Bendamustine +Rituximab (BR) for CLL

INDICATIONS

1. Treatment naïve TP53 wild-type CLL (NICE TA216)
2. Patients with relapsed B-cell chronic lymphocytic leukaemia (B-CLL) who are not eligible for treatment with BTK or BCL2 inhibitors. (not routinely commissioned by NHSE)

NB. BR has shown only limited efficacy in patients refractory to fludarabine or patients with TP53 deletions or mutations.

There are other bendamustine protocols, please ensure this is the correct one for patient.

TREATMENT INTENT

Disease modification.

PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage of disease - CT scan (neck, chest, abdomen and pelvis), presence or absence of B symptoms, clinical extent of disease, consider bone marrow aspirate and trephine.
3. Exclude presence of p53 del and/or mutation.
4. Blood tests - FBC, DAT, U&Es, LDH, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, β_2 microglobulin, HIV, hepatitis B core antibody and hepatitis B surface antigen, hepatitis C antibody.
5. **Send a "group and save" sample to transfusion and inform patient and transfusion laboratory that they will require irradiated blood products for all future transfusions**. Ensure irradiation card is attached to the patient's notes and copy given to the patient. See 'Guidelines for the use of blood components in adult haematology'.
6. Urine pregnancy test - before cycle 1 of each new chemotherapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy.
7. ECG +/-ECHO – *if clinically indicated*.
8. Record performance status (WHO/ECOG).
9. Record height and weight.
10. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent prior to treatment.
11. Fertility - it is very important the patient understands the potential risk of reduced fertility. All patients should be offered fertility advice by referring to the Oxford Fertility Unit.
12. Hydration - *in patients with bulky disease* pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 hours. For patients at high risk of tumour lysis, refer to the tumour lysis protocol.
13. Advise dental check is carried out by patient's own dental practitioner before treatment starts.

Treatment should be agreed in the relevant MDT.

DRUG REGIMEN

For **FIRST line** CLL treatment

Days 1 to 2 **Bendamustine** 90 mg/m^2 IV infusion daily in 500 mL sodium chloride 0.9% over 30-60 minutes

Day 1 **Pre med** - paracetamol 1g PO, chlorphenamine 10 mg IV, hydrocortisone 100 mg IV 30 minutes before rituximab
RITUXIMAB 375 mg/m^2 IV infusion in 500 mL sodium chloride 0.9%. (cycle 1)
RITUXIMAB 500 mg/m^2 IV infusion in 500 mL sodium chloride 0.9%. (cycles 2-6)
(Refer to rituximab care plan for titration of infusion rate. If first dose well tolerated, consider rapid infusion rituximab for dose 2 onwards).

Cycle 1: If lymphocyte count >25 x 10^9/L:
Give 50 mg/m^2 (or 100 mg flat dose) of Rituximab on day 1
Give the rest (i.e. 325 mg/m^2) on day 2
Give 500 mg/m^2 on day 1 of subsequent cycles

For **RELAPSED** CLL treatment

Days 1 to 2 **Bendamustine** 70 mg/m^2 IV infusion daily in 500 mL sodium chloride 0.9% over 30-60 minutes

Day 1 **Pre med** - paracetamol 1g PO, chlorphenamine 10 mg IV, hydrocortisone 100 mg IV 30 minutes before rituximab
RITUXIMAB 375 mg/m^2 IV infusion in 500 mL sodium chloride 0.9%. (cycle 1)
RITUXIMAB 500 mg/m^2 IV infusion in 500 mL sodium chloride 0.9%. (cycles 2-6)
(Refer to rituximab care plan for titration of infusion rate. If first dose well tolerated, consider rapid infusion rituximab for dose 2 onwards).

Cycle 1: If lymphocyte count >25 x 10^9/L:
Give 50 mg/m^2 (or 100 mg flat dose) of Rituximab on day 1
Give the rest (i.e. 325 mg/m^2) on day 2
Give 500 mg/m^2 on day 1 of subsequent cycles

NOTE: Interaction with allopurinol – see under 'Concurrent medications'.

CYCLE FREQUENCY

Cycle repeats every 28 days to a maximum of 6 courses.

RESTAGING

Staging and response assessment are by clinical examination. Consider CT neck, chest, abdomen and pelvis only if clinical trial or otherwise indicated.

DOSE MODIFICATIONS

Haematological Toxicity

If neutrophil count <1 x 10^9/L or platelets <100 x 10^9/L, consider delaying treatment by one week.

Bendamustine:

Renal impairment	Hepatic impairment
No dose adjustment required	Mild: Bili <20micromol/L Give 100% Moderate: Bili 20-51micromol/L Give 70% Severe: Bili >51micromol/L Not recommended

CONCURRENT MEDICATION

Allopurinol (see ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS below).	There have been rare skin reactions and other toxicities associated with the administration of allopurinol and Bendamustine when given together. It is suggested that allopurinol is omitted on the days of Bendamustine administration. Low risk of tumour lysis: allopurinol should be commenced following the administration of Bendamustine (i.e. day 3) at a dose of 300 mg OD. High risk of tumour lysis: allopurinol 300mg OD for 3 days prior to the administration of Bendamustine and for 5-7 days following Bendamustine.
Aciclovir	200 mg three times a day for duration of treatment and for 3 months after completion
Co-trimoxazole	480 mg daily on Monday / Wednesday / Friday for duration of treatment and for3 months afterwards (consider reducing the dose to 480 mg twice weekly during neutropenic periods)

INVESTIGATIONS

FBC, U&E, LFT.

EMETIC RISK

Moderate (avoid the use of Dexamethasone).

