Treatment for relapsed and/or refractory myeloma

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This talk will cover...

- What is relapsed myeloma and refractory myeloma
- Treatment options for relapse
- Treatment options for refractory disease
Take home messages

- Myeloma is a very complex individual cancer
- Patients will relapse following successful treatment and a period of remission/plateau
- Many patients who relapse can be successfully treated again, and will have a second period of remission/plateau

Outlook for myeloma patients has improved

1970 ..... melphalan, cyclophosphamide, prednisolone

1990s ..... Autologous stem cell transplantation for younger patients

1997 onwards ..... novel agents

- Thalidomide
- Velcade (bortezomib)
- Revlimid (lenalidomide)

Newer drugs (carfilzomib, pomalidomide, ixazomib, monoclonal antibodies (daratumumab, elotuzumab), bendamustine)
Myeloma – treatment algorithm 1999

We had…

Chemotherapy (melphalan, cyclophosphamide, CVAD)

Steroids (dexamethasone, prednisolone)

Stem cell transplants

Thalidomide was experimental

Now in 2014…so many more options
Use combination of drugs

Proteasome inhibitors
- Bortezomib
- Carfilzomib
- Ixazomib

OR

Immunomodulatory drugs
- Thalidomide
- Lenalidomide
- Pomalidomide

Chemotherapy
- Melphalan
- Cyclophosphamide
- Adriamycin

Steroid
- Prednisolone
- Dexamethasone

New drugs
- Monoclonal antibodies

Natural course of myeloma

MGUS: Monoclonal gammopathy of undetermined significance
Some definitions

Remission: Absence of paraprotein in blood and myeloma cells in bone marrow following treatment

Plateau: Stable disease following good response to treatment, reduced but detectable paraprotein levels

Relapse: Disease progression following a previously successful course of treatment

Refractory: No response to treatment whether initial treatment or treatment at relapse

Relapsed and refractory: Disease progression on a specific treatment or within 60 days of stopping treatment

Relapse

Relapse: Increase in paraprotein by 25% from baseline and at least 5g/L

Repeat tests to confirm

Treatment required if symptoms return

Relapse often picked up by blood test showing rising paraprotein before any symptoms
First relapse

Progression of myeloma after a period of remission/plateau following successful initial treatment

- Timing, nature and pace of relapse is very variable
- Some people relapse less than six months after completing their first line treatment
- Some people have more than five years of remission after their first line treatment

**VERY HARD TO PREDICT AT DIAGNOSIS**

- Generally wait for a significant rise in paraprotein/light chains or CRAB symptoms before starting next treatment

www.myeloma.org.uk
Relapse often picked up by blood test showing rising paraprotein before any symptoms

Relapse less commonly picked up by new symptoms

Evidence of relapse with a rising paraprotein without symptoms or new organ damage may be observed

Often difficult to know when to restart treatment

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**Treatment at relapse**

Deciding next treatment. Factors to consider

- Length of first remission/plateau
- Tolerability to previous treatments
- Existing illnesses (comorbidities)
- Number of previous relapses
- Type(s) of previous treatment
- Patient wishes
- What we are allowed to prescribe (NICE, Cancer Drugs Fund)
First relapse options

- Same as first line treatment? (if good response)
- Second transplant?
  – for patients who had a reasonable response to first transplant (>18 months)
- Velcade® (bortezomib)
- Different treatment – may depend on NICE approval or Cancer Drugs Fund
- Clinical trial - may provide options not otherwise available, Not all patients will be eligible
- Supportive treatment as necessary

Velcade (bortezomib)

- First proteasome inhibitor to be used in myeloma
- Current NICE–approved treatment for first relapse
- Originally IV injection, now subcutaneous injections. Once or twice weekly
- Generally combined with dexamethasone +/- chemotherapy
- 21 or 35 day cycles (3rd or 5th week rest week)
- 4 – 8 cycles
Velcade (bortezomib)

- Proteasome inhibitor
- Side-effects
  - Nausea
  - Constipation
  - Diarrhoea
  - Low platelets
  - Neuropathy (damage to nerves typically feet and hands)

Other options at first relapse

- Same treatment again if first remission lengthy
- Thalidomide usually in combination
- Lenalidomide (if allowed by NICE or Cancer Drugs Fund)
- Second transplant if first transplant remission >2yrs
- Enter a clinical study
- Hoping to get better access to other drugs such as lenalidomide (NICE, Cancer drugs fund)
Second autologous transplant

Data from Myeloma X study suggests benefit of doing a second autologous transplants if good response to first transplant

If second transplant is delayed and done later on, the long term outcome is no different from having two transplants together earlier on

