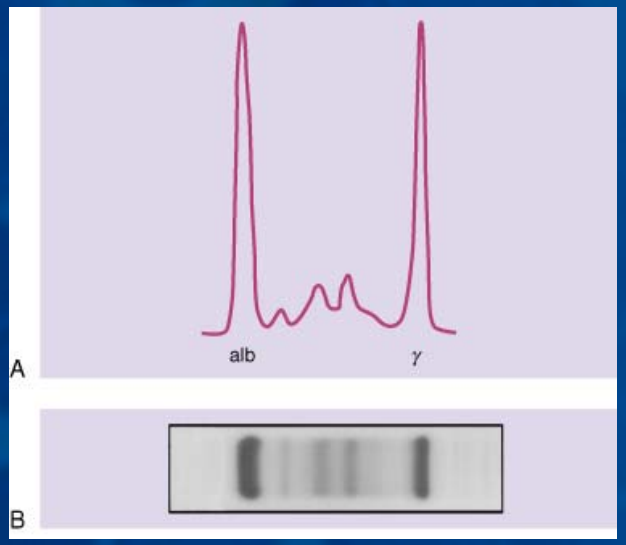
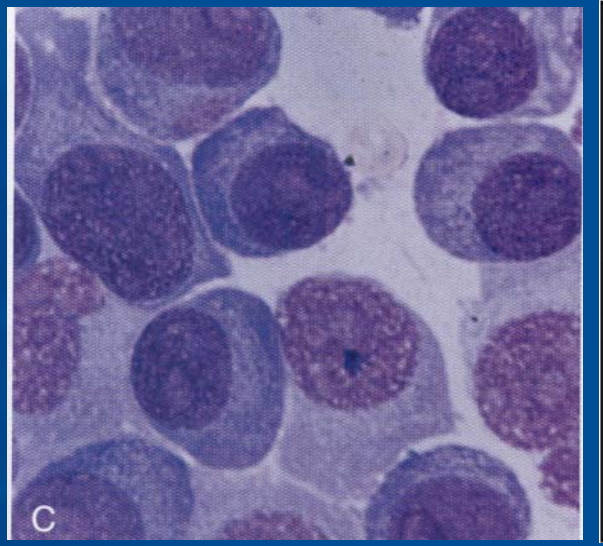
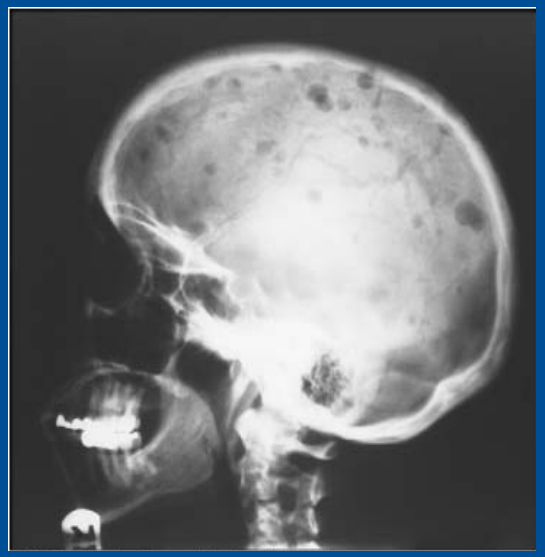
# *Managing Myeloma* Virtual Grand Rounds
## *Newly Diagnosed, Transplant Eligible Patient*



Case Study 2
2011

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# Newly Diagnosed Patient

- The patient is a 61-year-old Caucasian female
- History of high blood pressure which is under control with diuretic, but otherwise in good general health
- The disease was detected after the patient tripped on a curb and suffered a vertebral compression fracture
  - Patient is now ambulatory after kyphoplasty and is on treatment with bisphosphonates

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# Newly Diagnosed Patient

- Laboratory Results
  - β2-microglobulin: **3.8 mg/L**
  - Serum albumin 3.6 g/dL

**ISS Stage II**

**ISS Criteria**

**Stage I**
**β2-microglobulin <3.5 g/dL**
**Serum albumin ≥3.5 g/dL**
**Stage II:**
**Serum β2-microglobulin <3.5 mg/L**
**But**
**Serum albumin <3.5 g/dL**
***Or***
**Serum β2-microglobulin 3.5-5.5 mg/L irrespective of the serum albumin level**
**Stage III**
**β2-microglobulin ≥5.5 g/dL**

