(R) Bendamustine (Subsequent line for CLL)

Indication
Subsequent line treatment of Chronic Lymphocytic Leukaemia (CLL).

Funding must be approved 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 C91.1

Regimen details

Day	Drug	Dose	Route
1	Rituximab	375mg/m^2 (cycle 1) then 500mg/m^2 for subsequent cycles	IV infusion
1 and 2	Bendamustine	70mg/m^2	IV infusion

If high tumour burden consider splitting the first dose of rituximab to give 50mg/m^2 (or 100mg) 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.

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

Pre-medication
Pre-hydration may be required if bulky disease.
Antiemetics as per local policy.
Rituximab premedication:

- Paracetamol 1g PO 60 minutes prior to rituximab infusion
- Chlorphenamine 10mg IV bolus 15 minutes prior to rituximab infusion
- 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
Potassium	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.
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
Potassium*	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.

- **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%
1-3	70%
> 3	Discuss with consultant (no information)

- **Other toxicities**

For any grade 3-4 toxicity (except alopecia) delay treatment until toxicity ≤ grade 1 and reduce subsequent doses to 50%.

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

- **Serious side effects**

Myelosuppression
Cardiotoxicity
Infertility
Cytokine syndrome (rituximab)

- **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 6 May 2015 via www.medicines.org.uk
- National Institute for Clinical Excellence. Technology Appraisal Guidance 216. Accessed 6 may 2015 via www.nice.org.uk
- Knauf WU, et al. Phase III randomised study of Bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukaemia. J. Clin Oncol 2009; 27 (26): 4378-84

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Date: November 2017 (updated with heading change)