Consider mini-allogeneic (donor) transplant for some patients if appropriate

Second relapse

Duration of remission/plateau usually shorter

Myeloma changes in character – drug resistance develops

First line treatment
Second line treatment
Third line treatment

First Relapse
Second Relapse
Second relapse options

- Same as previous treatment?
- Revlimid® (lenalidomide)
- Different treatment – may depend on NICE approval or Cancer Drugs Fund
- Non-approved drugs – access schemes, bendamustine (not licensed for relapsed myeloma but on CDF)
- Other drug combinations e.g. DT-PACE, ESHAP
- Clinical trials – if eligible

Revlimid (lenalidomide)

- Immunomodulatory drug (IMiD), similar to thalidomide but more potent and less toxic
- Oral capsule taken daily on days 1 – 21 of 28 day cycle, treat until disease progression
- NICE–approved for second relapse and beyond, in combination with dexamethasone
- Recommended starting dose of 25mg (lower for patients with kidney damage)
**Revlimid (lenalidomide)**

Potential side-effects:

- Less constipation and neuropathy than thalidomide
- Neutropenia and thrombocytopenia
- Increased risk of blood clots
- Fatigue
- Muscle cramp

**Next lines of treatment**

- Consider previous treatments that have given lengthy remission
- Increasing dose or add drugs to existing treatment
- Pomalidomide
- Bendamustine
- Other strategies for younger patients such as DT-PACE or ESHAP
- Non-approved drugs via access schemes
- Enter clinical study
Subsequent relapse… Imnovid® (pomalidomide)?

- From November will no longer be obtained through CDF (England). Only allowed for patients who have had Velcade and Revlimid. Approved in Scotland and Wales.
- Oral capsule taken daily on days 1 – 21 of 28 day cycle.
- Low side-effect profile – infection, low blood counts.
- Usually used at third relapse in UK.
- Combined with steroids.

Refractory options

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

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**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, 2 days every 4 weeks

- Effective as a monotherapy but better in combination with other drugs e.g. thalidomide and/or dexamethasone

- Potential side-effects:
  - Nausea, vomiting
  - Neutropenia, thrombocytopenia

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**Allogeneic (donor) transplant in myeloma**

**Factors to consider:**

- Age
- Comorbidities (other illnesses/diseases)
- Nature of the myeloma

- Mini-allogeneic (donor) transplant can be considered for some patients if appropriate
- Clinical trial when possible
Mini-Allogeneic stem cell transplant

- Transplant using matched bone marrow stem cells from another human being (brother, sister, unrelated but matched individual)

- Reduced intensity transplants can be done up to 65+ years of age

Mini-Allogeneic stem cell transplant

- Serious procedure – risks involved
- Can be beneficial but graft versus host disease a problem
- Myeloma must be under control first
- Exact role in myeloma unclear

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Future strategies

- Clinical trials – novel drugs
  - Imnovid® (pomalidomide)
  - Kyprolis® (carfilzomib)
  - Ixazomib (MLN 9708)
  - Elotuzumab
  - Daratumumab
  - Panobinostat

Newer drugs – in trial

Carfilzomib

- Very promising proteasome inhibitor
- Same family as bortezomib but little neuropathy
- Intravenous injection currently two days a week
- Better than bortezomib?
Newer drugs – in trial

Ixazomib (MLN9708)
- Oral proteasome inhibitor
- Same family as bortezomib but little neuropathy
- Possible side effects: Fatigue, nausea, diarrhoea, rash, low platelets

Daratumumab
- Antibody against myeloma cells (against target called CD38)
- Given intravenously, Optimal schedule unclear weekly? Less frequently?
- Possible side effects: Reaction to infusion, low blood counts
Clinical studies

• Not possible to have every study open at each hospital (study may be open at another hospital in the region)

• There are strict criteria for being eligible for a trial (inclusion and exclusion criteria)

• Need to have a detailed discussion with health care professionals as to benefits and drawbacks of a particular trial

• You can withdraw from a study without having to give a reason

• Your doctor may withdraw you from a study if they feel it is in your best interests

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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
  - Velcade-based treatment if previously treated with thalidomide
  - Revlimid-based treatment at subsequent relapse
  - Clinical studies
  - Second transplant

Treatment of myeloma is changing so options and how we treat patients with myeloma will inevitably change!
This talk has covered...

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- Treatment options for refractory disease

Take home messages

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www.myeloma.org.uk
MUK resources signpost

- Myeloma – Your Essential Guide
- Velcade Infoguide
- Revlimid Infoguide
- Horizons Infosheets
- Clinical Trials Infoguide
- Myeloma TV
- Infoline
- ** please visit the Myeloma UK Patient Information stand in the foyer area for further information

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