  - Hemoglobin 11 g/dL
  - Calcium 8.0 mg/dL
  - Creatinine 1.1 mg/dL
  - Multiple lytic bone lesions on bone survey, magnetic resonance imaging shows multiple heterogeneous marrow lesions
  - SPEP 4.3 g/dL M-component protein IgG λ

**Durie-Salmon Stage IIIa**

  - 21% plasma cells by bone aspirate; hyperdiploid
  - FISH: Showed 30% t(11;14)

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Greipp PR, et al. *J Clin Oncol*. 2005;23:3412-3420.; Durie B, et al. *Cancer*. 1975;36:842-854.; IMWG. *Br J Haematol*. 2003;121:749-757.

# Newly Diagnosed Patient

- How would you manage this patient's myeloma?
  - What are your treatment goals for this patient?
  - Consider whether the patient is a transplant candidate
    - Stem cell harvest and transplant: timing (is ASCT necessary in the era of novel therapies?)
    - Choice of induction therapy
      - These are only examples: bortezomib/dexamethasone (category 1)[*]; lenalidomide/dexamethasone (category 1)[†*]; bortezomib/thalidomide/dexamethasone (category 1)*, lenalidomide/bortezomib/dexamethasone (category 2A)*[†]
    - Risk factors, comorbidities and MM associated sequelae and management of potential treatment-related side effects which may affect your choice of induction therapy and supportive care
  - Subsequent grand-rounds activities in this series will address stem cell transplantation, maintenance therapy and supportive care in greater depth, so we will focus primarily on induction therapy selection today

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*NCCN Clinical Practice Guidelines - Multiple Myeloma 2011 (version 1.2012).
†Lenalidomide is not currently approved by the FDA for use as first-line therapy in multiple myeloma.

# Patient Case

- Patient is 62 years of age (<65), in otherwise good health
  - Is she a transplant candidate?

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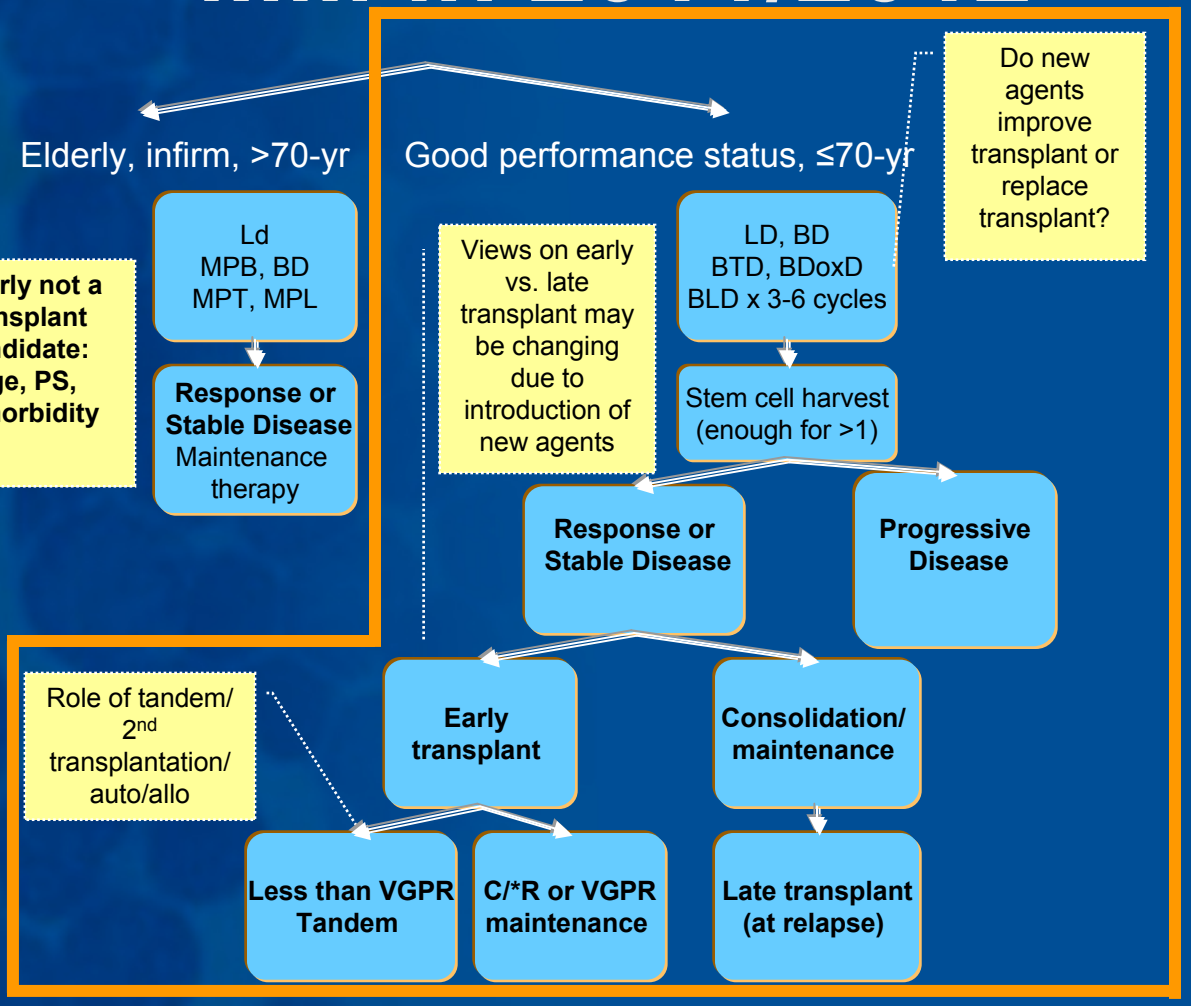
# Initial Approach to Treatment of MM in 2011/2012




