Future strategies for myeloma: new insights and treatments in development

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This talk will cover.

- Promising new treatments
- Area where research needs to focus
- Future prospects for myeloma treatment

Take home messages

- Survival and quality of life has improved for myeloma patients
- New drugs attack new targets
- Myeloma treatment will become more personalised in the future
Developments to date

Major advances in treatment over last 10-15 years with corresponding improvements in outcomes
Wide range of new treatments in development
What will be available and what are the key challenges?

Melphalan and prednisolone → Autologous SCT → Bortezomib → Lenalidomide → Pomalidomide


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

Mayo Clinic, Blood Journal, March 2008
More to be done

**Survival rates have improved but:**

- Less toxic treatments are needed
- Newer drugs have specific targets so may not all be effective for all patients
- Relapsing and remitting – need for next treatments
- Need to target effective early treatment for patients with high risk of progression
- Need to know which combinations of drugs are best, and for which type of patient

Cytogenetics and molecular genetics
Key genetic events in myeloma

2015:
FISH to identify high risk myeloma:
• t(4;14)
• t(14;16)
• t(14;20)
• Gain of 1q
• Loss of 1p and 17p

Which combinations are best and for whom?
Current combinations

- Alkylating chemotherapy drug
  - Cyclophosphamide
  - Melphalan

- 'Novel' drug
  - IMiD
    - Thalidomide
    - Lenalidomide
  - Proteasome inhibitor
    - Bortezomib

- Steroid
  - Dexamethasone
  - Prednisolone

New combinations

- Alkylating chemotherapy drug
  - Cyclophosphamide
  - Melphalan

- 'Next generation' IMiD
  - Pomalidomide

- 'Next generation' proteasome inhibitor
  - Carfilzomib
  - Ixazomib
  - Marizomib

- Steroid
  - Dexamethasone
  - Prednisolone

- New emerging drug
  - HDAC inhibitor
  - Monoclonal antibody
  - Cell cycle inhibitor
Promising new treatments

Categories or types of new treatments:
• New IMiDs and new proteasome inhibitors
• Monoclonal antibodies
• Cell-cycle inhibitors
• HDAC inhibitors

Plus new treatments to improve:
• Quality of life, supportive care

IMMUNOMODULATORY DRUGS (IMIDS)
Immunomodulatory drugs (IMiDs)

IMiDs are derived from thalidomide
- act on several different targets in myeloma
- Newer versions are more easily tolerated
- less toxic, more effective
- still have marked side-effects

Latest ImiD: Pomalidomide

Closely related to thalidomide and lenalidomide
More potent and generally well tolerated, works in patients refractory to bortezomib and lenalidomide

Oral schedule
- Pomalidomide 4mg daily days 1-21
- Dexamethasone 20-40mg weekly

Most common side-effects:
- neutropenia (32%), leukopenia (17%), fatigue (17%)
- VTE risk

Hepatic clearance
Renal studies underway
Pomalidomide

- Latest data shows that it enhances survival
- Licence in UK/Europe late 2013
- Available from Cancer Drugs Fund until November 2015:

**Pomalidomide** The treatment of relapsed and refractory multiple myeloma where the following criteria are met:

1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
2. Multiple myeloma
3. PS 0-2
4. Previously received treatment with adequate trials of at least all of the following options of therapy: bortezomib, lenalidomide and alkylating agents
5. Failed treatment with bortezomib or lenalidomide as defined by progression on or before 60 days of treatment or progressive disease 6 or less months after achieving a partial response or intolerance to bortezomib
6. Refractory disease to previous treatment
7. No resistance to high dose dexamethasone used in the last line of therapy
8. No peripheral neuropathy of grade 2 or more

**Clinical study in UK:**

**MUK seven study:**

Pomalidomide and dexamethasone +/- cyclophosphamide

www.myeloma.org.uk

PROTEASOME INHIBITORS

www.myeloma.org.uk
Proteasome inhibitors

- Proteasomes get rid of worn-out or unwanted proteins from cells
- Blocking proteasomes poisons the cell
- Myeloma cells are particularly vulnerable
- Velcade (bortezomib), Kyprolis (carfilzomib), ixazomib

