

## R-CHOP-21 / CHOP-21

### INDICATION

Lymphoma

**Omit rituximab if CD20-negative.**

### TREATMENT INTENT

Curative or disease modification depending on clinical circumstances

### PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage and IPI of disease - CT scan (neck, chest, abdomen and pelvis), and/or PET-CT, presence or absence of B symptoms, clinical extent of disease, consider bone marrow aspirate and trephine.
3. Blood tests – FBC, U&Es, LDH, ESR, urate, calcium, Vitamin D level, magnesium, creatinine, LFTs, glucose, Igs,  $\beta_2$  microglobulin, hepatitis B core antibody and hepatitis B surface Ag, hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent, group and save.
4. Urine pregnancy test - before cycle 1 of each new chemotherapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy.
5. ECG +/- Echo and baseline BP in all patients with a cardiac history or at risk of cardiac complications (hypertension, smokers, diabetes).
6. Record performance status (WHO/ECOG).
7. Record height and weight.
8. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
9. Fertility - it is very important the patient understands the potential risk of infertility. All patients should be offered fertility advice by referring to the Oxford Fertility Unit.
10. Hydration – *in patients with bulky disease* pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 hours. For patients at high risk of tumour lysis, refer to the tumour lysis protocol.
11. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts.
12. Consider mesna prophylactic treatment in any patient with a history of a bladder disorder (see Concurrent Medications below).
13. Treatment should be agreed in the relevant MDT.

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**DRUG REGIMEN**

**Day 1 Pre med** – Paracetamol 1g PO, Chlorphenamine 10 mg IV, and Day 1 Prednisolone 30 minutes before rituximab.

**RITUXIMAB** 375 mg/m<sup>2</sup> IV infusion in 500 mL sodium chloride 0.9%.

(Refer to rituximab care plan for titration of infusion rate. If first dose well tolerated, consider rapid infusion rituximab for dose 2 onwards).

**DOXORUBICIN** 50 mg/m<sup>2</sup> IV bolus.

**VINCRIStINE** 1.4 mg/m<sup>2</sup> (maximum 2 mg\*) IV infusion in 50 mL sodium chloride 0.9% over 10 minutes.

**CYCLOPHOSPHAMIDE** 750 mg/m<sup>2</sup> IV bolus or IV infusion over 20 mins in 100 mL sodium chloride 0.9%.

**Days 1 to 5 PREDNISOLONE** 40 mg/m<sup>2</sup> PO daily.

(Give first dose before rituximab as pre-med).

\* Vincristine 1 mg in patients over 70 years of age.

**Pretreatment with steroids:**

Some older patients may benefit from a steroid pre-phase consisting of 7 days of oral prednisolone at a dose of 50-100 mg daily.

**G-CSF primary prophylaxis:**

Consider for all patients from day 6 for 5 or 7 days.

**CYCLE FREQUENCY**

Cycle repeats every 21 days.

**RESTAGING**

Consider scanning after 3 or 4 cycles (not needed if obvious clinical improvement seen). Typically 6 cycles for advanced stage disease

Abbreviated cycles (typically 3 or 4) can be given for early stage disease with or without radiotherapy after discussion in the MDT.

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**DOSE MODIFICATIONS****Haematological Dose Reductions (Discuss with consultant)****On the day of treatment:**

Neutrophils $\geq 1 \times 10^9/L$	100% dose
Neutrophils $0.5 - <1 \times 10^9/L$	If patient is fit and well, proceed with chemo and give G-CSF from Day 6 if not already prescribed. If patient is unwell, delay for 1 week.
Neutrophils $<0.5 \times 10^9/L$	Consider delay by one week
Platelets $\geq 75 \times 10^9/L$	100% dose
Platelets $50 - 74 \times 10^9/L$	Consider 75% of cyclophosphamide and doxorubicin dose
Platelets $<50 \times 10^9/L$	Consider delay by one week

Consider G-CSF secondary prophylaxis after 1 episode of febrile neutropenia.

**Doxorubicin:**

Renal impairment	Hepatic impairment	
GFR $>10\text{mL}/\text{min}$ : no dose adjustment is needed GFR $<10\text{mL}/\text{min}$ : no need for dose adjustment is expected Hemodialysis: 75% of the original dose may be considered	Bilirubin micromol/L	Dose
	20-50	50%
	51-86	25%
	$>86$ or Child-Pugh C	omit

Doxorubicin maximum cumulative dose (additive to other anthracyclines):

450-550  $\text{mg}/\text{m}^2$  (in normal cardiac function)

400  $\text{mg}/\text{m}^2$  (in patients with cardiac dysfunction or exposed to mediastinal irradiation).

