## 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>Paracetamol</td>
<td>1gram</td>
<td>Oral</td>
<td></td>
<td>Once Only</td>
</tr>
<tr>
<td></td>
<td>Chlorphenamine</td>
<td>10mg</td>
<td>IV bolus</td>
<td>via 0.9% Sodium Chloride Drip</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone</td>
<td>100mg</td>
<td>IV bolus</td>
<td>via 0.9% Sodium Chloride Drip</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Rituximab</strong></td>
<td>375mg/m²</td>
<td>IV infusion</td>
<td><strong>250ml 0.9% Sodium Chloride</strong></td>
<td>See below</td>
</tr>
<tr>
<td></td>
<td><strong>Bendamustine</strong></td>
<td>90mg/m²</td>
<td>IV Infusion</td>
<td>500ml 0.9% Sodium Chloride</td>
<td>60 minutes</td>
</tr>
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**Pre-med not required if taking oral anti-emetics**

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**Bendamustine** 90mg/m² IV Infusion 500ml 0.9% Sodium Chloride 60 minutes

**Some centres may supply rituximab in 500ml on the first cycle to make the infusion rates easier to work with.**

### WARNING – Bendamustine doses and frequency vary according to protocol and when given in combination with rituximab

### CYCLE LENGTH AND NUMBER OF DAYS

28 Day cycle, Total 6 cycles depending on response and toxicity

### APPROVED INDICATIONS

Indolent Non Hodgkin’s Lymphomas (NHL) as in patients who have progressed longer than 6 months following treatment with rituximab or rituximab containing regimens.

Induction treatment for indolent NHLs where patients are unable to tolerate standard treatment with R-CVP

### 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
- Risk of hypersensitivity and anaphylaxis – particularly during the first cycle for the first two hours of administration. Monitor patient every 15 minutes for first hour then every 30minutes. Symptoms usually resolve with interruption of rituximab and administration of antipyretic and antihistamines. Some patients will require oxygen, intravenous fluids (0.9% Sodium Chloride), bronchodilators (e.g. nebulised salbutamol), and glucocorticoids (e.g. IV hydrocortisone).
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- Risk of severe hypersensitivity (cytokine release syndrome) increases when Peripheral Lymphocytes > 25 cells x10^9/l – treatment should only proceed with caution in this setting. Reducing the infusion rate or using a different therapy first line may be appropriate.
- Rituximab Infusion Rates:
  - First cycle of rituximab should commence at 50mg/hour and increase in rate by 50mg/hour every 30 minutes (to a maximum of 400mg/hour) provided the patient does not develop any signs of infusion reaction.
  - Subsequent cycles (provided the previous cycle has been tolerated well) can start at 100mg/hour and increase by 100mg/hour every 30 minutes to a maximum of 400mg/hour. (Rapid infusion – see below)
  - The infusion rate can be calculated by:
    \[ \text{Infusion Rate (ml/hour)} = \frac{\text{Infusion Volume (ml)} \times \text{Rate (mg/hour)}}{\text{Total Dose (mg)}} \]
  - Blood Pressure, Pulse and Respiration rate should be measured every 15 minutes for the first hour of infusion, and then every 30 minutes subsequently.
  - Rapid Infusion: a few small studies have demonstrated that it is possible to give rituximab at a faster rate for the second or third cycle. This practice is unlicensed and clinicians wishing to follow this practice should check with their own trust prior to adopting this practice. The unlicensed nature of the infusion rate should be explained to patients at the time of consent.
  - The rapid infusion rate used is 20% of the dose over 30 minutes (100ml/hour), followed by the remaining 80% over just 60 minutes (200ml/hour). Rapid infusion should only be considered for patients who have shown no signs of adverse reaction during previous infusions, and is contra-indicated in patients with high tumour bulk/burden or with high circulating lymphocyte counts.

TOXICITIES
- Myelosuppression
- Fatigue
- Leukopenia,
- Thrombopenia
- Dermatologic toxicities
- Allergic reactions (see above)
- Fever
- Nausea and vomiting
- Hypersensitivity Reactions, Lethargy

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
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If treatment is delayed for more than 14 days:

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<tr>
<th>ANC</th>
<th>PLT</th>
<th>Bendamustine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 -1.5</td>
<td>50 - 100</td>
<td>50%</td>
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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>
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<tr>
<td>&lt; 21μmol/l</td>
<td>100% Dose</td>
</tr>
<tr>
<td>21 – 51μmol/l</td>
<td>70% Dose</td>
</tr>
<tr>
<td>&gt; 51μmol/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 1162010 106-14
- Freidberg JW, Cohen P, Ling Chen K et al. Bendamustine in patients with Rituximab refractory, indolent and transformed NHL. Results from a multicentre phase II single agent study J Clin Oncology 26 (2)200 204-210

Document Control

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<tr>
<td>Author:</td>
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<td>Approved by:</td>
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<tr>
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