(R) CHOEP

Indication

Treatment of stage IA - IV T cell non-Hodgkin lymphoma as an alternative to CHOP in younger, fitter patients with normal LDH level.

May be used for stage IA - IV Diffuse Large B Cell non-Hodgkin lymphoma in combination with rituximab.

(Rituximab NICE TA243)

ICD-10

Codes with a prefix C84, C86.
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	Cyclophosphamide	750mg/m^2	IV
1	Doxorubicin	50mg/m^2	IV
1	Vincristine	1.4mg/m^2 (maximum dose 2mg)	IV infusion
1	Etoposide	100mg/m^2	IV infusion
1-5	Prednisolone	100mg	Oral
2 and 3	Etoposide	200mg/m^2	Oral

Cycle frequency

21 days
May be given on a 14 day cycle with GCSF support (as per local policy).

Number of cycles

Maximum of 6 cycles
Offer radiotherapy for bulky disease (mass >=7.5cm diameter, 36Gy) or extranodal sites of disease whenever feasible. Consider autograft.

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.

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

Etoposide is administered in 1000mL sodium chloride 0.9% over 60 minutes

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

Oral etoposide is available as 50mg and 100mg capsules. The dose should be rounded to nearest 50mg and swallowed whole on an empty stomach or an hour before food. In the event that the patient cannot swallow capsules, etoposide injection can be taken orally (diluted with orange juice immediately prior to administration) at a dose of 70% of the usual oral capsule dose. (This is an unlicensed use based on medical information from Bristol- Myers Squibb). Alternatively an additional IV dose may be given as above. Note: oral absorption of etoposide is variable.

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.
H2 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)
Etoposide is an irritant (group 3).

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT	14 days
Calcium	14 days
Glucose	14 days

Other pre-treatment investigations:
Hepatitis B and C serology
Bone marrow aspirate and trephine biopsy
LDH
ECG and 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*
LFT	7 days*
Calcium	If clinically indicated
Glucose	If clinically indicated

*If the 14 day regimen is used then 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)	≥ 50ml/min
Bilirubin	≤ ULN
AST / ALT	≤ 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 G-CSF prophylaxis for subsequent cycles.

- **Renal impairment**

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

Creatinine clearance (mL/min)	**Etoposide dose**
> 50	100%
15-50	75%
< 15	Consider 50% - discuss with consultant

Doxorubicin - no dose adjustment required, consultant decision if severe renal impairment.
Vincristine - consultant decision if CrCl < 30mL/min.

- **Hepatic impairment**

Bilirubin (x ULN)	**Doxorubicin dose**	**Cyclophosphamide dose**
≤ 1.0	100%	100%
>1.0 - 2.5	50%	100%
> 2.5 - 4.0	25%	Consider dose adjustment (discuss with consultant)
> 4.0	Omit	Consider dose adjustment (discuss with consultant)

Etoposide

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Etoposide dose**
≤ 1.25	and	< 1.0	100%
> 1.25 - 2.5	or	> 1.0 - 3.0	50%
> 2.5	or	> 3.0	Discuss with consultant - consider 25% or omit

Vincristine

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 – discuss with consultant

- **Other toxicities**

For patients who develop ≥ grade 3 ileus, delay treatment until ≤ grade 1 and then continue with 75% vincristine. If ≥ grade 3 ileus recurs, vincristine should be discontinued.

Neurotoxicity

Monitor for signs of peripheral sensory loss. Consider reducing vincristine dos to 50% if Grade 2 (moderate symptoms). If grade 3-4 discontinue vincristine. Discuss with consultant.

Cardiac toxicity

Further doxorubicin is contraindicated in patients already treated with the maximum cumulative dose of doxorubicin of 450mg/m^2 or other anthracyclines.

Patients with a baseline ejection fraction < 50%, consider withholding doxorubicin / monitoring cardiac function; if, > 20% reduction on repeat ECHO patients should not receive further anthracyclines.

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 5 Jul 2017 via www.medicines.org.uk
- Summary of Product Characteristics Doxorubicin (Hospira) accessed 5 Jul 2017 via www.medicines.org.uk
- Summary of Product Characteristics Cyclophosphamide (Sandoz) accessed 5 Jul 2017 via www.medicines.org.uk
- Summary of Product Characteristics Etoposide (BMS) accessed 5 Jul 2017 via www.medicines.org.uk
- NICE TA243 (Rituximab) accessed 5 Jul 2017 via www.nice.org.uk
- F. d'Amore, et al, on behalf of the ESMO Guidelines Committee. Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up..Annals of Oncology 26 (Supplement 5): v108–v115, 2015
- Michael Pfreundschuh, et al. for the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL) Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. Blood 104(3): 626-633, 2004

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