Addressing Challenges in Multiple Myeloma Management in an Era of New Therapeutics

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Featured Articles

The Role of Maintenance Therapy in the Treatment of Multiple Myeloma
Ashraf Badros

In the Age of Novel Therapies, What Defines High-Risk Multiple Myeloma?
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Complications of Multiple Myeloma Therapy, Part 2: Risk Reduction and Management of Venous Thromboembolism, Osteonecrosis of the Jaw, Renal Complications, and Anemia
Ruben Niesvizky and Ashraf Badros

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third-line therapies; managing the side effects of

to know more about choosing first-, second-, and

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immunomodulation, proteasome inhibition),

have multiple functions (e.g., antiangiogenesis,

health care providers to understand the newer

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United States, after non-Hodgkin lymphoma.

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Program Overview

Multiple myeloma (MM) remains the second most common hematologic malignancy in the United States, after non-Hodgkin lymphoma. Historically, MM has been a difficult and frustrating disease for patients and their health care providers. Since the reintroduction of thalidomide and the development of lenalidomide and bortezomib, outcomes have improved considerably, particularly when these newer agents are combined with conventional chemotherapeutic agents or with each other. Obviously, it is vitally important for today’s health care providers to understand the newer agents, but this is a challenge because the drugs have multiple functions (e.g., antitumor effects, immunomodulation, proteasome inhibition), have different toxicity profiles, and can be used in myriad combinations and sequences. Hematologists/oncologists have indicated a need to know more about choosing first-, second-, and third-line therapies; managing the side effects of the new agents; the role and timing of stem cell transplantation in the era of the new therapies; guidelines for maintenance therapy; and what new therapeutic combinations will be a major factor in treating myeloma in the coming years.

Learning Objectives

Upon completion of this activity, participants should be able to:

- Evaluate the need for, and propose appropriate maintenance therapy options in, MM
- Evaluate the current importance of assessing MM patients for risk, especially in the face of emerging and novel agents, and integrate this knowledge into management plans
- Describe the most appropriate techniques for monitoring treatment of MM
- Formulate evidence-based management plans for patients with MM based on their age, risk, and comorbidities

The opinions expressed in this publication are those of the participating faculty and not those of the National Comprehensive Cancer Network, MediCom Worldwide, Inc., Millennium Pharmaceuticals, Inc., or the manufacturers of any products mentioned herein.

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Drs. Anderson, Badros, Laubach, Mitsiades, Niesvizky, Richardson, and Schlossman indicated that their materials would include the discussion of unlabeled uses of commercial products or investigational/unapproved products not yet approved by the FDA for certain uses in the United States.

Dr. Jagannath indicated that his material would not include the discussion of unlabeled uses of commercial products or investigational/unapproved products not yet approved by the FDA for any use in the United States.

Activity Instructions

This activity is eligible for credit through February 15, 2011. After this date, this activity will expire and no further credit will be awarded.

Expected time to complete this activity as designed: 2.5 hours

There are no fees for participating in this activity. All participants must read the entire supplement and complete the Activity Evaluation Form. Participants must receive a minimum score of 70% on the self-assessment portion of the form to qualify for CE credit. Certificates will be mailed 4 weeks after receipt of a completed, qualified form.

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Addressing Challenges in Multiple Myeloma Management in an Era of New Therapeutics

**Featured Articles**

**S-1 Introduction: Addressing Challenges in Multiple Myeloma Management in an Era of New Therapeutics**

*Sundar Jagannath, MD*

Hematologists, oncologists, and other physicians can expect to encounter an increasing number of patients with multiple myeloma. Historically, multiple myeloma has been a difficult and frustrating disease, but since the reintroduction of thalidomide and the development of lenalidomide and bortezomib, outcomes have improved considerably. This supplement is part of a 3-supplement series planned at a roundtable discussion held in 2009, and this introduction discusses the articles in this supplement as well as those in earlier and later planned publications not included in *JNCCN*.

**S-4 Complications of Multiple Myeloma Therapy, Part 1: Risk Reduction and Management of Peripheral Neurpathy and Asthenia**

*Paul Richardson, MD; Jacob P. Laubach, MD; Robert L. Schlossman, MD; Constantine Mitsiades, MD, PhD; and Kenneth Anderson, MD*

Peripheral neuropathy and asthenia (fatigue) occur as both disease- and treatment-related complications in patients with multiple myeloma. Treatment-related peripheral neuropathy has an estimated incidence of 37% to 83% among patients with multiple myeloma, and asthenia is the most common adverse effect of cancer treatment, occurring in approximately 76% to 96% of patients receiving chemotherapy. These conditions are often dose-limiting, and they may interfere with optimal therapy and substantially affect patient quality of life. Regular screening and monitoring procedures, combined with patient education and effective management strategies, can reduce the risk of these treatment-related complications.

**S-13 Complications of Multiple Myeloma Therapy, Part 2: Risk Reduction and Management of Venous Thromboembolism, Osteonecrosis of the Jaw, Renal Complications, and Anemia**

*Ruben Niesvizky, MD, and Ashraf Badros, MD*

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.

**S-21 The Role of Maintenance Therapy in the Treatment of Multiple Myeloma**

*Ashraf Badros, MD*

Maintenance therapy in multiple myeloma has been under investigation for more than 3 decades, without evidence of clear benefit until recently. The role of the novel agents thalidomide, lenalidomide, and bortezomib as maintenance is emerging. Most reported maintenance studies have evaluated thalidomide, alone or in combination with a corticosteroid. Several of these studies suggest that thalidomide-based maintenance prolongs overall survival after autologous stem cell transplantation but important questions have not yet been resolved. Ongoing randomized trials are also evaluating lenalidomide and bortezomib maintenance therapies to better define the role of these drugs as maintenance in multiple myeloma.

**S-28 In the Age of Novel Therapies, What Defines High-Risk Multiple Myeloma?**

*Ashraf Badros, MD*

Multiple myeloma is characterized by clinical and biologic heterogenicity. Recently, genetic analysis has provided predictable prognosis across different types of treatment. These advances have allowed patients to be categorized into different risk groups and have been particularly useful in defining a high-risk group. Preliminary studies have shown promising outcomes after the use of novel agents in high-risk patients. The application of risk-based therapy and the potential of the new agents to abrogate the influence of adverse prognostic features may improve outcomes in these patients.

**S-35 CME Post-Test and Evaluation**
Introduction: Addressing Challenges in Multiple Myeloma Management in an Era of New Therapeutics

Hematologists/oncologists and other physicians can expect to encounter an increasing number of patients with multiple myeloma (MM) in the coming years. Between 1997 and 2006, the incidence rate of myeloma declined in the United States, but the burden (number of incident cases) increased. An analysis of population-based cancer registries in 9 countries detected modest increases in the incidence of MM in most between 1973 and 1992, with further increases projected by 2007. MM remains the second most common hematologic malignancy in the United States after non-Hodgkin's lymphoma.

Historically, MM has been a difficult and frustrating disease for patients and physicians. Since the reintroduction of thalidomide and development of lenalidomide and bortezomib, outcomes have improved considerably, particularly when these newer agents are combined with conventional chemotherapeutic agents or each other. Using the first-line regimens common in 1983, typical 2-year survival rates were 48% to 66%. In trials of triple combination therapy reported in 2008, the 2-year survival rates ranged from 83% to 90%. In the United States, the 5-year survival rate improved from 26% in 1975 to 1977 to 34% in 1996 to 2003, a statistically significant difference.

Obviously, it is vitally important for today’s physicians to understand the newer agents, but this is a challenge because the drugs have multiple functions (e.g., antiangiogenesis, immunomodulation, proteosome inhibition), have different toxicity profiles, and can be used in myriad combinations and sequences. Hematologists/oncologists have indicated a need to know more about choosing first-, second-, and third-line therapies; side effects of the new agents; the role and timing of stem cell transplantation in the era of new therapies; guidelines for maintenance therapy; and what new therapeutic combinations will be major factors in treating myeloma in the coming years.

This supplement is part of a 3-supplement series planned by myeloma experts via a roundtable discussion held April 24, 2009, in Philadelphia. Our charge was to develop outlines of 10 articles about myeloma therapy that would convey the information currently of most importance to community oncologists. The first 2 of the 4 articles in this supplement address risk reduction and management of the most common complications of myeloma therapy. Dr. Paul Richardson and colleagues focus on how thalidomide- and bortezomib-induced peripheral neuropathy usually can be effectively managed with dose reduction, schedule modification, optimized agent sequencing, or a combination of nonpharmacologic and pharmacologic therapy for symptom relief. They also discuss asthenia (fatigue), an important topic that is too infrequently addressed in myeloma reviews. The companion article, by Drs. Ruben Niesvizky and Ashraf Badros, explains the measures that oncologists should take to protect patients from a life-threatening complication, venous thromboembolism, the risk of which is elevated with thalidomide and lenalidomide. That article also reviews the latest data on osteonecrosis of the jaw, renal complications, and anemia.

Dr. Badros has contributed 2 additional articles to this supplement: one on maintenance therapy and the other on defining and treating high-risk myeloma. He explains that only recently, after 3 decades of investigation, have certain maintenance regimens shown promise in myeloma. In particular, several studies suggest that thalidomide, alone or with a corticosteroid, prolongs overall survival after autologous stem cell transplantation (ASCT). However, other studies have failed to support this
conclusion, and several important questions remain. Bortezomib- and lenalidomide-based maintenance therapies are being evaluated in ongoing randomized trials.

In the final article, Dr. Badros notes that advances in genetic analysis have allowed better estimates of prognosis for patients with myeloma. An effective means of risk stratification is required so that patients at high risk may be offered more aggressive treatment or be entered into clinical trials of investigational agents as first-line therapy. Dr. Badros discusses evolving risk stratification systems and the potential of the newer agents to improve outcomes in patients with newly diagnosed high-risk myeloma.

The first supplement in this series was published in Community Oncology. In the opening article on treatment goals, I review the indications for treating MM, help set goals for first-line treatment and treatment of relapsed/refractory disease, and suggest how to reconcile different schools of thought about treating MM.

In the second article in the Community Oncology supplement, Dr. Sergio Giralt reviews recent data on the use of novel therapies in the transplant setting and discusses why ASCT remains a standard of care in myeloma.

