Newly Diagnosed, Transplant-Eligible Patient

Case Study 1
2011

Case Study

- 62-year-old Caucasian man with increasing fatigue for the last three months presented to the ER with diffuse bony aches and back pains
- Admitted for further evaluation
- History past six months:
  - 20 pound weight loss
  - Increasing fatigue
  - Nausea and malaise
- Previous health – hypertension and type II diabetes for the past 10 years that has been poorly controlled. He has mild diabetic peripheral neuropathy for the past three years
- The patient was subsequently referred to an oncologist due to laboratory test findings during the ER visit

ER=emergency room

Initial Diagnostic Evaluation

- History and physical examination
- Blood workup
  - CBC with differential and platelet counts
  - BUN, creatinine
  - Electrolytes, calcium, albumin, LDH
  - Serum quantitative immunoglobulins
  - Serum protein electrophoresis and immunofixation
  - β_2-microglobulin
  - Serum free light chain assay
- Urine
  - Protein electrophoresis (UPEP)
  - Immunofixation electrophoresis (UIFE)
- Other
  - Skeletal survey
  - Unilateral bone marrow aspirate and biopsy evaluation with immunohistochemistry or flow cytometry, cytogenetics, and FISH
  - MRI as indicated

CBC=complete blood count; BUN=blood urea nitrogen; LDH=lactate dehydrogenase; FISH=fluorescence in situ hybridization; MRI=magnetic resonance imaging

Refer to the *Managing Myeloma* Initial Diagnostic tool available at: *www.managingmyeloma.com/index.php?option=com_content&view=article&id=613&Itemid=132*

Dimopoulos, M et al. *Blood*. 2011;117(18):4701-4705.

NCCN Clinical Practice Guidelines. Multiple Myeloma. Version 1..2011 released 10/15/2010.

Key Laboratory Findings Post-ER Visit

Test	Value	Common Laboratory Values
CBC, differential & platelets	**Hg 10.8 g/dL Platelet count 180,000**	Hg 13.5-16.5 Platelet count 100,000-450,000
BUN	**16 mg/dL**	7 - 20 mg/dL
Creatinine	**2.0 mg/dL ↑**	0.5 - 1.4 mg/dL
Electrolytes		
Calcium	**8.0 mg/dL ↓**	8.8 - 10.3 mg/dL
Lactate dehydrogenase (LDH)	**120 IU/L**	56 - 194 IU/L
Beta-2 microglobulin	**3.0 mg/L ↑**	< 2.5 mg/L
Albumin	**2.2 g/dL ↓**	**3.2 - 5 g/dL**
24-h urine total protein		
Serum free light chain assay	**κ 6.6 mg/L; λ 410 mg/L; κ / λ : 0.016**	κ 3.3 - 19.4 mg/L; λ 5.7-26.3 mg/L; κ/λ: 0.26 - 1.65
Serum quantitative immunoglobulins,		
Serum protein electrophoresis (SPEP)	**3.2 g/dL M-component**	**0.6 to 1.2 g/dL**
Serum immunofixation electrophoresis (SIFE)	**IgA λ**	
24-h urine for total protein		
Urine protein electrophoresis (UPEP)		
Urine immunofixation electrophoresis (UIFE)		
Skeletal Survey	**Skeletal survey shows fractures at T6 and T8**	
Unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and/or bone marrow flow cytometry	**Bone marrow biopsy shows 70% plasma cells**	

International Staging System (ISS)

- ISS identifies three groups with validated and confirmed survival differences

	Median survival (mo)
Stage 1: (β2M <3.5 mg/L & albumin ≥3.5 g/dL)	62
Stage 2: (neither stage 1 or 3)	44
Stage 3: (β2M ≥5.5 mg/L)	29

- ISS prognostic regardless of
  - Age, geographic region, individual institution or cooperative group, standard or transplant therapy, method of albumin

Greipp PR, et al. *J Clin Oncol.* 2005;23:3412-3420.

Newly Diagnosed Patient
ISS Staging and Key Test Findings

- Laboratory results
  - β2-microglobulin 3.0 mg/L
  - **Albumin 2.2 g/dL**

ISS Stage II

Stage II:
Serum β2-m <3.5 mg/L
But
Serum albumin <3.5 g/dL

  - Hemoglobin 10.8 g/dL
  - Calcium 8.0 mg/dL
  - Creatinine 2.0 mg/dL
  - SPEP **3.2 g/dL** M-component protein IgA λ
  - Serum free light chain assay- κ 6.6 mg/L; λ 410 mg/L; κ/λ: 0.016
  - Skeletal survey shows fractures at T6 and T8

  - Rouleaux on peripheral smear
  - No circulating plasma cells
  - Platelets 180,000/uL
  - Urine: 1+ protein, 2+ RBC
  - PT/PTT normal

An ultrasound might be in order for this patient. With red blood cells in the urine, a nephrologist may want to ask themselves, is it possible that this patient has renal cancer?

