Thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), are among the adverse events that can affect patients with multiple myeloma. Patients are at risk for the serious and potentially life-threatening events because of their disease, the presence of individual risk factors, and antimyeloma agents or other medications. Although use of the novel immunomodulatory drugs lenalidomide (Revlimid®, Celgene Corporation) and thalidomide (Thalomid®, Celgene Corporation) and the proteasome inhibitor bortezomib (Velcade®, Millennium Pharmaceuticals, Inc.) have increased response rates and survival times for patients with multiple myeloma in recent years (Ghobrial et al., 2007; Manochakian, Miller, & Chanhan-Khan, 2007; Rajkumar et al., 2005; Richardson & Anderson, 2006; Richardson, Hideshima, Mitsiades, & Anderson, 2007), their use has been associated with an increased risk of thromboembolic events. The increase is related, in part, to administration of concomitant medications, including dexamethasone (Bennett et al., 2006; Celgene Corporation, 2007a, 2007b; Durie et al., 2006; Palumbo et al., 2008; Rajkumar et al.; Rajkumar & Gertz, 2006; Zonder et al., 2006). Thromboembolic events have been reported in patients receiving single-agent bortezomib, but at a much lower rate than that observed in patients with multiple myeloma treated with other agents, including lenalidomide or thalidomide (Celgene Corporation, 2007a, 2007b; Harousseau et al., 2006; Lonial et al., 2007). However, patients receiving bortezomib may be at risk for DVT and PE as a result of other risk factors, including some concomitant therapies.

Patients with myeloma are at risk for serious and life-threatening thromboembolic events because of their disease, individual risk factors, and antimyeloma or other medications. The International Myeloma Foundation’s Nurse Leadership Board developed this consensus statement for assessment and prevention of thromboembolic events. Prophylactic measures are categorized as mechanical, regimen related, and antithrombotic drug, based on individual and myeloma-related risk factors. Aspirin is suggested for patients with no or one risk factor, low-molecular-weight heparin or full-dose warfarin for patients with two or more risk factors, and low-molecular-weight heparin or full-dose warfarin for all patients with therapy-related risks, including high-dose dexamethasone, doxorubicin, or multiagent chemotherapy.

At a Glance

- Patients with multiple myeloma are at risk for thromboembolic events (deep vein thrombosis and pulmonary embolism) because of the disease, individual risk factors, and treatment.
- Patients must be monitored and, if indicated, receive prophylaxis for thromboembolic events, which are serious and potentially life altering and life threatening.
- Measures to prevent thromboembolic events associated with novel therapies include mechanical, myeloma regimen related, and antithrombotic pharmaceutical and are based on individual patient-related and myeloma-related risk factors.
The International Myeloma Foundation’s Nurse Leadership Board, in recognition of the need for specific recommendations on managing key side effects of the novel antimyeloma agents, developed this consensus statement for the assessment and prevention of thromboembolic events, including DVT and PE, associated with novel therapies. The recommendations are designed to be used by healthcare providers in any type of medical institution (Bertolotti et al., 2007, 2008).

**Issue Statement**

Certain populations are at increased risk for thromboembolic events, including DVT and PE. Patients with cancer are among those with an increased risk for thromboembolic events (Heit et al., 2000, 2002; Otten et al., 2004; Prandoni, 2005; Van Gerpen & Mast, 2004), and patients with multiple myeloma may incur an even higher incidence (Hussein, 2006; Palumbo et al., 2008). Some combination treatments and concomitant therapies for multiple myeloma also may increase the incidence of thromboembolic events (Palumbo et al.).

Disruption of the vascular endothelium by trauma, surgery, or disease can expose the subendothelium to clotting elements in the blood. In normal coagulation, platelet activation, granule secretion, and aggregation are followed by activation of the plasma coagulation cascade, ultimately leading to fibrin formation. Thrombosis can result from the unregulated activation of coagulation that occurs with continued endothelial damage, reduced blood flow in deep veins, and hypercoagulability. The resulting thrombus may obstruct blood vessels partially or completely or may dislodge from the site of formation to become an embolus (Handin, 2005; Story, 2006; Viale & Schwartz, 2004).

