National Myeloma Day
Your Immune System and Medications

Julie Adams
Managing Director and
Clinical Pharmacist
Chemo@home
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we see health differently


• I Lost my voice
• This session will now be 100% interpretive dance
#eval14
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Talk Outline

- Treatment, highlighting new agents
  - Patients suitable for transplant
  - Patients not suitable for transplant
  - Patients with relapsed disease
- Managing of medications and side effects

Treatment Decision

- Once there is a diagnosis of myeloma …. a decision between the specialist and patient about the most suitable treatment is made
- When does treatment start?
  - Symptomatic (active) disease
    - C = High Calcium Levels
    - R = Altered Kidney (Renal) Function
    - A = Anaemia (Low Haemoglobin)
    - B = Bone disease
- What to consider when deciding on which treatment to have?
  - Depends on
    - Age (chronological vs biological)
    - Performance Status (fitness)
    - Other co existing conditions e.g. diabetes, heart problems
    - Clinical presentation of disease (aggressiveness)
  - Determine suitability for High Dose Therapy (HDT) + Autologous Stem Cell Transplant (ASCT)

Patients Suitable for Transplant

- More intensive treatment option
- Starts with **Induction Therapy**
- Usually 4 “cycles” of induction therapy
- Induction therapy normally 2 to 3 drugs given together
  - Novel agent (thalidomide, lenalidomide, bortezomib)
  - Steroid (dexamethasone/prednisolone)
  - +/- Chemotherapy agent (cyclophosphamide, doxorubicin)
- Induction completed → mobilisation stem cell collection
  - Filgrastim +/- Cyclophosphamide
- After stem cell collection
  - ASCT with high dose melphalan

