Treatment of Multiple Myeloma
Novel Approaches

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Toronto, ON
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Plasma cells in bone marrow

Adhesion Molecules and Growth Factors in Multiple Myeloma

Algorithm for Cytogenetic Analysis for MM at PMH

Approach to Initial Therapy

Approach to Progressive MM
**Novel Agents in Myeloma**

- **Agents**
  - Thalidomide
  - Bortezomib (Velcade)
  - Lenalidomide (Revlimid)

- **Settings**
  - Relapsed/refractory disease
  - Part of initial therapy
  - Maintenance

**Thalidomide in Multiple Myeloma**

- First “novel agent” for myeloma
- Has apoptotic, anti-angiogenic and immunomodulatory effects
- In relapsed/refractory disease, response rate ~30% as single agent and ~50% with dexamethasone
- Toxicities: sedation, constipation, rash, peripheral neuropathy and DVT

**Thalidomide Trials in MM**

- Newly diagnosed patients
  - Thal + Dex versus Dex before ASCT
  - Combinations before ASCT
  - MP + thal versus MP in newly diagnosed elderly patients

- Thalidomide as maintenance therapy after ASCT

**Phase III Trial: Thal/Dex vs Dex in Patients With Newly Diagnosed MM**

- N=207 Newly diagnosed MM
- Thal + Dex × 4 cycles† or PD
- Dex × 4 cycles† or PD

- Primary End Point: Best response at 4 mo (ITT)

- Off Study for SCT
- Continue Therapy*

*Treatment beyond 4 cycles was permitted at physician discretion
†Cycle duration=1 month

**Thal/Dex vs Dex in Newly Diagnosed MM**

- Results after 4 Cycles

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Thal/Dex (n=100) (%)</th>
<th>Dex (n=101) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best response (ECOG)</td>
<td>58</td>
<td>42</td>
</tr>
<tr>
<td>Best response, corr.</td>
<td>69</td>
<td>51</td>
</tr>
<tr>
<td>Median time to response (mo)</td>
<td>1.1 (0.7-4.1)</td>
<td>1.1 (0.7-2.9)</td>
</tr>
<tr>
<td>CR (%)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Disease progression</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Successful harvest</td>
<td>91</td>
<td>100</td>
</tr>
</tbody>
</table>

**Thal/Dex vs Dex in Newly Diagnosed MM**

- Grade 3 or 4 Toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Thal/Dex (n=100) (%)</th>
<th>Dex (n=101) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Heme</td>
<td>68</td>
<td>43</td>
</tr>
<tr>
<td>DVT</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Any &gt;/= gr 4</td>
<td>34</td>
<td>17</td>
</tr>
</tbody>
</table>
New Trials of Thalidomide in Newly Diagnosed Before ASCT

- Thal/Dex vs Dex
- Combinations
  - Velcade, thalidomide and Dex (VTD)
  - Pegylated liposomal doxorubicin + velcade + low dose Dex + thalidomide (Doxil + VdT)
  - VAD + thalidomide (VAD-thal)
  - VTD-PACE in Total Therapy 3
  - Cyclophosphamide + thalidomide + Dex (CTD)
  - Adriamycin + dex (AD) followed by thalidomide + Dex (DT)

Thalidomide With Melphalan and Prednisone in Elderly Patients With MM

**Thalidomide With Melphalan and Prednisone in Elderly MM Patients**

<table>
<thead>
<tr>
<th>Response</th>
<th>MPT, %</th>
<th>MP, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR + nCR</td>
<td>28*</td>
<td>5</td>
</tr>
<tr>
<td>PR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% - 74%</td>
<td>16</td>
<td>28</td>
</tr>
<tr>
<td>75% - 99%</td>
<td>34</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>41</td>
</tr>
<tr>
<td>Median EFS, mo</td>
<td>25.2*</td>
<td>13.7</td>
</tr>
</tbody>
</table>

*<0.001
 Median follow-up, 13.6 months

**Thromboembolism in MPT Treated Elderly Patients Reduced With Prophylaxis**

<table>
<thead>
<tr>
<th>Incidence, %</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No LMWH</td>
<td>With LMWH</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>(n=61)</td>
<td>(n=28)</td>
</tr>
<tr>
<td>DVT*</td>
<td>21.3</td>
<td>7.1</td>
</tr>
<tr>
<td>PE</td>
<td>4.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Arterial occlusion</td>
<td>1.6</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*p=0.003
*Enoxaparin, 0.4 mL/day for 4 months

