Getting Clear Answers to Complex Treatment Challenges in Multiple Myeloma: Case Discussions

Friday, December 8, 2017
Atlanta, Georgia

Friday Satellite Symposium preceding the 59th ASH Annual Meeting & Exposition.
This activity is supported by educational grants from Amgen, Celgene Corporation, Janssen, Karyopharm, Takeda Oncology, and The Binding Site.
Discussion 5
Current and Future Options for Therapy in Patients with Late Relapse

Presented by Brian G.M. Durie, MD
Cedars-Sinai Medical Center
Program Director and Presenting Faculty

Brian G.M. Durie, MD
Co-Chair Myeloma Committee, SWOG
Chairman, International Myeloma Foundation
Specialist in Multiple Myeloma and Related Disorders
Cedars-Sinai Outpatient Cancer Center
Los Angeles, California

Brian G.M. Durie, MD, has disclosed that he has received consulting fees from Celgene, Johnson & Johnson, Amgen, and Takeda.
Patient Case 7

- A 68-year-old man with standard-risk myeloma was treated with frontline Rd
- He achieved VGPR and received len maintenance
- Relapse occurred 2 years later while on len maintenance
- The patient was switched to Vd (with bortezomib SQ) and achieved a partial response for 5 months after which new bone lesions developed as part of clinical relapse
# How would you treat this patient?

<table>
<thead>
<tr>
<th>Expert</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brian G.M. Durie, MD</td>
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</table>
Relapsed/Refractory Disease

- Asymptomatic
- Symptomatic
- MGUS or Smoldering Myeloma
- Active Myeloma
- Plateau Remission
- Relapse
- Refractory Relapse

M Protein (g/L)
Prognostic Markers for Relapsed Myeloma

- **Good**
  - Remission duration > 2yr
  - Favorable cytogenetics
  - Biochemical progression
  - Young age
  - Low risk GEP

- **Bad**
  - Remission < 1 year
  - t(4, 14), t(14, 16)
  - 17p deletion
  - High LDH
  - Low Platelets
  - Secondary PCL
  - GEP-high risk
Selecting Treatment for Relapsed Myeloma

- **Patient related factors**
  - Age
  - Performance status
  - Prior toxicity
  - Convenience
  - Organ function
    - Renal
    - Hepatic
  - Stem cells stored?
  - Donor?

- **Disease related factors**
  - Duration of remission
  - First, second …. Relapse
  - Refractory relapse
  - Genetics
    - 17p
    - t(4,14), t(14,16)
    - Complex
  - GEP
Options for Relapsed/Refractory Myeloma

**Initial Therapy**

- **> 12 months**
  - Repeat initial therapy
  - A different initial therapy regimen
  - Clinical trial

- **≤ 12 months**
  - Refractory/Relapse
    - Triplet therapy
    - Chemotherapy
    - Clinical trial
    - AutoSCT
    - AlloSCT

**Relapse Therapy**

- Relapse after Lenalidomide and Bortezomib
  - Carfilzomib/Dex
  - Pom + dex
  - Clinical trial
  - Daratumumab
  - 2nd/salvageSCT

- Triple for 1-3 priors
  - KRD
  - Dara/Bort/Dex
  - Elo/len/Dex
  - Ixazomb/Len/Dex
  - Dara/Len/Dex

International Myeloma Foundation
Options for Relapsed/Refractory Myeloma

Relapse Therapy

Relapse after Lenalidomide and Bortezomib
- Carfilzomib/Dex
- Pomalidomide/dex
- Clinical trial
  - Daratumumab
  - 2nd/salvageSCT

Triplet for 1-3 priors
- KRD
- Dara/Bort/Dex
  - Elo/Len/Dex
  - Ixazomib/Len/Dex
  - Dara/Len/Dex
Summary of Combination Therapy in RR MM

**IMiD-Based**
- Rd[1]*
- CyRd[2]
- PomD[3]*
- CyPomD[4]
- KD[5]
- KrD[6]*
- KPomD[7]
- CyKD[8]
- VD[9]*
- VRd[10]*
- VPomD[11]
- CyBorD[12]*

**PI-Based**
- Rd[1]*
- PomD[3]*
- CyPomD[4]
- KD[5]
- KrD[6]*
- KPomD[7]
- VRd[10]*
- VPomD[11]
- CyBorD[12]*

**ORR, %**
- IMiD-Based: 60, 65, 65, 55, 87, 95, 67, 70
- PI-Based: 50, 64, 70

**Survival, months**
- IMiD-Based: 30, NR, NR, NR, 26, 21, 14, 10
- PI-Based: 11, 13, 10, 4, 20, 7, 10, 10

*Data from phase III trials, all others from phase I or II trials*

103 patients with ≥2 prior lines of Tx including ≥2 consecutive cycles of lenalidomide/bortezomib
  - Daratumumab 16 mg/kg IV weekly C1-2, q2wk C3-6, q4wk until PD
  - Pomalidomide 4 mg PO days 1-21
  - Dexamethasone 40 mg IV/PO per wk

