VR-CAP

Indication

Previously untreated mantle cell lymphoma in patients for whom haematopoietic stem cell transplantation is not suitable.

Bortezomib is NICE approved for this indication (NICE TA370)

ICD-10 codes

Codes with a prefix C83.

Regimen details

Day	Drug	Dose	Route
1, 4, 8 and 11	Bortezomib	1.3mg/m^2	SC
0 or 1	Rituximab*	375mg/m^2	IV infusion
1	Doxorubicin	50mg/m^2	IV bolus
1	Cyclophosphamide	750mg/m^2	IV bolus
1-5	Prednisolone	100mg/m^2	PO

* if appropriate

For patients over 70 years of age, use starting doses of 50% for prednisolone and 75% for doxorubicin and cyclophosphamide – consultant decision.

At least 72 hours must elapse between doses of bortezomib

Cytokine release syndrome: The risk is low but omitting Rituximab if peripheral blood lymphocyte count is greater than 30-50 x 10^9/L for the first cycle may reduce risk.

Cycle frequency

21 days

Number of cycles

6 cycles plus 2 further cycles (to a maximum of 8 cycles) if first response documented in cycle 6.

Administration

Bortezomib is administered by SC injection over 3-5 seconds.

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.

Doxorubicin is administered by slow IV bolus into the arm of a fast running drip of sodium chloride 0.9%.

Cyclophosphamide is administered as an IV bolus or as an IV infusion in 250-500mL sodium chloride 0.9% over 30 minutes.

Prednisolone is available as 5mg and 25mg tablets. The dose should be taken each morning for 5 days with or after food.

Pre-medication

Consider steroid pre-treatment (prednisolone 50-100mg OD for 7 days) for older patients.
Consider IV hydration for patients with bulky disease.
Rituximab premedication:

- Paracetamol 500mg-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 (may be omitted if day 1 prednisolone has been taken at least 30 minutes prior to the start of the rituximab infusion)

Emetogenicity

This regimen has moderate - high emetic potential

Additional supportive medication

Allopurinol 300mg OD (or 100mg OD if creatinine clearance <20mL/min) for the first 1-2 cycles.
H_2 antagonist or proton-pump inhibitor as per local policy.
Antiviral and antifungal and PCP prophylaxis as per local policy.
Antiemetics as per local policy.
Loperamide if required.
GCSF as per local policy if age >65 years or previous neutropenic sepsis (Note: theoretical risk of enhanced myelosuppression if given within 24 hours of Bortezomib)

Extravasation

Doxorubicin and vincristine are vesicant (Group 5)
Cyclophosphamide and rituximab are neutral (Group 1)

Investigations – pre first cycle

Investigation	Validity period
FBC (with film)	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Calcium	14 days
Glucose	14 days
Blood pressure (lying and standing)	On day 1

Other pre-treatment investigations:
Hepatitis B and C and HIV serology
Immunoglobulin levels and Direct antiglobulin
Baseline echocardiogram if pre-existing cardiac disease (risk of bortezomib-induced cardiomyopathy)

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours*
U+E (including creatinine)	7 days*
LFTs	7 days*
Glucose	If clinically indicated
Blood pressure	On day 1

* In addition, a FBC is required within 24 hours of day 8 Bortezomib. If platelet count <50 x 10^9/L please check FBC before each further dose of Bortezomib.

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	≥ 1.5 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine Clearance (CrCl)	> 20 mL/min
Bilirubin	≤ ULN
AST/ALT	< 2 x ULN

Dose modifications

Doses of bortezomib are modified according to the following table:

Full dose	1.3mg/m^2
First dose reduction	1.0mg/m^2
Second dose reduction	0.7mg/m^2
Third dose reduction	0.5 mg/m^2

- **Haematological toxicity**

If neutrophils <1.5 x 10^9/L and/or platelets < 100 x 10^9/L delay 1 week or until recovery.

If febrile neutropenia consider reducing doses of cyclophosphamide and doxorubicin by 25% and prescribe GCSF prophylaxis for all subsequent cycles. If neutrophils < 0.5 x 10^9/L for more than 1 week prescribe GCSF prophylaxis for all subsequent cycles.

On day of bortezomib administration, if neutrophils ≤ 0.75 x 10^9/L **or** platelets ≤ 30 x 10^9/L withhold bortezomib. If several doses within a cycle are withheld, dose reduce Bortezomib for subsequent cycles. Reduce doses of cyclophosphamide and doxorubicin by 25% for future cycles if thrombocytopenia recurs despite omission of Bortezomib. Consider stopping chemotherapy if grade 4 thrombocytopenia despite omission of Bortezomib and 50% dosing of cyclophosphamide and doxorubicin.

