Chemotherapy Protocol

LYMPHOMA

BENDAMUSTINE

There are multiple versions of this protocol in use. Please ensure you have the correct protocol for the relevant diagnosis.

Regimen

- Lymphoma – Bendamustine

Indication

- Indolent Non-Hodgkin Lymphoma where the disease has progressed during or within six months of rituximab based therapy

Toxicity

Drug	Adverse Effect
Bendamustine	Transfusion related GVHD, Gastro-intestinal disturbances, fatigue, insomnia, cardiac dysfunction, hypotension/hypertension, hypersensitivity reactions, hypokalaemia.

Patients treated with bendamustine carry a lifelong risk of transfusion associated graft versus host disease (TA-GVHD). Where blood products are required these patients must receive only irradiated blood products for life. Local blood transfusion departments must be notified as soon as the decision to treat is made and the patient must be issued with an alert card to carry with them at all times.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- FBC, LFTs and U&Es prior to day one of treatment
- Ensure close monitoring of potassium levels in patients with pre-existing cardiac disorders

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and some drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent. Low counts can be a consequence of bone marrow infiltration as well as drug toxicity.

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL. **Irradiated blood products must be used.**

Neutrophils ($x10^9$/L)	**Dose Modifications**
More than 1.5	100%
0.5-1.5	Delay until recovery and then give 100%
Less than 0.5 or febrile neutropenia	1st occurrence - delay until recovery and give 75% of the original dose 2nd occurrence - delay until recovery and give 50% of the original dose
Platelets ($x10^9$/L)	**Dose Modifications**
More than 100	100%
25-100	Delay until recovery and give 100%
less than 25 or bleeding	1st occurrence - delay until recovery and give 75% of the original dose 2nd occurrence - delay until recovery and give 50% of the original dose

Hepatic Impairment

Drug	**Bilirubin (µmol/L)**	**Dose (% of original dose)**
Bendamustine	less than 21	100%
	21-51	70%
	more than 51	no information

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Bendamustine	more than 10	100%
	10 or less	no information

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

In general for all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 2 or below. The dose should then be reduced to 75% of the original dose. If toxicity recurs' delay until recovery and further dose reduce to 50% of the original dose or discontinue as appropriate.

Skin

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis have been reported in patients who received bendamustine and allopurinol simultaneously. If patients experience any skin reactions during treatment, they should be monitored closely and, in the case of any suspicion of the skin reaction evolving to a serious muco-cutaneous reaction, treatment with bendamustine should be withheld until complete resolution of the event or discontinued. Other potential causes of skin toxicity should be evaluated and suspected agents discontinued accordingly.

Infusion Reactions

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, paracetamol and corticosteroids must be considered in subsequent cycles in patients who have previously experienced infusion related reactions.

Regimen

21 day cycle for 6 cycles

Drug	Dose	Days	Administration
Bendamustine	120mg/m^2	1 and 2	Intravenous infusion in sodium chloride 0.9% 500ml over 30 minutes

Consider initiating treatment with lower doses in elderly, frail or heavily pre-treated patients.

Dose Information

- Bendamustine will be dose banded according to the nationally agreed bands (2.5mg/ml)

Administration Information

Extravasation

- Bendamustine – vesicant

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy – Day 1

  - ondansetron 8mg oral or intravenous

  As take home medication – Day 1

  - metoclopramide 10mg three times a day when required oral
  - ondansetron 8mg twice a day oral for 3 days

  On day 2 please ensure the patient has taken the ondansetron at home

- Patients at high risk of tumour lysis syndrome (TLS) should be started on allopurinol 300mg once a day for 14 days. The course should be kept as short as possible to reduce the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with concomitant bendamustine and allopurinol use. Allopurinol should not be used where the risk of TLS is deemed low.

- Mouthwashes according to local or national policy on the treatment of mucositis

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- Bendamustine metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme. Therefore, the potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, aciclovir and cimetidine exists.

Coding (OPCS 4.6)

- Procurement – X71.2

- Delivery – X72.2 & X72.4

References
1.Friedberg JW, Cohen P, Chen L et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. J Clin Oncol 2008;26(2):204-10.
2.Kahl BS, Bartlett NL, Leonard JP et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a Multicenter Study. Cancer. 2010;116(1):106-14.
3.Summary of Product Characteristics; Levact 2.5mg/ml powder for concentrate for solution for infusion, Napp Pharmaceuticals Ltd., 3rd August 2010.

REGIMEN SUMMARY

Bendamustine

Cycle 1 Day One

1. Warning – Check blood transfusion status
   Administration Instructions
   Patients treated with bendamustine carry a lifelong risk of transfusion associated graft versus host disease.
   Where blood products are required these patients must receive ONLY IRRADIATED BLOOD PRODUCTS for life.
   Ensure transfusion departments are notified and the patient has been issued with an alert card to carry with them at all times.

2. Ondansetron 8mg oral or intravenous

3. Bendamustine 120mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes

Take home medicines

4. Metoclopramide 10mg three times a day when required oral

5. Ondansetron 8mg twice a day oral for 3 days starting on the evening of day one of treatment

Cycle 1 Day Two

1. Warning – Check supportive medication taken
   Administration Instructions
   Please ensure that the patient has taken ondansetron 8mg oral on the morning of treatment. If not please administer ondansetron 8mg oral or intravenous bolus 15-30 minutes prior to chemotherapy.

2. Bendamustine 120mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes

Cycles 2, 3, 4, 5 and 6 Day One

1. Ondansetron 8mg oral or intravenous

2. Bendamustine 120mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes

Take home medicines

3. Metoclopramide 10mg three times a day when required oral

4. Ondansetron 8mg twice a day oral for 3 days starting on the evening of day one of treatment

Cycles 2, 3, 4, 5 and 6 Day Two

1. Warning – Check supportive medication taken
   Administration Instructions
   Please ensure that the patient has taken ondansetron 8mg oral on the morning of treatment. If not please administer ondansetron 8mg oral or intravenous bolus 15-30 minutes prior to chemotherapy.

2. Bendamustine 120mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.4	July 2018	May require funding removed Dose banding statement change to national dose bands	Donna Kimber Pharmacy Technician	Dr Deborah Wright Pharmacist
1.3	February 2017	Bendamustine changed to vesicant as per EONS guidelines	Donna Kimber Pharmacy Technician	Dr Deborah Wright Pharmacist
1.2	Jan 2015	Header changed Toxicities removed "a diagnosis" replaced with "the decision to treat" in TA-GVHD warning Metoclopramide dose changed to 10mg Bolus removed from intravenous bolus throughout text Mucositis recommendation changed Ondansetron TTO clarified "Warning – Check blood transfusion status" added to cycle 1 Minor formatting changes Document control reordered Disclaimer added	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1.1	July 2012	Ondansetron added to TTA	Rebecca Wills Pharmacist	Dr Debbie Wright Pharmacist
1	April 2012	None	Rebecca Wills Pharmacist Dr Debbie Wright Pharmacist	Dr Andrew Davies Consultant Medical Oncologist Dr Alison Milne Consultant Haematologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospitals NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.