Our patient doesn't fit here

Our patient fits here

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NCCN Clinical Practice Guidelines - Multiple Myeloma 2011 (version 1.2012). Also see the *Managing Myeloma Compendium of Drug Regimens* at *www.managingmyeloma.com* under tools.

# Patient Case

- Yes, this patient is a candidate for autologous stem cell transplantation (ASCT)
  - Is ASCT still necessary in the era of novel therapies?
    - See support slides following this case presentation

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# Patient Primary and Adjunctive Treatment

- After discussing treatment goals and options with the patient, she agrees to induction therapy followed by stem cell collection and to be referred for transplantation – she lives close to the treatment center and is committed to adhering to her office visits and treatment
- After a baseline evaluation for symptoms of peripheral neuropathy (PN), and educating the patient to report any symptoms and change in symptoms of PN, she is started on bortezomib + dexamethasone [BD]
  - Bort 1.3 mg/m$^2$ d 1, 4, 8, 11; dex 40 mg PO QAM on days 1–4 and 9–12 for cycles 1–2 and days 1–4 for cycles 3–4. Administered for four 21-day cycles [IFM 2005-01]. Remember: prophylax for herpes zoster: acyclovir
- We also continue her treatment of bone disease with the bisphosphonate zoledronic acid

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Harousseau JL, et al. 2008 ASCO abstract 8505.; Harousseau JL, et al. *Haematologica*. 2006;91(11):1498-505.

# Further Discussions Regarding Bortezomib-Based Therapy

- This protocol has been reported to have an ORR of 66% with a 21% CR and 10% VGPR
- Off-protocol use of subcutaneous bortezomib could be used if one seeks to reduce risk of PN, but this is decision must be made by the practitioner based on his/her experience*
  - Peripheral neuropathy of any grade subcutaneous bort vs. IV bort (56 [38%] vs. 39 [53%]; *P*=.044), grade 2 or worse (35 [24%] vs. 30 [41%]; *P*=.012), and grade 3 or worse (9 [6%] vs. 12 [16%]; *P*=.026)
  - Grade ≥3 skin and subcutaneous tissue disorders were reported in 3% of patients; other AEs are similar

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*Subcutaneous bortezomib administration is not approved by the FDA for the treatment of MM.

Harousseau JL, et al. *Haematologica*. 2006;91(11):1498-505.; Moreau P, et al. *Lancet Oncol*. 2011;12(5):431-440.

# Patient Case After Two Cycles of Primary Treatment - Addressing Peripheral Neuropathy

- After two cycles of bortezomib (1.3 mg/m$^2$), the patient achieves a PR but complains of painful neuropathy in the hands and feet [grade 1 with pain]
- What options do we have?
  - We can keep the same dose schedule but reduce bortezomib to 1.0 mg/m$^2$
  - An alternative dose schedule we could have used is once-weekly bortezomib, which has been shown to reduce the incidence of PN with similar efficacy

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PR=partial response

Velcade (bortezomib IV) Prescribing Information. December 2010 Rev 11
*www.velcade.com/pdf/VELCADE_PRESCRIBING_INFORMATION.pdf*
Bringhen S, et al. *Blood*. 2010;116(23):4745-453.

