(R) COCKLE

Indication
Palliative chemotherapy for non-Hodgkins and Hodgkins lymphoma.

ICD-10 codes
Codes with a prefix C81.

Regimen details

Day	Drug	Dose	Route
0 or 1	Rituximab*	375mg/m^2	IV infusion
1	Lomustine	80mg STAT	PO
1-10	Cyclophosphamide	100mg OD	PO
1-10	Etoposide	50mg OD	PO
1-7	Prednisolone	60mg OD	PO

* if appropriate for CD20 positive NHL.

Cycle frequency
21-28 days

Number of cycles
At consultant discretion, depending on tolerability and response.

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 by 50mg/hour every 30 minutes to a maximum of 400mg/hour. Subsequent infusions should be initiated at 100 mg/hour and if tolerated increased by 100mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

Lomustine is available as 40mg capsules. Lomustine capsules should be swallowed whole with water.

Cyclophosphamide is available as 50mg tablets. Tablets should be swallowed whole with a full glass of water.

Oral etoposide is available as 50mg and 100mg capsules. The dose should be swallowed whole, with a glass of water, on an empty stomach or an hour before food.

In the event that the patient cannot swallow etoposide 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).
Note: oral absorption of etoposide is variable.

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

Pre-medication

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 low emetic potential with high on day 1 due to lomustine.

Additional supportive medication

Allopurinol 300mg OD (100mg OD if CrCl< 20mL/min) for first 2 cycles.
Antiemetics if required.
H_2 antagonist or PPI as per local policy.
Antibacterial, antiviral and PCP prophylaxis as per local policy.

Extravasation

Rituximab is neutral (Group 1)

Investigations – pre first cycle

Investigation	Validity period
FBC and film	14 days
Clotting screen	14 days
U+E (including creatinine)	14 days
LFTs	14 days

Other pre-treatment investigations:
Hepatitis B and C and HIV serology

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours
U+E (including creatinine)	96 hours
LFTs	96 hours

Urine dip test for microscopic haematuria.

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)	> 60 mL/min
Bilirubin	≤ 1.5 ULN
AST/ALT	≤ 1.5 x ULN

Dose modifications

- **Haematological toxicity**

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

- **Renal impairment**

CrCl (mL/min)	**Etoposide dose**
> 50	100%
15-50	75%
< 15	Omit or further dose reduction – discuss with consultant

CrCl (mL/min)	**Lomustine dose**
> 60	100%
45-60	75%
30-44	50%
< 30	Discontinue

CrCl (mL/min)	**Cyclophosphamide dose**
> 20	100%
10-20	75%
< 10	Omit or consider 50% dose – discuss with consultant

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Etoposide dose**	**Lomustine dose**
≤1.5	And	≤ 1.5	100%	100%
>1.5-3.0	Or	>1.5-3.0	50%	100%
>3.0	Or	> 3.0	Omit (discuss with consultant)	Consider dose reduction

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

- **Other toxicities**

If any grade 3 toxicity withhold treatment until ≤ grade 1 and then continue at 80% dose. If toxicity recurs discuss with consultant.

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

- **Serious side effects**

Myelosuppression
Hepatotoxicity

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Alopecia
Diarrhoea, constipation
Mucositis, stomatitis
Haemorrhagic cystitis

- **Other side effects**

Fluid retention
Electrolyte disturbances
Fatigue

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.

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.

Etoposide:
Phenylbutazone, sodium salicylate and salicylic acid: may displace etoposide from plasma protein binding thereby increasing systemic exposure.
Ciclosporin: May increase exposure to etoposide.
Phenytoin: May increase etoposide clearance and therefore reduce efficacy.

Additional comments

Lomustine can cause pulmonary problems after high, lifetime cumulative doses (>1,100mg/m^2). Onset of symptoms may occur months/years after treatment discontinued.

References

Adapted from archived ASWCS Haematology Chemotherapy Protocol accessed via http://www.avon.nhs.uk/aswcs-chemo/HCP/Part7/Cockle.pdf

- Summary of Product Characteristics Cyclophosphamide accessed via http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs (15 June 2016)
- Summary of Product Characteristics Lomustine (medac). Accessed 22 June 2016 via www.medicines.org.uk
- Summary of Product Characteristics Etoposide (Hospira) accessed 22 June 2016 via www.medicines.org.uk
- Summary of Product Characteristics Ritiximab (Roche). Accessed 7 September 2016 via www.medicines.org.uk

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