Managing Myeloma Virtual Grand Rounds
Newly Diagnosed, Transplant Eligible Patient

Case Study 2
2011
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
**Newly Diagnosed Patient**

- Laboratory Results
  - β2-microglobulin: 3.8 mg/L **ISS Stage II**
  - Serum albumin 3.6 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
  - 21% plasma cells by bone aspirate; hyperdiploid
  - FISH: Showed 30% t(11;14)

**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

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

†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?
Initial Approach to Treatment of MM in 2011/2012

Elderly, infirm, >70-yr
Good performance status, ≤70-yr

Role of tandem/2nd transplantation/auto/allo
Response or Stable Disease Maintenance therapy
Ld MPB, BD MPT, MPL

Views on early vs. late transplant may be changing due to introduction of new agents
Response or Stable Disease
LD, BD BTD, BDoxD BLD x 3-6 cycles
Stem cell harvest (enough for >1)

Consolidation/maintenance
Early transplant
Late transplant (at relapse)
Less than VGPR Tandem
C*/R or VGPR maintenance
Progressive Disease

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
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/m² 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

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 \( \geq 3 \) skin and subcutaneous tissue disorders were reported in 3% of patients; other AEs are similar

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

- After two cycles of bortezomib (1.3 mg/m²), 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/m²
  - 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

PR=partial response

Velcade (bortezomib IV) Prescribing Information. December 2010 Rev 11
www.velcade.com/pdf/VELCADE_PRESCRIBING_INFORMATION.pdf
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/m²
• 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
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/m² of cyclophosphamide by mouth on d 1, 8, 15, 22; 1.3 mg/m² 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/m²
    ▪ 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/m² 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/m² was shown to have comparable responses in phase 1/2 trial
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 patient’s 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

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