**MP vs MP-Thal and MP vs Mel100 in Newly Diagnosed MM Aged 65–75 Years**

*IMF 99-06 Trial Design*

- Newly diagnosed MM; aged 65–75 years (N=500)
- 1st Endpoint: Overall survival

**MP vs MP-Thal and MP vs Mel100 x2 in Newly Diagnosed MM Aged 65–75 Years**

*IMF 99-06 Trial Response to Treatment*

<table>
<thead>
<tr>
<th>% of Patients at 12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category of Response</td>
</tr>
<tr>
<td>Complete response (%)</td>
</tr>
<tr>
<td>≥90% (%)</td>
</tr>
<tr>
<td>≥50% (%)</td>
</tr>
</tbody>
</table>

*2nd planned interim analysis; median follow-up time = 28 months

IFM 99-06 Trial: Adverse Events Overview

<table>
<thead>
<tr>
<th>Incidence of DVT*, n (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP (n= 153)</td>
</tr>
<tr>
<td>MP-Thal (n= 99)</td>
</tr>
<tr>
<td>MEL 100 x2 (n= 92)</td>
</tr>
<tr>
<td>8 (5%)</td>
</tr>
<tr>
<td>12 (12%)</td>
</tr>
<tr>
<td>6 (6.5%)</td>
</tr>
</tbody>
</table>

- No toxic deaths related to DVT
- MP-Thal arm: DVT at median 3 mos (range 0.1-13 mos)
- MP-Thal arm: 36% peripheral neuropathy
- Hematologic/other adverse events as expected in each arm

Patients with history of DVT were excluded from trial


dimensions: 612.0x792.0

Maintenance With Thalidomide After ASCT for MM

<table>
<thead>
<tr>
<th>Preliminary Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endpoint</td>
</tr>
<tr>
<td>Patients, n</td>
</tr>
<tr>
<td>Progression, %</td>
</tr>
<tr>
<td>Median PFS, mo</td>
</tr>
<tr>
<td>3-yr PFS, %</td>
</tr>
<tr>
<td>Bone events, %</td>
</tr>
<tr>
<td>3-yr risk of bone events, %</td>
</tr>
</tbody>
</table>


Maintenance With Thalidomide After ASCT for MM

Vaccad (Bortezomib): PSI 341
Proteasome Inhibition

Velcade (Bortezomib)

Ubiquitin-Proteasome Pathway

Velcade (Bortezomib)

VELCADE

SUMMIT: Prior Therapy

- 6 median lines of prior therapy
- 92% of patients received at least 3 of the drug therapies listed (excluding stem cell transplant)

SUMMIT: Response Rates with Bortezomib (N=193)*

- 35% overall response (CR+PR+MR)
- 27% CR+PR
- 24% stable disease (SD)
- 59% of patients SD or better

SUMMIT: Updated Time-to-Progression

- Median TTP: overall ~7 mo, responders ~13.9 mo, nonresponders ~1.3 mo

SUMMIT: Response Rates Independent of the Types of Prior Therapy

Percent response (CR+PR) to bortezomib alone by types of prior therapy in SUMMIT trial

Bortezomib Trials in MM

- Velcade versus Dex in relapsed MM (APEX study)
- Velcade combinations as part of initial therapy
APEX: Study Design

• International, randomized, open-label study in pts with relapsed or refractory MM
  – 669 pts enrolled at 94 centers
  – Endpoints
    • Primary: time to progression (TTP)
    • Secondary: survival, response rate (RR) and duration, time to skeletal events (TSE), incidence of ≥ G3 infection, safety
    • Exploratory: quality of life (QOL), pharmacogenomics
  • Companion crossover study (M34101-040): bortezomib for pts progressing on Dex

APEX: Treatment Plan

**Induction**
- Bortezomib: 1.3 mg/m² IV push D 1, 4, 8, 11 q 3-wk cycle
- Dexamethasone: 40 mg PO D 1–4, 9–12, 17–20 q 5-wk cycle