- ORR (≥PR): 66%
- Median PFS: 9.9 months; Median OS: 25.1 months
- D/C due to AEs: 17%
Open Label Phase II of Pomalidomide, Cyclophosphamide, and Dexamethasone in Relapse Multiple Myeloma Patients Initially Treated with VRd ± ASCT

- 100 patients relapsing after VRd ± ASCT (IFM 2009)
- Pomalidomide 4 mg days 1-21
  Cyclophosphamide 300 mg days 1, 8, 15, 22
  Dexamethasone 40 mg days 1-4; 15-18
- ORR (≥PR): 91%
- Dose reductions in 35-46%
- Promising relapse and re-induction regimen

Patient Case 8

- A 58-year-old woman was diagnosed with stage II A IgAk myeloma
  - Initial FISH testing not performed
  - She was treated with VRd followed by ASCT and lenalidomide as maintenance; maximum response was traditional CR

- After 18 months, relapse occurred and the patient received KRd re-induction
  - A PR was achieved but after 8 months, there was further relapse

- Dara/pomalidomide/dexamethasone had just been approved and was used as salvage combination therapy
  - An excellent response occurred but was again followed by relapse after 5 months

- A repeat bone marrow revealed presence of the t(11;14) translocation as well as other changes, including the Igq plus abnormality
Which clinical trial option(s) would you recommend for this patient?

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# Classes of Drugs With Anti-MM Activity

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<td>Atezolizumab</td>
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<td>Marizomib</td>
<td>BCNU</td>
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- **MAbs**: Daratumumab, Elotuzumab, Isatuximab, Pembrolizumab, Atezolizumab
- **Immunomodulatory Agents**: Thalidomide, Lenalidomide, Pomalidomide
- **Proteasome Inhibitors**: Bortezomib, Carfilzomib, Ixazomib
- **Cytotoxic CT**: Melphalan, Cyclophosphamide, PLD, DCEP
- **HDAC Inhibitors**: Vorinostat, Panobinostat
- **BCL2 Inhibitor**: Venetoclax
- **Other**: Selinexor, CB-5093, CAR T-cell

*International Myeloma Foundation*
**Phase I Trial: Venetoclax Monotherapy**

**Study Population:** RRMM (N = 66)
- Median age: 63 yrs
- ISS stage II/III: 62%
- Median prior therapies: 5 (1-5)
- Prior BTZ: 94% (70% ref); Prior Len: 94% (77% ref)

**Dosing & Schedule:**
VEN: initial 2 week lead in period with **weekly dose-escalation**
- Final doses: daily at 300 mg, 600 mg, 900 mg, or 1200 mg
- Pts who progressed could receive VEN + dex and remain on study

- Median time on VEN: 2.5 mo (0.2-23);
- 26% received VEN + dex for a median of 1.4 mo (0.1-11)

**Safety, n (%):**

<table>
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<th>Safety Category</th>
<th>Venetoclax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr 3/4 (≥ 10%)</td>
<td>Thrombocytopenia (26%), neutropenia (21%), lymphopenia (15%), anemia (14%), and decreased white blood cells (14%)</td>
</tr>
<tr>
<td>SAEs ≥ 2 pts</td>
<td>Pneumonia (n=5), sepsis (3), pain, pyrexia, cough, and hypotension (2 each)</td>
</tr>
<tr>
<td>Deaths</td>
<td>8 (all considered unrelated to VEN)</td>
</tr>
</tbody>
</table>

**ORR by t(11;14) Status**

- ORR: 21%
  - t(11;14) (n = 30)
  - ORR: 40%
  - t(11;14) (n = 30)
  - ORR: 6%
  - Non-t(11;14) (n = 36)

