ORAL MELPHALAN +/- PREDNISOLONE

INDICATION

Treatment for patients who are not candidates for autologous stem cell transplantation and who are treated with a palliative intent.

TREATMENT INTENT

Palliative

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
   - FBC & film
   - Clotting screen
   - U&Es
   - LFTs
   - Calcium
   - Albumin
   - Uric acid
   - CRP
   - Baseline random blood glucose level
   - Virology : HIV, Hepatitis B (including core antibody), and Hepatitis C
   - Calculated creatinine clearance (CrCl), urine protein/ creatinine ratio
   - Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins.
   - Serum free light chain assay (Freelite)
   - β_2 microglobulin
   - LDH
   - Myeloma FISH should be performed in all patients at diagnosis, and in selected patients at relapse/progression to help guide treatment decisions Samples should be sent to Wessex Regional Genetics Laboratory (address below)
   - Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
   - Group and save
   - Imaging as per NICE/network guidance and clinical presentation
   - Bone marrow aspirate and trephine (with immunophenotyping for kappa/lambda if appropriate)

Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust
Salisbury Disctrict Hospital
Salisbury
Wiltshire
SP2 8BJ

Additional Investigations
- Plasma viscosity if hyperviscosity suspected

2. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given.
3. Fertility - all patients should be offered fertility advice, as appropriate.
4. Hydration - fluid intake of at least 3 litres /day should be attempted.
5. Document patient's height and weight, dose on actual body weight.
6. Document patient's performance status.
7. Treatment must be agreed at the relevant MDT.

DRUG REGIMEN

Melphalan	7 mg/m^2 po daily (tablets are 2 mg in strength)	Days 1 to 4
	WITH OR WITHOUT	
Prednisolone	20-60 mg po daily NB: Dose reduction may be necessary in the elderly.	For 5 days

CYCLE FREQUENCY

Every 4-6 weeks until plateau phase (paraprotein level stable for 3 months) then stop.

DOSE MODIFICATIONS

Haematological toxicity:
- Neutrophil count should be > 1.0 x 10^9/L and platelet count should be > 75 x 10^9/L before starting treatment unless low counts are thought to be disease related.
- The dose should be reduced if Grade 3 or 4 myelotoxicity occurs, alternatively consider changing to cyclophosphamide.
- If the nadir neutrophil count is > 1.5 and nadir platelets > 100, consideration may be given to a cautious *increase* in dose for subsequent cycles.

Renal/Hepatic Impairment

Melphalan**:**

Renal	Hepatic
SPC for oral melphalan states that In patients with moderate to severe renal impairment currently available pharmacokinetic data do not justify an absolute recommendation on dosage reduction when administering the oral preparation to these patients, but it may be prudent to use a reduced dose initially.. In myeloma patients with renal damage, temporary but significant increases in blood urea levels have been observed during melphalan therapy.	No recommendations. If excess toxicity, consider dose reduction on subsequent cycles

INVESTIGATIONS - First and Subsequent Cycles

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC.
- U&Es, LFTs, Creatinine, glucose, Ca^{++}.
- Alternate cycles Ig's, paraprotein.
- 24 hr urine for Bence Jones protein and / or Freelite assay at alternate cycles in light chain myeloma.
- Consider bone marrow assessment after four cycles for non-secretory myeloma.
- Consider blood glucose monitoring in patients with diabetes and those with signs of glucose intolerance

CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 7 days for cycle 1 only
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min)
- Consider prophylactic fluconazole 50mg OD if steroid related side effects.
- Consider prophylactic co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.
- Consider prophylactic levofloxaxin 500mg od for 12 weeks, if treating a newly diagnosed patient.
- Proton pump inhibitor or H2 antagonist at clinician's discretion.
- Bone protection as per NSSG Bone Protection protocol MM.3

EMETIC RISK

Low-moderate emetic risk

ADVERSE EFFECTS/ REGIMEN SPECIFIC COMPLICATIONS

Myelosuppression, nausea, vomiting and diarrhea, stomatitis, alopecia. Temporary significant elevation of the blood urea has been seen in the early stages of melphalan therapy in myeloma patients with renal damage

REFERENCES

1. Bird J M, Owen R G, D'Sa S, , et all on behalf of the Haemato- oncology Task Force of the British Committee for Standards in Haematology (BCSH), UK Myeloma Forum. 2014. Internet. Guidelines for management and diagnosis of multiple myeloma. Online. Available at: http://www.bcshguidelines.com/documents/MYELOMA_GUIDELINE_Feb_2014_for_BCSH.pdf (last accessed on 27/6/16).
2. Melphalan 2mg tabs eMC UK Summary of Product Characteristics , Aspen, March 2014

REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche, Pharmacist	Cycle frequency section updated, dose modifications, reference section	May 2016	4.3	May 2018
Manuela Sultanova Service Coordinator	Formatting, Standardisation of General pre-assessment section and correction of Wessex lab address	August 2017	4.4	May 2018
Network Protocol Review	Treatment intent. Emetic risk Standardisation of assessment, investigations, supports, formatting, Melphalan renal dosing. Adverse events	June 2018	4.5	June 2020
NSSG Myeloma Group	Annual protocol review, update to renal impairment section, concurrent medication	June 2022	4.6	June 2023