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Main side effect of Bendamustine is myelosuppression and dose might have to be titrated. Also: hypersensitivity, liver enzyme rise, cardiac disorders, nausea, vomiting, headache, alopecia, amenorrhea, anorexia, diarrhoea, constipation, mucositis, fatigue, possible risk of secondary malignancies, increased risk of opportunistic infections, and hepatitis B reactivation.

Rituximab - Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, angioedema, and hepatitis B reactivation.

All patients who are at risk of tumour lysis syndrome (TLS) must receive prophylaxis prior to initiation of treatment. An appropriate hydration (a fluid intake of approximately 3 L per day) starting before treatment is mandatory. Taking into account the degree of TLS risk and existing co-morbidities, the administration of allopurinol or an alternative can be considered if clinically appropriate. All patients should be carefully monitored during the initial days of study treatment with a special focus on renal function, potassium, and uric acid values.

Cases of Stevens-Johnson syndrome 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.

Non-melanoma skin cancer, evidence from clinical trials on an increased risk for non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) in patients treated with bendamustine containing regimens. Periodic skin examination is recommended for all patients, particularly those with risk factor for skin cancer.

EXTRAVASATION RISK

Rituximab: neutral
Bendamustine: vesicant/ irritant

TREATMENT RELATED MORTALITY

< 1%.

REFERENCES

1. Cheson BD, Rummel MJ. Bendamustine: rebirth of an old drug. J Clin Oncol. 2009 Mar 20;27(9):1492-501.s for skin cancer.
2. Fischer et al. Blood. 2008; 112: abstract 330.
3. MHRA. Drug Safety Update- Bendamustine (Levact): increased mortality observed in recent clinical studies in off-label use; monitor for opportunistic infections, hepatitis B reactivation. Published 20/07/2017. [Link]

4. NICE. TA 216 Bendamustine for the first-line treatment of chronic lymphocytic leukaemia. Published 23/02/2011. Available at https://www.nice.org.uk/guidance/ta216.
5. Accord Healthcare Limited. Bendamustine Summary of Product Characteristics. Updated 15/05/2021. Accessed on 31/05/2021via http://www.medicines.org.uk/emc.
6. Roche. Mabthera Summary of Product Characteristics. Updated 25/05/2021. Accessed on 31/05/2021 via http://www.medicines.org.uk/emc.
7. The Lancet Oncology. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20:e201-08.

Review

Name	Revision	Date	Version	Review date
Sara Castro (Advanced Haematology Pharmacist)	Annual Protocol review	May 2021	3.1	

Nursing Care Plan R-BENDAMUSTINE FOR CLL

Indication: Patients with relapsed B-cell chronic lymphocytic leukaemia (B-CLL)
IMPORTANT: there are several different protocols for Bendamustine make sure you are looking at the right protocol and care plan.
Frequency: Given every 28 days, maximum 6 cycles.
Alopecia: Hair thinning
Emetic Risk: Moderate
Send a group and save sample to blood transfusion and inform patient and laboratory that they will require irradiated blood products for all future transfusions. Give patient an irradiated blood product booklet and card

RITUXIMAB: Monoclonal antibody for CD 20.
Administered as IV infusion on day 1 of cycle
Classification of extravasation: neutral.
Emetic risk: low.
Side effects: risk of anaphylaxis, severe dyspnoea, bronchospasm and hypoxia

- Infusion reactions (Most common during first infusion - PREMED 30 MINS PRIOR TO INFUSION): fever, chills, rigors, urticaria, nausea, hypotension, dizziness, cough, chest tightness, back pain.
- Rituximab can cause hypotension. Consider withholding anti-hypertensives 12 hours prior to Rituximab (especially first dose).
- Risk of tumour-lysis syndrome, especially with bulky disease.
- Post infusion side effects: flu-like symptoms, fever, diarrhoea
- **For first Rituximab:**
    - Ensure patient is treated on a bed.
    - In DTU Setting *(where the patient is visually in front of the nursing station with very close observation):* Record baseline vital observations and then if patient reacts. On the ward setting: record vital observations every 30 minutes for the first two hours and then hourly. To have close observation.
    - Have anaphylaxis box nearby.
    - Increment drug infusion rate as per protocol. *Note there are different rates for first and subsequent treatments and for different doses.*
    - Educate patients re possible reactions and the importance of reporting any symptoms immediately.
- **If patient reacts to Rituximab:**
    - Stop infusion.
    - Record observations.
    - Seek an immediate medical review.
    - Consider administration of Hydrocortisone, Chlorphenamine, Oxygen, Salbutamol nebuliser depending on type and severity of reaction.

- Restart infusion at same or previous rate after 30 minutes if symptoms resolved.

BENDAMUSTINE : Alkylating agent
Administered as IV infusion over 30-60 minutes on **days 1 and 2**.
Classification of extravasation: vesicant
Emetic risk: moderate.
Side effects: tumour lysis syndrome, fever, chills, pruritis, rash, nausea and vomiting, myelosuppression, anorexia, diarrhoea, constipation, mucositis, fatigue, raised LFT's, hypokalaemia, cardiac impairment, hypo/hypertension, insomnia, skin disorders, alopecia, amenorrhoea, risk of secondary malignancies.

Regime Specific Considerations

- Note that patients with bulky disease may have split doses of Rituximab on cycle 1 (see protocol).
- Patients with a high white cell count/bulky disease are at increased risk of reacting to Rituximab.
- If over 2 months elapsed since last Rituximab, treat as first infusion.

Risk of skin reactions (Steven-Johnson Syndrome) when Allopurinol is given concomitantly with Bendamustine. For patients with a low risk of tumour lysis syndrome Allopurinol to be started on day 3. Check prescription on Aria for start dates of Allopurinol.