Treatment of Relapsed and Refractory Multiple Myeloma in Canada

September 2014
Toronto
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BC Cancer Agency, Vancouver General Hospital
# Disclosures

<table>
<thead>
<tr>
<th>Category</th>
<th>Organization</th>
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<tbody>
<tr>
<td>Honoraria</td>
<td>Celgene, Janssen, Novartis</td>
</tr>
<tr>
<td>Speaker</td>
<td>Celgene, Janssen</td>
</tr>
<tr>
<td>Research Support</td>
<td>Celgene, Janssen</td>
</tr>
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<td>Stocks</td>
<td>None</td>
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Objectives

• Discuss available drugs for myeloma
• Discuss some of the current drug trial in relapsed refractory myeloma
  – Not an exhaustive discussion
• Discuss challenges to obtaining drugs in Canada
Classes of medications

• Alkylators (Cyclophosphamide and Melphalan)
• Corticosteroids (Dexamethasone, Prednisone)
• **Immunomodulatory Drugs (thalidomide, lenalidomide)**
• **Proteosome inhibitors (bortezomib)**
Proteosome Inhibition

NF-κB = Bad

NF-κB = Good
Bortezomib APEX trial

<table>
<thead>
<tr>
<th></th>
<th>Bortezomib N=333</th>
<th>Dexamethasone N=336</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TTP</td>
<td>6.2 mos</td>
<td>3.5 mos</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ORR</td>
<td>43%</td>
<td>18%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median OS</td>
<td>29.8 mos</td>
<td>23.7 mos</td>
<td>.027</td>
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</tbody>
</table>

62% crossover rate

Richardson et al. Blood 2007;110:3557
Immunomodulatory Drugs

Cereblon !!
MM-009/MM-010 Pooled Analysis: Updated Overall Survival

Survival benefit retained despite 47% cross-over

- Placebo/Dex: Median 31.6 months
- Len/Dex: Median 38.0 months

$p = 0.045$

Dimopoulos et al Leukemia 2009
Post-Relapse Survival Pre and post 2004: Survival benefit is from post-relapse treatment

Survival Functions

P < 0.001

28 months improvement!!!
Patients Refractory to Bortezomib and Lenalidomide or Thalidomide Have a Poor Prognosis

Patients Refractory to Bortezomib and Lenalidomide or Thalidomide Have a Poor Prognosis

Main Targets and Drugs being tested in Myeloma

Relapsed/Refractory Options

- Len / Dex
- Bor / Dex

Len / Dex Plus
- Bor / Dex Plus

Newer Drugs
- single agent
- with Dex

- Pomalidomide
- Bendamustine
- Carfilzomib
- Elotuzumab
- Panobinostat
- Daratumumab
Pegylated liposomal doxorubicin (Doxil) plus bortezomib in relapsed/refractory MM

• **Rationale:**
  – Synergy of bortezomib with anthracyclines
  – Doxorubicin suppresses bortezomib-mediated induction of stress response proteins (eg. HSP)

• **Study regimen:**
  – Bortezomib 1.3mg/m2 IV days 1,4,8,11
  – PLD 30mg/m2 IV day 4

• **Results:**

<table>
<thead>
<tr>
<th></th>
<th>Bortezomib N=322</th>
<th>Bortezomib + PLD N=324</th>
<th>P value</th>
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<tbody>
<tr>
<td>ORR</td>
<td>41%</td>
<td>44%</td>
<td>NS</td>
</tr>
<tr>
<td>Median TTP</td>
<td>6.5 mos</td>
<td>9.3 mos</td>
<td>.000004</td>
</tr>
<tr>
<td>Duration of response</td>
<td>7 mos</td>
<td>10.2 mos</td>
<td>.0008</td>
</tr>
<tr>
<td>15 mo OS</td>
<td>65%</td>
<td>76%</td>
<td>.03</td>
</tr>
<tr>
<td>Grade 3-4 toxicity</td>
<td>64%</td>
<td>80%</td>
<td>&lt;.001</td>
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</table>

Orlowski et al. JCO 2007; 25: 3892-3901
### Phase I-II trial of the of bortez, cyclo and prednisone in relapsed/refractory MM

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Bortezomib Dose (mg/m²)</th>
<th>BTZ Day</th>
<th>Cyclophosphamide dose per week (mg/m²)</th>
<th>Prednisone Dose q 2 days (mg)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>0.7</td>
<td>1,8,15</td>
<td>150</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>0.7</td>
<td>1,8,15</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>1,8,15</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>1,4,8,11</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>1.3</td>
<td>1,4,8,11</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>1,8,15</td>
<td>300</td>
<td>100</td>
</tr>
</tbody>
</table>