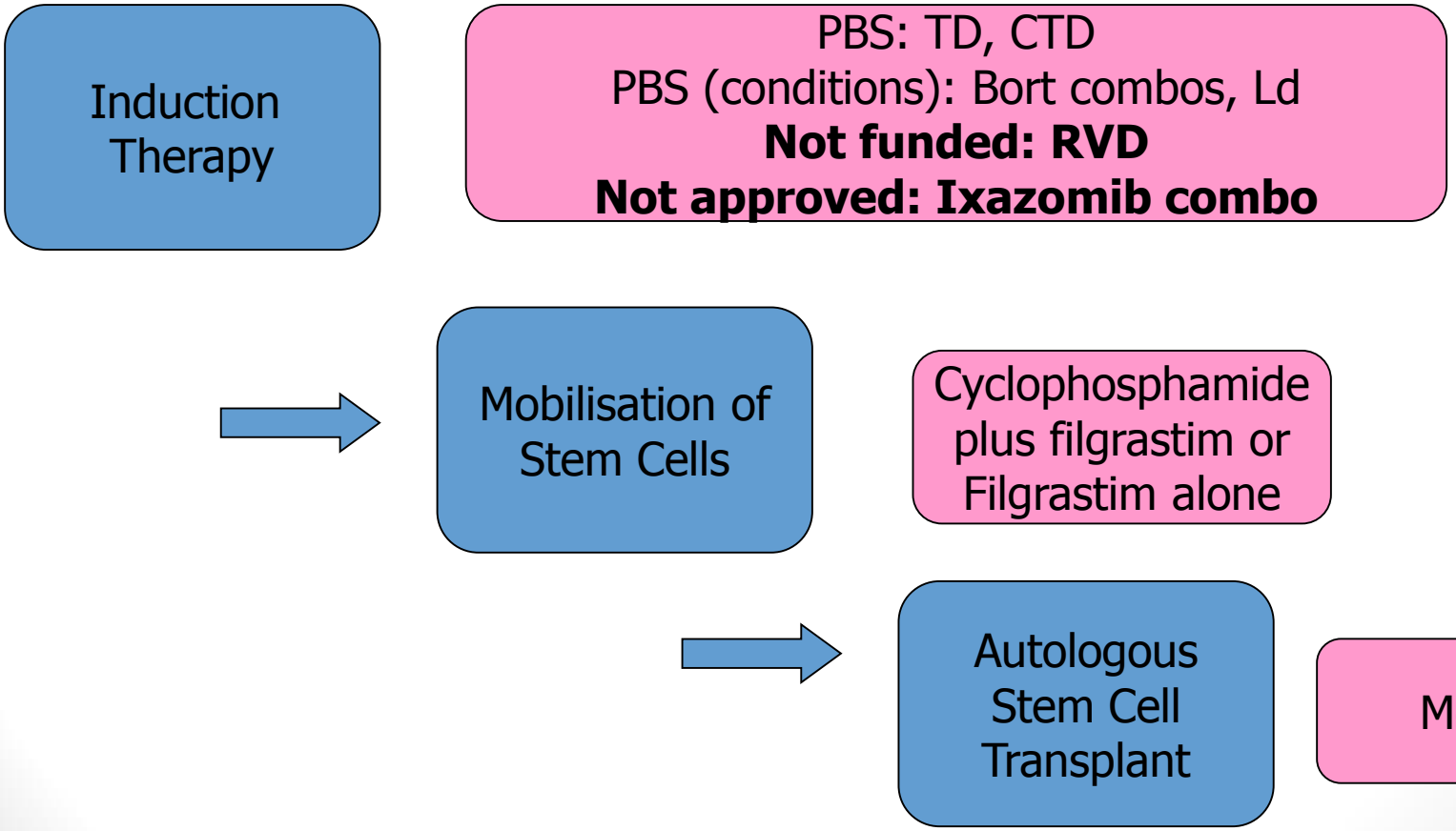
Patients suitable for transplant

- Traditional “gold standard” induction chemotherapy regimen with and without transplant
  - Chemotherapy
  - Followed by cyclophosphamide and filgrastim to mobilise stem cells
  - Then autologous stem cell transplant
    - 7 year overall survival 42% with transplant vs 27% without transplant
- Introduction of novel agents in the past decade have improved outcomes
  - Immunomodulatory Drugs
    - Thalidomide (Thalomid®)
    - Lenalidomide (Revlimid®)
  - Proteasome Inhibitor
    - Bortezomib (Velcade®)

Induction regimens for patients suitable for transplant

- **Funded** by the Pharmaceutical Benefits Scheme (PBS)
  - Thalidomide + Dexamethasone (TD)
  - Cyclophosphamide + Thalidomide + Dexamethasone (CTD)
- **Funded** by the PBS in **specific patient populations**
  - Bortezomib + Dexamethasone (Vel/Dex)
  - Bortezomib + Cyclophosphamide + Dexamethasone (CyBorD)
    - Bi weekly 1.3mg/m^2 versus weekly 1.5mg/m^2 (not PBS funded at this dose)
  - Bortezomib + Thalidomide + Dexamethasone (VTD)
- **Funded** by PBS, **after failure of first line therapy**
  - Lenalidomide + Dexamethasone (Rd)
- **Not funded** by the PBS
  - Bortezomib + Lenalidomide + Dexamethasone (RVD)
- **Not approved** by the Therapeutic Goods Administration (TGA)
  - Ixazomib + Lenalidomide + Dexamethasone

Treatment Schema for Patients Suitable for Transplant



Bortezomib, Lenalidomide and Dexamethasone (RVD)

- **PBS unfunded** (bortezomib TGA approved, lenalidomide not TGA approved for upfront therapy)
- Large trial showed improvements in response rates and survival compared with Rd
  - Response rate 71% versus 64%
  - Survival not reached versus 63 months
- **Grade 3/4 peripheral neuropathy was 24%**
  - Severe symptoms; limiting self care; assistive device indicated
  - Life-threatening consequences; urgent intervention indicated
- In context, compared with CyBorD
  - Response rates approx. 80%
  - Survival at 5 years 70%
  - Peripheral neuropathy approx. 10%

