



## TABLE OF CONTENTS

Introduction

Cell Biology of Multiple Myeloma

Overall Goals of Therapy and Treatment Options for MM

Individualizing Induction Therapy

Individualizing Maintenance Therapy

Guidance for the Use of Maintenance and Induction Therapies

Individualizing Management of Patients in Relapse

Individualizing Second Transplants After Relapse

Individualizing Treatment Based on Bone and Renal Disease

Individualizing Patients With Amyloidosis

Managing Patients on Novel Agents and Steroids

Conclusion

Full Interview With Charise Gleason, NP

Faculty

Posttest/Evaluation

References

CME Information

## Developing Individualized Treatment Strategies Based on Biology and Physiology of the Multiple Myeloma Patient

Sagar Lonial, MD, With Additional Commentary From

Charise Gleason, MSN, NP-C, AOCNP

March 9, 2011

### Introduction

Multiple myeloma (MM) is a plasma cell disorder associated with renal, bone, immunologic, and hematopoietic complications. Treatment results in frequent early responses of variable duration that are followed by treatment relapses. For any given treatment, long-term outcomes differ among MM patients, highlighting the innate heterogeneity within this patient population. Until recently, there have been very few effective therapies for MM. For approximately 4 decades, treatment consisted of alkylating agents and corticosteroids.<sup>1</sup> Several novel agents for the disease are now available, including the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide, as well as the proteasome inhibitor bortezomib, which has resulted in unprecedented response rates in both newly diagnosed and relapsed MM. However, relapse still remains a universal phenomenon. The variability in patient response profiles suggests that underlying influencing factors exist that should be considered when selecting treatment options for each patient.

### Cell Biology of Multiple Myeloma

Novel drug combinations are becoming increasingly personalized, and clinical practice is guided by genetic testing as well as prognostic factors.<sup>1</sup>

The ability to individualize treatment to MM patients is based on cytogenetic abnormalities of the tumor, negative patient prognostic factors such as hypercalcemia, hyperviscosity, and coagulation/thrombosis, and the presence or absence of renal disease. This type of information can be used to tailor initial treatment of newly diagnosed, transplantation-eligible MM patients<sup>3</sup> and treatment for relapsed/refractory disease.<sup>4</sup>

MM risk is routinely defined by laboratory parameters alone or in combinations with the Durie-Salmon staging system and the International Staging System (ISS).<sup>5</sup> Using high-throughput genomic analyses and data-mining techniques, a complete landscape of MM molecular pathogenesis is emerging. Gene expression patterns of large patient cohorts have revealed the innate heterogeneity of newly diagnosed cases of MM, allowing cases to be accurately stratified and cataloged. In standard clinical practice, when initial staging is performed, a bone marrow aspirate should be sent for a complete panel testing for del(13), del(17), t(4;14), t(11;14), t(14;16), and 1q21 abnormalities by fluorescent in situ hybridization (FISH) to determine risk classification. Based on the results from standard care testing with FISH, patients can be divided into 1 of 7 classes with different levels of risk (**Table 1**).<sup>5,6</sup> Importantly, the improved survival observed in specific classes through the use of new treatments, such as IMiDs and bortezomib, supports the concept of personalized treatment

**Table 1. Characteristics of Validated Molecular Classes as Defined by Unsupervised Hierarchical Clustering**

Molecular Subtype	% of Newly Diagnosed Patients	Genetic Characteristics	Risk
MS	17	t(4;14)	High
MF	6	t(14;16) or t(14;20)	High/moderate
CD-1	6	t(11;14) or t(6;14)	Low
CD-2	12	t(11;14) or t(6;14)	Low
HY	31	Typical trisomies +3, +5, +7, +9, +11, +15, +19	Low
LB	12	Typical HY trisomies; exception is frequent del13, gain of 1q, rare gain of 11	Low
PR	10	Made up of all subgroups	High

Adapted from Zhou Y, et al. *Leukemia*. 2009;23:1941-1956.

## Overall Goals of Therapy and Treatment Options for MM

The NCCN multiple myeloma panel has developed guidelines to address the diagnosis, treatment, and follow-up for MM.<sup>6</sup> The 3 case studies presented below demonstrate how the guidelines are applied and when consensus is lacking to generate a specific recommendation-how treatment can be individualized based on the unique attributes of the case.

