Updates in Myeloma Therapeutics: Bone Health, Smoldering Disease, and CAR-T Cells

R. Donald Harvey, PharmD, BCOP, FCCP, FHOPA
Associate Professor, Departments of Hematology and Medical Oncology and Pharmacology
Director, Phase 1 Clinical Trials Section

Disclosures

• Research funding to my institution that supports my salary
  — Acetylon, Amgen, Astra Zeneca, BMS, Calithera, Celgene, Cleave, Corvus, Eli Lilly, Halozyme, Incyte, Merck, Novartis, Pfizer, Regeneron, Takeda
• Consultant
  — BMS, Genentech

Learning Objectives

• Identify novel and emerging therapeutic options and mechanisms of action in bone disease, smoldering myeloma, and immunotherapy of myeloma with chimeric antigen receptor (CAR) T cell therapy
• Assess the efficacy and safety of current and emerging treatments for each area
• Apply evidence-based approaches to select myeloma patients who are likely to benefit from these options

MYELOMA AND BONE HEALTH

ARS #1

• A 78-yr-old man with newly diagnosed myeloma is planned for induction with lenalidomide, bortezomib, and dexamethasone (RVd), is coming in for counseling and therapy discussion.
• Upon PET imaging, he is noted to have spinal lytic lesions at the L3 and sacral levels, with multiple skull lesions.
• His past medical history is significant for coronary artery disease and hypertension, and his creatinine clearance per Cockcroft-Gault is 28 mL/min.
• Other significant lab values reveal: hemoglobin 9.3 g/dL, monoclonal IgG = 8.5 g/dL, and 53% plasma cells on bone marrow aspirate.
• Therapy with a bone modifying agent is being considered.

Myeloma Defining Events: CRAB Criteria Revised

• Calcium elevation
  — Serum calcium = 0.25 mmol/L (1.1 mg/dL) higher than UAN or > 2.75 mmol/L (> 11 mg/dL)
• Renal dysfunction
  — Creatinine clearance < 40 mL/min or serum creatinine > 177 μmol/L (> 2 mg/dL)
• Anemia
  — Hemoglobin > 2 g/dL, below low normal or < 10 g/dL
• Bone disease
  — One or more osteolytic lesions on skeletal radiography, CT, or PET/CT
• Other markers — bone marrow plasma cells > 60%, free light chain ratio > 100, > 1 focal lesion > 5 mm on MRI

Current Management of Bone Disease

- Treat the myeloma
- Novel therapies have benefits
  - Direct effect on inflammatory cytokines
  - Inhibition of bone resorption
  - Osteoclast stimulation
- Bisphosphonates
  - Pamidronate
  - Zoledronic acid
- Denosumab

International Myeloma Working Group Recommendations

<table>
<thead>
<tr>
<th>Factor</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Population</td>
<td>Newly diagnosed patients with MM who require antimyeloma treatment (regardless of bone status)</td>
</tr>
<tr>
<td>Administration</td>
<td>IV (zoledronic acid, pamidronate) or SC (denosumab)</td>
</tr>
<tr>
<td>Duration/ Frequency</td>
<td>Monthly during initial therapy and ongoing in patients who are not in remission</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Monthly creatinine clearance</td>
</tr>
<tr>
<td>Choice</td>
<td>Zoledronic acid (first option) Denosumab: preferred for patients with renal insufficiency Pamidronate (second option)</td>
</tr>
</tbody>
</table>

Bisphosphonate Use in MM: Adverse Events

- Flu-like symptoms
- Fever, myalgia, arthralgias
- Occurs usually 12–48 hours following infusion; lasts 6–24 hours
- Occurs in minority of patients (< 10%)
- Generally reduced with continued dosing
- Slow rate of infusion and use of steroids and antihistamines may help reduce intensity

Bisphosphonates and Osteonecrosis

- Uncommon complication causing avascular necrosis of maxilla or mandible
- Suspect with tooth or jaw pain or exposed bone
- May be related to duration of therapy
- Incidence between 3% and 4% with zoledronic acid or pamidronate
A 62-yr-old woman has been diagnosed with smoldering myeloma 5 years ago, and is asking about beginning therapy with daratumumab.

Her past medical history is significant for type II diabetes and hypertension.