  - Marrow 70% plasma cells
  - Conventional cytogenetics hypodiploid
  - FISH positive for t(4;14) and del 17p

Criteria for Diagnosis of Myeloma

MGUS
- **<3 g M-spike**
  <10% PC

Smoldering MM
- **≥3 g M spike**
- **OR ≥10% PC**

Active MM
- **Increased PC**

√ **• Any M-spike +**

AND

AND

YES

NO

Any one or more attributed to the disease end-organ damage

C - High calcium

√ **R - Renal dysfunction**

A - Anemia

√ **B - Bone lesions**

(also hyperviscosity, amyloidosis, recurrent infections)

MGUS=monoclonal gammopathy of undetermined significance; PC=plasma cell; MM=multiple myeloma

Kyle RA. *N Engl J Med.* 2002; 346:564.

IMWG Classification of Active MM

- High risk (25%)
  - FISH
    - Del 17p
    - t(4;14)*
    - t(14;16)
  - Cytogenetic deletion 13q
  - Cytogenetic hypodiploidy
  - PCLI ≥3%

- Standard risk (75%)*

  All others, including:
  - Hyperdiploidy
  - t(11;14)
  - t(6;14)

Patient is classified as high risk, he has hypodiploidy by conventional cytogenetics and is positive for t(4;14) and del 17p by FISH analysis

IMWG=International Myeloma Working Group; PCLI=plasma cell labeling index
*Patients with t(4;14), β2-M <4 mg/L and Hb ≥10 g/dL may have intermediate-risk disease.

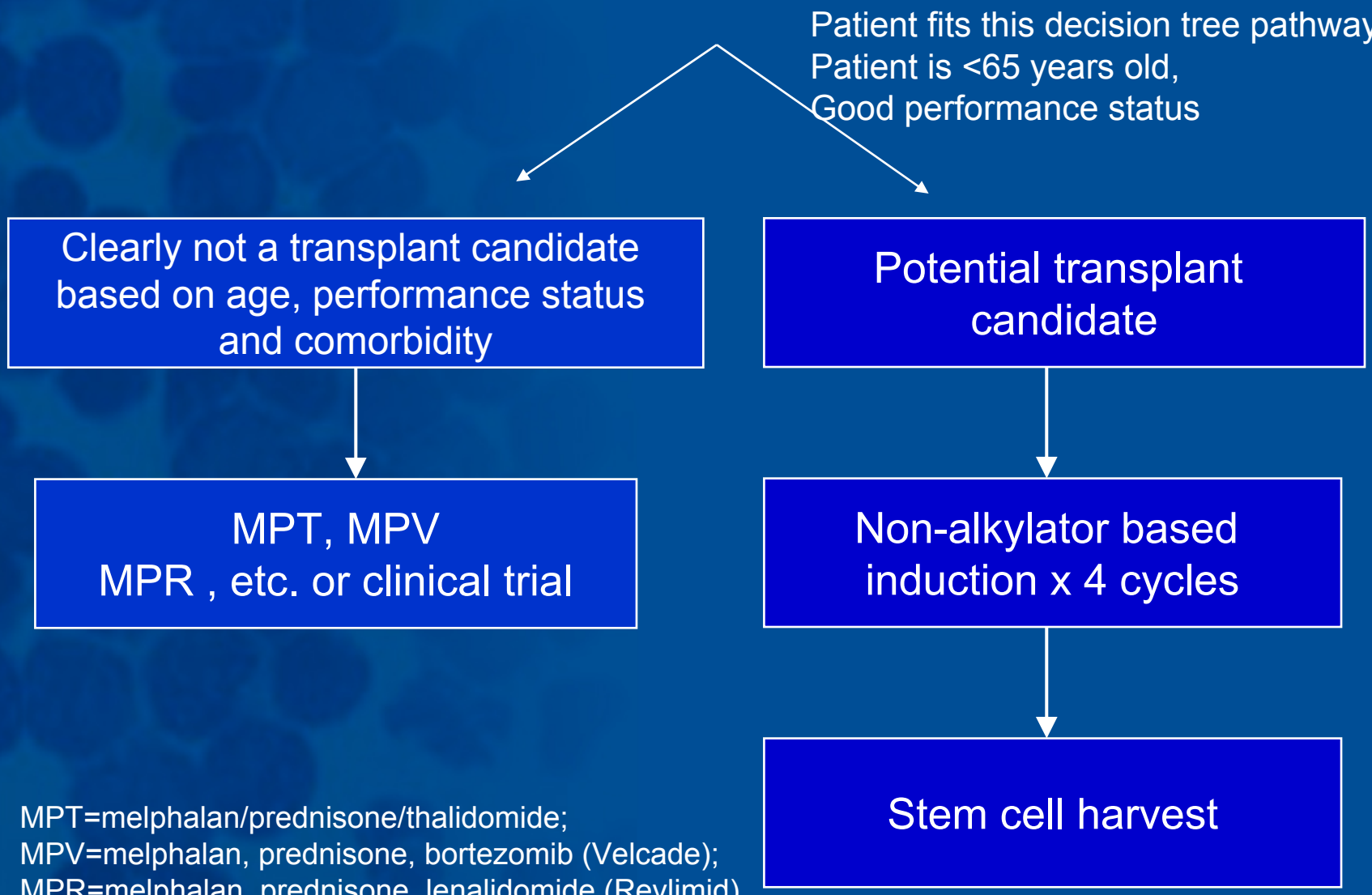
Dispenzieri A, et al. *Mayo Clin Proc*. 2007;82:323-341. v5 Revised and updated: Jan 2009.

