9.9 Thalidomide +/- pulsed dexamethasone

**Indications**

- **Relapsed and refractory myeloma:**
  
  Efficacy of Thalidomide as a single agent was first reported by Barlogie and colleagues in 1999 (1) in which 84 patients with relapsed and refractory myeloma received Thalidomide and attained a response rate of 32%. Similar findings in smaller series of patients have been reported by others. The optimal dose of Thalidomide has yet to be defined. It has been suggested that there is evidence of a dose-response effect (2). In contrast, other investigators have observed similar response rates with doses varying from 50-200 mg per day (3,4).

  Several studies in patients with relapsed or refractory disease have suggested that Thalidomide and Dexamethasone show synergistic activity with responses in patients displaying resistance to either agent alone (5).

- **Newly diagnosed patients:**
  
  Rajkumar et al from the Mayo Clinic have reported on the first 50 patients with active myeloma treated with Thalidomide and Dexamethasone (6). The observed PR rate was 64% which is comparable to VAD-like regimens. Venous thromboembolism was seen in 10% of patients, a significantly higher incidence than that generally observed with this regime in patients with relapsed disease and this observation has been supported by other studies. Randomised studies of Thalidomide as part of induction therapy are now underway.

For more detail of mechanism of action, results of clinical studies of Thalidomide in combination with other agents, Thalidomide analogues please consult UKMF/BCSH position paper ‘Thalidomide in multiple myeloma: current status and future prospects’ to be published soon on the UKMF website.


- **Pre-treatment Evaluation**

  - Document FBC (with film), plasma viscosity, U&E, creatinine, LFTs, calcium, glucose, serum protein electrophoresis and paraprotein quantitation, CRP, β₂-microglobulin and immunoglobulin levels.
  - Urine for BJP (and formal evaluation of 24 hour urinary BJP excretion if light chain only myeloma).
  - Baseline serum free light chain profile if BJP or non-secretory myeloma.
  - Bone marrow aspirate ± trephine (and cytogenetics if part of local protocol).
  - Skeletal survey.
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- Document height and weight and surface area.
- Give adequate verbal and written information for patients and relatives concerning patient’s disease, treatment strategy and side effects.
- Obtain written consent from patient or guardian.

### Drug Regimen

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<tr>
<th>Days</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Comments</th>
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<tr>
<td>Daily</td>
<td>Thalidomide</td>
<td>50-400mg/ day</td>
<td>PO</td>
<td>Start dose at 50mg daily and increase dose weekly in 50mg increments. (Normal max 200mg daily)</td>
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### Cycle Frequency

Continuously until relapse or significant side effects.

### Dose Modifications

Gradual escalation of dose until maximum dose tolerated by patient.

### Regular Investigations

- FBC, U&E, creatinine, LFTs, paraprotein level or urinary protein/BJP excretion/serum free light chain profile, plasma viscosity.

### Concurrent Medication

- Dexamethasone (if used) 20-40mg daily for 4 days every 2-4 weeks. Reduced side-effects are seen with 20mg dose.
- $H_2$-antagonist or PPI is advised for patients receiving Dexamethasone.
- Allopurinol 300mg (or 100mg if creatinine clearance <20mls/min) od po during the first two treatment cycles.
- Encourage 3l/24hrs oral fluid intake.
- Thromboprophylaxis should be considered. Low dose aspirin is recommended for low risk patients, and low molecular weight heparin or formal anticoagulation with warfarin is recommended for high risk patients.
- Bisphosphonates (Sodium Clodronate PO or Pamidronate IV or Zolendronate IV).

### Possible Side Effects

All patients should receive both verbal and written information about the side-effects of Thalidomide particularly those relating to its teratogenic potential.

- **Birth defects particularly phocomelia:**
  - All females of child-bearing potential who are candidates for Thalidomide therapy will be required to undergo pregnancy
testing before starting treatment and regularly thereafter and to use 2 methods of contraception.

– Men must be counselled to use barrier contraception if their partner is of child-bearing age since it is not known whether Thalidomide is present in semen.
– Patients must be clearly instructed to store the drug in a secure place and to return any unused drug to the hospital pharmacy.

• Sedation: The degree of sedation appears to decrease with continued administration at a constant dose and can be minimised by taking the drug in the evening. If the drug is taken approximately 3-4 hours before going to bed, then any ‘hang-over’ effect is minimised for the following morning.

• Constipation: This can be a significant problem particularly when doses over 400mg are taken. The use of extra dietary fibre and laxatives can usually overcome this problem.

• Peripheral neuropathy: This is a major potential problem since neuropathy can be irreversible if the drug is not promptly withdrawn. It is imperative that patients are monitored closely, especially during the first few months of therapy. Patients must know that they should stop the drug if significant numbness or paraesthesiae occur. It is recommended that nerve conduction studies be performed prior to commencing Thalidomide and should be repeated if necessary. However, for the patient who requires therapy, treatment should not be delayed if NCS cannot be performed immediately.

• Neutropenia: This has been reported as a rare side-effect.

• Hypothyroidism: One study has suggested that patients treated with Thalidomide are at increased risk of developing biochemical and clinical hypothyroidism (7).

• References

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