Venetoclax + Bortezomib/Dex

- ORR: 90%
  - PR: 8%
  - VGPR: 8%
  - CR: 24%
  - sCR: 20%

- ORR: 89%
  - PR: 8%
  - VGPR: 4%
  - CR: 24%
  - sCR: 4%

- ORR: 67%
  - PR: 24%
  - VGPR: 26%
  - CR: 23%
  - sCR: 15%

- ORR: 50%
  - PR: 23%
  - VGPR: 36%
  - CR: 24%
  - sCR: 33%

- ORR: 31%
  - PR: 11%
  - VGPR: 5%
  - CR: 5%
  - sCR: 15%

- ORR: 11%
  - PR: 11%
  - VGPR: 5%
  - CR: 5%
  - sCR: 5%

- ORR: 97%
  - PR: 10%
  - VGPR: 23%
  - CR: 40%
  - sCR: 24%

Published: Blood. 2017;30:2392-2400.
Selective Inhibitor Nuclear Exporter
**Phase II STORM Trial: Selinexor + Dex in R/R MM**

- **Median time to response:** 1 mo
- **Median DoR:** 5 mos

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 78)</th>
<th>Quad (n = 48)</th>
<th>Penta (n = 30)</th>
<th>6 Doses per Mo (n = 51)</th>
<th>8 Doses per Mo (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR:</strong></td>
<td>21%</td>
<td>20%</td>
<td>20%</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td><strong>CBR:</strong></td>
<td>33%</td>
<td>29%</td>
<td>40%</td>
<td>41%</td>
<td>41%</td>
</tr>
<tr>
<td><strong>Pts (%)</strong></td>
<td></td>
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</tr>
<tr>
<td>Overall</td>
<td>5 (15)</td>
<td>4 (17)</td>
<td>7 (13)</td>
<td>6 (14)</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Quad</td>
<td>35 (8)</td>
<td>44 (8)</td>
<td>20 (17)</td>
<td>41 (8)</td>
<td>22 (19)</td>
</tr>
<tr>
<td>Penta</td>
<td>12 (21)</td>
<td>19 (8)</td>
<td>23 (44)</td>
<td>22 (8)</td>
<td>22 (19)</td>
</tr>
<tr>
<td>6 Doses per Mo</td>
<td>41 (20)</td>
<td>41 (10)</td>
<td>22 (19)</td>
<td>41 (19)</td>
<td></td>
</tr>
<tr>
<td>8 Doses per Mo</td>
<td>4 (19)</td>
<td>4 (19)</td>
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*1 pt with t(14;16) achieved PR; 1 pt with del(17p) and t(14;16) had PD (not included in graph).
Phase IB Trial: Anti-CD38 MoAb Isatuximab (TCD14079) Plus Pom/Dex in R/R MM

ORR: 63%

- 5 mg/kg (n = 8)
  - PR: 13%
  - VGPR: 25%
  - CR: 25%

ORR: 75%

- 10 mg/kg (n = 12)
  - PR: 33%
  - VGPR: 33%

ORR: 50%

- 20 mg/kg (n = 6)
  - PR: 33%
  - VGPR: 33%

ORR: 65%

- All Pts (n = 26)
  - PR: 25%
  - VGPR: 31%

\[ \text{Isatuximab Dose QW/Q2W} \]

Pts with high-risk cytogenetics (del17p or t[4;14]): N = 5; 1 VGPR, 1 PR, 1 MR. Pts Len, PI, or IMiD/PI refractory: ORR of 60%, 50%, 47%, respectively.

Phase IB Trial: Anti-CD38 MoAb Isatuximab (TCD14079) Plus Pom/Dex in R/R MM

Maximum Change in Paraprotein

Data cut-off March 01, 2017. a Data represent dose escalation cohort (n=9) and expansion cohort (n=3) combined

Phase IB Trial: Anti-CD38 MoAb Isatuximab (TCD14079) Plus Pom/Dex in R/R MM

**Time on Treatment by Best (Confirmed) Response**

- **sCR**
- **CR**
- **VGPR**
- **PR**

**Time on treatment (weeks)**

- Median duration of response = 36.1 weeks
- Median time to first response = 4.3 weeks

Data cut-off March 01, 2017. *Data represent dose escalation cohort (n=9) and expansion cohort (n=3) combined. Other: patient discontinued due to unconfirmed disease progression. Data presented only for patients who achieved a best response of ≥PR. 13 patients remain on treatment.