Ixazomib, Lenalidomide and Dexamethasone

- **Not TGA approved,** unfunded
- Ixazomib is an oral proteasome inhibitor (i.e.like bortezomib)
- Has shown some good results
  - Response rate 78%
  - Overall survival measurements have not been reached
- BUT with some significant toxicity
  - Grade 3 and 4 adverse effects 74%
    - Rash 36%
    - Reduced neutrophils 19%
    - Reduced platelets 19%
    - Peripheral neuropathy 27% (all grades)

Summary in Transplant Eligible Patients

- No general consensus as to the “best” upfront induction regimen with the new agents
- No much in the way of direct comparisons between treatment regimens
- Patient and disease characteristics may suggest one approach over another
- Management of toxicity with the new agents, especially peripheral neuropathy, very important
- Transplant after induction still deemed necessary (at the moment)

Patients not suitable for transplant

- For elderly patients or those who are not suitable for transplantation, melphalan and prednisolone (MP) has been a standard treatment since 1960s
  - Overall response rate of 50%

- Trials with MP-based combinations have reported improved response rates, time to progression and overall survival compared with MP
  - MP + novel agent (thalidomide, lenalidomide, bortezomib)

Regimens for patients not suitable for transplant

- **Funded** by PBS
  - Melphalan, prednisolone + thalidomide (MPT)
  - Melphalan, prednisolone + bortezomib (MPV)
  - Melphalan, prednisolone + lenalidomide (MPR)
  - Cyclophosphamide, thalidomide + dexamethasone (CTD attenuated)
  - Lenalidomide + dexamethasone (Rd)
  - Cyclophosphamide, dexamethasone and bortezomib (CyBorD)
    - Bi weekly 1.3mg/m^2 versus weekly 1.5mg/m^2 (not PBS funded at this dose)
- **Not funded** (as yet) by the PBS
  - Bortezomib + Lenalidomide + Dexamethasone (RVD)

Summary in Transplant Ineligible Patients

- In patients not suitable for transplant, the addition of a novel agent to standard MP has provided improved response rates but may come with increased toxicity
- Bortezomib may improve kidney function in patients with kidney problems at presentation…making them transplant eligble?
- Care should be taken with thalidomide and lenalidomide therapy
  - Include clot prevention
- Care should be taken with bortezomib-based regimens
  - Include herpes zoster (shingles) prophylaxis

Relapsed Disease

Options include;

- Another Autologous Transplant
- More immunotherapy
  - Thalidomide +/- Dexamethasone
  - Lenalidomide +/- Dexamethasone
  - Bortezomib +/- Dexamethsone
- Chemotherapy
  - D(+/-T)-PACE given every 21-28 days (one cycle)
    - Dexamethasone
    - (Thalidomide)
    - Cisplatin)
    - Doxorubicin (Adriamycin)) All given together by infusion
    - Cyclophosphamide)
    - Etoposide)
      - Need to give blood clot prevention if using thalidomide
      - Requires white cell growth factors and blood product support

Relapsed Disease…. Newer Agents (PBS funded or TGA approved)

- Pomalidomide (i.e. like thalidomide and lenalidomide)
  - **PBS funded**, strict criteria
  - Less peripheral neuropathy
  - Still get responses in patients who have had prior lenalidomide and bortezomib

- Panobinostat (with bortezomib and dexamethasone)
  - **Not PBS funded, but TGA approved**
  - HDAC (Histone DeACetylase) modulator
  - Slows progression of myeloma
  - Survival data from trials yet not available
  - Side effects significant!
    - Reduced platelets (67%), reduced neutrophils (34%), diarrhoea (68%, severe 35%, death), heart effects (severe, death), fatigue, peripheral neuropathy

Relapsed Disease…
Not TGA approved

- Daratumumab (monotherapy)
  - **Not TGA approved**
  - Monoclonal antibody against CD38
  - Response rate 30%
  - Survival at 1 year 65%
  - Toxicity – fatigue, nausea, decreased platelets and some mild infusion reactions

