# Multiple Myeloma: Review Questions

*Jeffrey A. Zonder, MD*

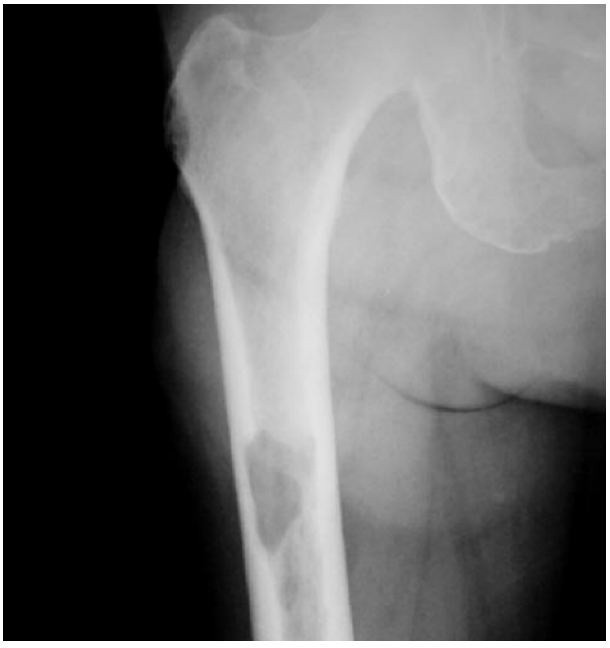

**Figure 1.** Lytic lesion found on the right femur of the patient described in questions 1 to 3.

## QUESTIONS

Choose the single best answer for each question.

**Questions 1 to 3 refer to the following case.**

A 76-year-old woman presents for a routine physical and is found to be mildly anemic (hemoglobin, 10.5 g/dL, decreased from 13.8 g/dL the previous year). She had a normal colonoscopy 2 years ago, and additional laboratory testing confirms that she is not iron-deficient. Serum protein electrophoresis with immunofixation demonstrates an IgG-kappa monoclonal protein (2.97 g/dL) with markedly reduced IgM and IgA levels. An extensive review of systems is negative, and physical examination reveals no abnormalities. A skeletal survey reveals osteopenia and several lytic lesions, but no fractures. The largest lesion is in the right femur (**Figure 1**). Multiple myeloma (MM) is strongly suspected.

1. **What is the next step in this patient's management?**
   (A) Biopsy of the femoral lesion
   (B) Bone marrow biopsy with cytogenetic analysis
   (C) Immediate chemotherapy combined with glucocorticoids
   (D) No further testing at present; the diagnosis of MM is certain and asymptomatic myeloma does not require immediate therapy

2. **Which of the following therapy options has the highest likelihood of inducing a major clinical response in this patient?**
   (A) MP (melphalan-prednisone)
   (B) MP-T (melphalan-prednisone-thalidomide)
   (C) TD (thalidomide-dexamethasone)
   (D) VAD (vincristine-Adriamycin-dexamethasone)

3. **Within 2 months of starting therapy, the patient's monoclonal protein level begins to decrease, and it is no longer detectable after 6 months of therapy. Three months later, the patient suddenly develops severe lower back pain with a band-like distribution. She also has developed modest constipation and very mild tingling in her toes over the past month, which is unchanged at the current visit. A radiograph of the lumbar spine demonstrates a compression fracture (Figure 2), and magnetic resonance imaging (MRI) reveals edema but no associated mass or cord compression. Which of the following measures would be most helpful in alleviating this patient's symptoms?**
   (A) Evaluation for vertebroplasty or kyphoplasty
   (B) Immediate switch in systemic therapy
   (C) Initiation of bisphosphonate therapy (eg, zoledronic acid, pamidronate)

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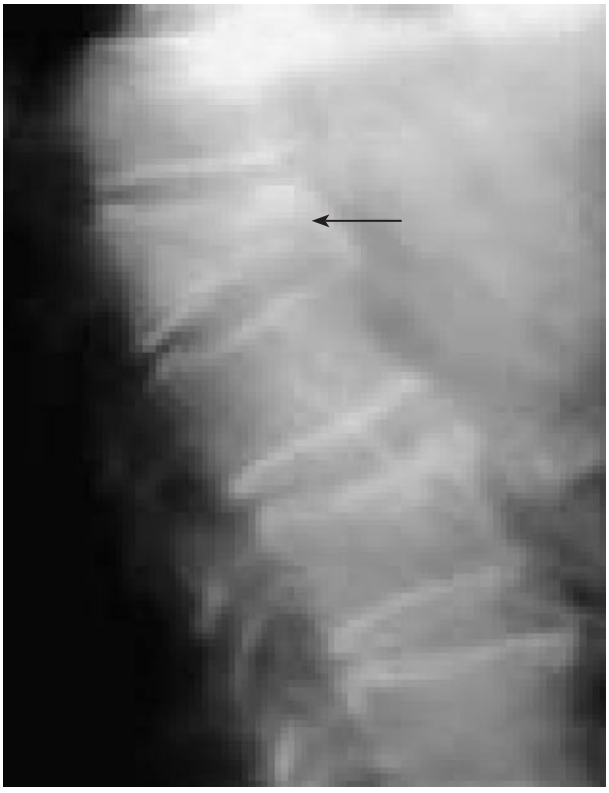

**Figure 2.** Radiograph of the lumbar spine demonstrating a compression fracture (*arrow*) in the patient described in questions 1 to 3.