Lab values reveal: hemoglobin 9.7 g/dL, monoclonal IgG = 5.6 g/dL, other values within normal limits.

**Historical Criteria for Diagnosis of Myeloma**

- **MGUS**
  - < 3 g/dL M spike
  - < 10% plasma cells
  - AND NO CRAB* features or end-organ damage

- **SMM**
  - ≥ 3 g/dL M spike
  - ≥ 10% plasma cells
  - AND CRAB* features

- **Active MM**
  - ≥ 10% plasma cells
  - M spike + in serum and/or urine
  - AND CRAB* features

*CRAB features: Calcium elevation (> 10.5 mg/dL or ULN), Renal dysfunction (serum creatinine > 2 mg/dL), Anemia (Hb < 10 g/dL or 2 g/dL < normal), Bone disease (lytic lesions)

**Updated IMWG Criteria for Diagnosis of Multiple Myeloma**

- **MGUS**
  - M protein ≤ 1 g/L
  - Clonal plasma cells in BM < 10%
  - No myeloma defining events

- **Smoldering Myeloma**
  - M protein ≥ 1 g/L, (≥ 3 g/L if without AL, ALW, or ALP)
  - Clonal plasma cells in BM ≥ 10% to 60%
  - No myeloma defining events

- **Multiple Myeloma**
  - Underlying plasma cell proliferative disorder
  - AND 1 or more myeloma defining events
  - AND ≥ 1 CRAB* feature
  - AND ≥ 1 bone lesions on skeletal radiography, CT, or PET-CT

**Biomarkers to Predict Risk of Progression**

- FLC ratio ≥ 100 predicts risk (P < .0001)
- Clonal plasma cells in BM predicts risk (P < .001)

**Smoldering Multiple Myeloma**

51% will convert in first 5 yrs

~ 10% per yr

51% will convert in remaining 15 yrs

~ 2% per yr

**HR: 13.7; P < .001**


**IMWG. Br J Haematol. 2003;121:749-757.**


**Kyle RA, et al. Leukemia. 2009;23:3-9.**
**CENTAURUS: Background**

- Current guidelines recommend monitoring for progression to MM in SMM pts.
  - More than 70% of pts with high-risk SMM progress to MM.
- Diagnostic criteria for MM updated in 2014 to include pts with ultrahigh risk of progression (≥ 60% BM plasma cells, ≥ 300 AL C ratio, ≥ 1 MRI focal lesion, CRAB).
- Before updated criteria, phase III QuiRedex study in SMM reported improved PFS with use of lenalidomide + dexamethasone followed by lenalidomide maintenance.
- Additional studies needed for identifying and treating remaining pts with SMM at high risk of progression.
- CENTAURUS assessed daratumumab monotherapy in pts with high- or intermediate-risk SMM.

**Diagnostic progression:**

- Primary endpoints: CR > 15%, PD/death rate per PY †< .0001.
- Secondary endpoints: PFS, safety.

**Other**

- ORR: 38%.
- Before updated criteria, phase III QuiRedex study in SMM reported improved PFS (from 10% to 19%) with lenalidomide + dexamethasone therapy, N = 259.
- Risk factors at screening (2014): ORR: 40% to 59%.

**Biochemical progression:**

- PFS defined as time to biochemical or diagnostic MM progression or death.
  - Biochemical progression: measurable disease increase from nadir by ≥ 25% in ≥ 2 subsequent assays per 2014 diagnostic criteria.
  - Diagnostic progression: 2014 diagnostic criteria for MM.

