Future strategies for myeloma: new insights and treatments in development

Prof Curly Morris

The situation with myeloma

• Very individual on almost all levels
• Relapsing and remitting – need for next treatments
• Increasing role of genetics/diagnostics – towards more personalised treatments
• Strong pipeline of new drugs in development
• Approval and access to new treatments still a problem
Developments to date

Melphalan and prednisolone
VAD
1962

Autologous SCT
1996

Thalidomide
1999

Velcade
2003

Revlimid
2005

?????
2013

Improved survival with new drugs

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

Mayo Clinic, Blood Journal, March 2008
What’s on the horizon?

- Better use of existing drugs
- Introduction of new drugs to existing combinations
- New treatment approaches
- Improving quality of life and supportive care

Current strategies

Combinations of different drugs

- Alkylating chemotherapy drug
  - Cyclophosphamide
  - Melphalan
  - Bendamustine
- ‘Novel’ drug
  - IMiD
  - Proteasome Inhibitor
- Steroid
  - Dexamethasone
  - Prednisolone
- Thalidomide
- Revlimid
- Velcade
New drugs

Alkylating chemotherapy drug
- Cyclophosphamide
- Melphalan
- Bendamustine

‘Novel’ drug
- ‘Next generation’ IMiD
- Pomalidomide
- ‘Next generation’ proteasome inhibitor
- Kyprolis
- MLN 9708
- NPI 0052

Steroid
- Dexamethasone
- Prednisolone

New emerging drug
- HDAC inhibitor
- Monoclonal antibody
- Cell cycle inhibitor
- Aminopeptidase inhibitor

Proteasome Inhibitors

- The proteasome is the cell’s ‘recycling’ bin
- Breaks down and recycles unused or damaged proteins
- Velcade was the first proteasome inhibitor
**Next generation**

**Kyprolis (carfilzomib)**
- Intravenous infusion
- Works in patients refractory to Velcade and/or Revlimid, 27% response rate
- Fewer side-effects, especially peripheral neuropathy
- Received FDA approval in July 2012 for relapsed AND refractory myeloma patients
- No approval submission yet in Europe
- Clinical studies in UK:
  - MUK five (Kyprolis/cyclo/dex vs Velcade/cyclo/dex)
  - Endeavour study (Kyprolis/dex vs Velcade/dex)

**Next generation (2)**

**MLN 9708 (ixazomib)**
- First oral proteasome inhibitor
- Effective on its own in multiply-relapsed patients
- Response rate of 90% in newly diagnosed patients in combination with Revlimid and dex
- Reduced incidence of neuropathy
- Clinical studies in UK:
  - MLN 9708 plus Rev/dex vs Rev/dex (relapsed patients)
  - MLN 9708 plus Melphalan/prednisolone (newly diagnosed patients)
Latest IMiD

Pomalidomide

- Closely related to thalidomide and Revlimid
- More potent and generally well tolerated, works in patients refractory to Velcade and Revlimid
- Latest data shows that it enhances survival
- Licence approval pending in both USA and Europe

Clinical study in UK:

- Pomalidomide plus low-dose dex (relapsed and refractory patients)

Monoclonal antibodies

Blocking antibodies to:
- CD66*
- IL-6 (siltuximab*)
- DKK1 (BHQ 880*)
- RANKL (denosumab)
- CS1 (elotuzumab*)
- CD38 (daratumumab*)

* Studies open in UK
**HDAC inhibitors**

**HDAC = Histone deacetylase**

- Histones are proteins that form a scaffold around DNA and help ‘package’ it within the cell
- Increased in some cancers
- Stops the production of ‘good’ genes that help prevent cancers or kill cancer cells
- HDAC inhibitors switch on these genes

---

**HDAC inhibitors**

- Panobinostat
- Vorinostat

**Clinical studies:**

- **Myeloma XI** – vorinostat as maintenance treatment (newly diagnosed patients)

- **MUK six**
  Panobinostat plus Velcade/thalidomide/dex followed by panobinostat maintenance (relapsed and/or refractory patients)
Future treatment

- 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?

