Complications of Multiple Myeloma Therapy, Part 2: Risk Reduction and Management of Venous Thromboembolism, Osteonecrosis of the Jaw, Renal Complications, and Anemia

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Key Words
Thalidomide, bortezomib, lenalidomide, deep vein thrombosis, pulmonary embolism, bisphosphonates, erythropoiesis-stimulating agents

Abstract
Venous thromboembolism (VTE), osteonecrosis of the jaw, renal failure, and anemia are all common complications of multiple myeloma therapy. Many of these adverse events have been documented only in the past 5 to 10 years, in conjunction with the introduction of a series of the newer therapies thalidomide, bortezomib, and lenalidomide. This article discusses these complications in detail and provides strategies for health care providers to best prevent, identify, and manage them. Preventive measures, such as VTE prophylaxis and appropriate dental hygiene, as well as patient education, dose adjustments, limited duration of drug treatment, and consideration of therapies that are associated with less burdensome adverse-event profiles, can contribute to substantially improved outcomes and quality of life. (JNCCN 2010;8[Suppl 1]:S13–S20)

Venous Thromboembolism
VTE typically manifests as deep vein thrombosis (DVT) or pulmonary embolism (PE). Both cancer and cancer treatments have been identified as discrete risk factors. Current evidence indicates that cancer increases thrombosis risk 4.1-fold and chemotherapy increases the risk 6.5-fold. Other key VTE risk factors include older age, recent surgery, acute medical illness, and immobility or bed rest. The risk of VTE is typically cumulative. Therefore, even if an independent relationship between VTE and specific cancers such as MM were excluded, the advanced age of most MM patients and other factors common in MM patients would tend to place them at heightened VTE risk. A recent, retrospective analysis of a managed care database of patients with MM (N = 1732) showed that 66.3% had at least 1 VTE risk factor and 48.3% had at least 2 risk factors.

It has been posited that the hypercoagulable state typical with MM and other cancers provides a prothrombotic baseline environment. The prothrombotic state associated with MM may be due to multiple hemostatic abnormalities, including activation of coagulation pathways, reduced natural anticoagulation mechanisms,
and an inflammatory milieu. Acquired resistance to activated protein C is a common coagulation abnormality in MM, and it has also been associated with increased thromboembolism risk. Conditions that result in hypercoagulable states include immunoglobulin interference with fibrin structure and paraprotein acting as an autoantibody against intrinsic anticoagulants and phospholipids. A small recent study (N = 49) of patients with MM receiving thalidomide confirmed that most patients who subsequently experienced a thrombotic episode had an underlying hypercoagulability abnormality.

Underlying VTE risk often escalates with therapeutic intervention and is typically greatest after initial therapy. For example, approximately half of VTE events in patients with MM occur within 2 months of treatment initiation. Varying risk levels are associated with specific therapies and therapeutic combinations. In particular, VTE rates are high in patients receiving the immunomodulatory drugs thalidomide or lenalidomide in combination with high-dose dexamethasone, doxorubicin, or combination chemotherapy. Dexamethasone alone has also been shown to somewhat increase thrombosis risk.

### Thalidomide

A recent systematic review and meta-analysis of 17 randomized, controlled trials found an overall VTE incidence of 11.7% in thalidomide-treated patients (95% CI, 8.1%–16.5%). This finding should be considered in the context of a systemic review by Zangari et al., who assessed relapsed/refractory versus newly diagnosed MM, as well as thalidomide monotherapy versus combination therapy, and found wide variation in VTE risk. Studies of thalidomide monotherapy showed VTE rates of less than 2% to 4% in both newly diagnosed patients and those with relapsed/refractory disease. Newly diagnosed patients receiving combination therapy had rates ranging from 17% to 28%. The rates of VTE in patients with relapsed/refractory MM who received combination thalidomide therapy tended to be lower (8% to 21%) but were still a cause for concern. The combination regimens evaluated included thalidomide/dexamethasone, thalidomide/melphalan/prednisone, and thalidomide plus conventional chemotherapy.

### Lenalidomide

As with thalidomide, the risk for VTE with lenalidomide is low, ranging from 0% to less than 5%, when it is administered as a single agent. However, studies have shown elevated VTE risk ranging from 8.5% to 15.0% when lenalidomide is combined with dexamethasone. More recent trials have shown that lowering the dexamethasone dosage reduces the risk of VTE with lenalidomide substantially.

Heightened VTE risk has also been associated with the use of erythropoiesis-stimulating agents (ESAs), such as epoetin alfa and darbepoetin alfa. Anemia is discussed in more detail in subsequent sections.