**CENTAURUS: Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Arm A: Long (n = 41)</th>
<th>Arm B: Intermediate (n = 41)</th>
<th>Arm C: Short (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>24 (59)</td>
<td>24 (59)</td>
<td>23 (59)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>62 (31-81)</td>
<td>62 (31-81)</td>
<td>62 (31-81)</td>
</tr>
<tr>
<td>Race (%)</td>
<td>White 24 (59)</td>
<td>23 (56)</td>
<td>21 (51)</td>
</tr>
<tr>
<td>Asian 8 (20)</td>
<td>9 (22)</td>
<td>13 (32)</td>
<td>29 (71)</td>
</tr>
<tr>
<td>Black 8 (20)</td>
<td>4 (10)</td>
<td>2 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other 2 (5)</td>
<td>(1)</td>
<td>(1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>BM plasma cells (%)</td>
<td>&lt; 2 27 (66)</td>
<td>23 (56)</td>
<td>18 (44)</td>
</tr>
<tr>
<td>≥ 2 14 (34)</td>
<td>18 (44)</td>
<td>18 (44)</td>
<td>14 (34)</td>
</tr>
<tr>
<td>SMM risk (≥ 60% BM plasma cells)</td>
<td>22 (53)</td>
<td>20 (49)</td>
<td>17 (42)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>24 (59)</td>
<td>23 (56)</td>
<td>21 (51)</td>
</tr>
<tr>
<td>Median age, yrs (range)</td>
<td>62 (31-81)</td>
<td>62 (31-81)</td>
<td>62 (31-81)</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Race (%)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>BM plasma cells (%)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>SMM risk (≥ 60% BM plasma cells)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Median age, yrs (range)</td>
<td>62 (31-81)</td>
<td>62 (31-81)</td>
<td>62 (31-81)</td>
</tr>
</tbody>
</table>

**CENTAURUS: Study Design**

**CENTAURUS: Efficacy**

**CENTAURUS: PFS**

**Based on 2014 Diagnostic Criteria**
CENTAURUS: Safety

### Adverse Events (AEs)

<table>
<thead>
<tr>
<th>Arm</th>
<th>Median duration of treatment, mos (range)</th>
<th>Grade 3/4 TEAEs, n (%)</th>
<th>Most common (&gt; 25%) any-gr AEs, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>14.9 (1.0-22.1)</td>
<td>15 (37)</td>
<td>Fatigue, cough, upper RTI, insomnia, headache</td>
</tr>
<tr>
<td>B</td>
<td>14.8 (1.9-22.1)</td>
<td>4 (10)</td>
<td>Fatigue, cough, upper RTI, insomnia, headache</td>
</tr>
<tr>
<td>C</td>
<td>1.6 (0-1.9)</td>
<td>6 (15)</td>
<td>Fatigue, cough, upper RTI, insomnia, headache</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm</th>
<th>Most common (&gt; 1 pt) gr 3/4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Hypertension</td>
</tr>
<tr>
<td>B</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>C</td>
<td>Hyperglycemia</td>
</tr>
</tbody>
</table>

### Study Conclusions

- Daratumumab monotherapy demonstrated clinical activity in intermediate- and high-risk SMM
  - ORR: 54% to 56% in longer-dose arms
  - 12-Month PFS: 88% to 95% in longer-dose arms vs 81% in short dose
- Acceptable safety profile
  - Few discontinued for treatment-emergent AEs
- Monotherapy using the SQ route is under investigation in ongoing phase III study (NCT03301220)
  - CENTAURUS data supports long dosing schedule for phase III trial

### CAR T-CELL THERAPIES

ARS #3

- A 65-yr-old male with R-ISS high risk stage III myeloma received bortezomib, lenalidomide and dexamethasone induction therapy followed by autologous BMT consolidation treatment. He received lenalidomide maintenance, relapsed, and is now on daratumumab and pomalidomide.
- He is interested in a clinical trial of BCMA directed CAR T cells, and wants to know more about the procedure

Immunologic Targets in Myeloma

- **CAR-BCMA T Cells in MM: Background**
  - **BCMA**: protein in TNF superfamily expressed by normal and malignant plasma cells and B cells
  - Autologous T cells can be genetically modified to express CARs targeted to malignancy-associated antigens
    - BCMA a potential target for myeloma CAR T-cell therapy
    - BCMA expressed uniformly on malignant plasma cells in 60% to 70% of patients
Example – KITE-585 CAR Molecule

Early Data – Study Design

- First-in-human phase I trial
- Pts with advanced R/R MM (≤ 3 prior lines of therapy; normal organ function; ≥ 3 prior lines of BCMA expression on MM cells (N = 12))
- CAR-BCMA T cells* single infusion
- CAR-BCMA expression determined by flow cytometry

CRB-401: Study Design

- Multicenter, open-label phase I trial in patients with R/R MM (N = 43; data cutoff: March 29, 2018)
  - Dose escalation (n = 21): ≥ 3 previous lines of therapy (excluding PI, IMiD) or double refractory, ≥ 50% BCMA
  - Dose expansion (n = 22): prior daratumumab, refractory to last therapy, any/no BCMA expression
- Primary endpoints: safety and tolerability
- Secondary endpoints: response per IMWG Uniform Response Criteria for Multiple Myeloma

