

Chemotherapy Protocol

LYMPHOMA

BENDAMUSTINE-POLATUZUMAB-RITUXIMAB

Regimen

- Lymphoma – Bendamustine-Polatuzumab-Rituximab

Indication

- Histologically diagnosed diffuse large B cell lymphoma (DLBCL) including;
 - DLBCL not otherwise specified including germinal cell B type (GCB) and activated B cell type (ABC)
 - primary mediastinal large B cell lymphoma
 - T cell rich B cell lymphoma
 - Epstein Barr virus (EBV) positive DLBCL
 - intravascular large B cell lymphoma
 - double and triple hit high grade B cell lymphoma
 - primary CNS lymphoma, Burkitt lymphoma and plasmablastic lymphoma are NOT included
- DLBCL which has either relapsed following or is refractory to standard routinely commissioned DLBCL chemotherapies;
 - has only received first line DLBCL (RCHOP or similar) responded to or relapsed or
 - has only received first line DLBCL chemotherapy (RCHOP or similar) and is refractory to it or
 - has received second or greater line chemotherapy (RICE/RIVE/RIGEV/RGDP/RGDCarbo/RESHAP/RDHAP/RGemOX) responded to it but has now relapsed
 - has received second or greater line chemotherapy (RICE/RIVE/RIGEV/RGDP/RGDCarbo/RESHAP/RDHAP/RGemOX) and is either refractory to it or had insufficient response to merit consideration of a stem cell transplant (SCT)
 - relapsed/refractory disease after previous autologous SCT
 - relapsed/refractory disease after previous allogeneic SCT
 - relapsed/refractory disease after previous CAR-T therapy
 - relapsed/refractory disease and the patient has been formally accepted by the national CAR-T cell clinical panel for CAR-T therapy and polatuzumab combination therapy is being used as a bridging therapy before CAR-T therapy
 - the patient is not a candidate for future haemopoietic stem cell transplantation (SCT) either as set out in formal local / regional lymphoma network guidelines or after discussion at a lymphoma multidisciplinary meeting which incorporates SCT centre representation. The patient may not be suitable for transplantation on account of;
 - a) fitness
 - b) co-morbidities
 - c) inadequate response to salvage chemotherapy

d) relapse after SCT

It is expected that patients with relapsed or refractory disease after standard chemotherapy and who are fit for SCT will proceed to standard salvage chemotherapy and consideration of SCT.

- The patient has either not been previously treated with polatuzumab or if continuing previous treatment with polatuzumab, this was either within the polatuzumab EAMS scheme and all other criteria stated above are fulfilled or within the interim SACT treatment options allowed for polatuzumab as bridging treatment to CAR-T therapy during COVID-19 pandemic and all other criteria are fulfilled
- The patient has not been previously treated with bendamustine for DLBCL or if the patient has been treated previously with bendamustine for DLBCL this treatment is to continue a previous registration for the polatuzumab EAMS scheme or the interim polatuzumab COVID-19 access or if treated with bendamustine outside of either of these two schemes then the response duration to that course of treatment with bendamustine for DLBCL exceeded one year
- a formal medical review as to whether treatment with polatuzumab in combination with bendamustine plus rituximab should continue or not will be scheduled to occur at least by the end of the first six weeks of treatment.
- WHO performance status of 0, 1, 2

Toxicity

Drug	Adverse Effect
Bendamustine	Transfusion related GVHD, Gastro-intestinal disturbances, fatigue, insomnia, cardiac dysfunction, hypotension/hypertension, hypersensitivity reactions, hypokalaemia, rash, immunosuppression
Polatuzumab	Infusion related reactions, peripheral neuropathy, progressive multifocal leukoencephalopathy, hepatotoxicity
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. Both polatuzumab and rituximab are withheld but not dose reduced.

Neutrophils (x10 ⁹ /L)	Dose Modifications (bendamustine)
More than 1	100%
0.5-1	If the neutrophils recover to 1 and above on or before day 7 of the cycle resume treatment with no dose reductions. If the neutrophils recover to 1 or above after day 7 then reduce the bendamustine dose from 90mg/m ² to 70mg/m ² or from 70mg/m ² to 50mg/m ² . If a dose reduction to 50mg/m ² has already occurred then discontinue the bendamustine.
Platelets (x10 ⁹ /L)	Dose Modifications (bendamustine)
More than 75	100%
25-75	If the platelets recover to 75 and above on or before day 7 of the cycle resume treatment with no dose reductions. If the platelets recover to 75 or above after day 7 then reduce the

	bendamustine dose from 90mg/m ² to 70mg/m ² or from 70mg/m ² to 50mg/m ² . If a dose reduction to 50mg/m ² has already occurred then discontinue the bendamustine.
--	---

Hepatic Impairment

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

Polatuzumab is known to cause hepatotoxicity. The pattern resembles hepatocellular injury, including elevations of transaminases and / or bilirubin.

Drug	Bilirubin (µmol/L)	Dose (% of original dose)
Bendamustine	less than 21	100%
	21-51	70%
	more than 51	no information
Polatuzumab	Equal to or less than 1.5xULN	No dose adjustment needed
	greater than 1.5xULN	Avoid
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
Polatuzumab	greater than or equal to 30ml/min	No dose adjustment necessary
	less than 30ml/min	Limited data
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.

Polatuzumab

Infusion Reactions

The infusion rate of polatuzumab should be slowed or interrupted if the patient develops an infusion related reaction. Polatuzumab should be immediately and permanently discontinued if the patient experiences a life threatening reaction.

Peripheral Neuropathy

For a NCI-CTC grade 2 or 3 peripheral neuropathy then withhold the polatuzumab until it resolves to a NCI-CTC grade 1 or below. If the peripheral neuropathy resolves to a grade 1 on or before day 14 of the cycle restart polatuzumab at a permanently reduced dose of reduced dose of 1.4mg/kg. If the neuropathy recurs despite this dose reduction then discontinue the polatuzumab. Treatment should also be discontinued if the peripheral neuropathy does not resolve within 14 days.

For a NCI-CTC grade 4 neuropathy then discontinue polatuzumab treatment.

Progressive Multifocal Leukoencephalopathy

Use of polatuzumab 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 polatuzumab must be permanently discontinued.

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

21 day cycle for 6 cycles

Cycle 1

Drug	Dose	Days	Administration
Bendamustine	90mg/m ²	2, 3	Intravenous infusion in sodium chloride 0.9% 500ml over 30 minutes
Polatuzumab	1.8mg/kg (maximum dose 240mg)	2	Intravenous infusion in 100ml glucose 5% (see below for infusion instructions)
Rituximab	375mg/m ²	1	Intravenous infusion in 500ml sodium chloride 0.9% (see below for infusion instructions)

Cycle 2, 3, 4, 5, 6

Drug	Dose	Days	Administration
Bendamustine	90mg/m ²	1, 2	Intravenous infusion in sodium chloride 0.9% 500ml over 30 minutes
Polatuzumab	1.8mg/kg (maximum dose 240mg)	1	Intravenous infusion in 100ml glucose 5% over 90 minutes (see below for infusion instructions)
Rituximab	375mg/m ²	1	Intravenous infusion in 500ml sodium chloride 0.9% (see below for infusion instructions)

[Dose Information](#)

- Bendamustine will be dose banded in accordance with the national dose bands (2.5mg/ml)
- Polatuzumab vedotin will be dose banded in accordance with the national dose bands (polatuzumab vedotin 20mg/ml)
- The maximum dose of polatuzumab is 240mg
- Rituximab will be dose rounded to the nearest 100mg (up if halfway)

[Administration Information](#)

[Extravasation](#)

- Bendamustine – vesicant
- Polatuzumab - neutral
- Rituximab - neutral

[Other](#)

- The first infusion of polatuzumab should be given over 90 minutes. Patients should be monitored for 90 minutes afterwards. If well tolerated subsequent infusions may be given over 30 minutes and the patients monitored for a further 30 minutes after the end of the infusion
- Polatuzumab must be administered using a sterile, non-pyrogenic, low protein binding 0.2µ or 0.22 µ filter.
- The rate of administration of rituximab varies. Please refer to the rituximab administration guidelines.

[Additional Therapy](#)

- Antiemetics

15-30 minutes prior to treatment – Day 2 Cycle 1 and day 1 of each cycle thereafter

- 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

- Polatuzumab and rituximab pre-medication

30 minutes prior to polatuzumab and rituximab

- chlorphenamine 10mg intravenous
- hydrocortisone 100mg intravenous (rituximab only)
- paracetamol 1000mg oral

- Treatment of infusion reactions

- hydrocortisone 100mg intravenous when required for infusion related reactions
- salbutamol 2.5mg nebule when required for infusion related bronchospasm
- consider pethidine 25-50mg intravenous for infusion 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.
- Bendamustine in this DLBCL indication is unlicensed. In July 2017 the MHRA issued a warning that increased mortality had been observed in recent clinical studies in off-label use of bendamustine and that patients needed to be monitored for opportunistic infections and hepatitis B re-activation

References

1. MHRA. Early Access to Medicines Scheme – Treatment Protocol – Information for Healthcare Professionals. www.assets.publishing.service.gov.uk. Accessed 08/10/2020

REGIMEN SUMMARY

Bendamustine-Polatuzumab-Rituximab

Cycle 1 Day One

1. Chlorphenamine 10mg intravenous
2. Hydrocortisone 100mg intravenous
3. Paracetamol 1000mg oral
Administration Instructions
The maximum dose of paracetamol is 4000mg/24 hours. Please check if the patient has taken this already.
4. Rituximab 375mg/m² intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines
5. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions
6. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

Cycle 1 Day Two

7. 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.
8. Chlorphenamine 10mg intravenous
9. Paracetamol 1000mg oral
Administration Instructions
The maximum dose of paracetamol is 4000mg/24 hours. Please check if the patient has taken this already.
10. Polatuzumab 1.8mg/kg intravenous infusion in 100ml glucose 5% over 90 minutes
Administration Instructions
The first infusion of polatuzumab should be given over 90 minutes. Patients should be monitored for 90 minutes afterwards. If well tolerated subsequent infusions may be given over 30minutes and the patients monitored for a further 30 minutes after the end of the infusion

Polatuzumab must be administered using a sterile, non-pyrogenic, low protein binding 0.2µ or 0.22µ filter.
11. Ondansetron 8mg oral or intravenous
12. Bendamustine 90mg/m² intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes
13. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions
14. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

Cycle 1 Day Three

15. 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 15-30 minutes prior to chemotherapy.

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

Take home medicines (Day 1)

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

Administration Instructions

Please supply 28 tablets or nearest equivalent pack size.

18. Ondansetron 8mg twice a day for three days oral starting on the evening of day two of the cycle

19. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday oral

Administration Instructions

This may be administered as 480mg twice a day according to local practice

Day 1 Cycles 2, 3, 4, 5, 6

20. Chlorphenamine 10mg intravenous

21. Hydrocortisone 100mg intravenous

22. Paracetamol 1000mg oral

Administration Instructions

The maximum dose of paracetamol is 4000mg/24 hours. Please check if the patient has taken this already.

23. Rituximab 375mg/m² intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines

24. Polatuzumab 1.8mg/kg intravenous infusion in 100ml glucose 5% over 90 minutes

Administration Instructions

The first infusion of polatuzumab should be given over 90 minutes. Patients should be monitored for 90 minutes afterwards. If well tolerated subsequent infusions may be given over 30 minutes and the patients monitored for a further 30 minutes after the end of the infusion

Polatuzumab must be administered using a sterile, non-pyrogenic, low protein binding 0.2µ or 0.22µ filter.

25. Ondansetron 8mg oral or intravenous

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

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

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

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

29. 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 15-30 minutes prior to chemotherapy.

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

Take home medicines (Day 1)

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

32. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday oral

Administration Instructions

This may be administered as 480mg twice a day according to local practice

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	December 2020	None	Dr Deborah Wright Pharmacist	Dr Rob Lown 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 which occur as a result of following these guidelines.