	30.1	71	20.6
Rash	55	15.9	28	8.1
Anorexia	47	13.6	30	8.7
Dyspnea (non–organ specific)	70	20.2	53	15.4
Deep vein thrombosis	27	7.8	11	3.2
Pulmonary embolism	11	3.2	3	0.9

Note. The severity of adverse events was assessed using the National Cancer Institute Common Toxicity Criteria Version 3 for the entire duration of therapy.

Note. Based on information from Celgene Corporation, 2006a.

growth-factor support are key approaches to maintain effective therapy. Dose interruptions and reductions are two essential approaches in the management of hematologic toxicities associated with lenalidomide and dexamethasone (Celgene Corporation, 2006b). Use of growth factors and blood products should be considered when clinically necessary.

Thromboembolic events such as deep vein thrombosis (DVT) and pulmonary embolism (PE) can be fatal; careful assessment during clinic visits is vital (Dimopoulos et al., 2005). Initiation of therapeutic anticoagulation therapy immediately after a thromboembolic event is critical. Confirmation by Doppler ultrasound (for suspected DVT) or ventilation/perfusion scan (for suspected PE) is very important. Starting thromboembolic prophylaxis using aspirin 81 mg daily, lower doses (1–5 mg daily) of warfarin (international normalized ratio of 2 or 3), or low-molecular-weight heparin (LMWH) immediately upon administration of lenalidomide (with or without dexamethasone) may prevent DVT and PE (Bennett et al., 2006).

Rash, a less serious adverse event, is manageable using antihistamine drugs. Gastrointestinal side effects such as mild cramping, diarrhea or constipation, and anorexia can be alleviated through diet modification (Celgene Corporation, 2006b). Constipation is highly manageable with a high-fiber diet, adequate fluid intake, stool softeners, and a judicious use of laxatives.

Although lenalidomide was found to be nonteratogenic in animal models, the FDA mandated a restricted drug-distribution program similar to the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) program (Zeldis, Williams, Thomas, & Elsayed, 1999). Patients, prescribers, and pharmacists must register through the RevAssist® Program. Similar to the S.T.E.P.S. program, the RevAssist program requires a complete patient-physician agreement form to be signed and faxed to Celgene Corporation. Once registration is complete, a prescriber must obtain an authorization number that must be written at the bottom of the prescription prior to dispensing of the drug. Women with childbearing potential must have a negative pregnancy test 14 days before and one day before the start of lenalidomide therapy. Men are required to use condoms when engaging in sexual activity with women who could be pregnant. All patients who are candidates for lenalidomide therapy must receive educational materials that explain the risks, pregnancy-prevention methods, and expected adverse events of the therapy (Celgene Corporation, 2006b).

Nurses have an important role in the management of patients with MM, including identifying patients who are candidates for oral therapy, educating patients, monitoring patient compliance with medication schedules, recognizing adverse events, and managing treatment-related side effects when they appear (Doss, 2006).

Conclusion

Lenalidomide is relatively well-tolerated and an active oral regimen alone or in combination with dexamethasone in patients with relapsed or refractory MM. It has convenient daily oral dosing, and no significant neuropathy or somnolence was found in clinical studies. The most commonly reported hematologic adverse events were neutropenia, anemia, and thrombocytopenia. The most common nonhematologic adverse events were constipation, diarrhea, anorexia, rash, dyspnea, DVT and PE. Monitoring complete blood counts at least every two weeks is necessary during the early phase of treatment (first three cycles) and less frequently (every month) later in the treatment phase (fourth cycle onwards). Frequent, weekly monitoring may be warranted based on a patient's clinical condition, such as previous grade 3 or 4 neutropenia while on lenalidomide therapy. Physicians, advanced practice nurses, oncology nurses, and all other healthcare providers should be cognizant of the signs and symptoms of myelosuppression. Initiation of growth-factor therapy as clinically indicated is pivotal to prevent fatal infection. Blood and blood-product transfusions also should be considered when clinically necessary. Prophylactic antithrombotic therapy such as daily aspirin 81 mg, low-dose warfarin, or LMWH should be considered during lenalidomide therapy, especially in combination with dexamethasone, to prevent DVT and PE (Bennett et al., 2006; Niesvizky et al., 2005; Zonder et al., 2005). Oncology nurses play a significant role in the management of patients receiving lenalidomide.