In the final article of the supplement, Dr. Donald Siegel and Elizabeth Bilotti discuss the investigational antimyeloma agents that are farthest along in clinical development.

The third supplement in this series, entitled “Essentials for Tailoring Multiple Myeloma Therapy,” will be published later this year by Oncology. It compares efficacy and safety data for the various therapies recommended for patients with newly diagnosed myeloma and those with relapsed/refractory disease. In it, Dr. Edward Stadtmauer provides guidance for choosing among the NCCN recommended regimens, with particular attention to patients who have cytogenetic abnormalities, renal disease, or other negative prognostic indicators. Dr. Niesvizky and colleagues discuss front-line treatment of patients with myeloma who cannot or choose not to undergo ASCT. Finally, Dr. Richardson and colleagues close the series by reviewing the treatment of relapsed/refractory disease.

An estimated 90% of oncology care in the United States is performed outside of academic medical centers, and data suggest that uptake of new evidence can be as fast in the community as at academic medical centers. The hope is that the information in these supplements will help community oncologists understand the latest standards for myeloma care and feel more confident about participating in this exciting, fast-changing field.

References


Complications of Multiple Myeloma Therapy, Part 1: Risk Reduction and Management of Peripheral Neuropathy and Asthenia

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Key Words
Fatigue, neurotoxicity, thalidomide, bortezomib

Abstract
Peripheral neuropathy (PN) and asthenia (fatigue) occur as both disease- and treatment-related complications in patients with multiple myeloma (MM). Risk factors for treatment-related PN, which has an estimated incidence of 37% to 83% among patients with MM, include therapy duration, dose intensity, cumulative dose, and the presence of preexisting neuropathy. Asthenia is the most common adverse effect of treatment, occurring in approximately 76% to 96% of patients receiving therapy. The severity of PN and asthenia can range from mild to potentially debilitating. These conditions can be dose limiting; they may interfere with optimizing duration of therapy and may also substantially affect patient quality of life. Regular screening and monitoring, combined with patient education and effective management strategies, can reduce the risk of these treatment-related complications, as well as their consequences. (JNCCN 2010;8[Suppl 1]:S4–S12)

Peripheral neuropathy (PN) and asthenia (fatigue) are among the most commonly seen complications in patients undergoing multiple myeloma (MM) therapy. These potentially debilitating adverse effects are frequently dose limiting, and they may interfere with optimal therapy and substantially affect patient quality of life as well as outcome. Effective strategies for preventing and managing these complications of MM therapy are thus critical.

Peripheral Neuropathy
Overview
PN occurs in MM both as a disease-related complication in newly diagnosed patients and as a side effect of MM therapy. The reported incidence is 1% to 20% in untreated patients with MM and 37% to 83% in previously treated individuals; neurophysiologic evidence of neuropathy may be detected in 11% to 52% and 39% to 46% of these populations, respectively.1-6 Risk factors for PN include treatment-specific characteristics, such as therapy duration, dose intensity, and cumulative dose, and patient-specific factors, such as age, comorbidities (e.g., diabetes mellitus, alcoholism), and the presence of preexisting neuropathy.6-11

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Dr. Richardson reports having participated in funded research for Celgene Corporation and Millennium and having participated as an advisory board member or consultant for Celgene Corporation; Millennium Pharmaceuticals, Inc.; and Johnson & Johnson. Dr. Laubach reports no potential conflicts of interest. Dr. Schlossman reports having served as a speakers’ bureau member for Celgene Corporation and Millennium Pharmaceuticals, Inc.
Dr. Mitsiades reports having participated in funded research for OSI Pharmaceuticals, Inc.; Amgen, Inc.; AVEO Pharmaceuticals, Inc.; EMD Serono, Inc.; and Sunesis Pharmaceuticals, Inc., and having participated as an advisory board member for Millennium Pharmaceuticals, Inc.; Novartis International AG; Merck & Co.; and Pharmacor Corporation. Dr. Anderson reports having received preclinical and clinical research support from Millennium Pharmaceuticals, Inc., Celgene Corporation, and Novartis, and having served as an advisory board member for Millennium Pharmaceuticals, Inc., Celgene Corporation, Novartis, and Merck & Co.
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Clinical Features

Treatment-related PN depends on the agents used, as described subsequently, and is typically a length-dependent, axonal, sensory, or mixed sensorimotor neuropathy with symmetric, distal, and progressive signs and symptoms. Clinical manifestations are usually agent-specific but range from temporary numbness, paresthesia, dysesthesia, hyperesthesia, loss of deep tendon reflexes, and muscle weakness or cramps to burning pain, muscle wasting, and paralysis. Autonomic involvement may result in orthostatic hypotension, constipation/ileus, and urinary bladder or sexual dysfunction. In the most extreme cases, the manifestations of treatment-related PN can be life-threatening but this is, fortunately, very rare.7,9,12

Thalidomide-Induced PN (TiPN)

Thalidomide has been shown to produce a small- and large-fiber sensory PN with distal symmetric loss of all modalities, primarily affecting the lower limbs. Associated clinical signs and symptoms typically include tingling or painful paresthesias and numbness in the feet and sometimes the hands.1,5,7,9,13 Motor neuropathy occurs infrequently with thalidomide treatment; if present, it is usually mild in severity.9,14 Autonomic manifestations are common, and include gastrointestinal (e.g., constipation, anorexia, nausea) as well as cardiovascular (e.g., hypotension, bradycardia) effects.15–17 Although the symptoms of thalidomide-induced PN are usually reversible after dose reduction or treatment stoppage, some effects may be permanent.15,17

The incidence of thalidomide-induced PN varies among different patient populations, treatment regimens, and diagnostic criteria, but estimates range from 37% to 83%.1,5,9,13,15–21 Most cases are mild to moderate, classified as grades 1 to 2 (Table 1).22 Evidence from numerous studies indicates that the risk and severity of thalidomide-induced PN increases with cumulative dose or treatment duration, particularly when therapy extends beyond 6 months,1,5,7,15,17,19,23 although neurotoxicity can also occur with short-term exposure.

Bortezomib-Induced PN (BiPN)

Bortezomib-induced PN is predominantly a small-fiber sensory neuropathy, characterized by distal symmetric loss of all modalities in the lower limbs.3,9,24,25 Clinical signs and symptoms include burning dysesthesia, numbness, hyperesthesia, and pain; effects are typically more pronounced in the lower limbs.9,25 Motor involvement is less likely with bortezomib than with thalidomide, but it may result in mild distal lower limb weakness.9 Autonomic dysfunction is frequently observed with bortezomib-induced PN; clinical manifestations include gastrointestinal adverse effects (e.g., diarrhea, nausea, constipation, vomiting, anorexia) and hypotension.25,26 The neurotoxic effects of bortezomib therapy are generally reversible with dose reduction or treatment discontinuation.3,4,11,14,24,27–31

The distinctive clinical features of bortezomib-associated neuropathy suggest fundamental differences in its pathogenesis compared with thalidomide and other agents.9,24,25,26 Findings from recent in vitro

| Table 1   National Cancer Institute Common Toxicity Criteria (Version 3) for Peripheral Neuropathy |
|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Adverse Event | Grade 0       | Grade 1       | Grade 2       | Grade 3       | Grade 4       | Grade 5       |
| Neuropathy:   | Normal        | Asymptomatic; | Symptomatic;  | Weakness      | Life          | Death         |
| motor         | weakness on   | weakness      | interference  | interfering   | threatening;  |                |
|               | examination/  | with function  | with ADL      | with ADL      | disabling (e.g.,|                |
|               | testing only  | but not       |              |              | paralysis)    |                |
| Neuropathy:   | Normal        | Asymptomatic; | Sensory       | Sensory       | Disabling     | Death         |
| sensory       | loss of deep  | alteration or  | alteration or | alteration or |               |                |
|              | tendon reflexes| paresthesia    | paresthesia   | paresthesia   |               |                |
|              | (including tingling) | (including tingling) | (including tingling) | (including tingling) |               |                |
|              | but not interfering with function | but not interfering with function | but not interfering with ADL | but not interfering with ADL |               |                |

Abbreviation: ADL, activities of daily living.

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and in vivo studies suggest that proteasome inhibitor-induced PN may be mechanism-based (a consequence of proteasome inhibition itself), with dorsal root ganglia identified as a primary target leading to secondary peripheral nerve degeneration.\(^\text{32}\) However, a separate preclinical study suggested that the dorsal root ganglia lesions seen with bortezomib administration did not occur with carfilzomib, a second-generation proteasome inhibitor currently being investigated for the treatment of MM, although other studies have suggested carfilzomib, and agents in its class do in fact cause dorsal root ganglion abnormality.\(^\text{32,33}\) Further research is necessary to determine whether the mechanism underlying bortezomib-induced PN represents a class effect of proteasome inhibitors. However, clinical studies to date suggest this to be true, but with the degree of PN being less with carfilzomib.\(^\text{34}\)

The reported incidence of treatment-emergent PN with bortezomib is 31% to 64%, with severe (grade 3 or 4) symptoms seen in 3% to 22% of patients.\(^\text{3,4,6,11,27–31,35–37}\) Evidence of the dose-related and cumulative nature of bortezomib-induced neurotoxicity has been provided in several phase II and III studies, with reversibility also demonstrated in each of these.\(^\text{4,11,24,27–29,35,38}\)

**Assessment/Monitoring**

A comprehensive neuropathy assessment may involve a combination of patient history, clinical neurologic examination, and neurophysiologic testing. Diagnosis of any underlying conditions or comorbidities that may increase the risk of treatment-related PN is a critical part of this evaluation. PN severity should be characterized at each assessment to monitor neuropathy progression and determine whether a regimen change or some other type of intervention is indicated. Patient education is important for improving awareness and encouraging the reporting of symptoms. Neurotoxicity assessment tools (see an example in Figure 1) may be useful for quantifying PN severity based on patient self-reports.\(^\text{12}\)

Patients should be evaluated for evidence of neuropathy at baseline, before initiating a change in therapeutic regimen, in conjunction with new or worsening signs or symptoms, and periodically throughout treatment. Patient- or agent-specific risk factors may necessitate more aggressive or targeted assessments. For example, because the incidence of thalidomide-induced PN has been reported to increase with longer duration of administration; monthly evaluation of patients is recommended during the first 3 months of treatment and regularly thereafter.\(^\text{15}\) In addition, neurophysiologic testing is suggested (e.g., sensory nerve action potential amplitudes) every 6 months for the detection of asymptomatic PN.\(^\text{15}\)