### Phase I/II Trial of Bendamustine + Pom/Dex in Pts with R/R MM: Response Rate

**Pomalidomide**
3 mg PO QD on days 1-21

**Bendamustine**
120 mg/m² IV on day 1

**Dexamethasone**
40 mg on days 1, 8, 15, and 22

28-day cycles

<table>
<thead>
<tr>
<th>Overall Response</th>
<th>N=34 (Treated @MTD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>23 (68%)</td>
</tr>
<tr>
<td>Stringent Complete Remission (sCR)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Very Good Partial Response (VGPR)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>17 (50%)</td>
</tr>
<tr>
<td>Minimal Response (MR)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>6 (18%)</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>2 (6%)</td>
</tr>
</tbody>
</table>

CBR: 71%

The CAR T Cell Preparation Process

1. T-cells collected from patient
2. Transduce with modified virus and expand patient T-cells ex vivo
3. Infuse CAR T-cells into patient
Chimeric Antigen Receptors (CAR)

First Generation
CD3ζ or FCRγ

Second Generation
One co-stim domain (CD28, 4-1BB, OX-40)
CD3ζ or FCRγ

Third Generation
Two co-stim domains (CD28, 4-1BB, OX-40)
CD3ζ or FCRγ

<table>
<thead>
<tr>
<th>Institution</th>
<th>CAR Construct</th>
<th>Conditioning Chemotherapy</th>
<th>Response</th>
<th>Reference</th>
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<tbody>
<tr>
<td>National Cancer Institute; Ali et al.</td>
<td>Gamma retrovirus; CD28 costim molecule; murine scFv</td>
<td>3 doses Cyclophosphamide 300 mg/m² 3 doses fludarabine 30 mg/m²</td>
<td>12 Patients treated; Best responses: 1 sCR; 2 VGPR; 1 PR; 8 SD</td>
<td>Blood 2016</td>
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<tr>
<td>Multi-Center; bluebird bio</td>
<td>Lentivirus; 4-1BB costim molecule; murine scFv</td>
<td>3 doses Cyclophosphamide 300 mg/m² 3 doses fludarabine 30 mg/m²</td>
<td>18 patients with ≥ 2 months follow-up Best responses: 4 CR, 7 VGPR, 5 PR, 2 SD</td>
<td>ASCO2017</td>
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<tr>
<td>University of Pennsylvania; Cohen et al.</td>
<td>Lentivirus; 4-1BB costim molecule; Human scFv</td>
<td>None</td>
<td>6 Patients treated; 1 sCR; 1 VGPR; 4 with minimal or no response</td>
<td>ASH2016</td>
</tr>
<tr>
<td>The Second Affiliated Hospital of Xi’an Jiaotong University; Fan et al.</td>
<td>Not published</td>
<td>Not published</td>
<td>19 patients 100% response rate with 18 pts achieving sCR or VGPR</td>
<td>ASCO2017</td>
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BCMA antigen expressed on MM tumor cells, in non-malignant plasma cells, and a small subset of B cells

International Myeloma Foundation

Anti-BCMA CAR T-Cells Producing Remission

Cytokine-release syndrome

IL-6 receptor antagonist tocilizumab

No. 8
Before treatment

2 weeks after treatment

No. 11

Example

Anti-BCMA CAR T-Cell Therapy

- Dose escalation; phase 1
- Refractory disease ≥ 3 prior therapies (3-14)
- Fludara/Cyclo “prep”
- 18 evaluable patients
- At > 50 x 10^6 bb2121 CAR T cells
  - ≥ PR = 100%
  - ≥ VGPR = 8/12 (67%) at 6 months
- Cytokine release syndrome (CRS): 71%; 2 Grade 3
- Promising efficacy; manageable toxicities

ASH Abstract 2017: Abstract #740
Phase 1; Part 1: ASH 2016

First in Human Study With GSK2857916, An Antibody Drug Conjugated to Microtubule-Disrupting Agent Directed Against B-Cell Maturation Antigen (n=30)

GSK 2857916: Anti-BCMA Mab/Drug Conjugate

- Humanized IgGI anti-BCMA Mab + auristatin-F
- Phase 1 study, Part 2 (expansion phase at 3.4 mg/Kg)
  - sCR 1
  - CR 2
  - VGPR 15
  - PR 3

- 35 patients: ORR = 21/35 (60%)
- Current median PFS: 7.9 months
- Most frequent AEs: thrombocytopenia; corneal events
- Encouraging single agent activity
- Manageable safety profile

### Classes of Drugs With Anti-MM Activity

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Final Thoughts

• Current “approved drug” options provide many excellent choices

• For truly refractory patients, there are several very effective and exciting new treatment trials to choose from
Go Online for More CCO Coverage of Myeloma!

On-demand Webcast of this event at myeloma.org

Capsule Summaries of all the key data for ASH 2017

Additional CME-certified slideset on myeloma with expert faculty commentary

Online treatment decision aid with recommendations from 5 experts for your individual patients with myeloma

ashsymposium2017.myeloma.org
clinicaloptions.com/oncology
clinicaloptions.com/MyelomaTool

International Myeloma Foundation
CLINICAL CARE OPTIONS® ONCOLOGY