# What Was Done in Response to Grade 2 Peripheral Neuropathy After Two Cycles of Primary Treatment

- We reduce the bortezomib dose to 1.0 mg/m$^2$
- The patient has achieved a PR, and the response may improve in subsequent cycles but the option of adding an additional agent was considered, discussed with the patient and implemented

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# Some Bortezomib-Based Regimen Tailoring Options

- Options to modify the bortezomib-based therapy:
  - Addition of cyclophosphamide to bort + dex (CyBorD) which has been shown to provide deeper responses: ORR (≥PR) 88%, with 61% ≥VGPR
    - 300 mg/m$^2$ of cyclophosphamide by mouth on d 1, 8, 15, 22; 1.3 mg/m$^2$ of bortezomib IV on days 1, 4, 8 & 11, and 40 mg of dexamethasone by PO d 1-4, 9-12, and 17-20
      - But keep bortezomib dose at 1.0 mg/m$^2$
    - Can use a once-weekly bortezomib schedule with this regimen, achieving similar efficacy, just wait until PN resolves at reduced bort dose
  - Addition of lenalidomide to bortezomib plus dexamethasone (LBD) which has been shown to provide some of the deepest responses to date: ORR (≥PR) 100%, with 67% ≥VGPR
    - Bort 1.3 mg/m$^2$ d 1, 4, 8, 11; len 25 mg d 1-14; and dexamethasone 20 mg PO d 1, 2, 4, 5, 8, 9, 11, 12
      - Bort 1.0 mg/m$^2$ was shown to have comparable responses in phase 1/2 trial

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Lenalidomide is not currently approved by the FDA for use as first-line therapy in multiple myeloma.

Reeder CB, et al. *Blood.* 2010;115(16):3416-3417.; Richardson PG, et al. *Blood*. 2010;116(5):679-686.

# What Was Done to Improve Response

- We opt to add lenalidomide to the patient's regimen
  - Thromboprophylaxis with aspirin (100 mg/d)
  - This regimen should be limited to no more than 4 cycles to ensure efficient PBSC collection
- The patients painful PN resolves, some grade 1 PN tingling remains in hands and feet not reported to be discernibly different than baseline
- After three cycles of LBD the patient achieves a CR (negative immunofixation on urine, serum; absence of plasmacytomas; ≤5% plasma cells in bone marrow) and is sent for PBSC collection and subsequent ASCT

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Cavallo F, et al. *Blood*. 2010;116(21):476-477 (Abstract 1092).

# Alternative Approach Using Lenalidomide-Based Therapy Would Also Have Allowed for Tailoring Options

- Had we made a different decision from the beginning, say initial treatment with LD, and observed less than anticipated or desired response, a similar approach to tailoring therapy for this patient would be possible, eg:
  - Addition of bortezomib to LD for (LBD)
    - ORR (≥PR) 100%, with 67% ≥VGPR
  - Addition of clarithromycin to LD (BiRD regimen)
    - ORR (≥PR) 90%; 39% complete response (sCR/CR), and 74% ≥VGPR
      - Dex 40 mg PO QAM days 1, 2, 3, 8, 15, and 22 during cycle 1 and weekly on days 1, 8, 15, and 22 of each subsequent cycle. Clarithromycin 500 mg PO BID, beginning on day 2 of cycle 1. Lenalidomide 25 mg PO QD days 3–21 of cycle 1 and on days 1–21 of subsequent cycles. Prophylactic treatments on protocol included aspirin 81 mg QD, daily; omeprazole 20 mg QD, daily; one double-strength tablet of trimethoprim/sulfamethoxazole BID, 3 times a week

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Lenalidomide is not currently approved by the FDA for use as first-line therapy in multiple myeloma.
Clarithromycin is not currently approved by the FDA for use in the treatment of multiple myeloma.
Richardson PG, et al. *Blood*. 2010;116(5):679-86.; Rossi AC, et al. *J Clin Oncol.* 2011;29: (suppl; abstr 8008).; Niesvizky R, et al. *Blood.* 2008;111(3):1101-1109.