**Management Strategies**

**Dose Reduction and Schedule Modification:** For patients with grade 1 PN, thalidomide therapy may be continued with a 50% dose reduction, particularly if no other treatment options are available.\(^\text{17}\) For grade 2 PN, thalidomide therapy should be discontinued until neuropathy has returned to baseline or less than a grade 1 severity; treatment may subsequently be resumed with dosage levels reduced by half.\(^\text{17}\) Some recommend restricting thalidomide therapy to short-term use (e.g., < 6 months) or low-dose regimens (e.g., 50 mg/d).\(^\text{5,18}\) In general, a conservative PN management approach is recommended for newly diagnosed MM patients, especially when treatment alternatives exist.\(^\text{17}\) Bortezomib dose modifications should be made according to the directions in the prescribing information,\(^\text{25}\) which are based on PN severity and the degree of associated neuropathic pain or impaired function (Table 2). The benefits of dose modification were shown in the pivotal phase III trial of bortezomib, with resolution or improvement of grade 2 or higher PN observed in 68% of patients who underwent a prespecified dose-reduction protocol, compared with 47% of those who did not.\(^\text{28}\)

**Therapeutic Intervention:** Nonpharmacologic management of sensory PN symptoms or neuropathic pain may involve the use of daily vitamins and nutritional supplements (e.g., multi-B complex vitamins [B₁, B₆, B₁₂], folic acid, magnesium, potassium, vitamin E, acetyl L-carnitine, α-lipoic acid, l-glutamine; see Table 3 for dosing), emollient creams (e.g., cocoa butter, menthol, and eucalyptus-based creams), and physical therapy, as well as therapeutic massage.\(^\text{12,39–41}\) These recommendations are largely based on anecdotal evidence, and controlled studies are needed to confirm their efficacy. Moreover, use of supplements on the day of bortezomib administration is not recommended based upon preclinical data suggesting the possibility of antagonism, although this has not been confirmed clinically.\(^\text{44}\)

If symptoms are inadequately controlled with nonpharmacologic intervention alone, pharmacologic therapy is advised. Because response is likely to vary substantially for each individual, a stepwise process may be necessary.\(^\text{41,45}\) Evidence of the therapeutic ben-
Peripheral Neuropathy and Asthenia

For additional symptomatic relief, the tricyclic antidepressant nortriptyline may be added at an initial dose of 25 mg every night at bedtime; dosing may be increased to 50 mg after 2 weeks, with further dose escalation of 25 mg monthly (as tolerated), up to a maximum of 100 mg every night at bedtime. If patient response remains inadequate, duloxetine, an antidepressant FDA approved for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, may be prescribed at a dose of 20 to 60 mg every day. Topical lidocaine, which is FDA approved for postherpetic neuralgia, is sometimes helpful for the control of neuropathic pain in the feet and hands.

Instructions for Patients

By circling one number per line, please indicate how true each statement has been for you during the past seven days using the following scale.

0 = not at all
1 = a little bit
2 = somewhat
3 = quite a bit
4 = very much

I have numbness or tingling in my hands
I have numbness or tingling in my feet
I have discomfort in my hands
I have discomfort in my feet
I have joint pain or muscle cramps
I feel weak all over
I have trouble hearing
I get a ringing or buzzing in my ears
I have trouble buttoning buttons
I have trouble feeling the shape of small objects when they are in my hand
I have trouble walking

Instructions for Healthcare Professionals

This assessment tool is provided to help you evaluate peripheral neuropathy in patients receiving chemotherapy. Healthcare professionals may find discussion of patients’ responses helpful in determining the grade of neuropathy as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (http://ctep.cancer.gov); however, no direct correlation exist between assessment scores and toxicity grades.

Figure 1  Tool for assessing severity of peripheral neuropathy.


This is a corrected copy of the article originally printed in the supplement to JNCCN. This corrected copy also includes additional material not in the original printed supplement.
Future Directions

The use of newer MM agents with improved neurotoxicity profiles can reduce the risk of treatment-related PN. Phase III trials have shown that with the potent thalidomide analogue lenalidomide, the incidence of grade 3 or 4 PN is less than 3%. The risk of treatment-emergent PN also appears to be decreased with the second-generation proteasome inhibitors carfilzomib (PR-171) and salinosporamide A (NPI-0052).

The risk of treatment-related PN may also be reduced by combining agents that have synergistic or neuroprotective effects. For example, a number of investigations have provided evidence of the potential synergy between proteasome inhibitors and immunomodulatory agents in terms of anti-tumor effect. Importantly, while neuropathy as a treatment-related side effect is a concern with this combination, the severity of PN has been less than expected. Specifically, studies have shown that the incidence of grade 3 PN is 5% to 10% with bortezomib/thalidomide/dexamethasone combination therapy. Importantly, no occurrences of grade 4 PN and only 1 case of grade 3 PN have been seen in a phase II trial of RVD in 66 subjects with newly diagnosed MM. In a phase II trial of RVD treatment in 64 patients with relapsed or refractory MM, only 1 case of grade 3 PN was seen, which occurred despite bortezomib reduction and required treatment discontinuation but subsequent improvement followed. This suggests that such combinations may favorably influence at least the severity of PN, perhaps through an anti-inflammatory mechanism, as well as allowing dose reduction without loss of therapeutic effect.

Initial findings suggest that the heat shock protein inhibitor tanespimycin may exhibit both synergistic and neuroprotective effects when combined with bortezomib for treatment of MM. In a phase I/II study, no cases of grade 3/4 treatment-emergent PN were detected in 72 patients treated with bortezomib plus tanespimycin for relapsed and refractory MM.

Asthenia

Asthenia, commonly referred to as fatigue, has been defined as a “distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion” that is not proportional to recent activity, interferes with usual functioning, and is not relieved by rest. Its symptoms can also include generalized weakness, lack of energy, and malaise. Many MM patients with asthenia have comorbidities such as depression, anxiety, and impaired psychosocial functioning, which can be exacerbated by medication effects, especially in combination with glucocorticoids.

Asthenia is a highly prevalent condition among patients with cancer in general and the most common side effect of cancer treatment. Clinical trial data suggest that asthenia of any grade affects approximately 40% to 75% of patients with newly diagnosed disease, 60% to 93% of individuals treated with radiotherapy, and 76% to 96% of patients treated with chemotherapy, depending on the type of primary neoplasia and treatment regimen. Examples of MM-specific rates in phase III trials are grade 3/4 asthenia has been reported by 15% of newly diagnosed patients receiving thalidomide/dexamethasone, by about 6% of patients with relapsed/refractory disease receiving bortezomib, by 6% of patients with relapsed/refractory disease receiving bortezomib/liposomal doxorubicin, and by 10% of newly diagnosed patients receiving lenalidomide/low-dose dexamethasone. The results

Table 2  Bortezomib Dose Modification Based on Severity of Bortezomib-Induced Peripheral Neuropathy

<table>
<thead>
<tr>
<th>Severity of Peripheral Neuropathy</th>
<th>Modification of Dose and Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (paresthesia or loss of reflex) without pain or loss of function</td>
<td>No action</td>
</tr>
<tr>
<td>Grade 1 with pain or grade 2 (interferes with function but not with activities of daily living)</td>
<td>Reduce bortezomib dose from 1.3 to 1.0 mg/m²</td>
</tr>
<tr>
<td>Grade 2 with pain or grade 3 (interferes with activities of daily living)</td>
<td>Withhold until toxicity resolves, then re-initiate bortezomib at 0.7 mg/m² once weekly</td>
</tr>
<tr>
<td>Grade 4 (permanent sensory loss that interferes with function)</td>
<td>Discontinue treatment</td>
</tr>
</tbody>
</table>


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A comprehensive primary asthenia examination is recommended for all patients reporting moderate to severe fatigue. No standardized guidelines for diagnosis of asthenia have been established, but the Tenth Revision of the International Classification of Disease (ICD-10) includes a proposed set of diagnostic criteria (Table 4).

Management approaches for asthenia include 1) treatment of contributing factors (e.g., anemia, pain, depression/anxiety, systemic disorders, such as hypothyroidism, sleep disturbances, nutritional deficiencies, and medication side effects); 2) patient education regarding the causes of asthenia and general strategies for fatigue self-management; 3) nonpharmacologic in-

of patient surveys suggest that asthenia exerts a more negative and longer-lasting effect on patients than pain, nausea, or depression, but that treatment is prescribed in as few as 14% to 40% of cases.59,62 This is true even though asthenia may persist for months or even years after treatment is completed.

According to the NCCN Clinical Practice Guidelines in Oncology: Cancer-Related Fatigue (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org), every cancer patient should be screened for asthenia at regular intervals, in conjunction with other vital-sign monitoring.56 During the initial screening, patients should be asked to assess their level of fatigue during the previous 7-day period, using a predefined scale. A comprehensive primary asthenia examination is recommended for all patients reporting moderate to severe fatigue. No standardized guidelines for diagnosis of asthenia have been established, but the Tenth Revision of the International Classification of Disease (ICD-10) includes a proposed set of diagnostic criteria (Table 4).65

Management approaches for asthenia include 1) treatment of contributing factors (e.g., anemia, pain, depression/anxiety, systemic disorders, such as hypothyroidism, sleep disturbances, nutritional deficiencies, and medication side effects); 2) patient education regarding the causes of asthenia and general strategies for fatigue self-management; 3) nonpharmacologic in-

*For either thalidomide-induced peripheral neuropathy (TiPN) or bortezomib-induced peripheral neuropathy (BiPN)

**Please note:** It is currently advised that patients do not take supplements on days of bortezomib infusions, and all supplements must be discussed with and approved by the treating physicians concerned. Supplements should be taken with food unless otherwise indicated.

**Additional Notes and Precautions:**

Nutritional supplements should be administered at low doses since there is preclinical evidence that the administration of pyridoxine (vitamin B6) and vitamin C at high doses may be harmful. Vitamin B6 can cause additional sensory neuropathy in patients with impaired renal function and in association with a protein-deficient diet. (Levine S, Saltzman A. Pyridoxine (vitamin B6) toxicity: enhancement by uremia in rats. Food Chem Toxicol 2002;40:1449–1451. Levine S, Saltzman A. Pyridoxine (vitamin B6) neurotoxicity: enhancement by protein-deficient diet. J Appl Toxicol 2004;24:497–500.)