**Maintenance**
- Bortezomib: 1.3 mg/m² IV push D 1, 8, 15, 22 q 5-wk cycle
- Dexamethasone: 40 mg PO D 1–4 q 4-wk cycle

**Duration**
- 8 cycles
- 4 cycles
- 3 cycles
- 5 cycles

APEX: Treatment Plan

**Time to Progression (N = 669)**

78% improvement in median TTP with bortezomib

**Adverse Events (All Pts)**

<table>
<thead>
<tr>
<th></th>
<th>Bortezomib (n = 331)</th>
<th>Dexamethasone (n = 332)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events ≥ G3</td>
<td>75%</td>
<td>60%</td>
</tr>
<tr>
<td>Adverse events G4</td>
<td>14%</td>
<td>16%</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>44%</td>
<td>43%</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>37%</td>
<td>29%</td>
</tr>
<tr>
<td>On-study deaths†</td>
<td>4%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Richardson et al. ASH 2004; Abstract 336.5.
Management of Thrombocytopenia

- 43% overall incidence\(^1\) of thrombocytopenia
  - 27% Grade 3 (10-50 x 10⁹/L)
  - 3% Grade 4 (< 10 x 10⁹/L)

![Mean Platelet Count (10⁹/L)](image)

Platelet nadir is ~40% of baseline

Del(13) in Multiple Myeloma
APEX: Matched-Pairs Analysis

Del(13) is Associated with Poor Survival in Dex-Treated Patients
HR (95% CI) = 3.11 (1.03, 9.46); \( P = 0.042 \)

![Proportion of Events](image)

Del(13) (\( n = 12 \))
No deletion (\( n = 20 \))

Del(13) Has No Impact on Survival in Bortezomib-Treated Patients
HR (95% CI) = 1.61 (0.35, 7.46); \( P = 0.79 \)

![Proportion of Events](image)

Del(13) (\( n = 8 \))
No deletion (\( n = 17 \))
Velcade Regimens Before ASCT

<table>
<thead>
<tr>
<th>Study</th>
<th>N/Eval</th>
<th>Regimen</th>
<th>CR/nCR</th>
<th>CR+PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jagannath</td>
<td>32/25</td>
<td>Velcade + DEX</td>
<td>30%</td>
<td>83%</td>
</tr>
<tr>
<td>Popat</td>
<td>21/21</td>
<td>PAD</td>
<td>29%</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>11/9</td>
<td>Velcade + Adria (2 dose levels) + DEX</td>
<td>22%</td>
<td>100%</td>
</tr>
<tr>
<td>Harousseau</td>
<td>30</td>
<td>Velcade + DEX</td>
<td>17%</td>
<td>83%</td>
</tr>
<tr>
<td>Alexanian</td>
<td>30</td>
<td>VTD</td>
<td>NA</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Velcade + thal + DEX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barlogie</td>
<td>57</td>
<td>Total Therapy F3</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VTD-PACE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uy</td>
<td>34</td>
<td>Velcade after thal or anthracycline</td>
<td>33%</td>
<td>89%</td>
</tr>
<tr>
<td>Chkowsk1</td>
<td>55/19</td>
<td>Velcade + DEX</td>
<td>5%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Lenalidomide (CC-5013; Revlimid™)

- More “potent” immunomodulator than thalidomide
- Fewer side effects: no significant constipation, neuropathy, or sedation
- DVT noted
- Not teratogenic

Lenalidomide (Revlimid) Trials

- Lenalidomide + Dex versus Dex alone in relapsed patients
- Pilot study of lenalidomide + Dex in newly diagnosed patients
- Others

Lenalidomide + Dex vs Placebo + Dex in Relapsed/Refractory MM

- Lenalidomide 25 mg/day PO, Days 1–21
- Dexamethasone 40 mg/day PO, Days 1–4, 9–12, 17–20 (n=170)

- Placebo 25 mg/day PO, Days 1–21
- Dexamethasone 40 mg/day PO, Days 1–4, 9–12, 17–20 (n=170)

Endpoints: TTP, Response Rate, Overall Survival

Interim Analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lenalidomide + Dex (n=170)</th>
<th>Placebo + Dex (n=170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTP (mos)</td>
<td>NYR</td>
<td>5</td>
</tr>
<tr>
<td>Response rate</td>
<td>51%</td>
<td>23%</td>
</tr>
<tr>
<td>CR</td>
<td>19%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Lenalidomide (CC-5013) and Dexamethasone for Newly Diagnosed MM

