

Chemotherapy Protocol

LYMPHOMA

BENDAMUSTINE-RITUXIMAB

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

Regimen

- Lymphoma – Bendamustine-Rituximab

Indication

- Relapsed or refractory Non-Hodgkin Lymphoma
- Relapsed or refractory Mantle Cell Lymphoma

Toxicity

Drug	Adverse Effect
Bendamustine	Transfusion related GVHD, Gastro-intestinal disturbances, fatigue, insomnia, cardiac dysfunction, hypotension/hypertension, hypersensitivity reactions, hypokalaemia.
Rituximab	Severe cytokine release syndrome, increased incidence of infective complications, progressive multifocal leukoencephalopathy

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
- Check hepatitis B status prior to starting treatment with rituximab
- 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.

Dose modifications based on haematological parameters apply to bendamustine only

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

Hepatic Impairment

Please note that the approach may be different where abnormal liver function tests are due to disease involvement.

Drug	Bilirubin (μmol/L)	Dose (% of original dose)
Bendamustine	less than 21	100%
	21-51	70%
	more than 51	no information
Rituximab	N/A	No dose adjustment needed

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Bendamustine	more than 10	100%
	10 or less	no information
Rituximab	N/A	No dose adjustment needed

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.

Bendamustine

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.

Rituximab

Infusion related adverse reactions have been observed in 10% of patients treated with rituximab.

Rituximab administration is associated with the onset of cytokine release syndrome. This condition is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. It may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, acute renal failure, elevated lactate dehydrogenase (LDH) and can lead to acute respiratory failure and death. This effect on the lungs may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray.

Cytokine release syndrome frequently occurs within one or two hours of initiating the first infusion.

Hypersensitivity reactions, including anaphylaxis, have been reported following the intravenous administration of proteins. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes of starting the infusion. Medicinal products for the treatment of allergic reactions should be available for immediate use in the event of hypersensitivity developing during the administration of rituximab.

Use of rituximab may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological, cognitive or psychiatric symptoms that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed the rituximab must be permanently discontinued.

The presence of a viral upper respiratory tract infection prior to treatment may increase the risk of rituximab associated hepatotoxicity. Patients should be assessed for any cold or flu-like symptoms prior to treatment.

Regimen

28 day cycle for 6 cycles

Drug	Dose	Days	Administration
Bendamustine	90mg/m ²	1, 2	Intravenous infusion in sodium chloride 0.9% 500ml over 30 minutes
Rituximab	375mg/m ²	1	Intravenous infusion in 500ml sodium chloride 0.9%

Dose Information

- Bendamustine will be dose banded according to the nationally agreed bands (2.5mg/ml)
- Rituximab will be dose rounded to the nearest 100mg (up if halfway)

Administration Information

Extravasation

- Bendamustine – vesicant
- Rituximab - neutral

Other

- The rate of administration of rituximab varies. Please refer to the rituximab administration guidelines.

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
- ondansetron 8mg twice a day for 3 days

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

- Rituximab pre-medication

30 minutes prior to rituximab

- chlorphenamine 10mg intravenous
- hydrocortisone 100mg intravenous
- paracetamol 1000mg oral

- Rituximab infusion reactions

- hydrocortisone 100mg intravenous when required for rituximab infusion related reactions
- salbutamol 2.5mg nebule when required for rituximab related bronchospasm
- consider pethidine 25-50mg intravenous for rituximab related rigors that fail to respond to steroids.

- 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.

- Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday oral
- Mouthwashes according to local or national policy on the treatment of mucositis.
- Gastric protection with a proton pump inhibitor or a H₂ 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

- Procurement – X71.5
- Delivery – X72.1, X72.2 & X72.4

References

1. Rummel M, Al-Batran S, Kim S et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. J Clin Oncol. 2005 May 20;23(15):3383-9.
2. Robinson K, Williams M, van der Jagt R et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. J Clin Oncol. 2008 Sep 20;26(27):4473-9.

REGIMEN SUMMARY

Bendamustine-Rituximab

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. Chlorphenamine 10mg intravenous
3. Hydrocortisone 100mg intravenous
4. Paracetamol 1000mg oral
5. Rituximab 375mg/m² intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines
6. Ondansetron 8mg oral or intravenous
7. Bendamustine 90mg/m² intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes
8. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions
9. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

Take home medicines

10. Metoclopramide 10mg three times a day when required oral
11. Ondansetron 8mg twice a day for three days oral starting on the evening of day one of treatment
12. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday oral

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 90mg/m² intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes

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

1. Chlorphenamine 10mg intravenous
2. Hydrocortisone 100mg intravenous
3. Paracetamol 1000mg oral
4. Rituximab 375mg/m² intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines
5. Ondansetron 8mg oral or intravenous
6. Bendamustine 90mg/m² intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes
7. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions
8. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

Take home medicines

9. Metoclopramide 10mg three times a day when required oral
10. Ondansetron 8mg twice a day for three days oral starting on the evening of day one of treatment
11. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday oral

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 90mg/m² 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 bands updated to reflect national dose bands	Donna Kimber Pharmacy Technician	Dr Deborah Wright Pharmacist
1.3	February 2017	Bendamustine extravasation changed to vesicant as per EONS guidelines	Donna Kimber Pharmacy Technician	Dr Deborah Wright Pharmacist
1.2	May 2015	Co-trimoxazole added as TTO OPCS version removed	Donna Kimber Pharmacy Technician	Dr Deborah Wright Pharmacist
1.1	Jan 2015	Header changed Toxicities removed "a diagnosis" replaced with "the decision to treat" in TA-GVHD warning Clarified that haematological dose modifications apply to bendamustine only Metoclopramide dose changed to 10mg Bolus removed from intravenous bolus throughout text Mucositis recommendation changed OPCS code updated "Warning-Check blood transfusion status" added to cycle 1 Ondansetron TTO clarified Disclaimer added	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1	July 2012	None	Rebecca Wills Pharmacist Dr Deborah 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.