In preclinical studies, the anticancer activity of bortezomib has been shown to be blocked by the polyphenols. It is speculated that the vicinal diols in the polyphenols interact with the boronic acid of bortezomib and convert the active triangular boronic acid of bortezomib to an inactive tetrahedral boronate, thus inhibiting the anti-myeloma activity of bortezomib. The restriction of the intake of natural polyphenols in foods or vitamin supplements (such as in green tea) during bortezomib treatment in MM patients should be considered. (Kim TY, Park J, Oh B, et al. for the Korean Multiple Myeloma Working Party (KMMWP). Natural polyphenols antagonize the antimielyoma activity of proteasome inhibitor bortezomib by direct chemical interaction. Br J Haematol 2009;146:270–281.)

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Interventions, including counseling, occupational therapy, cognitive behavioral therapy, exercise, dietary changes, and stress management; and 4) pharmacologic symptomatic therapy. Clinical trial data and anecdotal evidence suggest that psychostimulants, low-dose corticosteroids, and antidepressants may be helpful, but psychostimulants are investigational for this purpose and should be used with caution only after treatment- and disease-specific morbidities have been characterized or excluded. The optimal dose and schedule have not been established for use of psychostimulants in cancer patients. Specific measures in MM patients include attention to hydration, evaluation of novel-agent specific–effects (such as those seen with bortezomib, thalidomide, and lenalidomide); exclusion of important co-morbidities (e.g., thyroid deficiency, amyloidosis), and care regarding the possibility of progressive disease.

Among novel therapies associated with significant PN are bortezomib and thalidomide, both agents that have transformed the MM treatment paradigm through improvements in response rates, time-to-progression, and survival. Novel combination therapies for MM have the potential to reduce side effects, as well as enhance activity, thus improving the therapeutic index. In addition, effective management strategies are critical to reduce the risk of further treatment-related toxicities and improve the benefits of therapy in this otherwise incurable malignancy.

Conclusions
Peripheral neuropathy and asthenia are frequent complications of MM treatment. These complications interfere with optimum therapy and adversely affect patient outcomes as well as quality of life.

Acknowledgment
The authors thank Kimberly Cohen for medical writing assistance and Katherine Redman for administrative support. The authors also gratefully acknowledge the input of Kathleen Colson, RN, and Deborah Doss, RN.

References

Table 4 ICD-10 Criteria for Cancer-Related Fatigue

<table>
<thead>
<tr>
<th>A.</th>
<th>Six (or more) of the following symptoms have been present every day or nearly every day during the same 2-week period in the past month, with at least 1 symptom (A1) being significant fatigue:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1.</td>
<td>Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity</td>
</tr>
<tr>
<td>A2.</td>
<td>Complaints of generalized weakness or limb heaviness</td>
</tr>
<tr>
<td>A3.</td>
<td>Diminished concentration or attention</td>
</tr>
<tr>
<td>A4.</td>
<td>Decreased motivation or interest to engage in usual activities</td>
</tr>
<tr>
<td>A5.</td>
<td>Insomnia or hypersomnia</td>
</tr>
<tr>
<td>A6.</td>
<td>Experience of sleep as unrefreshing or nonrestorative</td>
</tr>
<tr>
<td>A7.</td>
<td>Perceived need to struggle to overcome inactivity</td>
</tr>
<tr>
<td>A8.</td>
<td>Marked emotional reactivity (e.g., sadness, frustration, or irritability) to feeling fatigued</td>
</tr>
<tr>
<td>A9.</td>
<td>Difficulty completing daily tasks attributed to feeling fatigued</td>
</tr>
<tr>
<td>A10.</td>
<td>Perceived problems with short-term memory</td>
</tr>
<tr>
<td>A11.</td>
<td>Postexertional malaise lasting several hours</td>
</tr>
</tbody>
</table>

| B. | The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning |

| C. | Evidence from the history, physical examination, or laboratory findings shows that the symptoms are a consequence of cancer or cancer therapy |

| D. | The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium |

Richardson et al.

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

Ruben Niesvizky, MD,* and Ashraf Z. Badros, MD; New York, New York, and Baltimore, Maryland

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)

Therapies such as thalidomide, bortezomib, and lenalidomide have provided meaningful benefits in multiple myeloma (MM), such as improved response rates and improved duration of response, but they have been associated with an increased risk of certain adverse events. Venous thromboembolism (VTE), osteonecrosis of the jaw (ONJ), renal failure, and anemia are all common complications of MM therapy. Community oncologists should be familiar with these potential complications and the strategies for preventing, identifying, and managing them.

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.1 Current evidence indicates that cancer increases thrombosis risk 4.1-fold and chemotherapy increases the risk 6.5-fold.2 Other key VTE risk factors include older age, recent surgery, acute medical illness, immobility or bed rest. The risk of VTE is typically cumulative.1 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.3 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.4

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. Because VTE risk is frequently cumulative, patients...
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.1,12,26

According to the IMWG, selection of candidates for thromboprophylaxis should be based on the baseline VTE risk associated with each therapy.12 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 2.12

For patients receiving epoetin alfa, the FDA recommends administration of an anticoagulant prophylactic.27,28 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.29 The combination of bortezomib with an ESA does not appear to increase the risk of VTE.30

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.12,31 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.12 Proposed DVT treatment strategies are outlined in Figure 1.

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.

Table 2 Recommendations for Thromboprophylaxis in Multiple Myeloma Patients Treated With Thalidomide or Lenalidomide

- ≤ 1 VTE risk factor: aspirin (81–325 mg once daily)
- ≥ 2 risk factors: LMWH (equivalent to enoxaparin, 40 mg/d)
- LMWH is also recommended for all patients receiving thalidomide or lenalidomide plus high-dose dexamethasone or doxorubicin
- Barring contraindications in the front-line setting, treatment strategies using dexamethasone should use low-dose dexamethasone and include aspirin prophylaxis
- Full-dose warfarin (target INR 2–3) is an alternative to LMWH, although limited data exist to support this strategy
- Anticoagulant prophylaxis is recommended in patients with relapsed disease and a high risk for VTE
- It may be reasonable to deliver anticoagulant prophylaxis for 4 to 6 months; longer treatment periods may be considered in the presence of additional risk factors
- If VTE occurs in patients receiving thalidomide or lenalidomide, it is reasonable to briefly discontinue therapy and resume once proper anticoagulation has been established

Abbreviations: INR, International Normalized Ratio; LMWH, low molecular weight heparin; VTE, venous thromboembolism.
For patients who do develop ONJ, a conservative, “supportive,” nonsurgical approach has been recommended: chlorhexidine 0.12% oral rinses, intermittent systemic antibiotics, and careful seques-trectomy. 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. Initiate therapy with LMWH*

Start oral anticoagulation within 24 hours (if concomitant thrombocytopenia risk is low)

Administer LMWH for a minimum of 5 days; do not stop treatment until INR is 2.0 to 3.0 for 2 consecutive days

Briefly discontinue thalidomide or lenalidomide until full anticoagulation has been established

Optimal treatment duration is unknown; extended LMWH treatment should be considered based on cost-benefit assessment

Figure 1 Recommended approach to treatment of VTE in patients with multiple myeloma.

Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.
*Treatment with unfractionated heparin is recommended for patients with renal failure.
therapy, and B₁₂ 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 \((P = .026; \text{95\% CI, 0.0026})\) 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 \((P < .001 \text{ for both comparisons})\). 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 prophylactically. 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.

Acknowledgment
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References


The Role of Maintenance Therapy in the Treatment of Multiple Myeloma

Ashraf Z. Badros, MD, Baltimore, Maryland

Key Words
Autologous stem cell transplantation, interferon, thalidomide, bortezomib, lenalidomide

Abstract
Maintenance therapy in multiple myeloma has been under investigation for more than 3 decades, without evidence of clear benefit until recently. Chemotherapy maintenance offers no benefit after conventional or high-dose treatment. Interferon-based maintenance is associated with minimal improvements in clinical outcomes, but is poorly tolerated. Results of corticosteroid maintenance studies have been conflicting; at least one randomized trial showed improved survival with prednisone maintenance after conventional chemotherapy. The role of the novel agents thalidomide, lenalidomide, and bortezomib as maintenance is emerging. Most reported maintenance studies have evaluated thalidomide, alone or in combination with a corticosteroid. Several of these studies suggest that thalidomide-based maintenance prolongs overall survival after autologous stem cell transplantation. Important questions that have not yet been resolved include the optimal dose and duration of thalidomide, whether clinical benefit depends on response to induction therapy and risk for relapse, and whether reported benefits are caused by cytoreduction or eradication of minimal residual disease, especially with bortezomib maintenance. Ongoing randomized trials are evaluating lenalidomide and bortezomib maintenance therapies to better define the role of these drugs as maintenance in multiple myeloma. (JNCCN 2010;8[Suppl 1]:S21–S27)

Maintenance After Conventional Chemotherapy

Because of the increased risk for acute myeloid leukemia with prolonged alkylating agent therapy, alternatives to this approach were being sought as early as the 1980s. Interferon-alpha was the subject of numerous trials that produced inconclusive results. Two meta-analyses, one performed using individual patient data and the other using published data, found a small but statistically significant survival benefit when interferon maintenance was used after conventional therapy. However, few patients can tolerate the substantial toxicities of interferon therapy, and therefore interferon maintenance is rarely used.

Several studies have evaluated corticosteroids, with or without interferon, as maintenance, but the data are insufficient to draw firm conclusions. When compared directly with interferon maintenance, dexamethasone, 20 mg/m², given orally on days 1 to 4 of a 28-day cycle produced a similar median duration of remission, but significantly fewer patients treated with dexamethasone maintenance responded to repeat melphalan/dexamethasone at relapse relative to those treated with inter-
Data on bortezomib-based maintenance strategies are beginning to emerge. A randomized phase III trial conducted by the Italian Multiple Myeloma Group is comparing bortezomib/melphalan/prednisone/thalidomide (VMPT) induction followed by bortezomib/thalidomide maintenance to bortezomib/melphalan/prednisone (VMP) induction without maintenance in elderly patients with newly diagnosed myeloma. \(^1\) Results presented at the 2008 American Society of Hematology Annual Meeting showed a higher response rate for VMPT relative to VMP (complete response \([\text{CR}]\) rate, 31\% vs. 16\%; \(P = .003\); very good partial response \([\text{VGPR}]\) rate, 55\% vs. 42\%; \(P = .02\)) but no difference in OS at 3 years.