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References

Anderson, K.C. (2005). Lenalidomide and thalidomide: Mechanisms of action—Similarities and differences. *Seminars in Hematology, 42*(4, Suppl. 4), S3–S8.

Bennett, C.L., Hussain, Z., Courtney, M., Yarnold, P., Raisch, D., & McKoy, J.M. (2006). RADAR update on thalidomide (Thal)- and lenalidomide (Len)-associated venous thromboembolism (VTE): Safety concerns persist for multiple myeloma (MM)

despite FDA approvals in this setting [Abstract # 3310]. Retrieved February 3, 2007, from http://meeting.bloodjournal.org/cgi/content/abstract/108/11/3310?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=1&title=lenalidomide&andorexacttitle=and&andorexacttitleabs=and&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT

Celgene Corporation. (2006a). Revlimid® in combination with dexamethasone sNDA granted approval by FDA for treatment of multiple myeloma. Retrieved January 30, 2007, from http://ir.celgene.com/phoenix.zhtml?c=111960&p=irol-newsArticle&ID=877894&highlight=

Celgene Corporation. (2006b). Revlimid® (lenalidomide) [Package insert]. Summit, NJ: Author.

Celgene Corporation. (2006c). Thalomid® sNDA granted FDA approval for treatment of newly diagnosed multiple myeloma. Retrieved January 30, 2007, from http://ir.celgene.com/phoenix.zhtml?c=111960&p=irol-newsArticle&ID=861181&highlight=

Celgene Corporation. (2006d). Thalomid® (thalidomide) [package insert]. Summit, NJ: Author.

Celgene Corporation. (2007). Product pipeline. Retrieved July 9, 2007, from http://media.corporate-ir.net/media_files/irol/11/111960/REVISED_20070209Rev_PIPELINE.pdf

Corral, L.G., Haslett, P.A., Muller, G.W., Chen, R., Wong, L.M., Ocampo, C.J., et al. (1999). Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. *Journal of Immunology, 163,* 380–386.

Davies, F.E., Raje, N., Hideshima, T., Lentzsch, S., Young, G., Tai, Y.T., et al. (2001). Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. *Blood, 98,* 210–216.

Dimopoulos, M.A., Spencer, A., Attal, M., Prince, M., Harousseau, J., Dmoszynska, A., et al. (2005). Study of lenalidomide plus dexamethasone versus dexamethasone alone in relapsed or refractory multiple myeloma (MM): Results of a phase 3 study (MM-010) [Abstract #6]. *Blood, 106,* 6a.

Doss, D.S. (2006). Advances in oral therapy in the treatment of multiple myeloma. *Clinical Journal of Oncology Nursing, 10,* 514–520.

Dredge, K., Marriott, J.B., Macdonald, C.D., Man, H.W., Chen, R., Muller, G.W., et al. (2002). Novel thalidomide analogues display anti-angiogenic activity independently of immunomodulatory effects. *British Journal of Cancer, 87,* 1166–1172.

Gupta, D., Treon, S.P., Shima, Y., Hideshima, T., Podar, K., Tai, Y.T., et al. (2001). Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: Therapeutic applications. *Leukemia, 15,* 1950–1961.

Hideshima, T., Chauhan, D., Podar, K., Schlossman, R.L., Richardson, P., & Anderson, K.C. (2001). Novel therapies targeting the myeloma cell and its bone marrow microenvironment. *Seminars in Oncology, 28,* 607–612.

Hideshima, T., Chauhan, D., Shima, Y., Raje, N., Davies, F.E., Tai, Y.T., et al. (2000). Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. *Blood, 96,* 2943–2950.

Jemal, A., Siegel, R., Ward, E., Murray, T., Xu, J., & Thun, M.J. (2007). Cancer statistics, 2007. *CA: A Cancer Journal for Clinicians, 57*(1), 43–66.

Lentzsch, S., Anderson, G., Kurihara, N., Honjo, T., Anderson, J., Mapara, M.Y., et al. (2005). Thalidomide derivative CC-4047 inhibits osteoclast formation by down regulation of PU.1 [Abstract #629]. *Blood, 106,* 187a.

Lokhorst, H. (2002). Clinical features and diagnostic criteria. In S. Singhal & J. Mehta (Eds.), *Myeloma* (pp. 151–168). London: Martin Dunitz Ltd.