- Elotuzumab (with lenalidomide and dexamethasone)
  - **Not TGA approved**
  - Monoclonal antibody against lymphocyte activation molecule F7 (SLAMF7) which is found on the surface of myeloma cells
  - Slows progression of myeloma
  - Toxicity – decreased lymphocyte count, decreased neutrophils, fatigue, pneumonia and infusion reactions

Relapsed Disease… Not TGA approved

- Carfilzomib (i.e. like bortezomib)
  - **Not TGA approved**
  - Slows progression of myeloma (19 v 9 months)
  - BUT toxicity with hypertension, cardiac failure, shortness of breathe and decreased kidney function

- Ixazomib (i.e like bortezomib but oral)
  - **Not TGA approved**
  - With lenalidomide and dexamethasone or just dexamethasone
  - Response rates improved over Rd
  - Slows progression of myeloma
  - Adverse cytogenetics did not seem important

Summary for Relapsed Disease

- There is no one standard treatment
- Individualise treatment taking into account
  - Previous treatment
  - Duration of response (remission) with prior therapy
  - How quickly disease is progressing
  - Patient's current physical state (toxicities/comorbidities)
- Try every agent possible
- Clinical trial of new agents

Managing your Medications

- Side effects from the disease and the treatment, play an important role in quality of life.
- Proper management side effects optimises the effectiveness of the treatment.
- Doses of medication can be adjusted due to age of the patient and any side effects experienced
- Side effects depending on their severity may lead to a dose reduction, treatment interruption or delay or change of therapy.
- Main Side Effects
  - **Peripheral Neuropathy**
  - Haematological Toxicity
  - Gastrointestinal Toxicity
  - Bone Disease

Managing Side Effects Peripheral Neuropathy

- Many agents that treat myeloma can cause peripheral neuropathy (thalidomide, bortezomib)
- Damage to different types of nerves
  - Motor (movement)
  - Sensory (touch, pain)
  - Autonomic (organ function eg. gut)
- Can affect quality of life and compromise cancer treatment
- Potentially dose-limiting toxicity for patients
- Neuropathy is cumulative and may not be reversible
- Important to understand about low-risk interventions to prevent injury from irreversible peripheral nerve damage
- Information leaflets available

Managing Side Effects Peripheral Neuropathy

- Signs and symptoms of peripheral neuropathy
  - Report any signs/symptoms as soon as they are noticed
- Safety strategies
  - Careful attention while walking
  - Removal of throw rugs and clutter in and around the home
  - Use of skid-free shower and bathroom mats
  - Use of a cane or walker if needed
- Inspect hands and feet frequently for sores and blisters
  - Wear properly fitting shoes
- Lowering temperature of home water heater and using a bath thermometer to ensure that water <50°C
- Dangling legs over side of the bed before rising to prevent blood pressure drops
- Adequate fluid intake, high fiber diet can reduce urine retention and constipation

Managing Side Effects Peripheral Neuropathy

- Management
  - Change therapy, dose adjustment, decrease frequency, change of administration eg. bortezomib s/c once weekly
  - Medication
    - Pain relief
      - Regular pain relievers (eg paracetamol, oxycodone)
      - Medication used for epilepsy (eg pregabalin)
      - Medication used for depression (eg amitriptyline)
      - Lignocaine injection or topical
    - Cocoa butter or capsaicin cream
    - Amino acids
    - Magnesium

Managing your medications

- Medication lists
- Pamphlets
- Booklets
- Ask questions if you are uncertain about how to take your medication
- Tell us if you are using or taking herbal/complimentary therapies

Useful websites

- www.myeloma.org.au
- www.leukaemia.org.au
- www.eviq.org.au
  - Australian site on treatment information, good patient info
- www.australiancancertrials.gov.au
  - Australian site on clinical trials

- www.cancer.gov
  - US site (NCI), particularly good for treatment information and clinical trials
- www.bccancer.bc.ca
  - Canadian site, good patient info
- www.mskcc.org
  - US site, very good info on herbal, complementary products

"With communication comes understanding and clarity. With understanding fear diminishes. In the absence of fear, hope emerges. And in the presence of hope, anything is possible."

Ellen Stovall