Multiple Myeloma and Treatment-Related Thromboembolism: Oncology Nurses’ Role in Prevention, Assessment, and Diagnosis

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Immunomodulating agents such as thalidomide and its newly emerged derivative, lenalidomide, are becoming increasingly popular in the treatment of multiple myeloma because of their ability to combat drug resistance. Clinical trials suggest that thalidomide and lenalidomide are effective in all stages of multiple myeloma treatment—new diagnoses, stem cell transplantations, maintenance therapy, and relapsed or refractory disease. The drugs are most efficacious when combined with additional chemotherapeutic agents and/or corticosteroids. However, deep vein thrombosis and other thromboembolic events are associated with the treatment regimens. Oncology nurses must understand the pharmacologic properties of the drugs and the potentially life-threatening complications associated with them. To provide the highest standard of care, oncology nurses must play a vital role in the prevention, diagnosis, and management of thromboembolic events through awareness of the clinical problem, assessment tools, and thromboembolic prophylactic regimens.

At a Glance

- Thalidomide and lenalidomide are quickly becoming the most frequently used drugs for the treatment of multiple myeloma; however, regimens containing the agents carry a high risk of thromboembolic events, including deep vein thrombosis and pulmonary embolism.
- Oncology nurses play a vital role in preventing life-threatening complications of thalidomide and lenalidomide through vigilant assessment and patient education.
- Thorough assessments, early thrombosis diagnoses, and patient education about possible complications and thrombosis prophylaxis are important components of nursing care.

Multiple myeloma (MM) is a malignancy of plasma cells, whose primary purpose is to produce immunoglobulins required to mount an immune response. MM causes excess production of one specific immunoglobulin, commonly known as the monoclonal protein, and underproduction of other immunoglobulins. The disease frequently is associated with skeletal, hematologic, and renal involvement. In 2007, an estimated 19,900 new cases of MM will be diagnosed and 10,970 will die from the disease (American Cancer Society, 2007). MM accounts for about 14% of all newly diagnosed cases of hematologic malignancies (Devenney & Erikson, 2004). Depending on prognostic factors and the disease stage at diagnosis, survival estimates range from several months to five years; the current median survival is about 42 months (Barber, 2006; Devenney & Erikson). However, the use of novel agents, such as thalidomide (Thalomid®, Celgene Corporation) or lenalidomide (Revlimid®, Celgene Corporation), in combination with a standard MM treatment regimen is associated with greatly improved response rates (Cavo & Baccarani, 2006; Richardson et al., 2006). As a result, the use of thalidomide in combination with dexamethasone (thal/dex) has become one of the most frequently prescribed regimens in patients newly diagnosed with MM. The treatment supported the investigation of lenalidomide with dexamethasone (Rev/dex) in relapsed or refractory and new onset MM (Fonseca & Stewart, 2007; Rajkumar, 2005). Although data from clinical trials involving thalidomide or lenalidomide continue to indicate encouraging increased response and disease-free survival rates (Rajkumar, Blood, Vesole, Fonseca, & Greipp, 2006; Richardson et al.), the use of these drugs in combination with dexamethasone and/or chemotherapeutic agents appears to
be associated with an increased occurrence of thromboembolic events (Doss, 2006; Zangari et al., 2001).

This article serves three purposes. It provides detailed information about two novel agents, thalidomide and lenalidomide, used in patients with MM and the rationale behind their increasing utilization in MM treatment. In addition, novel agents’ association with thromboembolic events is discussed. Lastly, thromboembolism prophylaxis and implications for nursing practice are reviewed.

**Select Novel Agents**

MM cells sometimes are able to resist systemic chemotherapy because they can attach themselves to the surface of bone marrow cells. Two factors promote MM cell growth and create an opportunity for drug resistance: Cytokines are released by the bone marrow, attracting MM cells to the bone marrow surface, and blood vessels are formed in the marrow, providing nourishment for MM cells (Anderson, 2007). Laboratory studies suggest that antiangiogenic and immunomodulator agents, such as thalidomide and lenalidomide, produce better response rates because they are able to combat such drug resistance by attacking the surface of the bone marrow at the site of MM cell adhesion (Bruno et al., 2004; Hideshima, Chauhan, Richardson, & Anderson, 2005) and inhibiting angiogenesis (Anderson; Multiple Myeloma Research Foundation, 2006). Figure 1 displays the theorized mechanisms of action of thalidomide and lenalidomide.