Niesvizky, R., Martinez-Banos, D.M., Gelbshtein, U.Y., Cho, H.J., Pearse, R.N., Zafar, F., et al. (2005). Prophylactic low-dose aspirin is effective as antithrombotic therapy in patients receiving combination thalidomide or lenalidomide [Abstract #3454]. *Blood, 106,* 964a.

Rajkumar, S.V., Hayman, S.R., Lacy, M.Q., Dispenzieri, A., Geyer, S.M., Kabat, B., et al. (2005). Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. *Blood, 106,* 4050–4053.

Richardson, P., & Anderson, K. (2004). Immunomodulatory analogs of thalidomide: An emerging new therapy in myeloma. *Journal of Clinical Oncology, 22,* 3212–3214.

Richardson, P., Jagannath, S., Hussein, M., Berenson, J., Singhal, S., Irwin, D., et al. (2005). A multicenter, single-arm, open-label study to evaluate the efficacy and safety of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma: Preliminary results [Abstract #1565]. *Blood, 106,* 449a.

Richardson, P.G., Jagannath, S., Schlossman, R., Zeldenrust, S., Rajkumar, S.V., Alsina, M., et al. (2003). A multi-center, randomized, phase II study to evaluate the efficacy and safety of two CDC-5013 dose regimens when used alone or in combination with dexamethasone (dex) for the treatment of relapsed or refractory multiple myeloma (MM) [Abstract #825]. *Blood, 100,* 235a.

Richardson, P.G., Schlossman, R.L., Weller, E., Hideshima, T., Mitsiades, C., Davies, F., et al. (2002). Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. *Blood, 100,* 3063–3067.

Singhal, S., Mehta, J., Desikan, R., Ayers, D., Roberson, P., Eddlemon, P., et al. (1999). Antitumor activity of thalidomide in refractory multiple myeloma. *New England Journal of Medicine, 341,* 1565–1571.

Streetly, M.J., Gyertson, K., Kazmi, M., Zeldis, J., & Schey, S.A. (2007). Prolonged survival with actimid (CC-4047) [Abstract PO-643]. *Haematologica, 92*(Suppl. 2), 166.

Tariman, J.D. (2003a). Thalidomide: Current therapeutic uses and management of its toxicities. *Clinical Journal of Oncology Nursing, 7,* 143–147.

Tariman, J.D. (2003b). Understanding novel therapeutic agents for multiple myeloma. *Clinical Journal of Oncology Nursing, 7,* 521–528.

Tariman, J.D., & Estrella, S.M. (2005). The changing treatment paradigm in patients with newly diagnosed multiple myeloma: Implications for nursing [Online exclusive]. *Oncology Nursing Forum, 32,* E127–E138. Retrieved July 3, 2007, from http://www.ons.org/publications/journals/ONF/volume32/issue6/32061098.asp

Weber, D.M., Chen, C., Niesvizky, R., Wang, M., Belch, A., Stadtmauer, E., et al. (2006). 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 # 7521]. *Journal of Clinical Oncology, 24*(18s). Retrieved February 2, 2007, from http://www.asco.org/portal/site/ASCO/menuitem.34d60f5624ba07fd506fe310ee37a01d/?vgnextoid=76f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=abst_detail_view&confID=40&index=y&abstractID=34363

Zangari, M., Tricot, G., Zeldis, J., Eddlemon, P., Saghafifar, F., & Barlogie, B. (2001). Results of phase 1 study of CC-5013 for the treatment of multiple myeloma (MM) patients who relapse after high dose chemotherapy (HDCT) [Abstract # 3226]. *Blood, 98,* 775a.

Zeldis, J.B., Williams, B.A., Thomas, S.D., & Elsayed, M.E. (1999). S.T.E.P.S.: A comprehensive program for controlling and monitoring access to thalidomide. *Clinical Therapeutics, 21,* 319–330.

Zonder, J.A., Durie, B.G.M., McCoy, J., Crowley, J., Zeldis, J.B., Ghannam, L., et al. (2005). High incidence of thrombotic events observed in patients receiving lenalidomide (L) + dexamethasone (D) (LD) as first-line therapy for multiple myeloma (MM) without aspirin (ASA) prophylaxis [Abstract #3455]. *Blood, 106,* 964a.

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