(D) Radiation oncology evaluation for possible external beam radiation
(E) Urgent neurosurgical evaluation for spinal decompression

**4. A 54-year-old man with IgA-lambda MM diagnosed 6 years ago is currently treated with lenalidomide plus dexamethasone. He also has received monthly infusions of zoledronic acid for the last 5 years. During a recent routine dental examination, the dentist noted a painless gingival defect with exposed bone along the lateral aspect of his mandible. What is the next step in this patient's management?**
(A) Full reevaluation of his myeloma
(B) Immediately discontinue lenalidomide
(C) Immediately discontinue zoledronic acid
(D) Referral for external beam radiotherapy

**5. A 50-year-old woman with kappa light-chain MM presents with modest renal insufficiency and bone pain. She is treated with thalidomide 200 mg daily plus dexamethasone, but her urine M-protein level continues to increase. After 2 months of therapy, her serum creatinine level has risen to 4.8 mg/dL, and she has progressive anemia and mild tingling in her fingers and toes. Which of the following treatment options is most appropriate at this time?**
(A) Bortezomib
(B) Lenalidomide
(C) MP
(D) TD, with an increased thalidomide dose (400 mg/day)

## ANSWERS AND EXPLANATIONS

**1. (B) Bone marrow biopsy with cytogenetic analysis.** Although this patient with a serum monoclonal protein level, immunoparesis (depressed normal immunoglobulins), anemia, and lytic bone lesions almost certainly has myeloma,[1] confirmation of the diagnosis with a bone marrow biopsy is essential. Patients with MM typically have more than 10% plasma cells in sheets and clusters. Although the patient has no physical symptoms, she does not meet the criteria for asymptomatic (ie, smoldering) myeloma, as she has multiple lytic bone lesions and mild anemia.[2] A biopsy of the large femoral lesion would likely confirm the diagnosis of MM, but a posterior iliac crest biopsy is simpler to perform. Cytogenetic analysis, including fluorescence in situ hybridization for common abnormalities such as deletion of chromosome 13, provides important prognostic information. This patient meets criteria for systemic antimyeloma therapy, but this should not be initiated until the diagnostic work-up is completed.

**2. (B) MP-T.** MP is an oral regimen combining an alkylating agent (melphalan) and a glucocorticoid (prednisone) that has been used to treat MM for over 3 decades, particularly in patients who are not candidates for autologous stem cell transplantation (ASCT). Because melphalan-containing regimens may impact stem cell mobilization and collection, they should be avoided in patients who could potentially be treated with ASCT. Approximately 50% of patients with newly diagnosed MM will have a major clinical response when treated with MP. VAD (an anthracycline-containing regimen administered via continuous infusion) and TD (an oral immunomodulatory regimen) are associated with somewhat higher response rates than MP (range, 60%–70%). Less than 10% of patients treated with MP, VAD, or TD achieve a complete response. Recently, 2 large randomized studies comparing MP-T with MP have been completed, and both demonstrated that MP-T therapy is associated with a higher response

rate, higher complete response rate, and longer time to disease progression.[3,4] Although neither of these studies compared MP-T with VAD or TD, the clinical efficacy of MP-T in both studies appears superior to what could be expected with VAD or TD based on previously reported experience with these regimens.

3. **(A) Evaluation for vertebroplasty or kyphoplasty.** This patient's pain is due to an acute compression fracture (Figure 2) and the resultant edema and inflammation. The MRI findings are typical of an acute fracture and have also ruled out an associated soft tissue mass (plasmacytoma) and cord compression; thus, neurosurgical decompression is not indicated. Likewise, this patient's symptoms are due to mechanical consequences of an acute fracture, and radiotherapy is not likely to relieve these symptoms. Vertebroplasty or kyphoplasty are minimally invasive spinal procedures that stabilize the fractured vertebral body and can provide rapid pain relief in many cases. The neurologic symptoms described predated the onset of back pain and are common side effects of thalidomide and vincristine, 2 commonly used therapies for MM. A compression fracture in a patient with previously documented skeletal disease is not necessarily evidence of myeloma progression, and other testing to reassess MM should be undertaken prior to switching therapy. Bisphosphonate therapy is considered standard therapy for MM patients with lytic bone disease, as randomized studies have shown that bisphosphonates are useful in preventing compression fractures and other skeletal complications of MM. This patient should have already been on either monthly zoledronic acid or pamidronate from the time of diagnosis; these drugs do not have any role in the management of an acute pathologic fracture.

4. **(C) Immediately discontinue zoledronic acid.** This patient likely has early osteonecrosis of the jaw (ONJ), an uncommon complication of bisphosphonate therapy. No definite link has been established between ONJ and other MM therapies (eg, lenalidomide, an immunomodulatory drug structurally related to thalidomide). While the overall incidence of ONJ is likely less than 5%, the risk appears to be related to the duration of bisphosphonate exposure and occurs more frequently with zoledronic acid than pamidronate, leading some experts to recommend the latter as the preferred therapy.[5] Although prospective data are lacking, patients with suspected ONJ generally should have bisphosphonate therapy discontinued, particularly in the setting of well-controlled myeloma. Radiotherapy—itself a risk for ONJ—would only be beneficial in the setting of progressive myeloma involving the jaw, such as a new lytic bone lesion. Early referral to an oral surgeon with experience managing patients with ONJ is strongly encouraged.

5. **(A) Bortezomib.** The patient's MM is not responding to TD therapy. Increasing the dose of thalidomide is unlikely to induce a response and will probably aggravate the early therapy-related peripheral neuropathy this patient is already experiencing. Although there is some risk that bortezomib may cause worsening neuropathy as well, it is the best choice from the remaining 3 options for a patient with significant renal insufficiency. It has been shown that bortezomib can be given at full dose in the presence of severe renal failure[6] and can induce responses in approximately 35% of patients with previously treated MM. Melphalan and lenalidomide are both problematic in the setting of advanced renal failure, although guidelines for dosage adjustment are available.

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