Future strategies for myeloma: An overview of novel treatments in development

Dr Supratik Basu
Consultant Haematologist
Royal Wolverhampton Hospitals

How far have we come?

Melphalan and prednisolone 1962
VAD
Autologous SCT 1996
Thalidomide 1999
Velcade 2003
Revlimid 2005
????? 2012?

Three new treatments available in the last 12 years, but still an urgent need for improved treatments and more options
Improved survival with new drugs

Average survival after relapse from transplant has doubled since introduction of new drugs (thalidomide, Velcade and Revlimid)

Cancer survival rate

Office of National Statistics: Five year survival rates in myeloma in the UK show largest increases compared to other cancers.

Published 10 April 2010
Room for improvement

• Improve patient outcome
• Control symptoms and complications
• Increase lengths of remission and survival
• Increase response rates and depths of response
• Decrease side-effects
• Improve quality of life

Current issues

• Which drugs are best used as first-line treatment?
• Which drugs are best used for relapse?
• Which combination of drugs work best together?
• Which combinations of drugs are least likely to cause serious side-effects
• Which treatment for which patient? – more genetic testing, moving towards personalised treatment
Individualised treatment plans

- Prognostic factors:
  - Age/fitness
  - Disease stage
  - Prior response to treatment
  - $\beta_2$ microglobulin levels
  - Cytogenetics
  - Gene profiling

Finding new drugs

Drug evolution

- Old targets:
  - DNA
  - Hormones
  - Cellular scaffold
  - Nuclear scaffold

- New targets:
  - Immune system
  - Cell signalling
  - Cell growth
  - Cell death
  - Proteasome
  - Blood vessel formation

- Future targets:
  - Genetic markers
  - Gene expression profile

Finding new drugs
Finding more effective combinations

- First-line treatment with currently used drugs
  - Velcade in combination
  - Revlimid in combination

- Novel treatment combinations
  - Velcade and thalidomide
  - Velcade and Revlimid

New combinations

- CTD better than VAD

- VTD better than TD

- VTD produces 66% CR (22% molecular CR)
  - If mol CR no relapse at 3 years

- In 2nd line and beyond combination therapy better
  - Overall response rate: Vel 38%; Vel/dex 50%; Vel/dex/bendamustine 72%
Toward a new therapeutic backbone in myeloma

Richardson, P. Blood 2007;109:2672-2673
Latest developments

- New immunomodulatory inhibitor
- Next generation proteasome inhibitor
- Histone deacetylase (HDAC) inhibitors
- Monoclonal antibodies
- Other existing chemotherapy drugs

Latest developments

- Bendamustine
- Carfilzomib
- Pomalidomide
- Elotuzumab
- HDAC inhibitors …
Pomalidomide

- Pomalidomide is an immunomodulatory drug (IMiD) - closely related to thalidomide and Revlimid

- It is more potent than either thalidomide or Revlimid and is generally well tolerated

- Thought to work in a number of ways to stop the growth of myeloma cells

- MM-002 Phase I/II study: Pomalidomide ± low-dose dex
  Heavily pre-treated patients including those refractory to Velcade and Revlimid
Pomalidomide + Low-Dose Dex

- ORR: 63%
  - 60% of patients refractory to both Revlimid and Velcade achieved ≥ partial response
  - Nearly all responders (97%) retained response through 6 months
- Length of remissions achieved
  - Median length of remission: 11.6 months
  - Median overall survival has not been reached
    - 94% of patients were alive at 6 months
    - Most common side-effects: neutropenia (32%), leukopenia (17%), fatigue (17%)


Pomalidomide in the UK

Phase III NIMBUS study – Finished Recruitment July 2012
For relapsed or refractory patients, who have had at least 2 previous lines of treatment

Pomalidomide + low-dose dex
- Pomalidomide: Days 1 - 21
- Low-dose dex: Days 1,8,15,22
- 28-day cycle
- Until progression

vs

High-dose dex
- High-dose dex Days 1 - 4
- Days 9 - 12
- Days 17 - 20
- 28-day cycle
- Until progression
**PEXIUS or MM010 trial**

- Study Opening ? Dec 2012

  Pomalidomide + low-dose dex
  - Pomalidomide; Days 1 - 21
  - Low-dose dex; Days 1,8,15,22
  - 28-day cycle
  - Until progression

**Carfilzomib**

- Next-generation proteasome inhibitor – targets a different area of the proteasome to Velcade

- More selective than Velcade and associated with less severe side-effects e.g. peripheral neuropathy

- Shows encouraging activity in newly-diagnosed, relapsed and/or refractory patients

- Recent fast-track FDA approval in the USA achieved for relapsed AND refractory patients
Carfilzomib in the UK

Phase III ASPIRE trial – Finished recruiting
For relapsed patients who have had no more than 3 prior treatments