### Bortezomib

The proteasome inhibitor bortezomib does not appear to increase VTE risk; in fact, it may exert antithrombotic actions. Proteasome inhibition is known to decrease expression of endothelial and vascular cell adhesion molecules; in addition, bortezomib has been shown to inhibit adenosine diphosphate–induced platelet aggregation. Two phase III studies indicate that bortezomib is associated with thrombocytopenia rates ranging from 20% to 26% (grade 3) and 4% to 17% (grade 4), but a very low (1%) VTE rate.

### Treatment and Prophylaxis Recommendations

Current VTE prophylaxis guidelines from the American College of Chest Physicians (ACCP) recommend primary antithrombotic prophylaxis for patients with cancer only if they are bedridden or undergoing surgical intervention. However, as discussed previously, without prophylaxis, the risk for VTE in treated MM patients is unacceptably high. In addition, PE is associated with a high case-fatality rate. One-week survival after PE is 71%, but one-quarter of all cases present as sudden death. Therefore, identifying high-risk patients and providing them with appropriate prophylaxis is essential. Unfortunately, very few randomized studies have assessed the impact of anticoagulant prophylaxis in patients with cancer.

The International Myeloma Working Group (IMWG) recently published guidelines for preventing VTE in myeloma. Primary data were lacking in many cases, so the IMWG recommendations are based on expert assessment or data extrapolation from studies not designed specifically to assess prophylaxis efficacy or safety. Therefore, they should not override the treating physician’s best judgment.
may present with a combination of disease-related and individual risk factors, as well as inherited and non-inherited risk factors. All of these must be considered alongside therapeutically mediated risk. Table 1 lists risk factors and related screening considerations for MM patients.

According to the IMWG, selection of candidates for thromboprophylaxis should be based on the baseline VTE risk associated with each therapy. The IMWG recommends reducing VTE risk to less than 10% using the safest and least cumbersome prophylaxis available. High-dose dexamethasone administration is considered an independent risk factor for VTE. At minimum, and coinciding with “black-box” warnings added recently to the prescribing information for thalidomide and lenalidomide, newly diagnosed MM patients being treated with either of those drugs in combination with dexamethasone should receive thromboprophylaxis. Proposed prophylaxis strategies include the use of a low-molecular-weight heparin such as enoxaparin, warfarin, or aspirin. Clinical experience suggests that full-dose warfarin may be used as prophylaxis, but low-dose warfarin is not acceptable. Specific IMWG recommendations are summarized in Table 2.

For patients receiving epoetin alfa, the FDA recommends administration of an anticoagulant prophylactically. The manufacturer of darbepoetin alfa does not recommend anticoagulant prophylaxis, but it specifies that the lowest dose needed should be used to reduce thromboembolism risk. The combination of bortezomib with an ESA does not appear to increase the risk of VTE.

Despite best efforts, prophylaxis cannot prevent all VTE incidents, and proper identification and management of VTE is critical. When DVT is suspected, the standard diagnostic test is compression ultrasonography. Suspected PE is typically investigated with imaging techniques, primarily CT pulmonary angiography. If this is contraindicated (due to baseline nephropathy, for example), magnetic resonance pulmonary angiography and/or nuclear medicine V/Q scan may be considered. In addition, all patients should be provided with education regarding the clinical symptoms of VTE (i.e., skin redness, pain in the extremities or chest, shortness of breath, rapid heartbeat) and instructed to inform their physician promptly if any concerns arise. If DVT is confirmed, the overall goals of treatment are symptomatic relief, prevention of emboli formation, and prevention of VTE recurrence. Proposed DVT treatment strategies are outlined in Figure 1.

