Chemotherapy Protocol

CHRONIC LYMPHOCYTIC LEUKAEMIA

BENDAMUSTINE (70)-RITUXIMAB

There are multiple versions of this protocol in use that vary depending on the indication. Please ensure you have the correct protocol for the relevant diagnosis.

Regimen

- CLL – Bendamustine (70)-Rituximab

Indication

- First line treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients for whom fludarabine combination chemotherapy is not appropriate

- Second, third or fourth line treatment of B-CLL (unlicensed indication)

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 before starting rituximab

- 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.

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 (80g/L). Irradiated blood products must be used.

Neutrophils ($x10^9$/L)	**Dose Modifications**
more than 1	100%
0.5-1	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

The approach may be different where abnormal liver function tests are due to disease.

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.

Potassium

In patients with cardiac dysfunction ensure the potassium remains above 3.5mmol/L during treatment with bendamustine.

Rituximab

Infusion Reactions

Infusion related adverse reactions have been observed in 10% of patients treated with rituximab. The administration of rituximab in those with a diagnosis of CLL is more complex than for lymphomas. The risk of an infusion related reaction is much greater. To prevent this reaction, the cycle one dose is split over two days. In general the higher the white cell count, the greater is the risk of a reaction.

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 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.

Neurological

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.

Regimen

28 day cycle for 6 cycles

Cycle 1

Drug	Dose	Days	Administration
Bendamustine	70mg/m^2	1, 2	Intravenous infusion in sodium chloride 0.9% 500ml over 30-60 minutes
Rituximab	375mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9% starting at a rate of 50mg/hour and, if tolerated, increasing by 50mg/hour every 30 minutes to a maximum rate of 400mg/hour

Cycle 2, 3, 4, 5, 6

Drug	Dose	Days	Administration
Bendamustine	70mg/m^2	1, 2	Intravenous infusion in sodium chloride 0.9% 500ml over 30-60 minutes
Rituximab	500mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines

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

  - metoclopramide 10mg oral or intravenous
  - ondansetron 8mg oral or intravenous

  As take home medication

  - metoclopramide 10mg three times a day when required for nausea oral
  - ondansetron 8mg twice a day for three days oral (on day two 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 with CLL are at risk of tumour lysis syndrome (TLS). The British Society of Haematology guidelines are a useful reference source. Oral allopurinol is one option for prophylaxis. 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. Intravenous rasburicase can be considered in high risk individuals.

- 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 exists. Always check for drug interactions.

Coding

- Procurement – X71.5

- Delivery – X72.1cycle 1, X72.2 cycle 2 onwards & X72.4

References

1.Fischer K, Cramer P, Busch R et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group.J.Clin.Oncol. 2011 Sep 10;29(26):3559-66.

REGIMEN SUMMARY

Bendamustine (70)-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/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per rituximab administration guidelines
   Administration Instructions
   The rate of administration of rituximab varies. Please refer to your local rituximab administration guidelines.

6. Metoclopramide 10mg oral or intravenous

7. Ondansetron 8mg oral or intravenous

8. Bendamustine 70mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes
   Administration Instructions
   Bendamustine may be given over 30-60 minutes

9. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions

10. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

Cycle 1 Day Two

11. Warning – Check supportive medication taken
    Administration Instructions
    Please ensure that the patient has taken metoclopramide 10mg oral and ondansetron 8mg oral on the morning of treatment. If not please administer metoclopramide 10mg oral or intravenous and ondansetron 8mg oral or intravenous 15-30 minutes prior to chemotherapy.

12. Bendamustine 70mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes
    Administration Instructions
    Bendamustine may be given over 30-60 minutes

Take home medicines (Day One)

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

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

15. Allopurinol 300mg once a day for 7 days

16. Aciclovir 400mg twice a day for 28 days oral

17. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 28 days oral
    Administration Instructions
    This may be administered as 480mg twice a day on Monday, Wednesday and Friday according to local practice

Cycle 2, 3, 4, 5, 6 Day One

18. Chlorphenamine 10mg intravenous

19. Hydrocortisone 100mg intravenous

20. Paracetamol 1000mg oral

21. Rituximab 500mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines
    Administration Instructions
    The rate of administration of rituximab varies. Please refer to your local rituximab administration guidelines.

22. Metoclopramide 10mg oral or intravenous

23. Ondansetron 8mg oral or intravenous

24. Bendamustine 70mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes
    Administration Instructions
    Bendamustine may be given over 30-60 minutes

25. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions

26. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

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

27. Warning – Check supportive medication taken
    Administration Instructions
    Please ensure that the patient has taken metoclopramide 10mg oral and ondansetron 8mg oral on the morning of treatment. If not please administer metoclopramide 10mg oral or intravenous and ondansetron 8mg oral or intravenous 15-30 minutes prior to chemotherapy.

28. Bendamustine 70mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes
    Administration Instructions
    Bendamustine may be given over 30-60 minutes

Take home medicines (Day One)

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

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

31. Aciclovir 400mg twice a day for 28 days oral

32. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 28 days oral
    Administration Instructions
    This may be administered as 480mg twice a day on Monday, Wednesday and Friday according to local practice

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	July 2018	Dose banding changed to national dose bnds	Donna Kimber Pharmacy Technician	Dr Deborah Wright Pharmacist
1	February 2017	None	Dr Deborah Wright Pharmacist	Dr Helen Dignum 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 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 that occur as a result of following these guidelines.