Treatment for relapsed and/or refractory myeloma

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Some definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
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<tbody>
<tr>
<td>Remission</td>
<td>Absence of both paraprotein in blood and myeloma cells in marrow after treatment</td>
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<tr>
<td>Plateau</td>
<td>Stable disease with a detectable paraprotein that follows a response to treatment</td>
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<tr>
<td>Relapse</td>
<td>Progression of myeloma following a previous response to treatment</td>
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<tr>
<td>Refractory</td>
<td>No response to treatment</td>
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<tr>
<td>Relapsed / refractory</td>
<td>Progression whilst receiving treatment or within 60 days of treatment.</td>
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Overview of Treatment for Myeloma

Presentation: 1st Relapse: 2nd Relapse: 3rd Relapse: Relapse

- Velcade
- Thalidomide
- Revlimid
- Bendamustine
- Conventional
- Autograft
- Clinical Trial
- Supportive Therapies

Modified from R. Popat

Relapse

- Treatment required if symptoms return
- Repeat tests to confirm
- Relapse: Increase in paraprotein by 25% from baseline

When do we need to treat at relapse?

- Treat when symptomatic
  - New bone complications
  - Anaemia
    - More tired, less energy, out of breath
  - Kidney impairment
  - High Calcium
  - Recurrent bacterial infections

Natural course of myeloma

- Asymptomatic
- MGUS or smouldering myeloma
- Active myeloma
- Plateau remission
- Relapse
- Refractory relapse

REMISSION

RELAPSE

Paraprotein

0%
50%
100%

100 50 0
Goals and Considerations at Relapse

- Patient factors
  - Age
  - Other illnesses
  - How fit?

- Myeloma features
  - Side effects
  - Response against myeloma

- Previous therapy
  - Type
  - Response
  - Cross resistance
  - Toxicity

- Other aspects
  - Quality of life
  - Hospital proximity
  - Funding
  - Choice

Treatment at relapse

Factors to consider:
- Length of first remission/plateau
- Time since diagnosis
- Number of previous relapses
- Type(s) of previous treatment

Relapse treatment options

- There is no standard approach
- Same again?

- Try different treatment?
  - May be governed by NICE recommendations

- Consider taking part in a clinical study (trial)
  - can take part at any point
  - provides another 'line of treatment'
  - must meet study criteria

- Supportive treatment as necessary

Refractory options

- Try different treatment
- Sequence of treatments similar to relapse
- Clinical study
  - good option as newer drugs can still be effective

First relapse

- Progression of myeloma in the absence of treatment following successful initial treatment

Treatment at first relapse

Velcade (bortezomib)
- The first proteasome inhibitor to be used in myeloma
- Current NICE-approved 2nd line treatment

- Originally IV injection
  - Now more often subcutaneous injections
  - Once or twice weekly
  - Each cycle usually 3 weeks
  - 2 - 4 injections per cycle
  - 4 – 8 cycles
Treatment at first relapse

Velcade (bortezomib)
- Generally combined with dexamethasone
- Better responses if used early in disease course and in combination with other drugs
- Potential side-effects:
  - Weakness, fatigue
  - Peripheral neuropathy
  - Low blood counts especially platelets
  - Nausea, diarrhoea or constipation
  - Postural hypotension

Other options at first relapse

- Same treatment again if first remission / response lengthy
- Thalidomide based therapy if not used at first line
- Enter a clinical study
  - May access newer drugs / newer combinations
- Second autologous stem cell transplant

Second autograft transplant

- Recent UK trial (Myeloma X) shows significantly better disease control for patients receiving second transplant
  - After having disease controlling chemotherapy
- If long response to first transplant
- If good response to relapse treatment
- If fit enough to undergo second transplant
  - Heart
  - Lungs
  - Kidneys

Allogeneic (Donor) transplants

- Stem cells from sibling or unrelated donor
- More side effects than autograft
  - Benefits and risks can be more difficult to balance
- Highly selected patients
  - Younger
  - Very fit
  - High risk genetics
- Ideally within a clinical trial

Repliromid (lenalidomide)

- Immunomodulatory drug (IMiD), similar to thalidomide but more potent and less toxic
- Current NICE approval at 3rd line and beyond, in combination with dexamethasone
- Oral capsule taken daily on days 1 - 21 of 28-day cycle
- Recommended starting dose of 25mg (lower for patients with kidney damage)
- Dose continued or modified, until disease progression
Revlimid

Potential side-effects:
• Less constipation and neuropathy than thalidomide
• Low white cells and platelets
• Neutropenia and thrombocytopenia
• Infections
• Increased risk of blood clots
• Fatigue
• Muscle cramp
• Diarrhoea

Next lines of treatment

• Consider previous treatments that have given lengthy remission
  • Alone or in combination

• Pomalidomide

• Other strategies such as DT-PACE or ESHAP

• Non-licensed drugs via access schemes
  • E.g. bendamustine

• Enter clinical study

Pomalidomide (Imnovid)

• Immunomodulatory drug (IMiD)
  – Closely related to thalidomide and Revlimid
  – More potent in the lab than both
  – Licensed to be given after Revlimid

• Given as a tablet
  – Daily and similar to Revlimid (day 1 – 21 on a 28 day cycle)

• In studies given alone or with dexamethasone

• Generally tolerated well

Bendamustine

• Chemotherapy drug

• Licensed for use in newly diagnosed patients unable to have thalidomide or Velcade

• Access at relapse via Individual Funding Request or Cancer Drugs Fund

• Intravenous infusion

• Effective as a monotherapy but better in combination with other drugs e.g. thalidomide and/or dexamethasone
  • First Myeloma UK study to report (MUK1)

• Potential side-effects:
  - nausea, vomiting
  - neutropenia, thrombocytopenia

Clinical studies / New drugs

• Multiple new drugs in clinical trials
  – Modifications of existing types
  – New classes of drugs
  – Lots of combinations
    • Kyprolis (carfilzomib)
    • MLN 9708 (Ixazomib)
    • Elotuzumab
    • Daratumumab
    • Panobinostat

Summary

• No standard best approach to treatment at relapse
  – adapting to meet patients’ needs important
  – identifying the best sequence of treatments is challenging

• Relapse options
  – Consider same treatment if lengthy first remission
  – Thalidomide-based treatment if not had it before
  – Velcade-based treatment if previously treated with thalidomide
  – Revlimid-based treatment at subsequent relapse
  – Pomalidomide-based treatment
  – Clinical studies
  – Second transplant
For information:

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