**Maintenance After Autologous Stem Cell Transplantation**

**Chemotherapy and Interferon Maintenance After Autologous Stem Cell Transplantation**

As with conventional induction regimens, chemotherapy is not currently recommended as a maintenance strategy after autologous stem cell transplantation (ASCT).\(^2\) Interferon is currently considered a maintenance option in the NCCN Clinical Practice Guidelines in Oncology for Multiple Myeloma (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org), based on low-level evidence and non-uniform NCCN consensus (category 2B).\(^2\) However, given the lack of clear activity and substantial toxicity associated with interferon and the availability of new agents, research into interferon maintenance has been largely abandoned.

**Novel Agents After ASCT**

Thalidomide is the best studied of the novel agents in the post-ASCT maintenance setting, although randomized clinical trials of bortezomib and lenalidomide are underway (Table 1).\(^1\) Four randomized phase III trials have been completed to establish the role of thalidomide-based maintenance after ASCT (Table 2).\(^1\)–\(^4\) In all 4 studies, improvements in response (CR) and PFS were seen. Of the 4 trials, 3 also reported significant improvements in OS, and a meta-analysis of these data showed a trend toward improved survival with maintenance thalidomide after ASCT (Figure 1).\(^7\) When the trial that in-

terferon maintenance (44\% vs. 82\%; \(P = .001\)).\(^5\) In the MY.7 study by the National Cancer Institute of Canada (NCIC), dexamethasone maintenance improved median progression-free survival (PFS) based on a hazard ratio (HR) of 0.61 (95\% CI, 0.47–0.79), but not overall survival (OS; HR, 0.88; 95\% CI, 0.65–1.18), relative to no maintenance.\(^6\) Similarly, when added to interferon, thrice-weekly prednisone, 50 mg, improved median PFS but not overall survival (OS), relative to interferon alone in the SWOG 9028 trial.\(^7\)

Only one trial, SWOG 9210, has shown a survival benefit with corticosteroid maintenance therapy.\(^8\) In this randomized trial, a prednisone regimen of 50 mg every other day significantly improved median PFS (14 vs. 5 months; \(P = .003\)) and OS (37 vs. 26 months; \(P = .05\)) relative to a physiologic dose regimen (10 mg every other day). These data support the use of steroids in this setting, although the efficacy of the SWOG 9210 regimen has not been confirmed in another controlled clinical trial.

Recently, several trials have focused on the role of novel agents as maintenance therapy. Offidani et al.\(^9\) conducted a randomized comparison of maintenance with either thalidomide (100 mg/d) plus dexamethasone (20 mg/d for 4 days per month) or interferon thrice weekly plus dexamethasone in 103 patients who experienced response to induction therapy with ThaDD (thalidomide, dexamethasone, and pegylated liposomal doxorubicin). Both 2-year PFS and OS rates were significantly better with thalidomide-based maintenance (PFS, 63\% vs. 32\%; \(P = .024\); OS, 84\% vs. 68\%; \(P = .030\)). The low-dose thalidomide regimen was generally well-tolerated, with peripheral neuropathy (6\%) and constipation (4\%) the most commonly reported grade 3/4 toxicities. More patients were compliant with thalidomide therapy long-term relative to interferon.

Preliminary data have been reported for maintenance therapy in elderly patients who experienced stable disease or better with thalidomide/dexamethasone or melphalan/prednisone induction.\(^1\) A total of 111 patients with nonprogressive disease were randomized to maintenance with thalidomide, 100 mg daily, with thrice-weekly interferon or interferon alone. At a median follow-up of 17.2 months, median survival from the start of maintenance was 53.1 months in the thalidomide/interferon arm and not yet reached in the interferon-alone arm (\(P = .49\)).

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cluded thalidomide during induction was excluded, the OS benefit became significant (HR, 0.49; 95% CI, 0.32–0.74).\textsuperscript{17} Peripheral neuropathy complicated the treatment course in all 4 studies, and, unsurprisingly, the incidence was highest when the duration of thalidomide maintenance was prolonged. None of the studies, however, determined the optimal dose or duration of thalidomide-based maintenance after ASCT.

A recent update to one of the trials, conducted at a median follow-up of 6 years, suggests that thalidomide may benefit patients with high-risk myeloma.\textsuperscript{18} The estimated OS rate at 5 years was 56% for patients with cytogenetic abnormalities treated with thalidomide versus 43% for those with cytogenetic abnormalities in the control group (\(P = .02\)).

Results from other randomized trials of thalidomide maintenance were presented at national meetings within the past year, none of which supports an improvement in OS. The United Kingdom Medical Research Council (MRC) Myeloma IX study evaluated thalidomide maintenance after primary treatment of myeloma (either ASCT or conventional chemotherapy, depending on the clinical situation).\textsuperscript{19} A total of 820 patients were randomly assigned to thalidomide maintenance (100 mg/d until relapse) or no maintenance, making this the largest trial conducted. Overall, PFS was numerically higher in the thalidomide arm, but the improvement was statistically significant only among patients who ex-

### Table 1 Ongoing Randomized Phase III Trials of Maintenance Therapy After ASCT in Patients With Newly Diagnosed Multiple Myeloma

<table>
<thead>
<tr>
<th>Clinical Trial and Accrual Goal</th>
<th>Primary Treatment</th>
<th>Maintenance Regimen(s)</th>
<th>Primary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCIC MY.10 (N = 324) [NCT00049673]</td>
<td>ASCT</td>
<td>• Thalidomide daily with alternate-day prednisone &lt;br&gt; • Observation Maintenance × 4 y</td>
<td>OS</td>
</tr>
<tr>
<td>NHLBI/ BMTCTN0102 (N = 710) [NCT00075829]</td>
<td>Tandem transplantation (no HLA-matched sibling) or ASCT followed by mini-allogeneic SCT (HLA-matched sibling)</td>
<td>• Thalidomide/dexamethasone &lt;br&gt; • Observation Maintenance × 1 y; only administered to patients undergoing tandem transplantation</td>
<td>3-y PFS</td>
</tr>
<tr>
<td>CALGB 100104 (N = 462) [NCT00114101]</td>
<td>ASCT</td>
<td>• Lenalidomide &lt;br&gt; • Placebo Maintenance continues as tolerated or until progression; only administered to patients with stable or responding disease after ASCT</td>
<td>TTP</td>
</tr>
<tr>
<td>IFM 2005-02 (N = 614) [NCT00430365]</td>
<td>ASCT</td>
<td>• Lenalidomide &lt;br&gt; • Placebo Duration not specified</td>
<td>Duration of post-ASCT response</td>
</tr>
<tr>
<td>Gesellschaft für Medizinische Innovation (N = 194) [NCT00891384]</td>
<td>ASCT</td>
<td>• Lenalidomide, 5 mg, days 1–21 q4w &lt;br&gt; • Lenalidomide, 25 mg/d, days 1–21 q4w Maintenance continues until disease progression</td>
<td>EFS</td>
</tr>
<tr>
<td>HOVON-65/GMMG-HD4 (N = 825) [NCT00891384]</td>
<td>Induction: VAD vs. PAD Stem cell collection: CAD ASCT: HDM</td>
<td>• Thalidomide 50 mg/d &lt;br&gt; • Bortezomib 1.3 mg/m² q2w Maintenance × 2 y</td>
<td>PFS</td>
</tr>
<tr>
<td>PETHEMA GEM05 (N = 390) [NCT00461747]</td>
<td>Induction: VBMCP-VBAD-bortezomib vs. TD vs. VTD followed by ASCT</td>
<td>• Interferon &lt;br&gt; • Thalidomide &lt;br&gt; • Thalidomide plus bortezomib Maintenance × 3 y</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

Abbreviations: ASCT, autologous stem cell transplantation; CAD, cyclophosphamide/doxorubicin/dexamethasone; EFS, event-free survival; HDM, high-dose melphalan; HLA, histocompatibility leukocyte antigen; OS, overall survival; PAD, bortezomib/doxorubicin/dexamethasone; PFS, progression-free survival; SCT, stem cell transplantation; TD, thalidomide/dexamethasone; TTP, time-to-progression; VAD, vincristine/doxorubicin/dexamethasone; VBMCP-VBAD, vincristine/carmustine/melphalan/cyclophosphamide/prednisone alternating with vincristine/carmustine/doxorubicin/dexamethasone; VTD, bortezomib/thalidomide/dexamethasone.
Two large studies have reported that the survival benefits with thalidomide were limited to patients who did not experience at least a VGPR, supporting the hypothesis that post-transplantation thalidomide provides additional cytoreduction rather than eradication or suppression of minimal residual disease. Currently, however, initial response to therapy should not be used to guide maintenance treatment decisions.

Furthermore, the optimal dose and duration of maintenance thalidomide remains to be determined. The incidence of neuropathy is clearly cumulative and dose-related, partly leading to the recommendation that thalidomide not be used throughout the entire treatment course. Doses of 200 mg daily or more are difficult to administer on a long-term basis. 22,23 Lower-dose (100 mg/d) and time-limited therapy (6–12 months) were efficacious in studies by the Tunisian Multiple Myeloma Study Group (TMMSG) and Australasian Leukaemia and Lymphoma Group (ALLG), but the United Kingdom MRC Myeloma IX study did not show a survival benefit with a 100-mg daily thalidomide maintenance regimen.

Therefore, although data support a role for thalidomide-based maintenance therapy after ASCT, several important questions remain, such as whether thalidomide given post-transplantation truly maintains response versus early initiation of salvage therapy. Two large studies have reported that the survival benefits with thalidomide were limited to patients who did not experience at least a VGPR, supporting the hypothesis that post-transplantation thalidomide provides additional cytoreduction rather than eradication or suppression of minimal residual disease. Currently, however, initial response to therapy should not be used to guide maintenance treatment decisions.

