Multiple Myeloma

3.14 Protocol Name: **Bortezomib +/- dexamethasone**

**Indication**

- Second line treatment of relapsed or refractory myeloma (as recommended by NICE guidance).

- Relapsed or refractory myeloma, heavily pre-treated or with no/limited other treatment options (OUTSIDE NICE guidance therefore requiring an individual funding application)

**NICE Guidance:**

Bortezomib (a proteosome inhibitor) monotherapy is recommended as an option for the treatment of progressive multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation, under the following circumstances:

- The response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in people who have a complete or partial response (that is, reduction in serum M protein of 50% or more or, where serum M protein is not measurable, an appropriate alternative biochemical measure of response) **and**

- The manufacturer rebates the full cost of bortezomib for people who, after a maximum of four cycles of treatment, have less than a partial response (as defined above).

**Bortezomib + Dexamethasone**

The manufacturers of bortezomib have not sought a specific licence for the combination of bortezomib with dexamethasone and therefore no submission was made to NICE for evidence to approve this combination specifically. Nevertheless there is an overwhelming body of evidence that the addition of dexamethasone to bortezomib enhances the response to this treatment, in the setting of relapsed and refractory MM as well as in newly diagnosed patients (reviewed by Manochakian et al, 2007, The oncologist). The NICE recommendation is not meant to discourage the use of dexamethasone in combination with bortezomib and should not invalidate the terms of the VRS (velcade response scheme)
Pre-treatment Evaluation

- Document FBC (with film), plasma viscosity, U&E, creatinine, LFTs, calcium, glucose, serum free light chain measurements, serum protein electrophoresis and paraprotein quantitation, serum-free light chain levels, CRP, β₂-microglobulin and immunoglobulin levels.
- Urine for BJP (and formal evaluation of 24 hour urinary BJP excretion if light chain only myeloma).
- Bone marrow aspirate ± trephine (and cytogenetics if part of local protocol).
- Skeletal survey.
- Document height and weight and surface area.
- Consider ECG ± echocardiogram if clinical suspicion of cardiac dysfunction.
- 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**  
(OPCS code: X71.5)

<table>
<thead>
<tr>
<th>Days</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1, D4, D8, D11</td>
<td>Bortezomib</td>
<td>1.3mg/m2</td>
<td>IV</td>
<td>Bolus over 3-5 seconds</td>
<td>Peripheral or central line. Flush with NaCl 0.9% after dose.</td>
</tr>
<tr>
<td>D1-2 D4-5 D8-9 D11-12</td>
<td>Dexamethasone</td>
<td>20mg</td>
<td>P.O.</td>
<td>In the morning</td>
<td></td>
</tr>
</tbody>
</table>

**Considerations**

Close monitoring of diabetic control

**Cycle Frequency**

- Repeat every 21 days.
Dose Modification

Haematological dose reductions:
- Withhold Bortezomib in the event of any Grade 4 haematological toxicities.
  Neutrophils < 0.5 x 10^9/l
  Platelets < 25 x 10^9/l
- Monitor Neutrophils and Platelets before each dose
  Platelets must be ≥ 75 x 10^9/l at Day 1 of each cycle.
- At any stage, withhold the dose until counts recover to:
  Neutrophils ≥ 1.0 x 10^9/l and
  Platelets ≥ 25 x 10^9/l before resuming treatment.
- Treatment should be re-initiated at 75% of full dose i.e.:
  1.3mg/m^2 reduced to 1.0mg/m^2
  1.0mg/m^2 reduced to 0.7mg/m^2.
- Consider extending the interval between doses as another way of dose modifying i.e. give a dose ONCE A WEEK FOR 4 WEEKS THEN BREAK FOR ONE WEEK.
- Consider growth factors if treatment delays are prolonged or frequent.
- This regime is not associated with increased risk of VTE

Neurological:

<table>
<thead>
<tr>
<th>Severity of Peripheral Neuropathy</th>
<th>Modification of dose &amp; regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (parasthesia &amp;/or loss of reflexes) with no pain or loss of function</td>
<td>No action</td>
</tr>
<tr>
<td>Grade 1 with pain, or Grade 2 (interfering with function but no activities of daily living)</td>
<td>Reduce to 1.0mg/m^2</td>
</tr>
<tr>
<td>Grade 2 with pain, or Grade 3 (interfering with activities of daily living)</td>
<td>Withhold treatment until symptoms resolve, then re-initiate at 0.7mg/m^2 ONCE a week</td>
</tr>
</tbody>
</table>
Renal impairment:
Monitor closely since increased incidence of adverse effects are seen with even mild to moderate renal impairment. Consider dose reduction if there is renal impairment, especially if creatinine clearance $\leq 30\text{ml/min}$.

Hepatic Impairment:
Use only with extreme caution since Bortezomib clearance is mainly via hepatic metabolism. Consider dose reduction.

Other toxicity:
Withhold bortezomib dose in the event of any Grade 3 or 4 non-haematological toxicities.

Investigations prior to subsequent cycles
- FBC, U & E, creatinine, LFTs, calcium, paraprotein level or urinary protein/BJP excretion, plasma viscosity
- Assess disease response after 2 cycles and again after 4 cycles.

Treatment Duration
- Review response after 4 cycles and only continue if > partial response achieved.
- It is recommended that patients with a confirmed complete response receive an additional 2 cycles beyond this, up to a total of 8 cycles.

Concurrent Medication
- Routine mouth care – refer to local protocol.
- Consider Allopurinol 300mg (or 100mg if creatinine clearance <20mls/min) od po during the first month.
- Consider oral systemic antibiotic, anti-viral and/or anti-fungal prophylaxis if patient is neutropenic - refer to local protocol.
- H$_2$-antagonist or PPI is recommended if dexamethasone is given, for at least the first 7 days of each cycle.
- Bisphosphonates.
- Loperamide – as per WLCN Diarrhoea Guidelines, if chemotherapy induced diarrhoea occurs, 4mg stat then 2mg every 4 hours until stool is formed, medical review at 24-48 hours.
- Avoid live vaccines
Anti-emetics
This regimen has low emetic potential - refer to local protocol.

Adverse Effects
See patient information or SPC, includes thrombocytopenia – rapid recovery, peripheral neuropathy, orthostatic postural hypotension, N&V, diarrhoea, constipation, rash.

References
http://theoncologist.alphamedpress.org/cgi/reprint/12/8/978


Bortezomib SPC

Patient Information


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