Next generation proteasome inhibitors

**Carfilzomib (Kyprolis)**
- Second generation proteasome inhibitor
- Irreversibly inhibits chymotrypsin-like site of proteasome
- Intravenous infusion
  - Twice a week
  - Days 1, 2, 8, 9, 15, 16 of a 28 day cycle
- Side effects
  - Infusion-related
  - Fluid retention/overload – uncertain mechanism
  - Minimal peripheral neuropathy
- As single agent om patients refractory to bortezomib and/or lenalidomide, 27% response rate
- Received FDA approval in USA July 2012 for relapsed AND refractory myeloma patients
- Awaiting European licence: has received CHMP
- ASPIRE study in combination with lenalidomide and dexamethasone:
  - Increase in progression free and overall survival
- Other studies
  - Weekly schedules
  - Other combinations including cyclophosphamide (MUK five)
Next generation proteasome inhibitors

**Oprozomib**
- Oral epoxyketone proteasome inhibitor
- Selective and irreversible
- Current data: promising activity
- Possible practical issues relating to GI toxicity and tablet formulation

**Ixazomib**
- Ixazomib: oral proteosome inhibitor
- Single agent activity in initial trials
- Combination with lenalidomide and dexamethasone – improved outcomes
- Low risk of peripheral neuropathy
- Current data: effective oral proteasome inhibitor
- GI toxicity
- Possible role following ASCT – trial to open C16019
- Combination studies
  - MUK eight
  - Myeloma XII

MONOCLONAL ANTIBODIES
Monoclonal antibodies

- Mimic antibodies produced naturally by the immune system
- Monoclonal antibodies recognise and attach to specific proteins on the surface of cancer cells
- This enables the immune system to target and destroy the cancer cells

Target different proteins on the surface of the myeloma cell

- CD38 (daratumumab)
- CS1 (elotuzumab)
- RANKL (denosumab)
- CD66
- IL-6 (siltuximab)
- DKK1 (BHQ 880)
## Monoclonal antibodies

### Elotuzumab
- **Anti-CS1 (SLAMF7)**
- Ineffective as monotherapy
- Intravenous days 1, 8, 15, 22 for 2 cycles then days 1 and 15
- Combined mode of action
  - Through antibody-mediated myeloma cell killing
  - By activation of natural killer cells resulting in immunostimulatory effect
- With lenalidomide and dexamethasone: Phase 3
- Relapsed MM
- Median progression-free survival in the elotuzumab group 19.4 months versus 14.9 months in the control group

### Daratumumab
- Fully humanised monoclonal antibody against CD38
- Monotherapy study: 42% PR, 25% MR
- Well tolerated, minor infusion related reactions
- Ongoing combination studies with:
  - Lenalidomide and dexamethasone: interim analysis overall response rates approaching 100%
  - Bortezomib and dexamethasone
- In smouldering myeloma
- **SAR650984**
- Anti CD38 monoclonal antibody
- With lenalidomide and dexamethasone: Phase 1b
- Relapsed/refractory myeloma
- ORR 64.5%
- Median PFS 6.2 months

www.myeloma.org.uk
CELL CYCLE INHIBITORS

Cell-cycle inhibitors

- Stop myeloma cells multiplying
- Multiplying cells go through stages with “checkpoints”
- Cell-cycle inhibitors block the cell cycle in multiplying myeloma cells
  - Arry-520
  - MLN8237
  - Selciclib
HISTONE DEACYLASE INHIBITORS (HDACI)

HDAC inhibitors

- Histones are part of DNA scaffolding and switch off genes
- Allow myeloma cells to grow and multiply
- HDAC inhibitors keep good genes switched on
- Stops myeloma cells growing and surviving
- Panobinostat
HDAC inhibitors

**Vorinostat**
- Myeloma XI
  - vorinostat as maintenance treatment
  - (newly diagnosed patients) – closed to new randomisations
- MUK four
  - Velcade, vorinostat and dexamethasone
  - Vorinostat maintenance
  - Closed: data to be presented this year

**Panobinostat**
- MUK six
  - Panobinostat plus Velcade/thalidomide/dex followed by panobinostat maintenance (relapsed and/or refractory patients):
  - Better tolerated than original studies with high response rates

www.myeloma.org.uk
Immunotherapy

Harness body’s own immune system
T cells play an important role in fighting infection but also in fighting malignancies
Once a tumour has developed, challenge is to re-programme body to recognise tumour cell as abnormal

Different potential strategies
  Monoclonal antibodies
  Drugs
  Allogeneic stem cell transplantation
  CAR-T cells
  Genetically modified autologous T cells

Oncolytic viral therapy

Measles virus
Small studies in myeloma and other haematological malignancies
Problem is of immunity to virus – need to overcome natural immunity with drugs or other delivery systems
Small number of very encouraging responses
Clinical Trials