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Another intriguing issue is whether patients who begin maintenance treatment with less than a VGPR should discontinue therapy once they experience VGPR or CR, given that those with VGPR/CR before maintenance therapy did not seem to benefit from additional therapy in some trials. The NCCN
Table 2  Published Randomized Trials of Thalidomide-based Maintenance Therapy After ASCT

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimens</th>
<th>Thalidomide Regimen</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT213</td>
<td>Newly diagnosed progressive or symptomatic MM, ≤ 75 y (N = 668)</td>
<td>Induction: 4 cycles of chemotherapy, with or without thalidomide&lt;br&gt;ASCT: tandem transplantation with melphalan-based preparative regimens, with or without thalidomide&lt;br&gt;Consolidation: randomized to 1 of 3 regimens, with or without thalidomide&lt;br&gt;Maintenance: IFN tid; with or without thalidomide; cycles of dexamethasone, 40 mg, given on days 1–4, 9–12, 17–20 q3mo for 4 cycles, first year only</td>
<td>Thalidomide vs. observation:&lt;br&gt;CR: 62% vs. 43%; &lt;br&gt;P = .001&lt;br&gt;MST after relapse: 1.1 vs. 2.7 y; &lt;br&gt;P = .001&lt;br&gt;Grade 2 AEs, thalidomide vs. observation:&lt;br&gt;Thrombosis/embolism: 30% vs. 17%; &lt;br&gt;P = .001&lt;br&gt;PN: 27% vs. 17%; &lt;br&gt;P = .001&lt;br&gt;Bowel obstruction: 14% vs. 8%; &lt;br&gt;P = .02&lt;br&gt;Tremor: 13% vs. 6%; &lt;br&gt;P = .003&lt;br&gt;Syncope: 12% vs. 4%; &lt;br&gt;P &lt; .001</td>
<td></td>
</tr>
<tr>
<td>IFM 99-0214</td>
<td>MM without or with one adverse prognostic factor, &lt; 65 y (N = 708)</td>
<td>Induction: VAD × 3–4 cycles&lt;br&gt;ASCT: tandem transplantation with melphalan-based preparative regimens&lt;br&gt;Randomization to maintenance with:&lt;br&gt;A) no maintenance&lt;br&gt;B) pamidronate, 90 mg, IV q4w until progression&lt;br&gt;C) pamidronate plus thalidomide</td>
<td>Maintenance arm C received thalidomide, 400 mg/d, with reduction to minimum of 50 mg/d allowed for toxicity; thalidomide given until disease progression</td>
<td>Arms A vs. B vs. C:&lt;br&gt;Best response after randomization (P = .001):&lt;br&gt;CR/VGPR: 55% vs. 57% vs. 67%&lt;br&gt;PR: 37% vs. 37% vs. 30%&lt;br&gt;MR: 7.5% vs. 5.5% vs. 3%&lt;br&gt;3-y probability of EFS: 36% vs. 37% vs. 52%; P &lt; .009&lt;br&gt;4-y probability of OS: 77% vs. 74% vs. 87%; P &lt; .04</td>
</tr>
<tr>
<td>TMMSG15</td>
<td>Stage II/III Durie-Salmon MM, &lt; 60 y (N = 202)</td>
<td>Induction: thalidomide with intermittent dexamethasone&lt;br&gt;ASCT: cyclophosphamide/GCSF for stem cell collection&lt;br&gt;Randomization:&lt;br&gt;A) Tandem transplantation with melphalan-based preparative regimens; thalidomide given at progression or relapse&lt;br&gt;B) Single transplantation with melphalan-based preparative regimen, with thalidomide maintenance; second ASCT at progression or relapse</td>
<td>Induction: 200 mg/d for 75 d&lt;br&gt;Tandem transplantation: salvage thalidomide, 200 mg/d&lt;br&gt;Single transplantation arm: 100 mg/d initiated 3 mo post-ASCT and continued for 6 mo</td>
<td>Arm A vs. B:&lt;br&gt;CR/VGPR:* 54% vs. 68%;&lt;br&gt;P = .04&lt;br&gt;PR:* 39% vs. 27%; P = NS&lt;br&gt;MR:* 3% vs. 3%; P = NS&lt;br&gt;3-y PFS: 57% vs. 85%;&lt;br&gt;P = .02&lt;br&gt;3-y OS: 65% vs. 85%;&lt;br&gt;P = .04</td>
</tr>
<tr>
<td>ALLG MM616</td>
<td>Newly diagnosed, symptomatic MM, ≤ 70 y (N = 269)</td>
<td>ASCT: Single transplantation with melphalan-based preparative regimen&lt;br&gt;Randomization to:&lt;br&gt;A) Prednisolone, 50 mg, every other day&lt;br&gt;B) Prednisolone plus thalidomide</td>
<td>Arm B received 100 mg/d, increased to 200 mg after 14 days as tolerated for up to 12 mo</td>
<td>Arm A vs. B:&lt;br&gt;CR/VGPR at 1 y: 40% vs. 63%; P &lt; .001&lt;br&gt;3-y PFS: 23% vs. 42%;&lt;br&gt;P &lt; .001&lt;br&gt;3-y OS: 75% vs. 86%;&lt;br&gt;P = .004</td>
</tr>
</tbody>
</table>

Abbreviations: AEs, adverse events; ALLG, Australasian Leukaemia and Lymphoma Group; ASCT, autologous stem cell transplantation; CR, complete response; EFS, event-free survival; GCSF, granulocyte colony-stimulating factor; IFN, interferon-alpha; MM, multiple myeloma; MR, minimal response; MST, median survival time; NS, not significant; OS, overall survival; PFS, progression-free survival; PN, peripheral neuropathy; PR, partial response; TT2, Total Therapy 2; TTMSG, Tunisian Multiple Myeloma Study Group; VAD, vincristine/Adriamycin/dexamethasone; VGPR, very good partial response.

*Assessed 6 months after second transplantation in arm A and 3 months after thalidomide maintenance in arm B.
guidelines currently do not address the dose or duration of maintenance thalidomide. Most centers currently continue patients on thalidomide for 1 to 2 years, depending on the patient's tolerance.

Finally, more research is needed to determine whether cytogenetics can be used to identify appropriate candidates for post-transplantation maintenance. Subgroup analyses from Total Therapy 2 suggest that thalidomide maintenance reduced the risk for death in patients with metaphase cytogenetic abnormalities, a well-known adverse prognostic factor, but not in those without these abnormalities. The IFM 99-02 trial showed that thalidomide was not effective in patients with del(13), and the United Kingdom MRC Myeloma IX trial showed that risk for death was significantly increased with thalidomide maintenance in patients with del (17p).

As these authors describe elsewhere in this supplement, increasing evidence suggests that the novel agents bortezomib and lenalidomide may overcome the poor prognosis associated with cytogenetic abnormalities in myeloma. How these findings from the induction setting translate into the maintenance setting remains to be determined in appropriately designed clinical trials.

Conclusions
The role of maintenance therapy after conventional chemotherapy remains to be determined, but there is a paucity of ongoing research in this setting. Much work is needed to evaluate maintenance therapy after ASCT, yet the optimal treatment regimen has not been identified. Thalidomide is the first novel agent to be studied as a maintenance therapy and shows the most promise. However, it may work through a direct cytoreductive effect rather than a true maintenance effect, given that several trials showed benefit only in patients who had not experienced at least a VGPR before initiating maintenance treatment. The optimal dose and duration of thalidomide maintenance remains to be determined, as does the appropriate patient population for routine treatment. Moreover, whether thalidomide should be used as maintenance or at relapse remains a matter of debate. More robust results of trials with lenalidomide and bortezomib maintenance therapies are eagerly awaited.

Acknowledgment
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References
In the Age of Novel Therapies, What Defines High-Risk Multiple Myeloma?

Ashraf Badros, MD, Baltimore, Maryland

Key Words
Chromosomal abnormalities, risk stratification, thalidomide, bortezomib, lenalidomide, allogeneic stem cell transplantation

Abstract
Multiple myeloma is characterized by clinical and biologic heterogeneity. Recently, genetic analysis has provided predictable prognosis across different types of treatment. These advances have allowed patients to be categorized into different risk groups and have been particularly useful in defining a high-risk group with short survival after standard- and high-dose chemotherapies. Preliminary studies have shown promising outcomes after the use of novel agents, such as bortezomib, thalidomide, and lenalidomide in high-risk patients, including those eligible for autologous stem cell transplantation and those who cannot or will not undergo transplantation. The application of risk-based therapy and the potential of the new agents to abrogate the influence of adverse prognostic features may improve outcomes in these patients. (JNCCN 2010;8[Suppl 1]:S28–S34)

Multiple myeloma (MM) is a clinically and pathophysiologically heterogeneous disease, as evidenced by variable response to treatment and variation in survival from a few months to more than 10 years. Nationwide U.S. data show that approximately 20% of patients survive longer than 10 years, irrespective of therapy. Genetic variations among myeloma cells appear to underlie much of the heterogeneity in clinical outcomes. Several groups have reported on the prognostic capability of genetic information in MM, which has led to re-evaluation of the definition of high-risk disease. The use of nonchemotherapeutic antimyeloma agents is also driving efforts for improved prognostication. Recent data suggest that agents such as thalidomide, bortezomib, and lenalidomide may neutralize the effects of negative prognostic factors. An effective means of risk stratification is required so that patients with poor risk may be offered more aggressive treatment or be entered into clinical trials of novel agents as first-line therapy. This article discusses evolving systems for risk stratification and the potential of novel agents to improve outcomes in high-risk patients newly diagnosed with MM.

Evaluation of Genetic Changes
Plasma cells in MM harbor multiple and complex chromosomal abnormalities. Studies in the past 7 to 8 years have shown the prognostic value of genetic aberrations, and the assessment of chromosomal abnormalities is an additional parameter that can refine the identification of high-risk patients.