Newly diagnosed MM (n=30)
Lenalidomide 25 mg/day Days 1–21
Dex 40 mg Days 1–4, 9–12, 17–20
Aspirin daily for DVT prophylaxis

SCT Planned: off treatment
CR/PR/ Stable at 4 months
No SCT: remain on treatment at MD discretion
Progressive disease: off treatment


Lenalidomide and Dex: Adverse Events Profile

Hematologic toxicity, %

<table>
<thead>
<tr>
<th>Grade 1/2</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>17</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>17</td>
</tr>
</tbody>
</table>

Non-hematologic toxicity, %

<table>
<thead>
<tr>
<th>Grade 1/2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT (all received prophylaxis)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>7</td>
</tr>
<tr>
<td>Sedation</td>
<td>30</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>17</td>
</tr>
<tr>
<td>Anxiety</td>
<td>7</td>
</tr>
</tbody>
</table>


Lenalidomide (CC-5013) and Dexamethasone for Newly Diagnosed MM

83% (25/30) achieved PR on intent-to-treat basis
Combination appears active
Final analysis awaited to confirm results
Randomized phase III trials of lenalidomide/Dex in newly diagnosed MM are ongoing (SWOG S0232, ECOG E4A03)


Novel Agents in Multiple Myeloma Summary/Conclusions

Effective in relapsed/refractory patients
Combinations can produce high response rates (up to 89-90%) in newly diagnosed patients
– CR/near CR rates up to 20-30%
Toxicities profile different from conventional chemotherapy, but potentially manageable (DVT, peripheral neuropathy)

Novel Agents as Part of Initial Therapy in MM: Unanswered Questions

Will the improved response rates translate into better overall survival?
Should novel agents/combinations be used upfront or reserved for relapse?
Will aggressive regimens replace ASCT?
Will they prove to be necessary as maintenance therapy after ASCT?

Ongoing/Pending PMH Multiple Myeloma Trials

Newly diagnosed myeloma
– Dex + Velcade + Doxil (DBd)
– Velcade in t(4;14) myeloma
Relapsed disease
– Cyclophosphamide + prednisone + Velcade
– Revlimid + Dex (expanded access)
– BCL inhibitor (GeminX)
– Irreversible proteasome inhibitor
– Histone deacetylase inhibitor (SAHA)
Thalidomide (Thalomid®)

- Oral immunomodulator
- Derivative of glutamic acid
- Anti-angiogenic and apoptotic properties

Thal/Dex vs Dex in Newly Diagnosed MM

Conclusions

- Addition of thal improves depth of response compared with Dex alone
- Significant increases in non-heme toxicity and DVT
  - DVT might be managed by prophylactic anticoagulation
- Thal + Dex is a reasonable alternative to VAD or Dex alone


Del(13) in Multiple Myeloma

APEX: Matched-Pairs Analysis

Del(13) is Associated with Poor Survival in Dex-Treated Patients

HR (95% CI) = 3.21 (1.03, 46.04); P = .0322

Del(13) Has No Impact on Survival in Bortezomib-Treated Patients

HR (95% CI) = 1.61 (0.35, 7.46); P = .79

Jagannath et al. ASCO 2005; Oral Abstract 6501
APEX: Final Results (N=669)

- **Time to Progression:** 78% improvement on bortezomib arm (p<0.0001)
  - Median TTP: Bortezomib 6.2 mos, Dex 3.5 mos
- **Survival:** Overall survival superior on bortezomib arm (p<0.0013) including patients on dex who crossed over to bortezomib
  - 1 year survival: bortezomib 80%, Dex 65%
  - 41% decreased risk of death at year on bortezomib arm (p=0.0005)

Richardson et al. ASH 2004; Abstract 336.5.

SUMMIT – Response Rates to VELCADE® Alone

- 193 evaluable patients
- 35% overall response (CR+PR+MR)
- 27% CR+PR
- 24% SD
- 59% of patients SD or better
- Assessed by Independent Review Committee

Novel Agents in Myeloma

**Thalidomide, Bortezomib (Velcade™), and Lenalidomide (Revlimid™)**

- In relapsed/refractory disease
- As part of first line therapy
  - Before ASCT
  - In patients ineligible for ASCT
- As maintenance therapy after ASCT