

Multiple Myeloma

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QUESTIONS

- A 53-year-old woman with a history of IgA/kappa multiple myeloma presents to the local emergency department with worsening nausea, fatigue, and mental status changes. She had achieved very good partial response after an autologous transplant 2 years ago. She tried a brief course of thalidomide maintenance therapy, which she did not tolerate. On physical examination, she is lethargic and oriented to person and place. She is afebrile and orthostatic. Results of serum chemistries reveal a markedly elevated serum calcium level at 15.9 mg/dL, a serum albumin level of 3.2 g/dL, and a total protein level that has increased to 10.4 g/dL from a recent value of 8.1 g/dL. Serum creatinine is 1.7 mg/dL (baseline, 1.0 mg/dL). What is the next step in the management of this patient?

 - Intravenous (IV) normal saline 1 L followed immediately by furosemide and IV zoledronate
 - IV normal saline and consideration of furosemide if fluid overload occurs, followed by IV zoledronate
 - IV normal saline and consideration of furosemide if fluid overload occurs, followed by zoledronate after achieving dental clearance
 - IV normal saline and consideration of furosemide if fluid overload occurs, followed by pamidronate
- A 64-year-old man presents with newly diagnosed International Staging System stage III IgG/lambda multiple myeloma with a monoclonal protein measuring 5.2 g/dL. He has a history of chronic kidney disease and a long-standing history of hypertension. Serum creatinine has increased from a baseline level of 1.8 mg/dL to 2.4 mg/dL. He has asymptomatic lytic bone disease. Metaphase cytogenetic testing shows deletion of chromosome 13. What is the most appropriate therapy for this patient?

 - Bortezomib and dexamethasone
 - Lenalidomide and high-dose dexamethasone
 - Oral melphalan, prednisone, and thalidomide
 - Pulse high-dose dexamethasone
- All of the following are associated with a poor prognosis in patients with multiple myeloma EXCEPT

 - Deletion of chromosome 13 by fluorescent in situ hybridization (FISH)
 - Elevated β_2 -microglobulin
 - Hypodiploid karyotypes
 - t(4;14) translocation by FISH
- A 72-year-old woman with relapsed multiple myeloma presents for cycle 3 of bortezomib therapy. Her monoclonal protein with the first 2 cycles of therapy has dropped from 3.4 g/dL to 1.8 g/dL. She reports to the infusion nurse that she has burning pain in both of her feet that keeps her awake at night. She has residual paresthesias from prior thalidomide exposure, which has not worsened. What is the next most appropriate step in the management of this patient?

 - Continue bortezomib with a 25% dose reduction
 - Continue full-dose bortezomib and add gabapentin
 - Discontinue bortezomib and initiate lenalidomide
 - Suspend bortezomib and then resume therapy at a reduced dose after the pain has resolved
- A 73-year-old woman with a history of rheumatoid arthritis presents to the emergency department with new left arm pain. Plain radiographs reveal a large lytic lesion in the left humerus. A skeletal survey reveals additional lytic lesions. She has stable anemia (hemoglobin, 10.1 g/dL) and stable renal insufficiency (serum creatinine, 1.6 mg/dL). Serum protein and urine electrophoresis and immunofixation reveal no evidence of a monoclonal protein; however, polyclonal immunoglobulins are suppressed. On serum free light chain assay testing, the kappa/lambda ratio is also suppressed at 0.01. A biopsy of the humeral lesion reveals lambda light chain-restricted malignant plasma cells. A bone

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marrow biopsy reveals lambda light chain–restricted plasma cells accounting for 60% of the cellular marrow. Which of the following tests can best assess this patient’s response to therapy?

- (A) Magnetic resonance imaging of the lytic lesion on the left humerus
- (B) Serum β_2 -microglobulin
- (C) Serum free light chain assay
- (D) Skeletal surveys