Responses

CAR-BCMA T Cells in MM: IL-6 Elevation

- Significant antimonyeloma responses associated with highest blood levels of CAR-BCMA T cells
- Serum IL-6 elevations observed in pts with clinical signs of cytokine-release syndrome
  - Pts 10 and 11, with the most severe cytokine-release syndrome, had markedly higher serum IL-6 levels as compared with other pts
- Concerns with potential impairment of hepatic metabolism


bb2121 (CRB-401): Background

- Anti-BCMA-CART bb2121: optimized autologous T-cell product expressing chimeric antigen receptors specific to BCMA, which is expressed by nearly all MM cells[1,2]
  - Contains 4-1BB costimulatory signaling domain, which is associated with more durable CAR T-cell persistence and less toxicity compared with CD28 costimulatory domain
  - Active against cell lines with low BCMA receptor density, not inhibited by high concentrations of soluble BCMA

- CRB-401: multicenter phase I trial of bb2121 in heavily pretreated patients with R/R MM[3,4]
  - Interim analysis of dose-escalation cohort reported high ORR, manageable safety[11]
  - Current analysis reports updated safety, efficacy results of 43 patients from dose-escalation and dose-expansion cohorts[11]

Most patients with grade 3/4 cytopenias recovered by Day 32
- ANC recovered to ≥ 1000/µL: 31/40 (78%)
- PLT recovered to ≥ 50,000/µL: 22/40 (55%)

CRB-401: Safety

<table>
<thead>
<tr>
<th>Treatment Emergent AE, n (%)</th>
<th>All Patients (N = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
</tr>
<tr>
<td>Cytokine Release Syndrome (CRS)</td>
<td>21 (50)</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>14 (33)</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>31 (73)</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>24 (56)</td>
</tr>
<tr>
<td>Anemia</td>
<td>24 (56)</td>
</tr>
<tr>
<td>Infection</td>
<td>20 (46)</td>
</tr>
</tbody>
</table>

- No grade 4 CRS
- Reversible grade 4 neurotoxicity observed without other events during expansion in 1 patient
- No deaths related to neurotoxicity or CRS

CRB-401: Response

<table>
<thead>
<tr>
<th>Dose of CAR T-Cells</th>
<th>BCMA Expression*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10^6</td>
<td>&gt; 10^6</td>
</tr>
<tr>
<td>82/10^6</td>
<td>57/10^6</td>
</tr>
<tr>
<td>100/10^6</td>
<td>50/10^6</td>
</tr>
</tbody>
</table>

- All 16 patients with response to bb2121 evaluated for MRD were MRD negative at ≥ 1 time point
- 44% of patients had durable bb2121 CART persistence ≥ 6 mos, higher peak expansion in responders

CRB-401: PFS

- Median PFS longest in MRD-negative responders (n = 16): 17.7 mos
- In dose-escalation cohort, median PFS longer at active doses
  - Active doses (150-800 x 10^6; n = 18): 11.8 mos
  - Inactive dose (50 x 10^6; n = 3): 2.7 mos

CRB-401: Conclusions

- bb2121 at doses ≥ 150 x 10^6 CAR T-cells achieved deep, durable responses in heavily pretreated patients
  - 100% CRMR in MRD-negative responders
  - Responses were dose-dependent, independent of BCMA expression
  - Greater peak CAR T-cell expansion observed in responders vs nonresponders
- Median PFS 11.3 mos in dose-escalation cohort
- Median PFS 11.3 mos in evaluable MRD-negative responders
- AEs, including CRS, manageable at bb2121 doses up to 800 x 10^6 CAR T-cells
  - Most CRS events grade 1/2, required infrequent use of corticosteroids and tocilizumab
- Global phase II KarMMa trial evaluating bb2121 CART open for enrollment (NCT0361748)

Conclusions

- Many new treatments are emerging in bone health, smoldering disease, and immune therapy targets
- Integration of these approaches, as well as combination strategies, continues to improve outcomes for patients
- Evolving development of existing and investigational agents means pharmacists will require continued education about agents and adverse event prophylaxis and management