Towards personalised treatment

Which treatment is best?
- Patient factors
- Myeloma factors
- Complications and side-effects
Individualised treatment plans

Prognostic factors
Conventional
– Age
– Disease stage
– Prior response to treatment
– β2 microglobulin
New
– Cytogenetics
– Gene profiling

Aim is to stratify patients

Living with myeloma

• Research focusing more on quality of life and supportive care - incorporated in new clinical studies

• Specific studies looking at:
  – role of supportive care and benefits of exercise
  – better management of complications, including pain control and management of peripheral neuropathy

• Multidisciplinary approach – individual care plan
Future strategies

Patient selection → Treatment decisions → Risk-adapted → Risk-adapted → Maintain QoL → Targeted → New drugs → Patient selection

For information:

www.myeloma.org.uk
0800 980 3332
Pomalidomide: background

- Pomalidomide is a distinct oral immunomodulatory drug with significant anti-myeloma activity in vitro1,2
- Pomalidomide has demonstrated promising activity in patients with relapsed/refractory multiple myeloma3
- When combined with low-dose dexamethasone, Pomalidomide has clinical efficacy in RRMM patients previously treated with lenalidomide and/or bortezomib4–6

Pomalidomide


PFS – Forest Plot of Subgroup Analyses

Updated March 1 2013

<table>
<thead>
<tr>
<th>Subgroup Analysis</th>
<th>HR (95%CI)</th>
<th>POM + LoDEX*</th>
<th>HIDEX*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT Population</td>
<td>0.48</td>
<td>233/302</td>
<td>133/153</td>
</tr>
<tr>
<td></td>
<td>(0.39-0.60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEN &amp; BORT Refractory</td>
<td>0.52</td>
<td>176/225</td>
<td>95/113</td>
</tr>
<tr>
<td></td>
<td>(0.41-0.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEN as Last Prior Tx</td>
<td>0.38</td>
<td>64/85</td>
<td>42/49</td>
</tr>
<tr>
<td></td>
<td>(0.26-0.58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BORT as Last Prior Tx</td>
<td>0.52</td>
<td>97/132</td>
<td>56/66</td>
</tr>
<tr>
<td></td>
<td>(0.37-0.73)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favors POM + LoDEX  Favors HIDEX

* Number of events/number of pts.
Based on IMWG criteria

San Miguel et al. ASCO 2013 (abstract 8510), oral presentation
Carfilzomib: A Novel Proteasome (Chymotryptic) Inhibitor

- Novel chemical class with highly selective irreversible proteasome binding
- Minimal neurotoxicity in animals
- Durable responses in relapsed and relapsed, refractory MM (ORR 23%) with reduced neuropathy (G1-2 15%, G3 1%)
- Carfilzomib Lenalidomide Dex versus Lenalidomide Dex ongoing (phase III trial for new drug approval – ASPIRE Study)
- Escalating dose trials in relapsed MM and combination trial with Len Dex as initial therapy promising (CRd in ND MM: ORR 94%, Jakubowiak et al, Blood 2012)


<table>
<thead>
<tr>
<th>Patients, %</th>
<th>Relapsed and refractory MM 003-A1 (73% BORT-refractory) Single agent + dex premed (N = 257)</th>
<th>Relapsed and/or refractory MM 004 (BORT-naive) Single agent (N = 67)</th>
<th>Relapsed MM 006 (75% prior BORT) CFZ + Rd (N = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>18 (5)</td>
<td>28 (24)</td>
<td>41 (37)</td>
</tr>
<tr>
<td>5 prior treatments</td>
<td>18 (13)</td>
<td>24 (12)</td>
<td>37 (2)</td>
</tr>
<tr>
<td>2 prior treatments</td>
<td>20</td>
<td>25</td>
<td>39</td>
</tr>
</tbody>
</table>

Efficacy Results of Carfilzomib in RRMM across Phase 2 Studies (Response Rate)

Direct comparisons across studies are not possible, given differences in study design and patient populations

Novel Proteasome Inhibitors Show *in vitro* and *in vivo* Activity

Marizomib and Ixazomib: 2nd generation proteasome inhibitors with promising activity in RRMM:

- **Marizomib (NPI-0052):**
  - induces apoptosis in cell lines resistant to conventional and bortezomib-based therapies
  - in animal models, NPI-0052 was well tolerated and prolonged survival
  - active in RRMM patients (ORR ~ 25% at MTD +/- dex)

- **Ixazomib (MLN9708):**
  - shows selective anti-MM activity in cell lines and an animal model
  - is currently being tested in clinical trials, with promising activity, esp. in combination, and has favourable tolerability