The different techniques currently used to detect genetic aberrations are conventional karyotyping, fluorescence in situ hybridization (FISH), and microarray technology. Nearly all patients with MM have abnormal chromosomes according to FISH (deletions, aneuploidy, and translocations), but standard metaphase analysis identifies aberrant karyotypes in approximately 30% of patients. Any abnormality detected conventionally identifies a subgroup with a higher proliferative rate and worse prognosis. Several chromosomal changes have been associated with shorter survival. The most widely recognized poor prognosticators of survival are deletions of chromosome 13 or its long arm (del[13]), translocations of the heavy-chain gene on chromosome 14 (t[4;14] or t[14;16]), and deletion of p53 on chromosome 17p13 (del[17p]). Deletion or structural anomalies of chromosome 13 are
detected in approximately 50% of patients with an abnormal karyotype and in 10% to 20% of patients overall. Patients with chromosome 13 anomalies in their metaphase cells have shorter survival and lower treatment response rates. The effect of del(13) on prognosis is greater when it is detected with karyotype analysis in metaphase cells than with interphase FISH.5,7–9 Recent data suggest that the prognostic significance of del(13) may depend on its association with t(4;14), del(17p), or a high serum level of β₂-microglobulin (β₂M).9

Chromosome translocations involving the immunoglobulin heavy-chain gene locus are detectable in 60% to 75% of patients with MM according to FISH. Translocations that have prognostic significance include t(4;14), t(14;16), t(11;14), and t(6;14). Of these, t(4;14) (detected in 15%–20% of patients) and t(14;16) (present in 2%–10% of patients) are unfavorable prognostic factors for patients with MM treated with either conventional or high-dose therapy (HDT).5,6,8,10 By contrast, t(11;14) (detected in 15%–20% of patients) characterizes a group of patients with neutral or somewhat favorable prognosis.8,9

Deletion of chromosome 17p13, present in 10% of patients, confers poorer survival. Patients with this deletion who undergo HDT followed by autologous stem cell transplantation (ASCT) have significantly shorter progression-free and overall survival than patients without this deletion.6–8

Aneuploidy occurs frequently in MM cells, and ploidy status has a significant impact on prognosis. Hypoploidy is associated with more aggressive disease and shorter survival. Hyperdiploid MM has a lower frequency of immunoglobulin heavy-chain translocations and is associated with good prognosis.5,9

Although chromosomal anomalies have a high impact on survival, they must be evaluated in the context of other parameters, especially the β₂M level. For example, subsets of patients with high-risk genetics, such as t(14;4) or del(17p), but with low β₂M level may have a similar or only marginally worse prognosis than other patients.9

A few teams have recently investigated the role of gene expression profiling (GEP) in the prognostication of myeloma, and several molecular classification systems have been proposed based on this technique.11–13 Although GEP is useful for risk stratification, it is currently limited by a lack of a uniform platform and widespread availability, and thus is not easily translated into clinical practice.

### Risk Stratification

Genetic changes display such a high prognostic value that myeloma experts have recently recommended including cytogenetic and FISH evaluations in a risk stratification system (Table 1).4,14 Routine molecular genetic testing is recommended for all patients with MM to identify the 25% with high-risk disease in whom conventional therapies perform poorly. The recommended basic test panel includes FISH detection of t(4;14), t(14;16), and del(17q); cytogenetic detection of del(13); and determination of serum β₂M, lactate dehydrogenase, or plasma cell labeling index as surrogate markers of tumor cell proliferation.

This risk-stratification model in Table 1 forms the basis of the Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART), an evidence-based algorithm of treatment decision-making that was developed at the Mayo Clinic for patients with newly diagnosed MM.15 In general, these high-risk features define a population of 25% to 30% of patients who have median survival of 2 to 3 years, even with stem cell transplantation, compared with

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**Table 1 Recommended Classification of High-Risk Myeloma**

<table>
<thead>
<tr>
<th>High Risk (25%)</th>
<th>Good Risk (75%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any of the following: t(4;14) according to FISH</td>
<td>Absence of high-risk features and presence of any of the following: Hyperdiploidy</td>
</tr>
<tr>
<td>t(14;16) or t(14;20) according to FISH</td>
<td>t(11;14) according to FISH</td>
</tr>
<tr>
<td>Del 17q13 according to FISH</td>
<td>Del 13 or aneuploidy according to metaphase analysis</td>
</tr>
<tr>
<td>Deletion 13 or aneuploidy according to metaphase analysis</td>
<td>Plasma cell labeling index &gt; 3%</td>
</tr>
</tbody>
</table>

Abbreviations: FISH, fluorescence in situ hybridization.

*Patients should be considered to be truly low-risk if genetic markers are accompanied by a β₂-microglobulin level less than 5.5 mg/L, lactate dehydrogenase less than 250 U/L, and/or a plasma cell labeling index less than 1%. Similarly, the presence of β₂-microglobulin level less than 3.5 mg/L may favorably modify the course for patients with otherwise high-risk genetics.

### Table 2  Selected Studies of New Agents in Newly Diagnosed High-Risk Patients Eligible for High-Dose Therapy/Autologous Stem Cell Transplantation

<table>
<thead>
<tr>
<th>First Author</th>
<th>No. of Patients</th>
<th>Patient Population</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bortezomib</strong></td>
<td></td>
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</tr>
</tbody>
</table>
| Dispenzieri et al.\(^1\) | 44 | Patients with high-risk newly diagnosed myeloma (del[13q], PCLI > 1%, t[4;14] or \(\beta_2M > 5.5\) mg/L) | Bortezomib for induction and maintenance | Response rate (> PR):  
• All = 48%  
• PCLI > 1%: 47%  
• \(\beta_2M > 5.5\) mg/L: 45%  
• del(13q): 33%  
• t(4;14): 50%  
After median follow-up of 41.6 months:  
• 1-y PFS/OS: 50%/88%  
• 2-y PFS/OS: 28%/76% |
| Knop et al.\(^2\) | 200 | Newly diagnosed myeloma \(\beta_2M: 3.75 \pm 3.38\) mg/L del(13): 55 (28%) del(17p): 20 (10%) t(4;14): 16 (8%) | Bort-dex-cyclophosphamide | Response rate on day 63  
ORR: 84%  
Normal cytogenetics: 86%  
Abnormal cytogenetics: 82%  
del(13): 82%  
del(17p): 70%  
t(4;14): 94% |
| **Lenalidomide** | | | | |
| Kapoor et al.\(^3\) | 100 | High-risk: at least 1 of the following: hypodiploidy, del[13], del(17p), t(4;14), t(4;16), or PCLI ≥ 3%  
Standard-risk: absence of all high-risk features | Len-dex (low- or high-dose) | Response rates:  
• CR + VGPR: high-risk, 38%; standard-risk, 45%  
• > PR: high-risk, 81%; standard-risk, 89%  
Median PFS: high-risk, 18.5 months; standard-risk, 36.5 months  
Median OS: not reached for either group |
| Zonder et al.\(^4\) | 198 | AK  
Len-dex: 13/54  
Dex: 12/43  
FISH-defined HRCA (del[13] or del[17p])  
Len-dex group: 8/37  
Dex group: 11/45 | Len-dex vs. placebo-dex | Estimated 1-y PFS (with AK vs. without):  
• Len-dex: 54% vs. 86% (\(P = N.S\))  
• Dec: 27% vs. 67% (\(P = .008\))  
Estimated 1-y PFS (with HRCA vs. without):  
• Len-dex: 100% vs. 71% (\(P = N.S\))  
• Dec: 55% vs. 57% (\(P = N.S\))  
Estimated 1-y OS (with HRCA vs. without):  
• Len-dex: 80% vs. 100% (\(P = N.S\))  
• Dec: 88% vs. 100% (\(P = N.S\)) |
| Kapoor et al.\(^5\) | 125 | High baseline PCLI (≥ 1%) vs. low baseline PCLI (< 1%) | Len-dex vs. TD | Median PFS (high PCLI vs. low PCLI):  
• Len-dex: 2.3 vs. 3.1 y (\(N.S\))  
• TD: 1.3 vs. 2.3 y (\(P = .01\))  
Median OS:  
• Len-dex: not reached for either group  
• TD: 2.3 vs. 6.9 y (\(P = .02\)) |
| **Thalidomide** | | | | |
| Zangari et al.\(^6\)  
Waheed et al.\(^7\) | 668 | Patients with or without cytogenetic abnormalities by metaphase analysis | TT2 protocol (induction, tandem transplantation, consolidation, maintenance) with thal vs. TT2 protocol without thal | 5-y follow-up (TT2 + thal vs. TT2 without thal)  
Median EFS:  
• With CA: 3.7 vs. 2.5 y (\(P = .03\))  
• Without CA: 6.3 vs. 5.4 y (\(P = .04\))  
Median OS:  
• With CA: NR vs. 4.1 y (\(P = .04\))  
• Without CA: NR vs. NR  
81-month follow-up (TT2 + thalidomide vs. TT2 without thalidomide)  
6-y EFS:  
• With CA: 38% vs. 20% (\(P = .008\))  
• Without CA: 56% vs. 45% (\(P = .02\))  
6-y OS:  
• With CA: 53% vs. 35% (\(P < .001\))  
• Without CA: 70% vs. 68% (\(P = N.S\)) |
| **Combinations** | | | | |
| Cavo et al.\(^8\) | 474 (464 evaluable) | ISS II + III: 54%-56%  
del(13): 46%-47%  
t(4;14): 19%-20%  
del(17p): 7%-8% | VTD vs. TD | ≥ nCR rate after induction:  
• ISS III: VTD, 24%; TD, 6% (\(P = .03\))  
• del(13q): VTD, 39%; TD, 12% (\(P < .001\))  
• t(4;14): VTD, 40%; TD, 9% (\(P < .001\))  
• del(17p): VTD, 27%; TD, 0% (\(P < .001\)) |
more than 6 to 7 years for patients with standard-risk MM.16 Furthermore, identifying the other 75% of patients as standard risk allows them to receive appropriate treatment with minimal toxicity.