### Table 1 Risk Factors to Consider When Screening Multiple Myeloma Patients for Thromboprophylaxis

<table>
<thead>
<tr>
<th>Individual Factors</th>
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<tr>
<td>General patient characteristics</td>
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<tr>
<td>• Age</td>
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<td>• Obesity and/or diabetes</td>
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<td>• Cardiovascular or renal disease</td>
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<tr>
<td>• Acute infection</td>
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<td>Inherited thrombophilic abnormalities</td>
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<tr>
<td>• Antithrombin III deficiencies</td>
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<tr>
<td>• Protein C and protein S deficiencies</td>
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<td>• Acquired protein C resistance</td>
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<tr>
<td>• Factor V Leiden mutation</td>
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<tr>
<td>• Prothrombin gene (G20210A) mutation</td>
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<tr>
<td>• Elevated homocysteine levels</td>
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<tr>
<td>Central venous catheter use</td>
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<tr>
<td>Prior deep vein thrombosis, pulmonary embolism, or superficial vein thrombosis</td>
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<th>Disease-Related Factors</th>
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<td>Recent (&lt; 3 mo) anesthesia, surgery, trauma, or hospital admission</td>
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<td>Confinement (i.e., to a nursing home), immobilization, or sedentary lifestyle</td>
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<td>Other malignant neoplasm, with or without chemotherapy</td>
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<td>Hyperviscosity or other blood-clotting disorders</td>
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<td>Neurologic disease with extremity paresis</td>
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<th>Therapy-Related Factors</th>
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<tr>
<td>High-dose dexamethasone</td>
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<td>Thalidomide, lenalidomide</td>
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<td>Adjuvant doxorubicin for other cancer</td>
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<td>Multiagent chemotherapies</td>
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<td>Erythropoietin use</td>
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Data from Refs. 2, 12, and 26.

### Osteonecrosis of the Jaw

A rare side effect recently documented in MM and other cancers, ONJ is linked to long-term use of bisphosphonates. The incidence of ONJ in bisphosphonate-treated MM patients is unknown. Manufacturer-sponsored epidemiologic studies re-
exposed bone in the jaw. The mandible is the main affected site, and most lesions occur posterior to the cuspid teeth.\(^{33,35,36}\) In a recent longitudinal study documenting the natural history of ONJ, 96 patients from the United States and Greece were followed up for 3.9 years after ONJ diagnosis.\(^{35}\) Dental extractions preceded diagnosis of ONJ in 47% of cases, and these procedures were more common in patients with a single episode of ONJ than in those with recurrent and nonhealing disease (58% vs. 30%). ONJ resolved in 62% of cases, recurred after healing in 12% (at the same or a new site) and did not resolve in 26% during 9 months of follow-up. The recurrence rate was higher among U.S. patients than Greek patients (22% vs. 7%, respectively). Discontinuation of bisphosphonate correlated with increased bone pain in the Greek cohort and increased fracture rates in the U.S. cohort; U.S. patients were more likely to restart bisphosphonate than were their Greek counterparts. Recurrence of ONJ was precipitated by re-initiation of bisphosphonate in 6 cases and dental treatment in 4 cases. The rate of MM relapse was higher in patients with recurrent or unresolved ONJ than in those who experienced a single such episode.

Management of ONJ is controversial because there are so many unknowns. No evidence-based consensus guidelines exist. A cornerstone of management is to attempt to prevent ONJ with good dental hygiene and avoidance of unnecessary dental procedures while on bisphosphonate therapy.
For patients who do develop ONJ, a conservative, “supportive,” nonsurgical approach has been recommended: chlorhexidine 0.12% oral rinses, intermittent systemic antibiotics, and careful sequestrectomy. Avoidance of bone curettage and surgical debridement is advised because most cases worsen after surgery. Ozone therapy, hyperbaric oxygen, and laser therapy have been used in several cases of ONJ, with mixed results.

In an effort to decrease the occurrence of ONJ, in 2007 ASCO updated its guidelines on the use of bisphosphonate in patients with MM. The guidelines now recommend limiting the duration of bisphosphonate use to 2 years in patients with responsive or stable MM, with drug resumption recommended in the case of new-onset skeletal-related events. The guidelines also recommend that, before bisphosphonate initiation, patients should obtain a comprehensive dental examination, with particular attention to identifying active oral infections and sites at high risk for infection.

The incidence of ONJ may be lower in patients receiving 3-monthly bisphosphonate therapy versus monthly infusions; however, the data are preliminary, and ongoing prospective clinical trials must be completed before such a schedule can be adopted.

**Renal Complications**

Renal impairment is common in patients with MM and may be present at diagnosis or a side effect of treatment. Bisphosphonates can cause renal function deterioration in the form of tubular necrosis and focal segmental glomerulosclerosis. If renal impairment is secondary to bisphosphonate use, discontinuation may lead to a partial recovery of function.

The updated zoledronic acid prescribing information and the updated ASCO guidelines recommend a reduced dosage for patients with an estimated creatinine clearance between 30 and 60 mL/min. The dose should be administered over a period of no less than 15 minutes; administration time may be prolonged for up to 30 minutes to decrease risk of renal toxicity. Zoledronic acid is not recommended for patients with severe renal impairment (creatinine clearance < 30 mL/min). No dosing guidelines have been established for the use of pamidronate in patients with severe renal failure; however, ASCO recommends a reduced dosage. In general, bisphosphonates should be used with extreme caution in MM patients with renal impairment, and all MM patients should be monitored for deterioration of kidney function.

