Treatment strategies for relapsing and refractory myeloma

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This talk will cover…

• The course of myeloma
• What is relapsed and refractory myeloma
• When to re-start treatment and factors to consider
• Treatment for relapsed and refractory myeloma
Three take home messages

1. Myeloma will return at some point but it is difficult to predict exactly when this will happen
2. Tests and symptoms/complications help to identify relapse
3. Treatment options are available for relapsed and refractory myeloma

Multiple Myeloma…..the facts

GLOBAL FACTS\(^1\,^2\)

<table>
<thead>
<tr>
<th>0.8%</th>
<th>229K</th>
</tr>
</thead>
<tbody>
<tr>
<td>of all cancer cases</td>
<td>5-year prevalence</td>
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</table>

• 28,700 & 19,920 new diagnoses p.a. in the EU & USA, respectively
• 37% are diagnosed through emergency routes rather than referral by GPs, compared to 23% across all cancer types.
• Patients diagnosed through emergency routes have less good outcomes compared to those diagnosed by GP referral.

≈4,000 new patients p.a in the UK

www.myeloma.org.uk
Myeloma – Not One Disease
Patients – Not One Host

cherry blossoms (sakura)

www.myeloma.org.uk

Definitions

- **Remission** – the period following treatment when myeloma cells and paraprotein are no longer detectable and no clinical symptoms of myeloma

- **Plateau** – a period of time when the myeloma and the paraprotein level is relatively stable

- **Relapse** – the point where myeloma returns or becomes more active after a period of remission or plateau

- **Refractory** – myeloma that has failed to respond to treatment

www.myeloma.org.uk
Myeloma.....the “natural” history

**Detecting relapsed / refractory myeloma**

Regular tests will indicate activity of myeloma and help to show when a patient has relapsed or is refractory

- Paraprotein
- Free light chains
- Imaging
- Blood tests
- Organ function

[www.myloma.org.uk](http://www.myloma.org.uk)
Treatment paradigm

Medication Developments

Financial impact

Legal impact

Patient Issues

Guidelines & algorithms

www.myeloma.org.uk

Treatment options: three approaches

REPEAT

ADD

NEW

Continue to monitor or repeat previous successful treatment

Add to the existing treatment combination e.g. steroid, chemotherapy

Try a new treatment with a different way of killing myeloma cells

www.myeloma.org.uk
Treatment decision tree for the treatment of MM at relapse

Treatment after relapse

Switch drug class after
- short remission
- long-term treatment
- toxicity

Re-treatment after*
- long remission
- short front-line treatment duration
- no toxicity concerns from first-line treatment

Re-intensification
- increase dosage of the current agent
- add additional agent

* Response usually shorter and smaller than original response.


www.mayeloma.org.uk

Treatment options

First relapse
- Velcade® (but no retreatment)
- Kyprolis® (but not if Velcade before)
- Thalidomide
- Steroid
- Chemotherapy
- Second ASCT +/- mini-allo SCT

Plus

Second relapse
- Revlimid®
- Farydak® (with Vel+dex)
- DT-PACE
- ESHAP

Plus

Third and subsequent relapse
- Imnovid®
- Bendamustine
- Chemotherapy

www.mayeloma.org.uk
Treatment options - first relapse

• Same as previous treatment if good response – but need to be aware of developing resistance
• Add to existing treatment +/- steroid +/- chemotherapy
• Second high-dose therapy and stem cell transplant
• Velcade® (bortezomib)
• Kyprolis® (carfilzomib)
• Clinical trial – if eligible

www.myeloma.org.uk

Transplantation in Myeloma

www.myeloma.org.uk
Reduced Intensity ("Mini")
allogeneic transplant

Rarely used but may be an option at relapse depending on:

- **Age** – younger patients
- **Comorbidities** (other illnesses/diseases)
- **Nature** of myeloma
- **Suitable** matched (sibling) donor

Carried out at doctor’s discretion, sometimes within a clinical trial, if a matched donor is available.
Reduced Intensity ("Mini") allogeneic transplant

Risk of graft-versus host disease (GVHD)
Higher risk if alternative donor used

Donated immune cells attack myeloma cells to produce long-term remission (immunotherapy)
Delays relapse

Treatment options - second relapse

• Same as previous treatment
• Add to existing treatment +/- steroid +/- chemotherapy
• Revlimid® (lenalidomide)
• Farydak® (panobinostat) (if had Revlimid® and Velcade®)
• Other combinations e.g. DT-PACE and ESHAP
• Clinical trial – if eligible

www.myeloma.org.uk
Treatment options - after second relapse

- Imnovid® (pomalidomide)
- Farydak® (panobinostat)
- bendamustine HCL

Treatment options - refractory myeloma

- Different combination of drugs
  +/- steroid  +/- chemotherapy
- Multi-drug combinations e.g. DT-PACE, ESHAP
- Clinical trial – newer drugs can still be effective

www.myeloma.org.uk
Future treatments – later talk

New myeloma drugs:

- **Kyprolis** (carfilzomib) for injection
- **NINLARO** (ixazomib) capsules
- **DARZALEX** (daratumumab)

[www.myeloma.org.uk](http://www.myeloma.org.uk)

Clinical Trials

[www.myeloma.org.uk](http://www.myeloma.org.uk)
**UK Myeloma Research Alliance**

**NCRI Haemato-Oncology CSG (Myeloma Sub-group)**

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**MUK CTN**

**Phase I**

**Phase I/II**

**Phase II**

**Phase IIb**

**Phase III**

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**MUK CTN – therapy accelerated programme**

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<tr>
<th>Trial</th>
<th>Concept</th>
<th>Set up</th>
<th>Recruiting</th>
<th>Closed</th>
<th>Target</th>
<th>Status</th>
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<tbody>
<tr>
<td>MUK one</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>96</td>
<td>(complete)</td>
</tr>
<tr>
<td>MUK three</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>38</td>
<td>Completed recruitment on 04Dec 2015, 22 pts recruited</td>
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<tr>
<td>MUK four</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>68</td>
<td>Closed early to recruitment, 16 pts recruited, Abstract presented at ASH 2015</td>
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<tr>
<td>MUK five</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>300</td>
<td>Open to recruitment, 245 pts recruited, 37 still open, Abstract presented at ASH 2015</td>
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<tr>
<td>MUK six</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>54</td>
<td>Closed to recruitment, Abstract presented at ASH 2015</td>
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<tr>
<td>MUK seven</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>250</td>
<td>Opened to recruitment 2 March 2016, 3 centres open, 0 pts</td>
</tr>
<tr>
<td>MUK eight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>212</td>
<td>Opened to recruitment on 17 Dec 2015, 11 centres open and 8 pts recruited</td>
</tr>
<tr>
<td>MUK nine HIGH RISK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>105</td>
<td>Expected to open Q3 2016</td>
</tr>
<tr>
<td>MUK 11 RELAPSED/REFRACTORY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>Finishing study design, due to open late summer 2016</td>
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<tr>
<td>MUK 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>In discussion with company</td>
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<td>MUK 14</td>
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<td>47</td>
<td>In discussion with company</td>
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Impact of UK Myeloma Trials

Clinical trials

- Clinical trials are designed to help develop better treatment for myeloma
- They often use newer drugs which are not yet used in routine care
- Follow strict rules as to what is done, when and where

www.myeloma.org.uk
IxaCyDex

Treat until PD

MUKeight

RRMM

Ixazomib
Cyclo Dex

Cyclo Dex

Treat until PD

Chief Investigator: Prof Gordon Cook

www.myeloma.org.uk

Oncolytic Virotherapy

www.myeloma.org.uk
Oncolytic viruses

Direct oncolysis

Potentiation of anti-tumour immunity

- Activation and enhancement of NK cell function
- Priming of tumour-specific CD8+ T cells

Coxsackievirus A21

Reovirus

25 nm

50-70 nm

www.myeloma.org.uk

MUKeleven

VIReL: Viral Immunotherapy in Relapse/Refractory Myeloma
Phase I/II Study Design

Lenalidomide

Pomalidomide

IMiD continuation

PD

Steroid Discontinuation

Reovirus

Immune response Biomarkers

Chief Investigator: Prof Gordon Cook

www.myeloma.org.uk
Clinical trials

Entry to a trial is determined by:

- What stage of disease (e.g. newly diagnosed or relapsed)
- Previous treatment
- Capacity within trials teams

<table>
<thead>
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<th>You can choose</th>
<th>You may/may not choose</th>
<th>You cannot choose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whether to become enrolled and treated on the trial</td>
<td>Where you have treatment</td>
<td>Whether you fit the criteria for a trial</td>
</tr>
<tr>
<td>To withdraw from the trial if you want to</td>
<td>When it starts</td>
<td>Exactly what treatment you get</td>
</tr>
<tr>
<td></td>
<td>Whether you have extra investigations</td>
<td>Whether doses change or drugs start or stop</td>
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clinicians.org.uk

Clinical trials: When to go on a trial

✓ If the trial treatment fits with what you need

✓ If you and your doctor believe in the trial treatments being offered

✓ If you are prepared for the additional trips and tests required at the trial centre

www.myeloma.org.uk
Patient hints and tips

“We all know that our myeloma will come back – obviously we all wish this takes as long as possible. When it does return, focus on what you can control, your thoughts, your actions.”

Tips from The small things that make all the difference book

This talk has covered...

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An Infopack for relapsed and refractory patients is currently in development and coming soon

Visit the Patient Information stand for other information

www.myeloma.org.uk
Three take home messages

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www.myeloma.org.uk

Myeloma UK resources

Treatment and clinical trials information

Videos featuring patients and healthcare professionals

3D animations about myeloma on our website

www.myeloma.org.uk
Thank you & any questions..........?

www.myeloma.org.uk