- Carfilzomib
- Revlimid
- Low-dose dex

• CFZ; 4 - 6 doses/cycle
• Revlimid; Days 1 - 21
• Low-dose dex Days 1, 8, 15, 22
• 28-day cycle
• Until progression

VS

- Revlimid
- Low-dose dex

• Revlimid Days 1 - 21
• Low-dose dex Days 1, 8, 15, 22
• 28-day cycle
• Until progression

Carfilzomib in the UK

Phase III FOCUS trial – Closed
For relapsed and/or refractory patients who have had 3 or more prior treatments

- Carfilzomib
  • 4 - 6 doses/cycle
  • 28-day cycle

VS

- Best supportive care
  • Dex or pred; every other day
  • Optional; cyclophosphamide Daily
NEW STUDY

ENDEAVOR opening soon

• For Relapsed myeloma 1-3 Lines of Treatment
• Head to head comparison of carfilzomib vs Velcade at 2 Dose levels
• Opening in November /December

Other drugs

• Daratumumab: antiCD38 (monoclonal antibody)
• 2 oral Proteasome inhibitors: Oprozomib
  MLN9708
Novel (next generation) proteasome inhibitors

OPROZUMIB

- Oral Carfilzomib
- Orally active
- Early dose-finding and safety studies being carried out

**MLN9708 oral single-agent, relapse**

<table>
<thead>
<tr>
<th>MLN9708 Weekly (Kumar abs 816)</th>
<th>N</th>
<th>Phase</th>
<th>Findings</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>32</td>
<td>Phase 1, dose escalation (D1, 8, 15; cycle 28 days up to 12 cycles)</td>
<td>Median 6 lines ttt (97% btz, 91% len) 56% refractory MTD 2.97 mg/m² No periph neuropathy</td>
<td>18 evaluable pts 1 VGPR, 1 PR, 8 SD</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>MLN9708 Bi-weekly (Richardson301)</th>
<th>N</th>
<th>Phase</th>
<th>Findings</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>56</td>
<td>56</td>
<td>Phase 1, dose escalation (26 pts), Expansion cohort (30 pts) (D1, 4, 8, 11 21-day cycles, up to 12 cycles)</td>
<td>Mediane 6 lines ttt (100% btz) 52% refractory MTD : 2 mg/m² No periph neuropathy</td>
<td>46 evaluable pts 6 &gt; PR (1 CR, 5 PR) 1 minim resp</td>
</tr>
</tbody>
</table>

Kumar et al.; ASH 2011; Abs 816; Richardson et al Abs 301
MLN9708 CC16006/CC16010 opening soon

- New class of ORAL proteasome inhibitors
- Less neurotoxic, as good efficacy as IV drugs
- Time line DEC 2012
- Both upfront and relapsed setting
Bendamustine in relapsed and refractory patients

Report of 110 patients enrolled in the French compassionate-use program

– Leukemia and Lymphoma, in press

<table>
<thead>
<tr>
<th>n</th>
<th>110 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>63 (34-83)</td>
</tr>
<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>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>Previous autologous SCT (n)</td>
<td>66</td>
</tr>
<tr>
<td>Single / Tandem</td>
<td>30 / 36</td>
</tr>
<tr>
<td>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>
<tr>
<td>Missing data</td>
<td></td>
</tr>
<tr>
<td>Response to bendamustine</td>
<td>110 patients (%)</td>
</tr>
<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>
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</table>

The median PFS and OS time for the entire cohort were 9.3 and 12.4 months, respectively.
BVD in relapsed multiple myeloma

- Bendamustine, Velcade, dexamethasone

Heat-shock protein inhibitors

- Phase I/II study of KW 2478 in combination with Velcade (open in the UK)

- Phase I/II study of AUY922 in combination with Velcade and dexamethasone (open in the US & other countries)

- Early data suggest that both drugs are well tolerated and have anti-myeloma activity
Monoclonal antibodies

Drugs designed to specifically target myeloma cells or molecules required for myeloma cell growth