Monitoring of creatinine levels during MM treatment is strongly recommended, although no current guidelines have been validated. Dosing adjustments are necessary for patients who exhibit a change in kidney function. There is currently no standard definition of renal failure, but most recent studies have used a serum creatinine level of 2 mg/dL as a cutoff point. Another useful marker is glomerular filtration rate, which has been suggested to be a more accurate measurement of renal function, especially for patients with mild or moderate renal impairment.

**Anemia**

Anemia may be present at the time of MM diagnosis, or it may develop subsequently. The most common trigger is the replacement of bone marrow by plasma cells, but anemia can also result from factors related to MM treatment, such as chemotherapy, radiation
therapy, and $B_{12}$ and folate deficiencies. Anemia often resolves when treatment for MM is swift and successful, but it will remain if the disease worsens.

Although anemia can be related to inadequate erythropoietin production, before initiating treatment, physicians should assess other possible causes. In particular, iron deficiency may be overlooked due to macrocytosis related to the treatment of MM. Patients with inadequate erythropoietin production may benefit from treatment with ESAs that mimic erythropoietin to stimulate red blood cell production. Treatment of anemia with ESAs has been successful in patients with a variety of cancer types, including MM. Studies specific to myeloma and lymphoma have shown improvement (response rates of 50%–70%) in anemia-related outcomes, such as quality of life, hemoglobin levels, and number of required transfusions. If ESA use is not effective, the most likely causes are functional iron deficiency, infection, surgery, or plasma-cell bone marrow dysfunction.

Unfortunately, recent evidence suggests that ESAs may contribute to solid tumor proliferation, thus reducing life expectancy. This was first noted in patients with breast or head and neck carcinoma. Research on ESA use in patients with MM has produced conflicting results. In a retrospective analysis, Baz et al. identified a trend toward increased overall survival. A hazard ratio of 0.6 ($P = .026$; 95% CI, 0.38–0.94) was identified for all patients except those with stage 1 disease, as defined by the Southwest Oncology Group staging system. No effect was found for patients with stage 1 disease. However, another retrospective analysis conducted by Katodrikou et al. found that ESAs might have a detrimental effect on both median overall survival and progression-free survival in patients with MM. Median overall survival was 31 months (95% CI, 25–37 months) for patients receiving ESAs and 67 months (95% CI, 55–79 months) for those not receiving ESAs. Median progression-free survival was 14 months (95% CI, 12–16 months) for patients who received ESAs and 30 months (95% CI, 24–36 months) for patients who did not ($P < .001$ for both comparisons). The authors concluded that their results do not contravene the therapeutic value of ESAs but might indicate that their administration should be limited to MM patients in whom a good response can be predicted. A randomized, prospective trial is needed to clarify the role and risk of ESAs in MM.

All ESAs are contraindicated for patients with uncontrolled hypertension. Revised FDA product labels for these drugs contain “black-box” warnings noting an increased risk of mortality, cardiovascular and thromboembolic events, and tumor progression or recurrence. In patients with renal failure, the FDA recommends individualized dosing with a goal of maintaining hemoglobin levels of 10 to 12 g/dL. In patients with cancer, ESAs are recommended for use only at the lowest doses and with concurrent chemotherapy. They are not recommended when myelosuppressive therapy is being used and a full recovery is expected. Based on these warnings, the NCCN recently released updated guidelines for the use of ESAs in cancer patients. The new guidelines eliminate hemoglobin level monitoring requirements and target hemoglobin ranges, reinforce the recommendation that only patients receiving chemotherapy should be treated with ESAs, and emphasize the risk for VTE with ESA administration.

For treatment with epoetin alfa, the FDA recommends administration of an anticoagulant prophylactic. Bortezomib combined with an ESA does not appear to be associated with increased VTE risk.

Conclusions

The identification over the past 10 years of new, more effective primary treatments for MM, such as bortezomib, lenalidomide, and thalidomide, has led to meaningful changes in patient outcomes. However, lenalidomide and thalidomide, used either alone or in combination, are associated with elevated VTE risk. Likewise, the treatment of MM-associated bony disease with bisphosphonate therapy provides clinical benefit but increases the risk for ONJ and renal impairment. Patients receiving MM therapy are also at heightened risk of anemia. The application of preventive measures, such as VTE prophylaxis, appropriate dental hygiene, and dose adjustments, can contribute to improved outcomes and quality of life for MM patients.

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References