Fonseca R, et al. *Leukemia*. 2009;23(12):2210-2221.

Case Study – Treatment Planning

- How would you manage this patient's myeloma?
  - Consider whether the patient is a transplant candidate
    - Stem cell harvest and transplant: timing
    - Choice of induction therapy
  - Risk factors, comorbidities and MM associated sequelae and management of potential treatment-related side effects
    - MM associated sequelae and risk factors: renal impairment, bone disease, FISH positive for t(4;14) and del 17p
    - Comorbidity: diabetes (may be affected by dexamethasone containing regimens)
- How would you monitor and assess response to treatment for this multiple myeloma patient?

Initial Approach to Treatment of Myeloma



MPT=melphalan/prednisone/thalidomide;
MPV=melphalan, prednisone, bortezomib (Velcade);
MPR=melphalan, prednisone, lenalidomide (Revlimid)

NCCN-listed Myeloma Therapies
(version 1.2011, released 10/15/2010)

- **Transplant-eligible candidates**
  - Bortezomib/dexamethasone [BD] **(category 1)**
  - Bortezomib/cyclophosphamide/dexamethasone [CyBorD] (category 2A)
  - Bortezomib/doxorubicin/dexamethasone [PAD] **(category 1)**
  - Bortezomib/lenalidomide/dexamethasone [LBD] (category 2B)
  - Bortezomib/thalidomide/dexamethasone [BTD] **(category 1)**
  - Dexamethasone (Category 2B)
  - Lenalidomide/dexamethasone [LD] **(category 1)**
  - Liposomal doxorubicin/vincristine/dexamethasone [DVD] (category 2B)
  - Thalidomide/dexamethasone [TD] (category 2B)

NCCN=National Comprehensive Cancer Network

Case Study Induction Therapy

- Patient is treated with bortezomib and dexamethasone with close monitoring for hyperglycemia and worsening of his neuropathy
  - Choice was guided by presence of renal dysfunction
    - Patient was also treated with the bisphosphonate pamidronate for his bone disease
    - Patient was given prophylaxis for herpes zoster- acyclovir according to PI
    - Patient educated to immediately report any symptoms of peripheral neuropathy and changes in blood glucose levels to be monitored daily
- After two cycles M-component protein has fallen to 0.5 g/dL
  - Dexamethasone is reduced from 40 to 12 mg due to hyperglycemia
  - Neuropathy and renal function are unchanged
- After completing three cycles of BD, his M-component protein is undetectable by immunofixation (urine, sera) and his bone marrow has <5% plasma cells.
  - Renal function improved, creatinine is now 1.2 mg/dL

PI=package insert

Roussou M, et al. *Leuk Res*. 2010;(10):1395-1397.; Dimopoulos MA, et al. *J Clin Oncol*. 2010;28(33):4976-4984.

Response Assessment

- According to IMWG Uniform Response Criteria, what is this patient's response to treatment?
  A. Stringent complete response (sCR)
  B. Complete response (CR)
  C. Very good partial response (VGPR)
  D. Partial Response (PR)

IMWG Uniform Response Criteria in Myeloma

- **Stringent complete response (CR):** CR as defined below plus normal free light chain (FLC) ratio; absence of plasma cells by immunohistochemistry (IHC) or immunofluorescence
- **Complete response (CR):** negative immunofixation on urine and serum; absence of plasmacytomas; ≤5% plasma cells in bone marrow
- **Very good partial response (VGPR):** serum and urine M-protein detectable by immunofixation but not on electrophoresis, or ≥90% reduction in serum M-protein + urine protein <100 mg/24 h
- **Partial response (PR):** ≥50% reduction of serum M-protein + ≥90% reduction in 24-h urinary M-protein (or <200 mg/24 h)

Durie BG, et al. *Leukemia.* 2006;20:1467-1473.

Response Assessment and Next Steps

- Patient achieved at least a CR
  - Free light chain test should be performed so should IHC to determine whether patient achieved sCR
- Patient to be referred for stem cell collection and autologous stem cell transplant