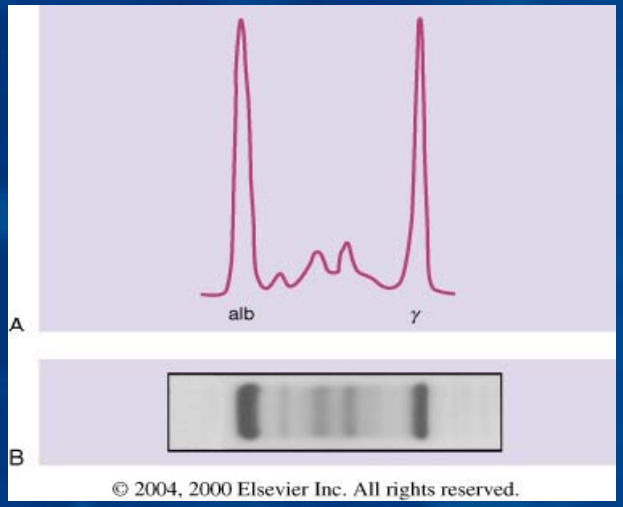
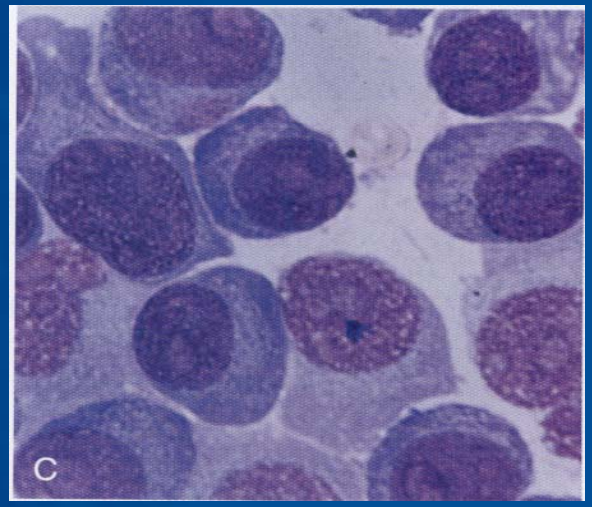
Practice Support Cases: Maintenance Therapy for Multiple Myeloma 2012





Patient Case 1

- 61-year-old Caucasian female
- Diagnosed after a vertebral compression fracture; kyphoplasty was performed, placed on bisphosphonates
- She was ISS II
  - Laboratory results
    - β2-microglobulin **3.8 mg/L**
    - Serum albumin 3.6 g/d
    - 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
    - 21% plasma cells by bone aspirate; hyperdiploid
    - FISH: Showed 30% t(11;14)

ISS=International Staging System; SPEP=serum protein electrophoresis; IgG=immunoglobulin G; FISH=fluorescence in situ hybridization

Richardson PG, et al. *Blood*. 2009;114:Abstract 1218.; NCCN Guidelines MM 1.2011.

Patient Case 1

- Treatment for myeloma
  - Bortezomib 1.3 mg/m^2 d 1, 4, 8, 11; dexamethasone 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
  - After 2 cycles of bortezomib, the patient achieves a PR but complains of painful neuropathy in the hands and feet [grade 1 with pain]
  - **Bortezomib dose was decreased to 1.0 mg/m^2 IV on days 1, 4, 8, and 11;** and **lenalidomide 25 mg PO QAM on days 1–14 was added**; Dex was left unchanged (LBD regimen*) - patient's painful PN resolved to baseline with only minor tingling
  - After 3 cycles of **LBD** the patient achieves an IF-CR; she underwent PBSC collection and ASCT

Lenalidomide is not approved by the FDA for treatment of newly diagnosed, treatment naïve multiple myeloma.

PO=orally/by mouth; QAM=once in the morning; PR=partial response; IV=intravenous; Dex=dexamethasone; LBD=lenalidomide, bortezomib, dexamethasone; PN=peripheral neuropathy; IF-CR=immunofixation negative complete response; PBSC=peripheral blood stem cell; ASCT=autologous stem cell transplant

Richardson PG, et al. *Blood*. 2009;114:Abstract 1218.; NCCN Guidelines MM 1.2011.