Emerging data suggest that novel therapies and combinations may ameliorate the adverse influence of these poor-risk features, underscoring the importance of including genetics into risk-stratification schemes. Current NCCN guidelines include cytogenetic and FISH evaluation as part of the initial diagnostic workup but note that further data are needed before cytogenetic information can be incorporated into patient management.17

**Outcomes With Novel Agents**

A major application of genetic stratification is in the selection of candidates for HDT-ASCT. Several large studies have shown that patients defined as being at high risk genetically do not develop durable responses to HDT as currently practiced, and many experience early relapse after ASCT.7-9,16 High-risk patients are therefore considered appropriate candidates for alternative approaches, including early incorporation of novel agents. Clinical trial data suggest that in patients with MM who are eligible for transplantation, newer agents may be able to overcome the adverse influence of cytogenetic abnormalities (Table 2).19-29

Two major combinations have emerged as treatment options for elderly patients and others who will not undergo transplantation: melphalan-prednisone (MP) plus an immunomodulatory agent, and MP plus bortezomib. Both of these approaches have resulted in outcomes superior to those with MP alone and are recommended induction therapies (NCCN category 1 recommendation) in patients ineligible for transplantation.17 These new combinations have also shown efficacy in high-risk patients ineligible for transplantation (Table 3).30-33

**Role of ASCT**

The introduction of reduced-intensity conditioning...
Badros

regimens with reduction in immediate transplantation-related mortality and stable engraftment has rekindled interest in allogeneic transplantation. In patients with poor-risk disease, nonmyeloablative conditioning regimens (mini-allogeneic transplantation) with or without donor lymphocyte infusions have resulted in excellent responses and stable engraftment, with lower transplantation-related mortality, although acute and chronic graft-versus-host disease remains a troubling complication.34,35 In a prospective trial, the Intergroupe Francophone du Myélome studied ASCT followed by nonmyeloablative allotransplantation in patients with newly diagnosed MM who had both elevated β2M and del(13),36 then compared the results with data on patients with the same high-risk features but had no donor and had undergone tandem ASCT.37 The median duration of overall (35 vs. 41 months) and progression-free survival (25 vs. 30 months) did not differ significantly between the regimens.36

Encouraging long-term follow-up results were recently reported for 102 patients who underwent ASCT followed by nonmyeloablative allogeneic hematopoietic stem cell transplantation from a human leukocyte antigen-identical sibling.38 After a median follow-up of 6.3 years, the median overall survival was not reached, and estimated 5-year overall and progression-free survival were 64% and 36%, respectively. Although cytogenetic studies were not performed at specific times or using uniform methods, the authors reported that cytogenetics had no effect on the risk for relapse, suggesting that allogeneic transplantation may overcome adverse genetic prognostic features. A recent analysis of the prognostic impact of the most frequent genetic abnormalities in patients who underwent allogeneic transplantation showed that del(17p) was the only significant prognostic factor, with a negative impact on complete response and length of event-free survival.39 In multivariate analyses, only del(13) and del(17p) significantly influenced the rate of relapse, whereas for event-free survival, only age and del(17p) remained negative prognostic factors. Major findings were that t(4;14) was not associated with a worse complete response rate or shorter event-free or overall survival, suggesting that the negative effect of t(14;4) might be overcome with allogeneic transplantation. These results may have implications for risk-adapted strategies.

Table 3 Selected Studies of New Agents in Patients With Newly Diagnosed High-Risk Disease Ineligible for High-Dose Therapy/Autologous Stem Cell Transplantation

<table>
<thead>
<tr>
<th>First Author</th>
<th>No. of Patients</th>
<th>Patient Population</th>
<th>Treatment</th>
<th>Results</th>
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<tr>
<td>Mateos et al.30,31 60 Elderly patients del(13); n = 13 IgH translocation: n = 8 Bort-melphalan-prednisone</td>
<td>Response rate: Rb del: 100% IgH tr: 88% TTP (months): β,M &lt; 3.5 mg/L: 23 IgS stage I: 37 Rb del: 25 (IgH tr)/no Rb del: 29</td>
<td>No Rb del: 66% No IgH tr: 82%</td>
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<td>San Miguel et al.32 682 Elderly patients ISS I: 19% ISS II: 47% ISS III: 34%–35% KPS ≤ 70%: 33%–35% Bort group: High-risk cytogenetics [t(4;14)/t(14;16)/del(17p)]; n = 26 Standard-risk: n = 142</td>
<td>Bort-melphalan-prednisone vs. melphalan-prednisone</td>
<td>Bort group: High-risk vs. standard-risk patients: CR: 28% in both TTP: P = .55 OS: P = .99</td>
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<td>Palumbo et al.33 54 Elderly patients Median age: 71 y ISS I: 34% ISS II: 32% ISS III: 32% β,M ≥ 3.5 mg/mL: 57% del(13): 38% Data missing: 21%</td>
<td>Lenalidomide-melphalan-prednisone</td>
<td>1-y EFS: β,M &lt; 3.5: 100% del(13): 85% t(4;14): 83%</td>
<td>β,M ≥ 3.5: 86% (P = .02) No del(13): 95% (P = NS) No t(4;14): 87.5% (P = NS)</td>
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Abbreviations: β,M, β2-microglobulin; bort, bortezomib; CR, complete response; EFS, event-free survival; NS, not significant; ISS, International Staging System; KPS, Karnofsky performance status; OS, overall survival; TTP, time to progression.
Conclusions

Defining a high-risk cohort of patients with MM with short survival regardless of treatment will be helpful in guiding management decisions. With the demonstrated adverse influence of chromosomal changes, various groups have endorsed a new risk stratification model that incorporates recently defined independent prognostic markers of underlying myeloma cell biology. Efforts have focused on defining a high-risk group that might merit a different management approach, such as early treatment with novel agents. The proposed risk stratification system remains a global stratification and is not therapy-based, although ongoing trials may uncover risk factors specific for individual therapies. The general agreement is that no definitive treatment can currently be managed based on the presence of risk factors. The use of genetic information for stratifying risk and making treatment decisions continues to be explored in clinical trials and will likely play a greater role in patient care in the near future.

New therapies with novel mechanisms of action may benefit patients for whom other therapies fail. Preliminary reports from several groups show high response rates with use of bortezomib, lenalidomide, and thalidomide in both the transplantation and nontransplantation settings in high-risk patients, suggesting that these new agents may ameliorate the effects of adverse prognostic factors. Long-term follow-up and confirmation in prospective, comparative trials will be required to determine whether clinical benefit can be sustained.

Acknowledgment

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References


Addressing Challenges in Multiple Myeloma Management in an Era of New Therapeutics

Release date: February 15, 2010
Expiration date: February 15, 2011

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Specialty: ___________________________ Years in practice: ________

Number of myeloma patients seen per week: ________

I certify that I have completed this educational activity as designed.

Signature ___________________________ Date ____________________________

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Please circle the correct answer below.

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**Self-Assessment Answer Sheet**

Please circle one answer per question. A score of at least 70% on the post-test is required.

<table>
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**ACTIVITY EVALUATION**

Addressing Challenges in Multiple Myeloma Management in an Era of New Therapeutics

Please rate the activity by filling in the most appropriate circle.

(A) Excellent  (B) Good  (C) Fair  (D) Poor

<table>
<thead>
<tr>
<th></th>
<th>Overall content</th>
<th>Format</th>
<th>How well did this activity achieve its educational objectives?</th>
<th>Evaluate the need for, and propose appropriate maintenance therapy options in multiple myeloma</th>
<th>Evaluate the current importance of assessing multiple myeloma patients for risk, especially in the face of emerging and novel agents, and integrate this knowledge into management plans</th>
<th>Describe the most appropriate techniques for monitoring treatment of multiple myeloma</th>
<th>Formulate evidence-based management plans for multiple myeloma patients based upon their age, risk, and comorbidities</th>
<th>Do you feel the activity was useful to you in your practice setting?</th>
<th>Do you feel that fair balance was maintained for all therapeutic options?</th>
<th>Would you participate in future self-study activities?</th>
<th>How long did it take you to complete this activity?</th>
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Please provide detailed comments and suggestions for future activities.

Please contact me regarding upcoming medical education opportunities.

Name: ________________________________

For additional information on multiple myeloma, please visit www.ManagingMyeloma.com
1. Which of the following is/are FALSE about peripheral neuropathy in patients with multiple myeloma (MM)?
   a. It occurs as both a disease-related complication and a side effect of therapy.
   b. Its clinical manifestations are usually agent-specific.
   c. It is not usually reversible.
   d. All of the above

2. If sensory peripheral neuropathy or neuropathic pain in patients with MM cannot be controlled nonpharmacologically, which of the following agents is/are recommended?
   a. Gabapentin
   b. Nortriptyline
   c. Topical lidocaine
   d. All of the above

3. Which of the following is/are TRUE about asthenia?
   a. It is the most common side effect of cancer treatment.
   b. According to patient surveys, it is the third most distressing side effect of MM therapy.
   c. According to NCCN guidelines, patients with severe asthenia should be treated with a psychostimulant.
   d. All of the above

4. The risk for venous thromboembolism in patients being treated for MM:
   a. Is greater with increased duration of antimyeloma therapy.
   b. Is regimen-specific.
   c. Warrants anticoagulant prophylaxis except in bedridden patients.
   d. All of the above

5. In their longitudinal study of osteonecrosis of the jaw in patients with MM, Badros et al. determined that more than half of cases:
   a. Were preceded by dental extractions.
   b. Resolved and did not recur.
   c. Recurred after healing.
   d. Did not heal during 9 months of follow-up.

6. What is the state of the evidence about whether use of erythropoiesis-stimulating agents (ESAs) leads to solid tumor proliferation in patients with MM?
   a. ESAs appear to be safe for MM patients younger than 70 years.
   b. The evidence in MM is inconclusive.
   c. ESAs are clearly contraindicated in MM.
   d. This question has not been studied in MM.

7. Which of the following MM maintenance regimen(s) has/have a category 1 recommendation from the NCCN?
   a. Prednisone
   b. Interferon
   c. Thalidomide
   d. All of the above

8. Which of the following is NOT a current research issue regarding post-transplant MM maintenance therapy with thalidomide?
   a. Whether it is safe when combined with prednisone
   b. Its optimal dosage
   c. Whether it should be discontinued if complete response is achieved
   d. Whether cytogenetics can be used to identify appropriate candidates

9. Which of the following is/are TRUE about genetic aberrations detected conventionally (i.e., by karyotyping) in MM patients?
   a. They occur in approximately 30% of patients.
   b. They are associated with a higher proliferative rate.
   c. They are associated with worse prognosis.
   d. All of the above

10. According to the recently developed Mayo Clinic algorithm, which of the following is/are NOT indicators for high-risk MM?
    a. Serum $\beta_2$-microglobulin level $\geq$ 3.5 mg/L
    b. $t(4;14)$ by fluorescence in situ hybridization
    c. Aneuploidy by metaphase analysis
    d. Plasma cell labeling index $> 3\%$