*Case 1. A newly diagnosed young patient with standard-risk MM who is a potential transplant candidate*

Management of a newly diagnosed patient depends on whether the patient is a transplant candidate. For those individuals who are potential transplant candidates, there are 4 regimens with evidence-based medicine to support their use.<sup>3,6</sup> The first regimen consists of thalidomide and dexamethasone (TD; category 2A), which is considered least appealing of the 4 options. TD does not result in the kind of posttransplant benefits one wants to see for induction therapy and does have potential risks. The remaining regimens have level 1 support. The second regimen consists of lenalidomide and low-dose dexamethasone (Rd), which provides a better depth of response and a better posttransplant outcome. The third option is bortezomib and dexamethasone (BD), which results in superior responses both before and after transplant compared with vincristine, doxorubicin, and dexamethasone (VAD). These results translate into improved progression-free survival. The final regimen consists of bortezomib with thalidomide and dexamethasone (VTD), which yields improved response rates, both before and after transplant compared to TD.<sup>6</sup>

## Treatment Strategies

The NCCN multiple myeloma panel has developed guidelines to address the diagnosis, treatment, and follow-up for MM.<sup>6</sup> The 3 case studies presented below demonstrate how the guidelines are applied and when consensus is lacking to generate a specific recommendation-how treatment can be individualized based on the unique attributes of the case.

*Case 1. A newly diagnosed young patient with standard-risk MM who is a potential transplant candidate*

Management of a newly diagnosed patient depends on whether the patient is a transplant candidate. For those individuals who are potential transplant candidates, there are 4 regimens with evidence-based medicine to support their use.<sup>3,6</sup> The first regimen consists of thalidomide and dexamethasone (TD; category 2A), which is considered least appealing of the 4 options. TD does not result in the kind of posttransplant benefits one wants to see for induction therapy and does have potential risks. The remaining regimens have level 1 support. The second regimen consists of lenalidomide and low-dose dexamethasone (Rd), which provides a better depth of response and a better posttransplant outcome. The third option is bortezomib and dexamethasone (BD), which results in superior responses both before and after transplant compared with vincristine, doxorubicin, and dexamethasone (VAD). These results translate into improved progression-free survival. The final

regimen consists of bortezomib with thalidomide and dexamethasone (VTD), which yields improved response rates, both before and after transplant compared to TD.<sup>6</sup>

#### *Case 2. A high-risk MM patient who is a potential transplant candidate*

The initial approach taken for a high-risk patient during induction is similar to that taken for a standard-risk patient. High-risk patients require the best induction regimen available, so they, too, will get RVD for initial therapy. The RVD regimen has demonstrated a high percentage of VGPR, and a significant percentage of patients with both low-risk and high-risk cytogenetic profiles are able to achieve 18-month progression-free survival.<sup>7</sup> After completion of the induction phase, treatment will be individualized for the high-risk patient in the maintenance setting covering both posttransplant maintenance and postinduction (pretransplant) maintenance.

#### *Case 3. Newly diagnosed MM in an older patient who is not a transplant candidate*

Age is one of the key factors influencing treatment options. Elderly patients are at increased risk of adverse events, have reduced tolerability to intensive chemotherapy, and are therefore less likely to receive high-dose therapy.<sup>2</sup> Three induction regimens with Level I evidence for elderly patients who are not transplant candidates include MPT (melphalan, predisone, and thalidomide), MPV (melphalan, predisone, and bortezomib), and RD (lenalidomide and dexamethasone).<sup>8,9</sup>

---

### Individualizing Induction Therapy

---

Treatment has progressively changed from alkylator-based therapies to multiagent combination therapies to triple combination therapies incorporating IMiDs and proteasome inhibitors.<sup>11</sup> Clinical studies have demonstrated that use of novel agents during induction results in higher response rates before transplant. TD, RD, BD, VTD, and RVD result in higher response rates than either dexamethasone alone or older combinations using alkylator agents. The response rates and depth of response that were previously achieved only when using high-dose therapy plus stem-cell transplantation (HDT-SCT) can now be achieved in MM patients using the new induction regimens containing the novel agents.<sup>12</sup> In a landmark study of RVD, the drug combination demonstrated favorable tolerability and was highly effective in the treatment of newly diagnosed myeloma.<sup>7</sup> RVD offers a platform for future combinations, beyond triple-drug combinations, but also 4-drug combinations. In addition to higher CR rates pretransplant, the use of novel agents during induction also may result in higher CR rates posttransplant, and superior long-term outcomes. A phase 3 study by the French Myeloma Study Group (IFM) found that BD was significantly superior to VAD with respect to response rates postinduction and posttransplant, as well as 2-year progression-free survival rate. The Italian myeloma group (GIMEMA) found that VTD was superior to TD in terms of CR + nCR and CR + VGPR rates pretransplant and posttransplant, and in terms of progression-free survival.<sup>13</sup>