At level 6:
- ORR 84%, CR 54%
- 1 yr PFS 83%, median OS not reached
- MTD not reached

Reece et al. JCO 2008; 26: 4777-4783
Revlimid + Bortezomib

Revlimid sensitizes MM cells to apoptosis-inducing effects of bortezomib and dexamethasone

Phase II Study Lenalidomide, Bortezomib and Dex in Patients with Relapsed or Refractory MM (N= 64)

- **Regimen:**
  - Revlimid 15mg daily x 14 days
  - Bortezomib 1.0 mg/m2 days 1,4,8,11
  - Dex 40/20mg day on and after bortez
    → subsequently amended to 10mg
  - Daily ASA, GCSF permitted

- **Responses:**
  - 64% PR or better (11% CR)
  - PFS 9.5 months
  - OS 30 months

Richardson et al Blood 2014; 123(10); 1461-1469
Agents available in the USA for patient previously exposed to iMIDS and bortezomib

• Carfilzomib (Kyprolis)
  – Produced by Amgen. Discussion initiated with Health Canada.

• Pomalidomide (Pomalyst)
  – Produced by Celgene. Health Canada Approved. Provincial funding in negotiations
Molecular Structure of Thalidomide, Lenalidomide, and Pomalidomide

Thalidomide
100-200 mg/d
Neuropathy
Constipation
Sedation
DVT

Lenalidomide
15-25 mg/d
Myelosuppression
Skin rash
DVT

Pomalidomide
1-4 mg/d

Stewart AK. Hematology 2009
Pomalidomide + LoDEX vs. HiDEX in Myeloma patients who failed Lenalidomide and Bortezomib (N=451)

RANDOMIZATION 2:1

(n = 302)

POM: 4 mg/day D1-21 +
LoDEX: 40 mg (≤ 75 y)
20 mg (> 75 y)
D1, 8, 15, 22

Follow-up for OS Until 5 Years Post Enrollment

PD or intolerable AE

(n = 153)

HiDEX: 40 mg (≤ 75 y)
20 mg (> 75 y)
D1-4, 9-12, 17-20

PD or intolerable AE

Companion trial MM-003C
POM 21/28 days

San Miguel JF, et al. ASH 2013 [abstract 686].
85 pts (56%) on the HiDEX arm received subsequent POM
Proteosome inhibitors

BORTEZOMIB

Peptide Boronates

CARFILZOMIB

Peptide Epoxyketones
Single-agent carfilzomib in relapsed and refractory multiple myeloma

A

Proportion of patients alive and without progression (%)

Median PFS: 3.7 months (95% CI: 2.8–4.6)

Censored observations
Confidence band

B

Proportion of patients alive (%)

Median OS: 15.6 months (95% CI: 13.0–19.2)

Censored observations
Confidence band

Siegel D S et al. Blood 2012;120:2817-2825
Carfilzomib (FOCUS trial)

Relapsed and advanced refractory myeloma (prior exposure to bortezomib and iMID)

- Carfilzomib
- Dex or Pred) +/- cyclophosphamide

did not meet its primary endpoint of improving overall survival

Amgen Press releases (August 2014)
Carfilzomib (ASPIRE trial)

Relapsed myeloma

- Rev/Dex
- Rev/Dex + Carfilzomib

met its primary endpoint of progression-free survival
- PFS 26.3 months vs 17.6 months) ($p<0.0001$)
- OS showed a trend in favor of KRd

Amgen Press releases (August 2014)
Bendamustine in relapsed/refractory myeloma patients: results from the French compassionate use program (N = 110)

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous line of treatment, median (range)</td>
<td>4 (1 – 9)</td>
</tr>
<tr>
<td>Any alkylating agents, n (%)</td>
<td>110 (100%)</td>
</tr>
<tr>
<td>Any steroids, n (%)</td>
<td>110 (100%)</td>
</tr>
<tr>
<td>Any anthracyclines, n (%)</td>
<td>57 (52%)</td>
</tr>
<tr>
<td>Bortezomib, n (%)</td>
<td>110 (100%)</td>
</tr>
<tr>
<td>Lenalidomide based, n (%)</td>
<td>93 (85%)</td>
</tr>
<tr>
<td>Thalidomide based, n (%)</td>
<td>57 (52%)</td>
</tr>
<tr>
<td>Others, n (%)</td>
<td>61 (55%)</td>
</tr>
<tr>
<td>Previous autologous SCT (n)</td>
<td>66</td>
</tr>
<tr>
<td>Single/Tandem</td>
<td>30/36</td>
</tr>
<tr>
<td>Type of response to the last treatment before bendamustine (n)</td>
<td>8</td>
</tr>
<tr>
<td>PR</td>
<td>11/71</td>
</tr>
<tr>
<td>SD/PD</td>
<td>20</td>
</tr>
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</table>