Thromboembolic events can produce life-altering complications, affecting physiologic functions such as breathing, cognition, and overall function, and should be considered medical emergencies. Thromboembolic events can permanently affect the lives of patients and their families. Impairment resulting from thromboembolic events can interfere with therapy, treatment options, drug combinations, and patient adherence.

**Patient and Caregiver Educational Recommendations**

Patient education, focused nursing assessment, and proactive prophylaxis against thromboembolic events may increase positive patient outcomes. Nursing opportunities include identifying and recommending prophylaxis against thromboembolic events in conjunction with the healthcare team and implementing prophylaxis algorithms such as those included in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™ for venous thromboembolic disease (NCCN, 2007), the International Myeloma Working Group (IMWG) consensus statement recommendations (Palumbo et al., 2008), this consensus statement, and other nursing practices that have been identified to reduce the risk of thromboembolic events.

**Global Statement**

Recommendations for prevention and prophylaxis of thromboembolic events in patients with multiple myeloma depend on institutional practices, drug therapies and combinations, and factors specific to individual patients (e.g., concomitant illnesses, medical history, cost of therapy, insurance, patient abilities, adherence, allergies and sensitivities).

**Tool for Grading Thromboembolic Events**

Healthcare professionals can quantify the severity of thromboembolic events with the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). The NCI CTCAE are used for identifying treatment-related adverse events to facilitate the evaluation of new cancer therapies, treatment modalities, and supportive measures. For most adverse events, the NCI CTCAE defined grades 1 through 5 using unique clinical descriptions; each grade is assigned a severity: grade 1 is mild, grade 2 is moderate, grade 3 is severe, grade 4 is life threatening or disabling, and grade 5 is death related to the adverse event. Table 1 defines the NCI CTCAE version 3.0 vascular toxicity

### Table 1. National Cancer Institute Common Terminology Criteria for Adverse Events: Vascular Toxicity Grades

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>GRADE 2 (MILD)</th>
<th>GRADE 3 (SEVERE)</th>
<th>GRADE 4 (LIFE THREATENING OR DISABLING)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis/embolism (vascular access related)</td>
<td>Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated</td>
<td>Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated</td>
<td>Embolic event, including pulmonary embolism or life-threatening thrombus</td>
</tr>
<tr>
<td>Thrombosis/thrombus/embolism</td>
<td>Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated</td>
<td>Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated</td>
<td>Embolic event, including pulmonary embolism or life-threatening thrombus</td>
</tr>
</tbody>
</table>

*Note. Vascular toxicity has no grade 1 (mild). Note. Based on information from National Cancer Institute, 2006.*
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Assessment of Risk Factors

Ongoing and focused nursing assessment, proactive prophylaxis, and prompt recognition and diagnostic workup of potential or actual thromboembolic events, particularly DVT and PE, can help patients with multiple myeloma achieve positive outcomes. Figure 1 lists general risk factors for thromboembolic events. Assessment tools to determine risk for venous thromboembolism and DVT are available for practitioners and patients (Caprini, 2006; Coalition to Prevent Deep-Vein Thrombosis, 2006). The IMWG consensus statement for the prevention of thromboembolic events associated with thalidomide and lenalidomide in the treatment of patients with multiple myeloma relies on the number of individual and myeloma-related risk factors to determine specific recommendations (Palumbo et al., 2008).

If a thromboembolic event is suspected, a complete history should be taken and a laboratory workup should be performed. Figure 2 lists the signs and symptoms of DVT and PE, which can be used for physical assessment. Table 2 summarizes the tests that are used to diagnose DVT and PE.