It is important to understand that the excellent response to therapy was NOT dependent on cytogenetics. This patient had negative cytogenetics/FISH and was ISS stage III at diagnosis. Another consideration is whether and when such a young patient should be considered for allotransplant, since the disease is considered incurable. The role of allo treatment is experimental at this point. There are no randomized data showing improved outcomes for allogeneic versus autologous transplants, and morbidity is very high for allotransplant. Therefore, allotransplantation would not be supported for this type of patient.

---

### Individualizing Maintenance Therapy

---

It is not known whether all patients can benefit from maintenance therapy or what the appropriate duration of such therapy is in different patient subtypes. Long duration of treatment appears to have compensatory effects in individuals who cannot tolerate high-dose treatment and those at high risk of relapse. Therefore, when individualizing maintenance therapy, myeloma biology and patient convenience and ease are two key considerations. One must decide which dosing schedule to use and for what duration to treat. For each specific situation, it is important to consider the available evidence supporting use of maintenance for individual patients and which agents are best suited for each patient. For example, the adverse events associated with a particular maintenance drug can be

a deciding factor. To reduce the risk of deep vein thrombosis in high-risk patients, combined melphalan, prednisone, and bortezomib is preferable for reduced thrombogenicity, whereas combined melphalan, prednisone, and lenalidomide is preferable for patients with increased risk of peripheral neuropathy.<sup>14</sup>

Certain MM patients are more appropriate candidates for maintenance therapy than others. Promising results have been observed with maintenance therapy in the posttransplant setting using sequential maintenance therapy with VTD following single autologous peripheral SCT. The regimen has been well tolerated and resulted in 55% CR, with 22% upgrading their response following 6 months of maintenance.<sup>15</sup> Favorable results also have been observed with the addition of bortezomib to standard high-dose melphalan therapy prior to tandem autologous transplantation (MVD) together with use of RVD posttransplantation maintenance therapy in patients with high-risk cytogenetic abnormalities.<sup>16</sup>

If patients have a complete response and a respectable progression-free survival following induction therapy, they may still benefit from maintenance therapy. For patients with high-risk disease, achieving a CR is not necessarily indicative that the CR will last. New tests such as flow cytometry and PCR can be used to assess minimal residual disease (MRD) in patients with CRs because a CR, even as currently defined, means a patient still has some disease. It therefore becomes important to determine how to minimize disease activity and the impact of MRD on patient outcomes. The purpose of maintenance therapy is to achieve a better depth of response and a longer duration of response that not only translates into improved event-free survival, but improved overall survival as well.

The elderly patient population can also benefit from maintenance therapy. Data are beginning to emerge on the use of a reduced-intensity induction in this cohort (eg, a bortezomib-based regimen followed by a specially designed maintenance regimen). Bortezomib with either thalidomide (VT) or prednisone (VP) has been shown to be a safe and effective maintenance treatment for elderly patients with MM.<sup>17</sup>

---

## Guidance for the Use of Maintenance Therapy Following Induction Treatment Without Intent of Upfront Transplant vs Induction Followed by Upfront Transplant and Maintenance Therapy Posttransplant

---

Prior to the use of the novel targeted agents, when the conventional approach to consolidation was high-dose melphalan and autologous stem cell transplantation (ASCT), the question of early versus delayed SCT was addressed by the MAG90 trial. This study concluded that early intervention in the disease course was associated with better quality of life.<sup>18</sup> The introduction of IMiDs and bortezomib has led to a need to reinvestigate the question of early versus delayed transplant. However, randomized controlled trials are still lacking in this area.<sup>18</sup>

Advantages of early transplant include the very long remission duration (particularly as more effective induction regimens are used), during which patients have an excellent quality of life and require no drug treatment. Because the median age at diagnosis of MM is 70 years, a number of patients initially eligible for early transplant will no longer be eligible if it is delayed for several years, and they will miss their opportunity to receive an effective therapy. Advantages of delayed transplant include the excellent results and tolerability of the continued use of newer induction regimens. These advantages have led to increased use of delayed transplant in patients with MM in conjunction with continued initial therapy. In a landmark analysis of the E4A03 clinical trial that compared lenalidomide and 2 doses of dexamethasone, patients who continued to receive primary therapy had a 3-year overall survival of 79% compared with 92% for those who proceeded directly to high-dose melphalan therapy.<sup>18</sup>