National Phase 3 studies (UKMRA)
- Myeloma XI/XI+
- Myeloma XII
- Myeloma XIV
- Myeloma XV
- Commercial studies

Phase 2 studies
- Myeloma UK CTN
- Commercial studies

Phase 1/2 studies
- Myeloma UK CTN
- Commercial studies
## Current Portfolio of MUK Trials

<table>
<thead>
<tr>
<th>MUK No.</th>
<th>Test Drug</th>
<th>Title</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>one</td>
<td>Bendamustine</td>
<td>An open label, multi-centre, randomised, parallel group phase II selection trial to identify the optimal starting dose of bendamustine (60 vs 100 mg/m²) when given in combination with thalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma.</td>
<td>COMPLETED patient recruitment, published</td>
</tr>
<tr>
<td>three</td>
<td>CHR3996 &amp; Tosedostat</td>
<td>A Phase I/II, Dose-Escalation, Study of CHR-3996 in Combination with Tosedostat in Subjects with Relapsed, Refractory Multiple Myelomas.</td>
<td>OPEN Recruiting patients to Phase I</td>
</tr>
<tr>
<td>four</td>
<td>Vorinostat</td>
<td>An open label, single arm, phase II trial to assess the efficacy, safety and tolerability of vorinostat in combination with bortezomib and dexamethasone (VVD) in patients with relapsed or relapsed refractory multiple myeloma.</td>
<td>COMPLETED patient recruitment, in analysis</td>
</tr>
<tr>
<td>five</td>
<td>Carfilzomib</td>
<td>A phase II randomised trial of carfilzomib, cyclophosphamide and dexamethasone (CCD) vs cyclophosphamide, Velcade and dexamethasone (CVD) for first relapse in myeloma patients.</td>
<td>OPEN Recruiting patients</td>
</tr>
<tr>
<td>six</td>
<td>Panobinostat</td>
<td>A Phase IIa trial of Velcade, thalidomide and dexamethasone (VTD) with panobinostat in relapsed and relapsed/refractory multiple myeloma patients who have received 1-4 prior lines of therapy.</td>
<td>COMPLETED patient recruitment, in analysis</td>
</tr>
<tr>
<td>seven</td>
<td>Pomalidomide</td>
<td>Pomalidomide Specific Targeting in Relapsed and Refractory Myeloma (POST Study) A single arm Phase II study in which all patients will receive treatment with Pomalidomide and Dexamethasone.</td>
<td>OPEN Recruiting patients</td>
</tr>
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**MUK Trials in development**

<table>
<thead>
<tr>
<th>MUK No</th>
<th>Test Drug</th>
<th>Phase and population</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUK eight</td>
<td>Ixazomib (Takeda)</td>
<td>3 – relapsed myeloma</td>
<td>In set-up</td>
</tr>
<tr>
<td>MUK nine</td>
<td>Daratumumab, lenalidomide and multi-agent</td>
<td>2 – high risk newly diagnosed myeloma</td>
<td>In development</td>
</tr>
<tr>
<td>MUK ten</td>
<td>Panobinostat combinations</td>
<td>In development</td>
<td>In development</td>
</tr>
<tr>
<td>MUK eleven</td>
<td>Oncolytic virus</td>
<td>1 – relapsed myeloma</td>
<td>In development</td>
</tr>
</tbody>
</table>

**Quality of life**

- As patients live longer, improving quality of life is even more important
- This includes effects of the myeloma and its treatment on you as a person

**Supportive care**

- A key factor in prolonging life is better supportive care
- Specific studies looking at e.g. benefits of exercise, infection control, better management of complications (e.g. pain and peripheral neuropathy)
Areas for improvement

Myeloma is a very individual cancer, treatment needs to be personalised

Approval/access

• Drugs can only help when patients have access to them
• Health Technology Assessment bodies

Increased role of genetics and diagnostics

This talk has covered...

Promising new treatments

Area where research needs to focus

Future prospects for myeloma treatment
Take home messages

• Survival and quality of life has improved for myeloma patients
• New drugs attack new targets
• Myeloma treatment will become more personalised in the future

MUK resources

• Clinical Trials Infoguide
• Clinical Trial Tracker and
• New Drug Scanner
• Horizons Infosheets
• Myeloma TV
• Infoline

** please visit the Myeloma UK Patient Information stand in the foyer area for further information