(R) CVP

Indication

Primary treatment of CD20 positive stage III or IV follicular and other indolent lymphomas.
Waldenström's macroglobulinaemia, chronic lymphocytic leukaemia (CLL) and aggressive lymphomas where more intensive chemotherapy is not indicated.
Omit rituximab if CD20 negative.

(Rituximab NICE TA243)

ICD-10 codes

Codes with a prefix C82, C88, C91

Regimen details

Day	Drug	Dose	Route
0 or 1	Rituximab*	375mg/m^2	IV infusion
1	Cyclophosphamide	750mg/m^2	IV bolus
1	Vincristine	1.4mg/m^2 (maximum dose 2mg)	IV infusion
1-5	Prednisolone	60mg/m^2 (maximum dose 100mg)	PO

* if appropriate

Consider vincristine 1mg dose for patients > 70 years of age or > 60 years of age with pre-existing constipation or neurological problems.

Cyclophosphamide may be given orally as an alternative at a dose of 400mg/m^2 OD for 5 days.

Cycle frequency

21 days

Number of cycles

6 - 8 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 30minutes to a maximum of 400 mg/hour.

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

Vincristine is administered in 50mL sodium chloride 0.9% over 10 minutes, as per national guidance. Nurse to remain with patient throughout infusion.

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.
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 (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 2 cycles.
H_2 antagonist or proton-pump inhibitor as per local policy.
Antiviral and antifungal prophylaxis as per local policy.
Antiemetics as per local policy.
Loperamide if required.

Extravasation

Vincristine is 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

Other pre-treatment investigations:
Hepatitis B and C serology
Immunoglobulin levels
Direct antiglobulin
Bone marrow aspirate and trephine biopsy

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Glucose	If clinically indicated

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

- **Haematological toxicity**

If neutrophils <1.5 x 10^9/L and/or platelets <100 x 10^9/L delay 1 week or until recovery. Reduce cyclophosphamide dose to 80%.

- **Renal impairment**

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

- **Hepatic impairment**

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

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Vincristine dose**
< ULN	and	≤ 2	100%
1 – 2.5	or	> 3	50%
> 2.5	and	< ULN	50%
> 2.5	and	> 3	Omit

- **Other toxicities**

Neurotoxicity

Monitor for signs of peripheral sensory loss or constipation. Consider reducing vincristine dose. If grade 3-4 discontinue vincristine. Discuss with consultant.

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

- **Serious side effects**

Secondary malignancy
Myelosuppression
Infertility/Early menopause
Tumour lysis syndrome
Neurotoxicity

- **Frequently occurring side effects**

Constipation
Fatigue
Nausea and vomiting
Mucositis
Myelosuppression
Alopecia

- **Other side effects**

Fluid retention
Haemorrhagic cystitis

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.

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

Vincristine:
Itraconazole, voriconazole, posaconazole: increase severity of neuromuscular side effects. Avoid for 72 hours either side of vincristine dose if concurrent use cannot be avoided.

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.

References

- Summary of Product Characteristics Rituximab (Roche) accessed 8 July 2015 via www.medicines.org.uk
- Summary of Product Characteristics Vincristine (Hospira) accessed 8 July 2015 via www.medicines.org.uk
- Summary of Product Characteristics Cyclophosphamide accessed 8 July 2015 via http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs
- NICE TA243 (Rituximab) accessed 8 July 2015 via www.nice.org.uk
- Marcus, R et al; Blood 2005; 105: 1417-1423.
- Sehn et al; Blood 2007; 109 (10): 4171 - 4173

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