---

## Individualizing Management of Patients in Relapse

---

As previously noted, despite significant advances in therapy, all MM patients still relapse. Whereas the goal initially was to treat to CR, the goal of treatment after relapse is not as clearly defined. At this juncture, the goal is to maximize the depth of response. The first decision that needs to be

made is whether to repeat the initial front-line treatment or switch to a different therapy from that used previously. Once again, there is an opportunity to individualize therapy. The choice of treatment for the relapsed patient is dependent on several factors: how long the last remission was; how aggressive the relapse is; what the patient received at induction; and what toxicities were experienced during induction. If a long ( $\geq 12$  months) remission was obtained following a distinct short course of treatment and adverse events were acceptable, then rechallenging with the front-line regimen may be possible. However, if only a short ( $\leq 6$  months) remission was obtained and the duration of the initial therapy was long, then it may be advisable to switch to a different treatment.<sup>13</sup> When considering a treatment change, if the patient initially received a proteasome inhibitor, but not an IMiD, then it is probably best to use an IMiD during relapse, and if the patient received an IMiD initially, but not a proteasome inhibitor, then it is probably appropriate to use a proteasome inhibitor to manage relapse. Aggressive relapse tends to use more combination therapy versus single agents. A bortezomib-based approach would be a rational choice for a patient who presents with aggressive relapse disease and renal dysfunction, to try and reduce light chain burden quickly and reverse any level of chronic renal dysfunction.

---

## Individualizing Second Transplants After Relapse

---

Even if transplant were part of the first therapy, there may still be a role for a second transplant in the relapse setting for select individuals. The patients with a duration of remission following the first transplant of approximately 2 years are the ones most likely to benefit from a second transplant. However, the duration of remission after the second transplant will be shorter than duration after the first transplant. For patients who had 5 to 6 years' remission, resalvaging with therapy such as RD or BD may result in duration of remission just as long, if not longer, than the duration of remission from a second transplant.

In patients with limited hematologic reserve, the goal of a second transplant is not necessarily to improve long-term disease control, but rather, to reset the immunologic clock and thus improve cell and platelet counts so that such patients can be treated. The second transplant may therefore be appropriate for patients with a white count of 1.5, a hemoglobin of 8, and a platelet count that is persistently in the 30s or 40s; these are patients who cannot be treated with standard regimens because of the degree to which their marrow is damaged.

---

## Individualizing Treatment Based on Bone Disease and Renal Disease: The Use of Bisphosphonates for Patients With Renal Failure and Extensive Bone Disease

---

Bisphosphonates prevent, reduce, and delay MM-related skeletal complications; therefore, they are an essential component of MM therapy.<sup>19</sup> However, bisphosphonates can potentially cause nephrotoxicity, especially when given for any extended time. There are concerns about bisphosphonate dosing in patients with dialysis-dependent renal failure. There is no real evidence-based approach for managing patients in this situation.

New and emerging agents designed to address the problem of skeletal complications may protect bone somewhat better and hopefully not have similar side effects such as renal complications. It may be possible to use drugs such as denosumab or the DKK1 inhibitor BHQ, regardless of renal function. The potential for these alternative agents awaits efficacy data from ongoing studies.

---

## Individualizing the Treatment Approach for Patients Who Have Amyloidosis as Part of Their Myeloma Disease Manifestation

---

Approximately 12% to 15% of MM patients develop overt clinical amyloidosis through the course of their disease, resulting in amyloid deposits in subcutaneous fat pads, bone marrow, and other vital organs such as heart, liver, and kidneys. Because amyloidosis patients appear to be susceptible to side effects from most any treatment and complications tend to be magnified, it is crucial to recognize the presence of AL amyloidosis in the setting of MM, particularly when making therapeutic decisions regarding the choice of induction therapy or the intensity of the conditioning regimen.<sup>20</sup>

For these patients, it is necessary to reduce the intensity of treatment, especially treatments with known cardiotoxicity, neurotoxicity, and nephrotoxicity. Anticipate that even reduced-intensity treatment can cause potential gastrointestinal side effects including nausea, vomiting, and diarrhea. It is also important to monitor the body weight of these patients closely. When administering steroids as part of a treatment regimen, clinicians must appreciate that these patients tend to have cardiac dysfunction and are at higher risk of dysrhythmias and congestive heart failure, as steroid use can further increase the tendency to accumulate body fluid.