G. Damaj et al, Leukemia & Lymphoma, April 2012; 53(4):632-634
Response to bendamustine: PFS and OS

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>33 (30)</td>
</tr>
<tr>
<td>CR</td>
<td>2 (2)</td>
</tr>
<tr>
<td>PR</td>
<td>31 (28)</td>
</tr>
<tr>
<td>SD</td>
<td>22 (20)</td>
</tr>
<tr>
<td>PD</td>
<td>55 (50)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>9.3 months</td>
</tr>
<tr>
<td>OS</td>
<td>12.4 months</td>
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</tbody>
</table>

G. Damaj et al, Leukemia & Lymphoma, April 2012; 53(4):632-634
Possible options for Patients previously exposed to iMiDs and bortezomib

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>RR</th>
<th>EFS/PFS</th>
<th>OS</th>
<th>HC approved</th>
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<tbody>
<tr>
<td>Pomalidomide plus Dex</td>
<td>31%</td>
<td>4.0mo</td>
<td>12.7mo</td>
<td>No</td>
</tr>
<tr>
<td>High-dose Dex</td>
<td>10%</td>
<td>1.9mo</td>
<td>8.1</td>
<td>yes</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>24%</td>
<td>3.7mo</td>
<td>15.6mo</td>
<td>No</td>
</tr>
<tr>
<td>RVD</td>
<td>46%</td>
<td>3mo</td>
<td>7.5mo</td>
<td>Yes</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>30%</td>
<td>9.3mo (?responders)</td>
<td>12.4mo</td>
<td>Yes</td>
</tr>
</tbody>
</table>

• San Miguel et al ASCO 2013
• Siegel et al Blood 2012
• Jimenez-Zepeda et al Leuk/Lymph 2013
• Damaj et al Leuk/Lymph 2012
Panobinostat ~ a Pan-Deacetylase Inhibitor: 

Introduction

- Panobinostat (PAN): potent, oral pan-DACi
- PAN was synergistic with bortezomib (BTZ) and dexamethasone (Dex) in preclinical studies of MM
- In phase 1 and 2 studies, PAN-BTZ-Dex demonstrated durable responses in relapsed or relapsed and refractory MM, including BTZ-refractory disease
- In Phase 3 Study BTZ-DEX vs PAN-BTZ-DEX (PANORAMA 1) increased PFS of 3.9 month

ARRY-520 (Filanesib)

• **Filanesib**: Kinesin Spindle Protein (KSP) inhibitor
  – KSP is a microtubule motor protein critical to the function of proliferating cells

• KSP inhibition induces aberrant mitotic arrest and rapid cell death
  – Novel mechanism of action for MM
  – Preferentially acts on MCL-1 dependent cells including MM
  – Not expected to be cross-resistant with other drugs

Algorithm for Relapsed MM

- **ASCT not an option**

  - **Bortezomib based**
  - **Lenalidomide based**

  - **Pomalidomide based**

  - Try older drugs
  - Combinations not previously used
  - Palliation

Consider clinical trials
## Cost of Myeloma Treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year of Approval</th>
<th>Monthly Medicare Price at time of Approval</th>
</tr>
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<tbody>
<tr>
<td>Melphalan</td>
<td>1992</td>
<td>$35</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>2003</td>
<td>$4-8,000</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>2005</td>
<td>$8,535</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>2006</td>
<td>$5,998</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>2012</td>
<td>$10,000</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>2013</td>
<td>$10,500</td>
</tr>
<tr>
<td>Inpatient ASCT</td>
<td>2012</td>
<td>$62,259</td>
</tr>
<tr>
<td>Outpatient ASCT</td>
<td>2012</td>
<td>$42,737</td>
</tr>
</tbody>
</table>

Bach *NEJM* 2009; 360:626-633  
Myeloma Beacon  
Holbro *BBMT* 2013; 19(4):547-51
Provincial Funding Issues

• Bortezomib
  – Retreatment: Some jurisdictions do not allow retreatment
  – Duration of treatment: Some jurisdiction allow bortezomib
    Administration until progression. Others only allow finite number
    of cycles
• Lenalidomide
  – Not approved in all provinces
  – Use in combination with bortezomib variable
• Other available drugs
  – Bendamustine
  – Doxil
• How do we align ourselves with other provinces
  (pCODR, PMPRB)
Summary

- Growing armamentarium of therapies for relapsed/refractory myeloma
- Key backbone agents:
  - thalidomide, bortezomib, lenalidomide
- New Drugs are on the horizon
- **Treatments must be simple, available and “affordable”**
- Literature does not guide for all situations
- Individualized approach is needed
Thank you!

Enjoy Toronto and CHC 2014