- **Renal impairment**

CrCl (mL/min)	**Doxorubicin dose**	**Cyclophosphamide dose**
> 20	100%	100%
10-20	100%	75%
<10	Discuss with consultant	50%

Bortezomib:
If CrCl < 20mL/min use with caution.

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Doxorubicin dose**
< ULN	and	< 2	100%
< ULN	and	2-3	75%
1 – 2.5	or	> 3	50%
2.5 – 4			25%
> 4			Omit

Cyclophosphamide is not recommended if bilirubin > 1.5 x ULN or AST/ALT > 3 x ULN (consultant decision).

Bortezomib:
If bilirubin > 1.5 x ULN consider starting dose of 0.7mg/m^2 for cycle 1. For subsequent cycles increase dose to 1mg/m^2 or reduce dose to 0.5mg/m^2 according to tolerability.

- **Other toxicities**

Bortezomib:

Toxicity	Definition	Bortezomib dose
Neuropathy	Grade 1 with no pain	100%
	Grade 1 with pain or grade 2 but not interfering with daily living	1.0mg/m^2 If bi-weekly switch to weekly dosing
	Grade 2 with pain or grade 3	Withhold until symptoms resolved Restart at dose of 0.7mg/m^2 weekly.
	Grade 4	Discontinue bortezomib

Any other ≥ grade 3 non-haematological toxicity: withhold treatment until ≤ grade 1. Recommence with 1 level dose reduction of bortezomib and consider dose reduction of doxorubicin and cyclophosphamide.

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

- **Serious side effects**

Secondary malignancy
Myelosuppression
Infertility/Early menopause
Tumour lysis syndrome
Cardiotoxicity
Neurotoxicity
Thromboembolism
Pulmonary hypotension

- **Frequently occurring side effects**

Constipation, diarrhoea
Peripheral neuropathy
Headache
Rash
Fatigue
Nausea and vomiting
Myelosuppression
Alopecia

- **Other side effects**

Fluid retention
Haemorrhagic cystitis
Altered LFTs
Confusion
Depression

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 direct oral anticoagulant during treatment. If the patient continues taking warfarin monitor the INR at least once a week and adjust dose accordingly.

Co-trimoxazole/trimethoprim: enhances antifolate effect. Avoid if possible, if essential, monitor FBC regularly.

Bortezomib:
Antihypertensives: Risk of additive hypotensive effect. Close monitoring of BP is required.
Oral anti diabetic agents: Hyper and hypo glycaemia has been reported. Close monitoring of blood glucose is required.

Ciclosporin: increased risk of severe neuropathy: avoid concomitant use.
Vitamin C: reduced efficacy of bortezomib: avoid concomitant use.
Cytochrome P34A inhibitors (ketoconazole and other azole antifungals, clarithromycin, erythromycin) may increase bortezomib levels: avoid concomitant use.
Cytochrome P34A inducers (rifampicin, carbamazepine, phenytoin, St Johns Wort) may reduce bortezomib levels: avoid concomitant use.

Cyclophosphamide:
Amiodarone: increased risk of pulmonary fibrosis – avoid if possible
Clozapine: increased risk of agranulocytosis – avoid concomitant use
Digoxin tablets: reduced absorption – give as liquid form
Indapamide: prolonged leucopenia is possible - avoid
Itraconazole: may increase adverse effects of cyclophosphamide
Phenytoin: reduced absorption - may need to increase dose of phenytoin
Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

Additional comments

Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

Discuss the need for contraception with both male and female patients if appropriate.

Doxorubicin has a life time maximum cumulative dose of 450mg/m^2

References

- Summary of Product Characteristics Bortezomib (Janssen) accessed 18 January 2017 via www.medicines.org.uk
- Summary of Product Characteristics Rituximab (Roche) accessed 18 January 2017 via www.medicines.org.uk
- Summary of Product Characteristics Doxorubicin (Hospira) accessed 18 January 2017 via www.medicines.org.uk
- Summary of Product Characteristics Cyclophosphamide (Baxter) accessed 18 January 2017 via www.medicines.org.uk
- NICE TA370 accessed 18 January 2017 via www.nice.org.uk
- Robak T., et al. Bortezomib-based therapy for newly diagnosed Mantle Cell Lymphoma. 2015. NEJM. 372; 10

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