## Management of Herpes Simplex Virus, Fungal Infections, and *Pneumocystis Carinii* (PC) in MM Patients Treated With Novel Agents and Steroids

Prolonged steroid treatment of patients with hematologic malignancies raises the risk of developing pneumocystis, a rare, but potentially lethal complication.<sup>21</sup> PC can occur in patients who are already in complete remission or who have undergone an autologous or allogeneic transplant. The latency between diagnosis of hematologic disease and PC infection is highly variable, with a median of 5 months.<sup>21</sup> Patients receiving steroids, such as dexamethasone, should therefore receive pneumocystis prophylaxis. The simplest care is a prophylactic regimen of sulfamethoxazole and trimethoprim (SMZ/TMP) 3 times weekly.<sup>21</sup>

Another concern is that immunosuppression with dexamethasone and treatment with bortezomib can contribute to varicella zoster virus (VZV) reactivation or shingles.<sup>22</sup> VZV reactivation and herpes simplex virus (HSV) reactivation can be easily minimized or prevented through the use of 400 mg oral acyclovir prophylaxis daily, irrespective of the MM therapy used.<sup>22</sup> The drug is administered when disease-specific therapy is initiated and continued indefinitely, unless patients show signs of toxicity. Other treatment options for VZV include valacyclovir and famciclovir (Table 2).<sup>22</sup> Corticosteroid use also increases the risk of fungal infections.<sup>23</sup> Fluconazole may be able to reduce the risk of these infections. Once a fungal infection is identified, prospective treatment is recommended.

Drug	Dose of mg Daily						
	200	250	300	350	400	450	500
Acyclovir <sup>1</sup>							
Acyclovir <sup>2</sup>							
Valacyclovir <sup>3</sup>							
Famciclovir <sup>4</sup>							

<sup>1</sup>The standard regimen, <sup>2</sup>Used if SCr >2 mg/dL, <sup>3</sup>Alternative to acyclovir, <sup>4</sup>Alternative to acyclovir.  
Adapted from Vickrey E, et al. *Cancer*. 2009;115:229-232.

## Conclusion

There are various points within the MM treatment continuum where therapy choices can be individualized to the specific patient. Table 3 provides a summary of the various points of management, ie, during the induction phase, maintenance phase, relapse, second transplant, and under specific conditions, such as development of skeletal involvement, amyloidosis, and infections. The care of patients with MM can be personalized based on a number of different treatment decisions, such as drug choice, treatment duration, and time to initiate treatment. By taking into account the underlying factors that contribute to variability in patient response profiles, clinicians can tailor treatment options for each MM patient.

**Table 3. Summary of Points Along the Treatment Continuum Where MM Therapy Can Be Individualized and Factors to Consider at Each Decision Point**

Point of Management	Areas for Individualized Treatment	Factors to Consider
<b>Induction</b>	1. Choice of drugs 2. Number of drugs 3. Number of cycles	1. Risk status 2. Transplant candidate 3. Age of patient
<b>Maintenance</b>	1. Before/after transplant 2. Choice of drug(s) 3. Duration of treatment 4. Managing a plateau	1. Myeloma biology 2. Patient convenience/ease 3. Adverse events of regimen 4. Response to induction 5. Patient age
<b>Relapse</b>	1. Treat/don't treat 2. Same treatment/different treatment 3. Single/combo drugs	1. How long was last remission? 2. How aggressive in relapse? 3. What did patient receive at induction? 4. What toxicities did patient experience?
<b>Second Transplant</b>	1. Yes/No	1. Duration of remission post first transplant 2. Amount of hematologic reserve
<b>Skeletal Complications</b>	1. Use bisphosphonate? 2. If yes, at what dose schedule?	1. Presence/absence of renal failure
<b>Amyloidosis</b>	1. Choice of induction 2. Intensity of conditioning	1. Severity of amyloidosis
<b>HSV/Fungus and PCP Prophylaxis</b>	1. Need for prophylaxis 2. Choice of prophylaxis agents	1. Use of dexamethasone in treatment regimen