Key Practice Reminders

- All patients, whether after ASCT or after induction therapy for patients not receiving ASCT, should be strongly considered for maintenance therapy*

*See *Managing Myeloma*'s Patient Care Support Tool: Maintenance Therapy Reference Resource for additional information and citations.

Practice Pearl

- If maintenance is to be given to a patient who has achieved an IF-CR, it should be delivered until progression*
  - Reason: Even patients who have achieved an immunofixation negative complete response still have residual disease

*See *Managing Myeloma*'s Patient Care Support Tool: Maintenance Therapy Reference Resource for additional information and citations.

Return to Patient 1 Case

- 61-year-old Caucasian female
- Treatment for myeloma
  - After 3 cycles of LBD the patient achieves an IF-CR; she underwent PBSC collection and ASCT
  - Maintenance options include both Bort or Len
- Patient was prescribed Len maintenance using 10 mg/d QAM daily (continuous therapy)
  - Patient was educated regarding the incidence of SPMs observed in clinical trial
  - Consideration: no high risk factors, convenience – patient still works and lives at a distance from the treatment center
  - Maintenance with Len improved the 3-year PFS from randomization in one trial, 35% placebo versus 68% with Len (HR=0.46, *P*<10-6). This benefit was observed both among patients achieving or not achieving a complete response after ASCT

Lenalidomide is not FDA approved as a maintenance therapy for multiple myeloma.

Bort=bortezomib; Len=lenalidomide; SPMs=second primary malignancies; PFS=progression free survival; HR=hazard ratio

Attal M, et al. *J Clin Oncol.* 2010;28:15s (suppl; abstr 8018).

What Could We Have Done Differently to Reduce the Risk of Side Effects?

- Patient Case 1 on lenalidomide maintenance
  - Reduce lenalidomide to 10 mg three weeks on, one week off

Patient Case 2

- 79-year-old African American male
- History of well-controlled hypertension, hyperlipidemia, prostatic hypertrophy, single-vessel coronary stent six years ago. Previously very active. Takes metoprolol, ASA, pravastatin, tamsulosin, fish oil
- Presents with five months progressive fatigue, dyspnea, bony pains, anorexia. ECOG PS of 1
  - Cardiac workup unremarkable
  - Found to have new normocytic anemia (Hgb 8.0), renal insufficiency (Cr 2.2), hypercalcemia (Ca 10.6 with albumin 3.0)
  - SPEP shows large M-spike (5.2 g/dL)

ASA=acetylsalicylic acid (aspirin); ECOG=Eastern Cooperative Oncology Group; PS=performance status; Hgb=hemoglobin; Cr=creatinine; Ca=calcium

Patient Case 2

- Laboratory results
  - β2-microglobulin 6.8 mg/L, **ISS stage 3**
  - Serum albumin 3.0 g/dL
  - **Hemoglobin 8.0 g/dL**
  - **Calcium 10.6 mg/dL**
  - **Creatinine 2.2 mg/dL** (CrCl = 31 mL/min)
  - **Multiple lytic bone lesions, mild L1 and L4 compression fractures on bone survey**
  - SPEP: M-spike 5.2 g/dL, serum immunofixation: IgG K, quant. IgG=6100 mg/dL
  - 24-hour urine: 1800 mg of Bence-Jones proteinuria (kappa light chains)
  - Serum free kappa light chains = 1450 mg/L with κ:λ ratio = 58.9
  - **60% plasma cells by bone marrow aspirate**; normal karyotype
  - **FISH: Showed 20% t(4;14)**