<table>
<thead>
<tr>
<th>Target</th>
<th>Antibody</th>
<th>Company</th>
<th>Type</th>
</tr>
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<tbody>
<tr>
<td>CS1</td>
<td>Elotuzumab</td>
<td>Abbot/BMS</td>
<td>Humanized</td>
</tr>
<tr>
<td>IL-6</td>
<td>Siltuximab</td>
<td>Orthobiotech</td>
<td>Chimeric</td>
</tr>
<tr>
<td>CD138</td>
<td>BT062</td>
<td>Biotest</td>
<td>Chimeric; conjugated to</td>
</tr>
<tr>
<td>Anti-KIR</td>
<td>IPH2101</td>
<td>Innate</td>
<td>Fully Human</td>
</tr>
<tr>
<td>CD40</td>
<td>SGN-40, HCD122, Dacetuzumab</td>
<td>Seattle Genetics</td>
<td>Humanized; Fully Human</td>
</tr>
<tr>
<td>CD56</td>
<td>IMGN901, Lorvotuzumab</td>
<td>ImmunoGen</td>
<td>Humanized; conjugated to</td>
</tr>
<tr>
<td>CD74</td>
<td>Immu-110</td>
<td>Immunomedicics</td>
<td>Humanized; conjugated to</td>
</tr>
<tr>
<td>IGF1-R</td>
<td>CP751,871</td>
<td>Pfizer</td>
<td>Fully Human</td>
</tr>
<tr>
<td>RANKL</td>
<td>Denosumab</td>
<td>Amgen</td>
<td>Fully Human</td>
</tr>
<tr>
<td>DKK-1</td>
<td>BHQ880</td>
<td>Novartis</td>
<td>Fully Human</td>
</tr>
<tr>
<td>FGFR3</td>
<td>PRO-001</td>
<td>Prochon Biotech</td>
<td>Humanized</td>
</tr>
</tbody>
</table>
Elotuzumab: Background

- Elotuzumab is a humanized IgG1 mAb targeting human CS1, a cell surface glycoprotein\(^1\)^\(^2\)
- CS1 is highly expressed on >95% of MM cells\(^3\)^\(^4\)
  - Lower expression on NK cells
  - Little to no expression on normal tissues
- MoA of elotuzumab is primarily through NK cell-mediated ADCC against myeloma cells\(^5\)^\(^6\)
- In a MM xenograft mouse model, antitumor activity of elotuzumab was enhanced by the addition of lenalidomide\(^7\)

ADCC, antibody-dependent cellular cytolysis; DMSO, dimethyl sulfoxide; mAb, monoclonal antibody; MED, maximum efficacious dose; MM, multiple myeloma; MoA, mechanism of action; NK, natural killer.


Moreau et al, EHA 2011

Phase 1/2 Study Design

Response Assessments

- **Elotuzumab**
- **Dosing**
  - CYCLE 1
  - CYCLE 2
  - CYCLE 3
  - CYCLE 4
  - CYCLE N-1
  - CYCLE N

- **Lenalidomide**
  - Cycle day
  - Cycle day
  - Cycle day
  - Cycle day
  - Cycle day

- **Dexamethasone**

- **Phase 1**
  - Dose escalation study of elotuzumab 5, 10, and 20 mg/kg IV in combination with:
    - Lenalidomide 26 mg PO
    - Low-dose dexamethasone 40 mg PO

- **Phase 2**
  - Pts randomized to elotuzumab 10 or 20 mg/kg IV as above
  - Treatment continued until disease progression or unacceptable toxicity

*First 5 pts limited to 6 cycles of therapy; remaining 23 pts treated until disease progression or unacceptable toxicity.
HDAC inhibitors

Two HDAC inhibitors being investigated:

- Phase III study of Vorinostat in combination with Velcade for relapsed/refractory patients (study name: VANTAGE-088)
  Also
- Phase II study of Vorinostat in combination with Velcade for Velcade resistant patients (study name: VANTAGE-095)

- Phase III study of Panobinostat in combination with Velcade and dexamethasone for relapsed/refractory patients (study name: PANORAMA 1) – Finished recruiting UK

- Phase I study of JNJ 26481585 – oral HDAC inhibitor in combination with Velcade and dex (available in France)
Monoclonal antibodies in the UK

- Elotuzumab binds to CS1 surface protein on myeloma cells and directs the immune system to destroy the myeloma cells

- Phase III study of Elotuzumab in combination with Revlimid and low-dose dexamethasone for relapsed and/or refractory patients – open in the UK

- Data so far suggest that elotuzumab/Rev/dex combination is tolerable and shows promising anti-myeloma activity

Other strategies

- Existing chemotherapy drugs
e.g. bendamustine
  MUK one – bendamustine/thalidomide/dex

- Different routes of administration
e.g. intravenous vs subcutaneous injection

- Change in dosing/schedule
e.g. once a week vs twice a week
  - Is MM « ?? chronic disease », « role of maintenance ???»
### Expectations

- Many new developments in the pipeline – patients are more informed and finding out about them sooner
- Not all treatments under development get through. They can fall at any clinical study hurdle
- Be realistic about treatment outcome – there is still no magic bullet
- Treatments are not routinely approved and provided to appropriate patients

### Living with myeloma

- Research is starting to focus more on quality of life and supportive care
- Specific studies looking at the role of supportive care and benefits of exercise
- Better management of complications, including pain control management of peripheral neuropathy
- Individualised care-management plans, with a multidisciplinary approach
Future strategies?

• New drugs
• Risk-adapted
• Targeted
• Patient selection
• Maintain QoL

For information
www.myeloma.org.uk
Infoline: 0800 980 3332