## REFERENCES

1. Fonseca R, Stewart AK. Targeted therapeutics for multiple myeloma: the arrival of a risk-stratified approach. *Mol Cancer Ther.* 2007;6:802-810.
2. Lonial S. Presentation and risk stratification-improving prognosis for patients with multiple myeloma. *Cancer Treat Rev.* 2010;36(suppl 2):S12-S17.
3. Stadtmauer EA. Tailoring initial treatment for newly diagnosed, transplantation-eligible multiple myeloma. *Oncology (Williston Park).* 2010;24(3 suppl 2):7-13.
4. Richardson PG, Laubach J, Mitsiades C, et al. Tailoring treatment for multiple myeloma patients with relapsed and refractory disease. *Oncology (Williston Park).* 2010;24(3 suppl 2):22-29.
5. Zhou Y, Barlogie B, Shaughnessy JD Jr. The molecular characterization and clinical management of multiple myeloma in the post-genome era. *Leukemia.* 2009;23:1941-1956.
6. National Comprehensive Cancer Network. NCCN Clinical Practice Guideline in Oncology: Multiple Myeloma. v1.2010.
7. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood.* 2010;116:679-686.
8. Lonial S. Frontline regimens for multiple myeloma patients. *Clin Adv Hematol Oncol.* 2010;8:331-332.
9. Palumbo A, Gay F. How to treat elderly patients with multiple myeloma: combination therapy or sequencing. *Hematology Am Soc Hematol Educ Program.* 2009:566-577.
10. San Miguel JF, Schlag R, Khuageva N, et al, for the VISTA Trial Investigators. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med.* 2008;359:906-917.
11. Nooka A, Gleason C, Lonial S. Improving induction therapy in multiple myeloma. *Curr Hematol Malig Rep.* 2010;5:119-128.
12. Lonial S, Cavenagh J. Emerging combination treatment strategies containing novel agents in newly diagnosed multiple myeloma. *Br J Haematol.* 2009;145:681-708.

13. Ludwig H, Beksac M, Bladé J, et al. Current multiple myeloma treatment strategies with novel agents: a European perspective. *Oncologist*. 2010;15:6-25.
14. Raab MS, Podar K, Breitkreutz I, Richardson PG, Anderson KC. Multiple myeloma. *Lancet*. 2009;374:324-339.
15. Sahebi F, Krishnan A, Somlo G, et al. A phase II study of sequential velcade/thalidomide/dexamethasone (VTD) as maintenance therapy post single autologous peripheral stem cell (PSCT) in patients with multiple myeloma. *Blood*. 2009;114:Abstract 3403.
16. Lee CK, Kaiser J, Myint H, Berg M, Kolhouse JF, Robinson W. An outcome study on survival and disease control in patients with high-risk multiple myeloma (MM) for relapse, treated with high-dose melphalan combined with bortezomib for autotransplant followed by post-transplant maintenance with bortezomib and lenalidomide. *Blood*. 2009;114:Abstract 3404.
17. Mateos MV, Oriol A, Martínez-López J, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. *Lancet Oncol*. 2010;11:934-941.
18. Kumar SK, Mikhael JR, Buadi FK, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. *Mayo Clin Proc*. 2009;84:1095-1110.
19. Terpos E, Sezer O, Croucher PI, et al. The use of bisphosphonates in multiple myeloma: recommendations of an expert panel on behalf of the European Myeloma Network. *Ann Oncol*. 2009;20:1303-1317.
20. Bahlis NJ, Lazarus HM. Multiple myeloma-associated AL amyloidosis: is a distinctive therapeutic approach warranted? *Bone Marrow Transplant*. 2006;38:7-15.
21. Pagano L, Fianchi L, Mele L, et al. *Pneumocystis carinii* pneumonia in patients with malignant haematological diseases: 10 years' experience of infection in GIMEMA centres. *Br J Haematol*. 2002;117:379-386.
22. Vickrey E, Allen S, Mehta J, Singhal S. Acyclovir to prevent reactivation of varicella zoster virus (herpes zoster) in multiple myeloma patients receiving bortezomib therapy. *Cancer*. 2009;115:229-232.
23. Merck Manual. Fungal infections. Available at: <http://www.merck.com/mmhe/print/sec17/ch197/ch197a.html>. Accessed November 3, 2010.

This initiative is supported by an educational grant from:



This initiative is jointly sponsored by:

