R – Bendamustine 90 (First line for relapsed low grade NHL)

Indication

First line treatment of CD20 positive low grade non-Hodgkin's lymphoma.

Relapsed low grade non-Hodgkin's lymphoma in patients who have not previously been treated with bendamustine and who are unable to receive R-CHOP, FCR or high dose therapy.

Note: funding should be secured prior to commencing treatment.

There are a number of bendamustine protocols – please ensure this is the correct one for your patient.

ICD-10 codes

Codes with a prefix C82.4, C82.9

Regimen details

Day	Drug	Dose	Route
1	Rituximab	375mg/m^2	IV infusion
1 and 2	Bendamustine	90mg/m^2	IV infusion

If high tumour burden consider splitting the first dose of rituximab to give 50mg/m^2 (or 100mg of total dose) on day 0 and the remainder of the total dose on day 1.

Cycle frequency

28 days

Number of cycles

Up to 6 cycles

Administration

Rituximab is administered in 500mL sodium chloride 0.9%. The first infusion should be initiated at 50mg/hour and if tolerated the rate can be increased at 50mg/hour every 30 minutes to a maximum of 400mg/hour. Subsequent infusions should be initiated at 100 mg/hour and if tolerated increased at 100mg/hour increments every 30 minutes to a maximum of 400 mg/hour. Also see note above regarding patients with high tumour burden

Bendamustine is administered in 500mL sodium chloride 0.9% over 30-60 minutes.

Pre-medication

Pre-hydration may be required if bulky disease (e.g. 1000mL sodium chloride 0.9% over 4-6 hours)
Antiemetics as per local policy.
Rituximab premedication:

- Paracetamol 1g (500mg in patients <50kg) PO 60 minutes prior to rituximab infusion
- Chlorphenamine 10mg IV bolus 15 minutes prior to rituximab infusion
- Consider dexamethasone 8mg IV bolus or Hydrocortisone 100mg IV bolus 15 minutes prior to rituximab infusion

Emetogenicity

This regimen has moderate emetic potential

Additional supportive medication

Allopurinol 300mg OD (100mg OD if CrCl < 20mL/min) for the first 2 weeks. Some patients may require for subsequent cycles. (**Omit allopurinol on days of bendamustine administration** – see interactions section).
Antiviral and PCP prophylaxis as per local policy.

Extravasation

Rituximab is neutral (Group 1)
Bendamustine is an irritant (Group 3)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days

Hepatitis B and C serology: HBV serology (aAg and cAb) must be checked before first dose rituximab. Avoid rituximab in active hepatitis B. Consider anti-viral (eg entecavir 500micrograms OD) where there is evidence of past infection.
HIV status.
TP53 mutational status (R-bendamustine has limited efficacy if TP53 mutated)

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC*	72 hours
U+E (including creatinine)	72 hours
LFTs	72 hours

*Serum potassium must be monitored in all patients with cardiac disorders. If serum potassium <3.5mml/L start potassium supplementation and perform an ECG.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine clearance (CrCl)	≥ 10ml/min
Bilirubin	≤ ULN

Dose modifications

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L delay treatment until recovery. Consider bendamustine dose reduction – discuss with consultant.

- **Renal impairment**

There is no information regarding use of bendamustine if CrCl ≤ 10mL/min. Discuss with consultant.

- **Hepatic impairment**

Bilirubin (x ULN)	**Bendamustine dose**
≤ ULN	100%
> ULN - 3 x ULN	70%
> 3 x ULN	Discuss with consultant (no information)

- **Other toxicities**

For any grade 3-4 toxicity (except alopecia) delay treatment until toxicity ≤ grade 1 and consider reducing subsequent bendamustine doses to 50% - discuss with consultant.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Cardiotoxicity including arrhythmia
Infertility
Cytokine release syndrome (rituximab)
Stevens-Johnson syndrome and toxic epidermal necrolysis (bendamustine with allopurinol)
Possible risk of secondary malignancies
Hypersensitivity

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Mucositis, stomatitis
Diarrhoea, constipation
Hypokalaemia
Renal impairment

- **Other side effects**

Raised transaminases
Alopecia
Fatigue
Insomnia
Rash, urticaria

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Bendamustine

Allopurinol: reports of Stevens-Johnson syndrome and toxic epidermal necrolysis – avoid concurrent administration.

CYP 1A2 inhibitors: metabolism of bendamustine by cytochrome P450 (CYP) 1A2 isoenzyme is a significant route of hepatic clearance so interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, aciclovir and cimetidine is possible. May increase toxicity – avoid concomitant use.

Additional comments

Patients must receive irradiated blood products for all future transfusions.

References

- Summary of Product Characteristics Bendamustine (Napp) accessed 10 August 2016 via www.medicines.org.uk
- Summary of Product Characteristics Rituximab (Roche) accessed 10 August 2016 via www.medicines.org.uk
- Rummel et al. Bendamustine plus Rituximab is effective and has a favourable toxicity profile in the treatment of mantle cell and low grade non-Hodgkin's lymphoma. JCO 2005, 23(15); 3383-89
- Robinson KS 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.

Written/reviewed by: Dr S Otton (Consultant Haematologist, North Bristol NHS Trust)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust)

Date: April 2017