As mentioned, therapy with lenalidomide or thalidomide may increase the risk of thromboembolic events for patients with multiple myeloma, particularly in combination with other antimyeloma agents and concomitant medications. Table 3 lists therapy-related risk factors for thromboembolic events. Although the risk for thromboembolic events with lenalidomide or thalidomide administered as a single agent is low, both immunomodulatory drugs are indicated in combination with dexamethasone for the treatment of multiple myeloma. Low-dose dexamethasone should be distinguished from high-dose dexamethasone, which is defined as 480 mg or more per month; low-dose dexamethasone, defined as less than 480 mg per month, is not a risk factor for thromboembolic events (Palumbo et al., 2008). In contrast, the proteasome inhibitor bortezomib is indicated for administration as a single agent; as such, it is not associated with an increased risk of thromboembolic events (Harousseau et al., 2006; Lonal et al., 2007; Millennium Pharmaceuticals, Inc., 2007). However, some evidence suggests that the addition of bortezomib to regimens including lenalidomide and other combination therapies associated with thromboembolic events may decrease the incidence of such events (Barlogie et al., 2005; Richardson et al., 2006). Erythropoietin administered with lenalidomide or thalidomide is a risk factor for thromboembolic events, but administration of erythropoietin with bortezomib does not result in an increased risk of thromboembolic events (Harousseau et al.; Palumbo et al.).

Recommendations for Prophylaxis

Clearly, recognizing factors that put patients at risk for thromboembolic events and instituting preventive measures are better than attempting to treat adverse events after they occur.
Deep Vein Thrombosis
- Slight fever
- Tachycardia
- Unilateral swollen, erythematous, warm extremity
- Cyanosis and cool skin if venous obstruction is present
- Dull ache, pain, or tight feeling over area and with palpation
- Positive Homans’ sign (calf pain when knee is flexed and foot is dorsiflexed); present in approximately 35% of patients; high false-positive rate
- Obvious swelling (may not be present early)
- Distension of superficial venous collateral vessels

Pulmonary Embolism (a medical emergency)
- Anxiety
- Sudden dyspnea
- Chest discomfort; may appear anginal at first, then pleuritic; increases with inspiration
- Tachycardia or tachypnea
- Low-grade fever
- Pleural friction rub, crackles followed by diminished breath sounds; wheezing also may be present.
- Electrocardiogram right axis deviation or new right bundle branch block

Prophylactic measures against thromboembolic events may be categorized as mechanical, myeloma regimen related, and antithrombotic pharmaceutical (clot-preventing agent). Figure

Figure 2. Signs and Symptoms of Thromboembolic Events
**Note.** Based on information from Story, 2006; Van Gerpen & Mast, 2004.

Prophylactic measures against thromboembolic events may be categorized as mechanical, myeloma regimen related, and antithrombotic pharmaceutical (clot-preventing agent). Figure

Table 2. Diagnostic Testing for Thromboembolic Events

<table>
<thead>
<tr>
<th>ASSAY TYPE</th>
<th>DEEP VEIN THROMBOSIS (DVT)</th>
<th>PULMONARY EMBOLISM (PE)</th>
</tr>
</thead>
</table>
| Imaging examinations            | Doppler ultrasonography; sensitivity/specificity of 95%; less reliable for diagnosing DVT in calf veins and upper extremities than venograph | Ventilation perfusion lung (V/Q) scan: If PE exists, lung perfusion is decreased without interfering with ventilation. If normal, no other studies are needed. 
Spiral (helical) computed tomography (CT) angiography: three-dimensional view; highly sensitive and specific for PE 
Pulmonary angiography: previous “gold standard” but invasive and not usually needed with availability of V/Q and spiral CT scans |
|                                 | Contrast venography: “gold standard” but invasive Impedance plethysmography: not method of choice for lower extremities or asymptomatic patients 
Radionuclide scintigraphy: less reliable in calf or in recurrent DVT |
| Laboratory tests                | Serum D-dimer (enzyme-linked immunosorbent assay) for fibrin degradation products: may be elevated in other conditions; high negative predictive value and sensitivity in presence of intermediate to high clinical risk; exclusionary test for DVT and PE in outpatients with low clinical probability 
Antithrombin level: Decrease corresponds to severity of thrombosis. If DVT or PE is diagnosed; prothrombin time, adjusted partial thromboplastin time, and baseline international normalized ratio |
|                                 | Serum D-dimer (enzyme-linked immunosorbent assay) for fibrin degradation products: may be elevated in other conditions; high negative predictive value and sensitivity in presence of intermediate to high clinical risk; exclusionary test for DVT and PE in outpatients with low clinical probability 
Antithrombin level: Decrease corresponds to severity of thrombosis. If DVT or PE is diagnosed; prothrombin time, adjusted partial thromboplastin time, and baseline international normalized ratio |

* Pulmonary embolism is a medical emergency.

