BDR – Bortezomib, Dexamethasone and Rituximab

Indication

Waldenstrom's macroglobulinaemia / lymphoplasamacytoid lymphoma

(Funding via CDF unless amyloid also present)

ICD-10 codes

Codes prefixed with D88

Regimen details

Cycle 1 (21 day cycle)

Days	Drug	Dose	Route
1, 4, 8 and 11	Bortezomib	1.3mg/m²	SC

Cycles 2 and 5 only (35 day cycle)

Days	Drug	Dose	Route
1, 8, 15 and 22	Bortezomib	1.6mg/m²	SC
1, 8, 15 and 22	Dexamethasone	40mg OD	PO
1, 8, 15 and 22	Rituximab	375mg/m²	IV

Cycles 3 and 4 only (35 day cycle)

Days	Drug	Dose	Route
1, 8, 15 and 22	Bortezomib	1.6mg/m²	SC

There should be at least 72 hours between doses of bortezomib.

Cycle frequency

As above
Cycle 1 - 21 day cycle
Cycle 2 to 5 - 35 day cycles

Number of cycles

Until disease progression or unacceptable toxicity to a maximum of 5 cycles (as above)

Administration:

Bortezomib is administered as a subcutaneous bolus injection.
Bortezomib is also licensed for IV administration as a slow IV bolus over 3-5 seconds, however this may lead to increased risk of neurotoxicity.

Dexamethasone is available as 500microgram and 2mg tablets. It is taken orally 30 minutes prior to rituximab.

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 30minutes to a maximum of 400 mg/hour.

Pre-medication:

Rituximab premedication:

- Paracetamol 1g PO 60 minutes prior to rituximab infusion
- Chlorphenamine 10mg IV bolus 15 minutes prior to rituximab infusion
- Dexamethasone 40mg PO 30 minutes prior to rituximab (as per dosing table above)

Emetogenicity:

This regimen has low emetic potential.

Additional supportive medication

Allopurinol 300mg OD (or 100mg OD if creatinine clearance <20mL/min) for the first 7 days.
H_2 antagonist or proton-pump inhibitor as per local policy.
Antiemetics as per local policy.
Loperamide if required.
Aciclovir 400mg BD continuously
Consider prophylactic co-trimoxazole
Patients who experience dizziness or low blood pressure may benefit from 500mL sodium chloride 0.9% with each dose of bortezomib.

Extravasation

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

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	7 days
U+E (including creatinine)	7 days
LFTs	7 days
DAT	7 days
Calcium	7 days
Magnesium	7 days
Glucose	7 days
Plasma viscosity	7 days
Blood pressure	7 days

ECG and/or ECHO if clinically indicated

Other pre-treatment investigations:
Immunoglobulin level
Paraprotein level
Hepatitis B core antibody , Hepatitis B surface antigen, Hepatitis C antibody
EBV, CMV
HIV 1 + 2
Group and Save

Investigations – pre subsequent cycles

Investigation	**Validity period**
FBC	48 hours
U+E (including creatinine)	48 hours
Plasma viscosity	48 hours
Blood pressure	On day 1

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	≥1.0x 10 ^{9}/L
Platelets	≥ 50 x 10^{9}/L
CrCl	>20 mL/min
Bilirubin	≤ 1.5 x ULN

Neuropathy assessment also required prior to each cycle.

Dose modifications

- **Haematological toxicity**

If neutrophils < 1.0 x 10 ^{9}/L and/or platelets < 50 x 10^{9}/L delay by one week or until resolved. Recommence bortezomib at reduced dose of 1.6mg/m² to 1.3mg/m² or 1.3mg/m² to 0.8mg/m².

- **Renal impairment**

If CrCl < 20mL/min consider bortezomib dose reduction (consultant decision).

- **Hepatic impairment**

Use with caution in mild to moderate hepatic impairment. If bilirubin > 1.5x ULN reduce bortezomib to 0.8mg/m² for cycle 1. Consider dose escalation to 1.0mg/m² or further dose reduction to 0.5mg/m² in subsequent cycles based on tolerability.
Contraindicated in severe hepatic impairment.

- **Other toxicities**

Toxicity	Definition	Bortezomib dose
Neuropathy	Grade 1	100%
	Grade 2 with moderate symptoms	1.3mg/m²
	Grade 2 with pain or grade 3	Withhold treatment until ≤ grade 1. Recommence at dose of 0.8mg/m²
	Grade 4	Discontinue

Patients should be advised to report pain, hypersensitivity, pins and needles, prickling, numbness and paraesthesia. If these occur, dose adjustments as above and consider use of amitriptyline, gabapentin and referral to specialist pain team.

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

- **Serious side effects**

Myelosuppression
Ileus
Progressive multifocal leukoencephalopathy (PML)
Pneumonitis

- **Frequently occurring side effects**

Myelosuppression
Neuropathic pain
Peripheral neuropathy
Dizziness
Orthostatic hypotension
Nausea, vomiting
Diarrhoea, constipation

- **Other side effects**

Reactivation of herpes zoster virus
Seizures

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.

Inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort): avoid co-administration as these may reduce exposure to bortezomib.

Inhibitors of CYP3A4 (e.g. ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone, atazanavir): use with caution.

Antihypertensives should be used with caution due to the risk of orthostatic hypertension.

Additional comments

Caution in patients with history of syncope or with pre-existing peripheral neuropathy.

Male and female patients of childbearing potential must be advised to use effective contraception during and for 3 months following treatment.

Patients taking oral antidiabetic agents require close monitoring during treatment.

References

- Ghobrial I M, Hong F, Padmanabham S, et al. Phase II trial of weekly Bortezomib in combination with rituximab in relapsed and refractory Waldenstrom's macroglobulinaemia. J Clin Oncol, 2010.2010Mar10;28(8)1422-8
- Agathocleous A, Rohatiner A, Rule S, et al. Weekly versus twice weekly Bortezomib given in conjunction with Rituximab, in patients with recurrent follicular lymphoma, mantle cell and Waldenström's macroglobulinaemia. Br J Haematol.2010 Nov; 151(4):346-353.
- Summary of Product Characteristics Bortezomib (Janssen) accessed via www.medicines.org.uk (08 Oct 2014)
- Summary of Product Characteristics Rituximab (Roche) accessed via www.medicines.org.uk (08 Oct 2014)

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Date: January 2015