### Ixazomib (MLN9708), lenalidomide and dexamethasone (“Rld”) : Study design

- Phase 1: oral MLN9708 dose-escalation
  - Standard 3+3 schema, 33% dose increments, based on cycle 1 dose-limiting toxicities (DLTs)
- Phase 2: oral MLN9708 at the RP2D from phase 1
- Stem cell collection allowed after 3 cycles, with autologous stem cell transplantation (ASCT) deferred until after 6 cycles
- MLN9708 maintenance continued until progression or unacceptable toxicity
- Mandatory thromboprophylaxis with aspirin or low-molecular-weight heparin

Kumar S. et al, ASH 2012
Progression-free survival

- 4 of 65 pts have progressed or died
- Estimated 1-year progression-free survival probability: 93%

Patients at risk: 65 59 26 7 5 0

Kumar S. et al, ASH 2012

MAb-Based Therapeutic Targeting of Myeloma

Antibody-dependent Cellular cytotoxicity (ADCC)
- Lucatumumab or Dacetuzumab (CD40)
- Elotuzumab (CS1)
- Daratumumab (CD38)
- XmAb®5592 (HM1.24)

Complement-dependent Cytotoxicity (CDC)
- Daratumumab (CD38)
- huN901-DM1 (CD56)
- nBT062-maytansinoid (CD138)
- 1339 (IL-6)
- BHQ880 (DKK1)
- RAP-011 (activin A)
- Daratumumab (CD38)

Apoptosis/growth arrest via targeting signaling pathways

Effector cells: MM

Tai & Anderson Bone Marrow Research 2011
Phase II: Elotuzumab + Len + Low-Dose Dex in Rel/Ref MM (Study 1703)

- Phase 2: Pts (n=73) with relapsed and/or refractory MM with 1-3 prior therapies were randomized to elotuzumab 10 or 20 mg/kg IV combined with
  - Lenalidomide 25 mg PO
  - Low-dose dexamethasone 40 mg PO
- Endpoints
  - Primary: ORR (≥PR per IMWG Criteria)
  - Key secondary endpoints: PFS and safety

**Efficacy: Maximum Percent Reduction in Serum M Protein***

- Maximum percentage decrease from baseline to 60 d after permanent discontinuation of elotuzumab or start of new line of MM therapy.
- Eight pts without measurable disease (baseline and all on-study serum M-protein levels <0.5 g/dL) were not included.
DARATUMUMAB, A CD38 MONOCLONAL ANTIBODY IN PATIENTS WITH MULTIPLE MYELOMA - DATA FROM A DOSE-ESCALATION PHASE I/II STUDY

Torben Plesner, Henk Lokhorst, Peter Gimsing, Hareth Nahi, Steen Lisby, Paul Richardson

Vejle Hospital, Denmark; University Medical Center Utrecht, Netherlands; Copenhagen University Hospital, Denmark; Karolinska Institutet, Stockholm, Sweden; Genmab A/S, Copenhagen, Denmark; Dana-Farber Cancer Institute, Boston, MA, USA

ASH 2012, IMW 2013

Daratumumab: A Human CD38 mAb with Broad-Spectrum Killing Activity

CD38 molecule

- CD38 is expressed on multiple myeloma, with (a) leukemia, B-CELL
- Myeloma, plasma cell leukemia, MM, including PC-MM
- Currently in two clinical trials for multiple myeloma

- Works in combination with other novel agents
- Inhibits killing in combination with other novel agents

- Efficacy kills CD38 tumor cells, e.g. in multiple myeloma
- Prevents ADCC, CDC, ADOP
- Inhibits CD38 enzymatic activity
- Apoptosis after cell lysis
- In vitro efficacy at very low doses in mouse models
Daratumumab
Response according to IMWG

Response rate (%)

0 10 20 30 40 50 60 70 80 90 100

N=32  N=20  N=12

MR  PR

Lokhorst et al. ASCO 2013 (Abstract 8512), oral presentation

Daratumumab
Progression-Free Survival

Estimated probability (%)

0 10 20 30 40 50 60 70 80 90 100

4-24 mg/kg (N=12)
median follow up time: 18.4 weeks (0-53)

0.005-2 mg/kg (N=20)
median follow up time: 8.6 weeks (0-29)

log-rank test: p=0.007

Lokhorst et al. ASCO 2013 (Abstract 8512), oral presentation