**Note.** Based on information from Qaseem et al., 2007; Story, 2006; Van Gerpen & Mast, 2004.
Low-molecular-weight heparin or full-dose warfarin for all patients with therapy-related risks, including high-dose dexamethasone, doxorubicin, or multiagent chemotherapy. The labeling for thalidomide and lenalidomide recommends monitoring for signs and symptoms of thromboembolic events. According to the thalidomide label, preliminary data suggest that patients who are appropriate candidates may benefit from concurrent prophylaxis with aspirin or an anticoagulant (Celgene Corporation, 2007b). The lenalidomide label states that the decision to use prophylaxis should be made after assessment of each patient’s risk factors (Celgene Corporation, 2007a).

Individual patient risk factors, the presence of multiple myeloma, and the use of antimyeloma therapies or other medications all contribute to the risk of serious and life-threatening thromboembolic events in patients with myeloma. Prophylactic measures based on individual and myeloma-related risk factors can reduce or eliminate the risk.
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Author Contact: Sandra Rome, RN, MN, AOCN®, CNS, can be reached at romes@cshs.org, with copy to editor at CJONEditor@ons.org.

References


Patient Education Sheet: Preventing Blood Clots and Thromboembolic Events With Novel Agents for Multiple Myeloma

**KEY POINTS**

Patients with cancer are at increased risk for developing blood clots (thromboembolic events). Patients with multiple myeloma may have an even higher risk of developing blood clots. Novel therapies used to treat myeloma include thalidomide and lenalidomide. These drugs, in combination with other medications, may increase the incidence of clots. Prevention of blood clots can reduce complications and contribute to successful treatment. Changes in your medication may be made by a healthcare provider based on your symptoms.

**TYPES OF THROMBOEMBOLIC EVENTS**

- Deep vein thrombosis (DVT): a small blood clot in the arm, leg, hand, or foot; DVT is the most common thromboembolic event.
- Pulmonary embolus (PE): a blood clot that travels to the lungs
- Cerebral infarction (stroke): a blood clot that travels to the brain

**SYMPTOMS OF DEEP VEIN THROMBOSIS**

- Swelling, aching, pain, tightness, or a hard or soft lump in the arm, leg, hand, or foot
- Fast heartbeat
- Veins larger than usual (distended)

**SYMPTOMS OF PULMONARY EMBOLUS**

- Anxiety
- Fast heartbeat and fast breathing
- Chest pain or new onset of shortness of breath
- Coughing up blood

**SYMPTOMS OF STROKE**

- Change in emotional or mental behavior and confusion

**TREATMENT**

- DVT, PE, and stroke are considered medical emergencies.
- Report any symptoms to your healthcare provider immediately.
- You will need regular examinations and may need to receive medications to prevent clots.
- The treatments or medications you receive will be based on your individual risk factors.
- Low-dose aspirin may be suggested if you have no risk factors or only one risk factor.
- Pills or injectable anticoagulant drugs may be prescribed if you have more than one risk factor.

**RISK FACTORS FOR CLOT FORMATION**

- Lack of activity
- Obesity
- Smoking
- History of blood clots in you or your family
- Taking estrogen compounds (hormone replacement)
- Taking drugs to increase the amount of red blood cells, such as erythropoietin, epoetin alfa, or darbepoetin alfa
- Recent surgery
- Prolonged air travel

**WAYS TO REDUCE CLOT RISK**

- Exercise, such as walking, ankle circles, and knee to chest lifts.
- Lose weight.
- Stop smoking.
- Take medications prescribed by your healthcare providers.

*Note. For more information, please contact the International Myeloma Foundation (1-800-452-CURE; www.myeloma.org). The foundation offers the Myeloma Manager™ Personal Care Assistant™ computer program to help patients and healthcare providers keep track of information and treatments. Visit http://manager.myeloma.org to download the free software.*

*Note. Patient education sheets were developed in June 2008 based on the International Myeloma Foundation Nurse Leadership Board’s consensus guidelines. They may be reproduced for noncommercial use.*