(R) CHOP

Indication

Primary treatment of CD20 positive stage IA - IV Diffuse Large B Cell (DLBC) Non-Hodgkins Lymphoma (NHL).
Relapsed/refractory CLL and low grade lymphoma in patients unsuitable for other treatment options.
Omit rituximab if CD20 negative.

(Rituximab NICE TA243)

ICD-10 codes

Codes with a prefix C82, C83, C85 and C91

Regimen details

Day	Drug	Dose	Route
0 or 1	Rituximab*	375mg/m^2	IV infusion
1	Doxorubicin	50mg/m^2	IV bolus
1	Vincristine	1.4mg/m^2 (maximum dose 2mg)	IV infusion
1	Cyclophosphamide	750mg/m^2	IV bolus
1-5	Prednisolone	50mg/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.

Cycle frequency

21 days

Note: R-CHOP may be given on a 14 day cycle with GCSF support (as per local policy) on days 4-10.

Number of cycles

6 cycles plus 2 further cycles (to a maximum of 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.

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

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

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.
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

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

Other pre-treatment investigations:
Hepatitis B and C serology
Immunoglobulin levels
Direct antiglobulin
Bone marrow aspirate and trephine biopsy
If aggressive NHL: LDH and CSF cytology
If clinical suspicion of cardiac dysfunction: ECHO and/or MUGA

Investigations – pre subsequent cycles

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

* More recent blood results required for 14 day regimen, usually within 48 hours.

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	≥ 75 x 10^9/L
Creatinine Clearance (CrCl)	> 20 mL/min
Bilirubin	≤ ULN
AST/ALT	< 2 x ULN

Dose modifications

- **Haematological toxicity**

If neutrophils <1.0 x 10^9/L and/or platelets <75 x 10^9/L delay 1 week or until recovery.

If febrile neutropenia or neutrophils < 0.5 x 10^9/L for more than 1 week consider GCSF prophylaxis for all subsequent cycles. Consider reducing doses of cyclophosphamide and doxorubicin to 80% for future cycles.

- **Renal impairment**

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

- **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).

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
Cardiotoxicity
Neurotoxicity

- **Frequently occurring side effects**

Constipation
Fatigue
Nausea and vomiting
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.

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

References

- Summary of Product Characteristics Vincristine (Hospira) accessed via www.medicines.org.uk (09 July 2014)
- Summary of Product Characteristics Doxorubicin (Hospira) accessed via www.medicines.org.uk (09 July 2014)
- Summary of Product Characteristics Cyclophosphamide accessed via http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs (09 July 2014)
- NICE TA243 (Rituximab) accessed 6 August 2014 via www.nice.org.uk
- Pfreundschuh M, et al; German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol. 2008 Feb;9(2):105-16.

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