**Thalidomide**

Results of research involving thalidomide are exciting not only in the laboratory but in the clinical setting as well. Subjects who received thal/dex for relapsed or refractory MM have experienced a 47%–60% reduction in serum monoclonal protein levels, whereas newly diagnosed subjects saw their levels decrease by 64%–72% (Doss, 2006). Clinical trials support the combination of thal/dex for the greatest degree of efficacy. In a trial comparing thalidomide alone versus thal/dex in treatment-naïve patients with MM, responses were achieved in 36% of subjects (n = 28) receiving thalidomide alone and in 72% of those (n = 40) also receiving dexamethasone. Furthermore, researchers determined the time to remission was faster in the cohort receiving thal/dex (0.7 months versus 4.2 months) (Weber, Rankin, Gavino, Delasalle, & Alexanian, 2003).

Despite its impressive efficacy, thalidomide has no shortage of side effects. Doses of thalidomide range from 50–400 mg daily. Doses in excess of 200 mg daily, although producing even more convincing response rates, are associated with a much higher toxicity profile (Devenney & Erikson, 2004; Doss, 2006). Well known for its teratogenic potential, thalidomide is associated with constipation, somnolence, dose-limiting peripheral neuropathy, rash, and cytopenias (Doss).

**Lenalidomide**

Because of the high toxicity profile of thalidomide, clinical researchers worked to develop a derivative that would produce similar response rates but be better tolerated by patients. As a result, in June 2006, lenalidomide was approved by the U.S. Food and Drug Administration for use in patients with MM. Lenalidomide appears to have greater antimyeloma potency and a lower side-effect profile than thalidomide (Rajkumar et al., 2006; Rajkumar et al., 2005). The most common side effects noted with lenalidomide, typically occurring at a dose of 25 mg daily, are neutropenia and thrombocytopenia. Patients often require a dose reduction because of severe cytopenias. Other side effects include diarrhea, constipation, nausea, rash, and fatigue (Celgene Corporation, 2006; Richardson et al., 2006). Rajkumar et al. (2005) reported that Rev/dex induced a partial response or better in 91% of subjects (n = 34) newly diagnosed with MM. The drug combination also shows promise in relapsed or refractory MM, with various early clinical trials indicating a partial response rate of 18%–44% and a complete response rate of 14%–27% (Doss, 2006).

Despite their side effects, thalidomide and lenalidomide undoubtedly will be used more frequently to improve the effectiveness of MM treatment. Consequently, oncology nurses must remain vigilant in assessing and managing the side effects of these agents that may cause dose-limiting toxicities or negatively impact patients’ quality of life.

**Risk of Thromboembolic Events**

As researchers evaluated the data from studies combining thalidomide or lenalidomide with standard MM chemotherapy,

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**Figure 1. Mechanisms of Action of Thalidomide and Lenalidomide**

*Note.* Based on information from Multiple Myeloma Research Foundation, 2006.
Therapeutic agents, a potentially life-threatening side effect emerged. Results suggested that combining thalidomide or lenalidomide with additional antmyeloma agents increased the risk of deep vein thrombosis (DVT) and other thromboembolic events (Baz et al., 2005; Fonseca & Stewart, 2007; Rajkumar, 2005; Zangari et al., 2004). The pathophysiology of the formation of DVT is not understood completely; however, researchers have hypothesized that the drugs create platelet hyperactivity, leading to a harmful interaction with the vascular endothelial lining (Baz et al.; Rajkumar). Although estimates of the incidence of thrombosis vary widely among published reports (Hirsch, 2007), identification of thrombosis as a threat to patients with MM is pervasive throughout the literature. Baz et al. noted that, when used to treat MM, dexamethasone alone is associated with a 3% incidence of a thromboembolic event, but thal/dex increases the incidence to 15%–26%. Furthermore, adding doxirubicin to the treatment regimen increased the likelihood of a thromboembolic event by another 12% (Zangari et al., 2002).

The Eastern Cooperative Oncology Group currently is conducting a clinical trial of dexamethasone alone versus Rev/dex in previously untreated MM. After enrolling 21 patients, the investigators noted an increase in the incidence of thromboembolic events in one of the arms and temporarily ceased enrollment. Nine of 12 subjects randomized to Rev/dex experienced a thromboembolic event, including one ischemic stroke. Enrollment resumed once the protocol was amended, mandating that all patients receive prophylaxis against clotting events. Although the trial continues to enroll, to date, fewer thromboembolic events have been reported since adding prophylaxis (Zonder et al., 2006).

Clinical research results provide oncology nurses with invaluable information to consider while educating patients about possible side effects of treatment and assessing them for complications of their regimens. Although DVT may develop at any time, it most often occurs within the first three months of treatment (Baz et al., 2005; Zangari et al., 2001). The lower extremities are the most frequent site of origination. About half of DVT cases progress to pulmonary embolism (Rajkumar, 2005). Oncology nurses caring for patients on thalidomide or lenalidomide in combination with other MM therapy must be aware of the potential for dangerous complications; they must conduct a thorough assessment for the development of DVT and pulmonary embolism and educate patients and families about the potential risks (see Table 1).