ANSWERS

1. **The correct answer is (B), IV normal saline and consideration of furosemide if fluid overload occurs, followed by IV zoledronate.** Hypercalcemia is a skeletal-related complication of multiple myeloma that is caused by increased osteoclastic activity. Aggressive management of this complication is required to prevent permanent and even fatal outcomes. Most patients with hypercalcemia of malignancy present with significant hypovolemia secondary to gastrointestinal and constitutional manifestations (eg, nausea, vomiting, delirium). Because volume depletion exacerbates hypercalcemia, it is essential to replace the fluid deficit as aggressively as the patient’s condition allows. Forced diuresis with loop diuretics such as furosemide can be beneficial, but loop diuretics should only be administered once the fluid deficit is fully corrected. Premature initiation of furosemide before the fluid deficit is corrected can worsen the hypercalcemia. Inhibition of the osteoclast with bisphosphonate therapy is also crucial. Zoledronate has been shown to be superior to pamidronate in the management of hypercalcemia of malignancy and is the treatment of choice.¹ Even in the setting of mild renal insufficiency, correction of the hypercalcemia is crucial and calls for prompt correction with bisphosphonate therapy. In randomized trials of zoledronate versus pamidronate, significant renal dysfunction (serum creatinine up to 4.5 mg/dL) was present in many patients and should not preclude zoledronate therapy. Other complications associated with bisphosphonate therapy include osteonecrosis of the jaw. Although dental evaluation is important prior to initiating prophylactic bisphosphonates, hypercalcemia of malignancy constitutes a medical emergency and zoledronate therapy should not be withheld.

Reference

1. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001;19:558–67.

2. **The correct answer is (A), bortezomib and dexamethasone.** Induction therapies should be individualized to each patient. The combination of oral melphalan, prednisone, and thalidomide is a potent therapeutic option; however, based on this patient’s age, autologous stem cell transplantation is a possible treatment option, and therefore therapy with stem cell toxic agents such as melphalan should be avoided. Pulse high-dose dexamethasone does not affect the ability to harvest stem cells, but this patient has evidence of high-risk disease based on the presence of the chromosome 13 deletion. Subset analyses of multiple trials have demonstrated that use of novel agents such as bortezomib and lenalidomide may overcome the negative prognostic effect of some high-risk cytogenetic abnormalities.^{1,2} Lenalidomide and high-dose dexamethasone has been associated with high response rates when used as first-line therapy in newly diagnosed, untreated, symptomatic patients with multiple myeloma; however, use of high-dose as compared with low-dose dexamethasone is associated with significant non-hematologic toxicity and decreased survival.³ In addition, lenalidomide is renally excreted and the current guidelines for dosing lenalidomide in renal impairment have not been validated prospectively.⁴

References

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4. Dispenzieri A, Rajkumar SV, Gertz MA, et al. Treatment of newly diagnosed multiple myeloma based on Mayo Stratification of Myeloma and Risk-adapted Therapy (mSMART): consensus statement. *Mayo Clin Proc* 2007; 82:323–41.

3. The correct answer is (A), deletion of chromosome 13 by FISH. Chromosome 13 deletions are associated with an adverse prognosis when detected on conventional metaphase cytogenetics. Isolated chromosomal 13 deletions by FISH have not been associated with an adverse prognosis. The t(4:14) translocation and other chromosomal losses are associated with an adverse prognosis.¹ Elevated β_2 -microglobulin is associated with a worse prognosis and is an essential part of the International Staging System.

Reference

1. Dispenzieri A, Rajkumar SV, Gertz MA, et al. Treatment of newly diagnosed multiple myeloma based on Mayo Stratification of Myeloma and Risk-adapted Therapy (mSMART): consensus statement. *Mayo Clin Proc* 2007; 82:323–41.

4. The correct answer is (D), suspend bortezomib and then resume therapy at a reduced dose after the pain has resolved. Aggressive dose modifications are essential for the safe administration of bortezomib. Peripheral neuropathy is a dose-limiting toxicity of bortezomib and can result in debilitating pain and loss of function if not addressed properly. With the development of pain, bortezomib therapy should be

held and restarted at a reduced dose after the pain has resolved. Adjunctive agents such as gabapentin may be used, but only in addition to the prescribed dose adjustments. Although switching this patient to lenalidomide would not be unreasonable, this patient's excellent response to bortezomib would likely encourage continued use.

5. The correct answer is (C), serum free light chain assay. Serum β_2 -microglobulin can provide a rough estimate of tumor burden but is also greatly affected by renal function. As such, it is not a reliable indicator of disease response. Magnetic resonance imaging of the lytic lesion on the left humerus would provide an accurate reflection of the response in the specific lesion but does not provide information regarding systemic response to therapy. Skeletal imaging will provide evidence of progressive disease, but the lesions can remain stable even in the setting of responsive disease. This patient would have been considered nonsecretory prior to the advent of serum free light chain assay testing. In this patient, the suppressed kappa/lambda ratio indicates that the patient has a lambda monoclonal protein and, as such, serum free light chains can be used to assess this patient's response to therapy and progression while in remission.

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