NECN CHEMOTHERAPY HANDBOOK PROTOCOL
Bendamustine for Non Hodgkins Lymphoma

DRUG ADMINISTRATION SCHEDULE

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ondansetron</td>
<td>8mg</td>
<td>IV Bolus</td>
<td>Via Sodium Chloride 0.9% Drip</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
<td>8mg</td>
<td>IV Bolus</td>
<td>Via Sodium Chloride 0.9% Drip</td>
<td>Over &gt;2 mins</td>
</tr>
<tr>
<td></td>
<td>Bendamustine</td>
<td>120mg/m²</td>
<td>IV Infusion</td>
<td>500ml 0.9% Sodium Chloride</td>
<td>60 minutes</td>
</tr>
<tr>
<td>2</td>
<td>Pre-med not required if taking oral anti-emetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bendamustine</td>
<td>120mg/m²</td>
<td>IV Infusion</td>
<td>500ml 0.9% Sodium Chloride</td>
<td>60 minutes</td>
</tr>
</tbody>
</table>

WARNING THERE ARE TWO BENDAMUSTINE PROTOCOLS WITH DIFFERENT DOSES – THIS IS FOR NHL
In NHL a higher dose (120mg/m²) is given more frequently = 21 day cycle

CYCLE LENGTH AND NUMBER OF DAYS
21 Day cycle, Total 6 to 8 cycles depending on response and toxicity

APPROVED INDICATIONS
Indolent Non Hodgkin’s Lymphomas (NHL) as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or rituximab containing regimens.

ELIGIABILITY CRITERIA
• As above

EXCLUSION CRITERIA
• Pregnancy / Breast Feeding

EXTRAVASATION
An extravasal injection should be stopped immediately. The needle should be removed after a short aspiration. Thereafter the affected area of tissue should be cooled. The arm should be elevated. Additional treatments like the use of corticosteroids are not of clear benefit.

RECOMMENDED TAKE HOME MEDICATION
Metoclopramide 10mg Three Times Daily on days 1 to 5.
Dexamethasone 8mg Once daily for 3 days (starting morning of day 2)
Ondansetron 8mg Twice Daily for 3 days (starting evening of day 1)
Consider addition of Allopurinol to the first cycle of treatment.
INVESTIGATIONS / MONITORING REQUIRED

Prior to first cycle: FBC, U&Es, LFTs, LDH, bone profile, DCT, bone marrow
Prior to each cycle:  FBC, U&Es, LFT, bone profile

ASSESSMENT OF RESPONSE

Haematological response
Palpable disease
B symptoms

REVIEW BY CLINICIAN

Prior to each cycle (unless being seen by a nurse / pharmacist – see below)

NURSE / PHARMACIST LED REVIEW

Nurse or pharmacist led review, within a locally agreed protocol, is acceptable on day 1 for all cycles except the first, and middle cycle.

ADMINISTRATION NOTES

• Bendamustine metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme
  Therefore, the potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir and cimetidine exists.
• Infusion reactions to bendamustine hydrochloride have occurred commonly in clinical trials. Symptoms are generally mild and include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred. Patients must be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids must be considered in subsequent cycles in patients who have previously experienced infusion reactions.
• May cause tumour lysis syndrome in susceptible patients
• Serum potassium must be monitored in all patients with cardiac disorders and potassium supplement must be given when K+ <3.5 mEq/l, and ECG measurement must be performed

TOXICITIES

• Myelosuppression
• Fatigue
• Leukopenia,
• Thrombopenia
• Dermatologic toxicities
• Allergic reactions (see above)
• Fever
• Nausea and vomiting

DOSE MODIFICATION / TREATMENT DELAYS

Haematological Toxicity:
(Note: where haematological disease is affecting bone marrow function, lower treatment parameters may be acceptable. This should be clearly documented for the specific patient.)
Delay treatment on Day 1 if ANC < 1.5 x 10^9 cells/l or PLT < 100 x 10^9 cells/l

If treatment is delayed for more than 14 days:

<table>
<thead>
<tr>
<th>ANC</th>
<th>PLT</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 - 1.5</td>
<td>50 - 100</td>
<td>50%</td>
</tr>
</tbody>
</table>

Renal Function:
It does not appear to be necessary to modify the dose of Bendamustine for renal impairment with CrCl > 10ml/min. Recommendation for patients less than 10ml/min is currently not possible.

Hepatic Function:
Clearance of bendamustine correlates with serum bilirubin levels.

<table>
<thead>
<tr>
<th>Bilirubin</th>
<th>Bendamustine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 21 µmol/l</td>
<td>100% Dose</td>
</tr>
<tr>
<td>21 – 51 µmol/l</td>
<td>70% Dose</td>
</tr>
<tr>
<td>&gt; 51 µmol/l</td>
<td>Possibly contra-indicated</td>
</tr>
</tbody>
</table>

TREATMENT LOCATION
Suitable for self administration in patients own homes, under the supervision of haematology teams from Level 1 – 4 Haematology Services.

REFERENCES:
- Kahl B, Bartlett NL, Leonard JP. Bendamustine is effective therapy in patients with Rituximab refractory indolent B cell non Hodgkins Lymphoma, Cancer 116 2010 106-14
- Freidberg JW, Cohen P, Ling Chen K et al Bendamustine in patients with Rituximab refractory, indolent and transformed NHL. Results from multicentre phase II single agent study J Clin Oncology 26 (2) 200 204-210