CrCl=creatinine clearance

Patient Case 2

- 79 M, HTN/CAD, new myeloma
  - Cr 2.2 (CrCl = 31 mL/min), Hgb 8.0, ISS III, t(4;14)
  - → hydrated, transfused, pain control
  - **Started on BMP on twice-weekly schedule (Bort 1.3 mg/m^2 days 1, 4, 8, 11, 22, 25, 29, 32)**
    - Melphalan 25% dose-reduced (from 9 to 6.75 mg/m^2) due to age/renal insufficiency
    - Acyclovir prophylaxis, proton pump inhibitor
  - **After 1 cycle, Cr is 1.4, has partial response**
    - Bisphosphonate started monthly, switched to weekly Bort schedule to decrease risk of neuropathy. (Bort weekly: 1.3 mg/m^2 days 1, 8, 15, 22 every 35 days)
  - **After 9 total cycles, has near complete response, Cr is normal, Hgb 10, Bort dose reduced last 2 cycles due to grade 1 painful peripheral neuropathy → resolved to grade 1 without pain (Bort weekly with dose reduction: 1.0 mg/m^2 days 1, 8, 15, 22 every 35 days)**
    - Bone marrow shows 4% residual kappa-restricted plasma cells, FISH now negative

HTN/CAD=hypertension and coronary artery disease; BMP=bortezomib, melphalan, prednisone

Practice Pearls

- Maintenance is indicated independently from the response achieved and independently from the prognosis of those patients*
  - Reason: Maintenance study data exists showing efficacy both in patients in CR or PR, and data showing efficacy both in patients with standard risk or high risk of disease (refer to the Maintenance Therapy Reference Tool on *Managing Myeloma* and the Grand Rounds – Maintenance Therapy Activity discussion by Dr. Antonio Palumbo for supporting reference citations)

CR=complete response

*See *Managing Myeloma*'s Patient Care Support Tool: Maintenance Therapy Reference Resource for additional information and citations.

Return to Patient 2

- Patient was placed on BP maintenance
  - Bortezomib 1.0 mg/m^2 on days 1, 8, 15 and 22 every 3 months, plus oral prednisone 50 mg every other day
    - Patient achieved a nCR while on BMP and has high-risk disease, thus maintenance therapy with bortezomib is a rational choice with prednisone
    - Elderly patients given BP maintenance have a PFS of 24 mos (95% CI 15–33); and a median survival of 60 months
      - Prednisone can be dropped from the regimen if prednisone associated toxicities occur; bortezomib can be administered SQ if painful neuropathy reoccurs

Bortezomib/prednisone and bortezomib are not approved by the FDA as maintenance therapy for multiple myeloma

BP=blood pressure; nCR=near-complete response; PFS=progression free survival; CI=confidence interval; SQ=subcutaneous

Mateos M-V, et al. *Blood*. 2011;Abstract 477.; Kapoor P, e al. *Int J Hematol*. 2011;94(4):310-320.

What Could We Have Done Differently to Reduce the Risk of Side Effects?

- Patient Case 2 on bortezomib/prednisone maintenance
  - Dose-schedule days of bortezomib (1.3 mg/m^2) could be further reduced to day 1 and 15 instead of day 1, 8, 15, and 22
    - Prednisone can be omitted

Practice Reminders

- MPL primary therapy followed by lenalidomide maintenance has demonstrated one of the longest PFS observed to date
  - Lenalidomide can be given continuously until disease progression; side effects are manageable; SPMs have been clinically observed, their incidence is low
  - Discuss the observed risk of SPMs with your patients
- Bortezomib maintenance has also shown one of the longest PFS to date in the elderly MM population; current clinical data is less mature than that for lenalidomide, and placebo control comparator arms are needed in future studies

Lenalidomide is not approved by the FDA for newly diagnosed, treatment naïve multiple myeloma patients.

MPL= melphalan/prednisone/lenalidomide; MM=multiple myeloma

Practice Reminders

- The best primary maintenance therapy combination has not been determined – NCCN lists Thal, Len and Bort as “preferred” maintenance regimens
  - Tailor therapy to patient needs and previous response to therapy and toxicities
    - If patient responded well to lenalidomide-based primary therapy, lenalidomide-based maintenance therapy may be preferred; this is a choice therapy for convenience
    - Conversely, if patient responded well to bortezomib-based primary therapy, bortezomib-based maintenance therapy may be preferred
    - Thalidomide-associated side effects may complicate the duration of therapy which can be achieved with this strategy, consider alternative choice of therapy
- Use strategies to limit toxicities while patients are on maintenance therapy
- Maintenance therapy is a long-term treatment; toxicities should not be allowed to exceed grade 1

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NCCN= National Comprehensive Cancer Network; Thal=thalidomide