**Prophylactic Recommendations**

Thrombosis prophylaxis is recommended for any patient receiving thalidomide or lenalidomide in combination with other anti-MM agents (Hirsch, 2007; Rajkumar et al., 2005; Zangari et al., 2001; Zonder et al., 2006). Aspirin, low-molecular-weight heparin (LMWH), and full-dose warfarin (maintaining an international normalized ratio of 2.0–3.0) all show efficacy in reducing the incidence of thromboembolic events in patients receiving thalidomide or lenalidomide-based regimens (Rajkumar et al., 2005; Weber et al., 2003; Zangari et al., 2004). However, no prophylaxis regimen is accepted universally for patients with MM (Fonseca & Stewart, 2007; Hirsch). Clinical trials continue to compare aspirin and anticoagulants, such as LMWH and warfarin, with thalidomide and lenalidomide-based regimens, yet the efficacy of one method over another has not been determined. All of the agents are safe for patients with MM, even in the presence of thrombocytopenia, without increasing the risk of bleeding (Rajkumar, 2005).

Aspirin usually is associated with the prevention of arterial clotting events. However, the process by which venous thrombosis occurs in patients receiving thalidomide and lenalidomide as part of MM treatment suggests that aspirin also will be effective against venous thrombosis. Until randomized clinical trials demonstrate one method to be superior, oncologists should use their preferred prophylactic therapy. However, the occurrence of DVT does not mandate discontinuation of treatment. Patients who experienced thromboembolic events were able to resume therapy safely after receiving either heparin or therapeutic warfarin (Rajkumar, 2005; Zangari et al., 2004).

**Nursing Implications**

MM treatment has four stages: initial treatment, stem cell transplantation, maintenance therapy, and relapsed or refractory treatment. Thalidomide already is being used in patients at each stage of treatment. Because use of combination regimens with thalidomide or lenalidomide has increased in the treatment of MM, oncology nurses undoubtedly will care for patients receiving these agents. Nurses must be aware that potentially life-threatening complications, including DVT and pulmonary embolism, may occur. Nurses are vital to the assessment, diagnosis, and prevention of thromboembolism.

**Assessment**

A thorough baseline assessment should be performed prior to initiating a treatment regimen with lenalidomide or thalidomide. Consideration should be paid to inherent risk factors as well as concomitant medications that may increase a patient’s risk for thromboembolism (Morrison, 2006). Figure 2 details risk factors that increase the likelihood of thromboembolic

| Table 1. Signs and Symptoms of Thromboembolic Events and Associated Nursing Assessments |
|------------------------------------------|------------------------------------------|
| **SIGNALS AND SYMPTOMS**                | **NURSING ASSESSMENT**                   |
| Deep vein thrombosis                    | Assess the report of pain and the presence of a positive Homan’s sign (pain after dorsiflection of the ankle). |
| • Calf pain or tenderness               | Measure the calf circumference.          |
| • Unilateral edema (with or without pitting edema) | Assess visually. |
| • Erythema                               | Palpate and interview the patient.       |
| • Warmth                                 |                                        |
| Pulmonary embolism                      | Measure the respiratory rate and interview the patient. |
| • Tachypnea or dyspnea                  | Assess the patient’s report of pain.     |
| • Pleuritic pain                        | Visually assess the patient.             |
| • Cyanosis                               | Interview the patient.                   |
| • Cough                                  |                                         |
| • Hemoptysis                             | Interview the patient and obtain a sputum sample. |

Note. Based on information from Morrison, 2006.
events. Awareness of additional risk factors helps to determine the best prophylactic regimen for each patient (Blann & Lip, 2006; Morrison). For example, aspirin may suffice for a patient without additional risk factors of thromboembolism (Baz et al., 2005). However, LWMH or warfarin, although more costly and inconvenient for patients, provides stronger prophylaxis and may be warranted in the presence of other risk factors such as prior thromboembolic episodes, obesity, immobility, or presence of an indwelling central catheter (Hirsch, 2007).

A thorough patient assessment of signs and symptoms suggestive of thromboembolism is crucial during every appointment. Unilateral pain is considered a hallmark sign of DVT (Morrison, 2006). However, oncology nurses must consider that patients with MM, secondary to the disease process, often take pain medication that may dull their pain perception. As a result, a patient’s subjective report of pain should not be the key factor triggering the nurse to perform a more thorough assessment.

Diagnosis

Early detection is pivotal in preventing pulmonary embolism and other potentially fatal thromboembolic events likely to arise from DVT. Nurses’ assessments often trigger the need to obtain radiologic examinations to document the presence of DVT or pulmonary embolism (Morrison, 2006). Currently, vascular ultrasound and chest computed tomography are the most efficient and widely used methods to confirm DVT and pulmonary embolism, respectively (Zierler, 2004). Some practitioners use coagulation tests to assist in the diagnosis of DVT. Blood tests may reveal an elevated D-dimer (> 500 ng/ml) among those experiencing venous thromboembolism; however, that method should be used only in conjunction with radiologic examinations and never as the single diagnosis and therapeutic anticoagulation (Zangari et al., 2001).

