INTERMEDIATE DOSE MELPHALAN WITH DEXAMETHASONE

INDICATION

Relapsed/ Refractory myeloma. AL amyloidosis where autograft is not an option.

TREATMENT INTENT

Disease modification

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
   - FBC & film
   - Clotting screen
   - U&Es
   - LFTs
   - Calcium
   - Albumin
   - Uric acid
   - CRP
   - 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
   - Formal assessment of performance status (WHO score)
   - 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.
- If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology

2. Consent - ensure patient has received adequate verbal and written information regarding their

disease, treatment and potential side effects. Document in medical notes all the information that has been given. Obtain written consent for the treatment.

3. Hydration - fluid intake of at least 3 litres /day should be attempted.
4. Document patient's height and weight, dose on actual body weight.
5. Document patient's performance status
6. Treatment must be agreed at the relevant MDT.

REGIMEN SPECIFIC PRE -ASSESSMENT

For amyloid patients Mayo staging for AL amyloid patients and Consider NAC review

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DRUG REGIMEN/ CYCLE FREQUENCY

Melphalan	25 mg/m^2 on Day 1 IV	In 100 mL 0.9% sodium chloride infusion over 30 minutes
	WITH	
Dexamethasone	40 mg PO daily on days 1 to 4 NB: The dose may need to be reduced on cycle 1 or subsequent cycles in the elderly or if steroid-related side effects develop.	

Intravenous melphalan at this dose can be safely administered as an outpatient without intravenous fluid hydration. Please ensure patient is well hydrated prior to start of therapy. Cycle length is 28 days. Number of cycles is usually 2-4.

DOSE MODIFICATIONS

Myelosuppression:

Intermediate dose melphalan therapy is associated with significant myelosuppression. Consider G-CSF support in patients developing Grade 3 - 4 neutropenia.

Recommended dose adjustments during treatment and to restart treatment: Next cycle should not commence until neutrophils are > 1 x 10^9/L and platelets > 75 x 10^9/L. If count recovery is delayed beyond 28 days, patients should receive G-CSF for 7 days from day 5 of the next cycle. Consider early G-CSF for count recovery if BM is heavily infiltrated with multiple myeloma or cytopenias before commencing chemotherapy.

Melphalan

Renal	Hepatic
GFR 10 – 50mL/min 75% dose GFR < 10 mL/min clinical decision 25mg/m^2 dose in dialysis dependent patients has proven efficacy without significant toxicity	No recommendations. If excess toxicity, consider dose reduction on subsequent cycles

INVESTIGATIONS - Pre-treatment and during treatment:

- Ensure all staging investigations (as listed under the PRE-ASSESSMENT heading above) are done. Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC & U&E's – consider fortnightly for first cycle, then monthly.
- Ca^{++}, LFTs – monthly.
- Ig's, paraprotein, urinary BJP and serum free light chain levels in patients with light chain disease - monthly.
- Random blood glucose/ blood sugar

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)
- Proton pump inhibitor or H2 antagonist at clinician's discretion
- Prophylactic fluconazole
- Bone protection as per NSSG Bone Protection protocol MM.3
    - Consider prophylactic co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.

EXTRAVASATION RISK

Melphalan- neutral

EMETIC RISK

Moderate emetic risk.

ADVERSE EFFECTS/REGIEMN SPECIFIC COMPLICATIONS

Gastrointestinal toxicity: Patients could develop nausea or diarrhoea with intravenous melphalan. Regular anti-emetic therapy and occasionally use of anti-motility drugs could be considered.

Mucositis, hair loss.

TREATMENT RELATED MORTALITY

<10% - for Myeloma, Amyloidosis (patient/stage as per MAYO specific)

REFERENCES

1. Schey SA, Kazmi M, Ireland R, Lakhani A. The use of intravenous intermediate dose melphalan and dexamethasone as induction treatment in the management of de novo multiple myeloma. Eur J Haematol. 1998 Nov;61(5):306-10.
2. Petrucci MT, Avvisati G, Tribalto M, Cantonetti M, Giovangrossi P, Mandelli F. Intermediate-dose (25 mg/m2) intravenous melphalan for patients with multiple myeloma in relapse or refractory to standard treatment. Eur J Haematol. 1989 Mar;42(3):233-7.
3 Vigneau C, Ardiet C, Bret M, Laville M, Fiere D, Tranchand B, Fouque D. Intermediate-dose (25 mg/m2) IV melphalan for multiple myeloma with renal failure. J Nephrol. 2002 Nov-Dec;15(6):684-9.
4 eMC UK Summary of Product Characteristics for Melphalan 50mg injection, Aspen, Dec 2014

REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche Pharmacist	Formatting, dose modification section, adverse effects and pre assessment section reviewed, gastrointestinal toxicity	May 2016	2.3	May 2018
Faouzi Djebbari (Haematology Pharmacist)	Updated drug regimen, concurrent medication, and references	July 2017	2.4	June 2019
Myeloma Protocol Review 2019	Updated general pre-assessment, dose modifications, concurrent medications, and extravasation risk	June 2019	2.5	June 2020