Prevention

The role that nurses play in the prevention of thromboembolism and the management of existing thrombi cannot be underestimated. One of the many advantages of thalidomide and lenalidomide-based regimens is that therapy does not require hospitalization. Consequently, patients and their caregivers become their own first line of defense in ensuring thromboembolic events are detected early. Therefore, nurses’ primary responsibility is to educate patients and their caregivers about the risk of thromboembolic events and their signs, symptoms, and sequelae (Morrison, 2006). Classic signs and symptoms of DVT, to which patients must be alerted, are pain, swelling, erythema, and/or warmth of the affected extremity (Morrison). Nurses must encourage patients to routinely monitor for specific signs and symptoms and seek immediate medical attention should any appear. A venous clot that originates in the lungs or travels from an extremity into the lung results in a pulmonary embolism. Signs and symptoms of pulmonary embolism include tachypnea, difficulty breathing, cough, hemoptysis, pleuritic pain, and cyanosis. Because of the high morbidity and mortality rate of pulmonary embolism, patients exhibiting its signs and symptoms require immediate medical attention (Blann & Lip, 2006). Patients must be comfortable identifying the signs and symptoms of DVT as well as pulmonary embolism, know that the symptoms cannot be overlooked, and seek immediate attention from their healthcare practitioner should any symptoms appear.

Immobility is well documented as a contributing factor to the development of DVT (Blann & Lip, 2006; Morrison, 2006; Zangari et al., 2004). Nurses should encourage frequent mobilization among patients with MM, but it can present a challenge to those with advanced MM experiencing bone involvement or compression fractures. Therefore, patients’ performance status should be evaluated when considering prophylaxis regimens. Every effort should be made to minimize a patient’s risk of thromboembolism by encouraging any possible mobility and discussing other modifiable risk factors, including obesity and smoking (Morrison). Pain should be managed adequately to enhance mobility.

Nurses must ensure patients’ adherence with their prescribed prophylaxis regimen (Morrison, 2006) by reviewing current medications at every patient visit. Clinical trials indicate that patients who received thrombosis prophylaxis experienced fewer thromboembolic complications than those who did not (Baz et al., 2005; Zangari et al., 2004). However, should thromboembolism occur, treatment does not need to be discontinued. Patients may remain on thalidomide or lenalidomide so long as their blood counts tolerate the concurrent anticoagulation that will be necessary for the remainder of treatment. Patients need to understand that the benefits of prophylactic therapy far outweigh the risks and consequences associated with thromboembolism and MM treatment regimen discontinuation.

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**Inherent Risk Factors**

- Age > 40 years
- Obesity
- Smoking
- Personal or familial history of thromboembolic events
- Medical history (e.g., diabetes, cancer)

**Acquired Risk Factors**

- Concomitant medication or therapy (e.g., erythropoietin, hormonal therapy and radiotherapy, oral contraceptives)
- Immobility (Eastern Cooperative Oncology Group performance status more than 3, in which patients are immobile more than 50% of their waking hours)
- Surgery
- Trauma

**Multiple Myeloma–Related Risk Factors**

- High-dose dexamethasone (40 mg on days 1–4, 9–12, and 17–20 of each 28-day cycle)
- Presence of an indwelling central catheter (implantable venous access device, Hickman, peripherally inserted central catheter line, pheresis catheter for chemotherapy administration or stem cell collections)

**Figure 2. Risk Factors for Thromboembolism**

*Note. Based on information from Fonseca & Stewart, 2007; Morrison, 2006; Zangari et al., 2004.*
Summary

To provide the highest standard of care to patients with cancer, oncology nurses must be aware of the complications associated with treatment regimens. Thalidomide and lenalidomide are used frequently in treating patients with MM (Davies, 2006; Rajkumar, 2005). Patients receiving regimens including thalidomide or lenalidomide may be seen and treated in the outpatient area or hospitalized because of pain, neutropenic fever, infection, or other treatment-related complications. Oncology nurses in inpatient and outpatient settings must be aware of the high risk of thromboembolism associated with the regimens. Crucial components of patient care include patient education regarding possible complications, thrombosis prophylaxis, thorough assessments, and early thrombosis diagnoses. Investigators continue to recommend additional randomized clinical trials that further analyze the efficacy of novel agents as part of MM treatment (Rajkumar et al., 2005, 2006; Richardson et al., 2005) and seek to determine the most effective thrombosis prophylaxis regimen for care that includes these agents (Baz et al., 2005; Hirsch, 2007; Rajkumar, 2005).

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References