Consider dose reduction in the event of cardiac impairment.

**Vincristine:**

Renal impairment	Hepatic impairment
Renal impairment or Hemodialysis: no need for dose adjustment is expected	Bilirubin $> 51$ micromol/L 50% dose

**Vincristine** In the presence of motor weakness or sensory symptoms, discuss reducing or withholding vincristine with a consultant.

**Cyclophosphamide:**

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Renal impairment		Hepatic impairment
<b>GFR (mL/min)</b>	<b>Dose</b>	Mild and moderate: no need for dose adjustment is expected.  Severe: not recommended, due to risk of reduced efficacy.
≥30	100%	
10-29	75%	
<10	Not recommended, if unavoidable consider 50%	
Hemodialysis	Not recommended, if unavoidable consider 50%	

## INVESTIGATIONS

FBC, renal and liver profiles.

## CONCURRENT MEDICATION

Allopurinol	300 mg daily for 7 days starting 24-48 hours prior to chemotherapy (first course / cycle only)
Omeprazole	20mg once a day for the duration of steroid treatment in regimen
Aciclovir	200 mg three times a day for duration of treatment and for 3 months after completion
Mesna (in patients with pre-existing bladder disorders)	Regimen 1: Mesna PO 300mg/m <sup>2</sup> (40% of IV cyclophosphamide dose), starting at 2 hours before cyclophosphamide injection, every 4 hours for 3 doses. Regimen 2: Mesna IV 150mg/m <sup>2</sup> (20% of IV cyclophosphamide dose), immediately before cyclophosphamide injection, followed by Mesna PO 300mg/m <sup>2</sup> (40% of IV cyclophosphamide dose) at 2 and 6 hours after the intravenous mesna dose.  In patients at high-risk of urothelial toxicity a shorter interval may be left between oral mesna doses, or the number of doses increased, or both.
G-CSF	Starting from Day 6 for 5-7 days. See "Drug Regimen" and "Dose Modification".
Bone Protection	See <b>Bone Protection in Lymphoma Supportive Care</b> document regarding Calcium supplementation and use of Zoledronic acid 5mg IV single dose with Cycle 1 (or Cycle 2 if a dental assessment is required)

Consider PCP prophylaxis if patient is being treated for post-transplant lymphoproliferative disorder or if another risk factor is present, e.g. immunosuppressive medication.

## EMETIC RISK

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High.

## EXTRAVASATION RISK

Cyclophosphamide: neutral  
Doxorubicin: vesicant  
Rituximab: neutral  
Vincristine: vesicant

## ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

- Rituximab - severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. Hepatitis B reactivation – see pathway for treatment and management of HBV positive patient.
- Cyclophosphamide may irritate the bladder mucosa. Patients should be encouraged to drink a minimum of three litres of fluid per 24 hours.
- Cardiotoxicity - monitor cardiac function. Doxorubicin may be stopped or replaced by a non-cardiotoxic agent in future cycles if signs of cardiotoxicity, e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.
- Vincristine may cause neurotoxicity.
- Steroid side effects – monitor BMs.

## TREATMENT RELATED MORTALITY

1-5%

## REFERENCES

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6. Pfreundschuh M et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006; 7:379-91.
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8. Zoledronic acid Operational Policy (L.132). Lymphoma NSSG Page.
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Review

Name	Revision	Date	Version	Review date
Cheuk-kie Jackie Cheung (Haematology Pharmacist)	Cycle frequency section updated with IPI scores	July 2017	1.2	
Cheuk-kie Jackie Cheung (Haematology Pharmacist)	Removal of fluconazole	May 2018	1.3	
NSSG Lymphoma Group	Annual protocol review	May 2019	1.4	
Cheuk-kie Jackie Cheung (Haematology Pharmacist)	Addition of PTLD under PCP prophylaxis consideration	Sep 2019	1.5	May 2021
Quality Manager	Addition of nursing care plan	July 2020	1.6	May 2021
Sara Castro (Advanced Haematology Pharmacist)	Annual protocol review	April 2021	1.7	May 2023

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## Nursing Care Plan: CHOP-21 +/- Rituximab

**Indication:** Lymphoma, Histiocytosis

**Frequency:** Given every 3 weeks for up to 6 cycles with curative intent. (May be 4 weekly for low grade NHL)

**Alopecia:** yes

**Emetic risk:** high

**C = CYCLOPHOSPHAMIDE:** Alkylating agent.

Administered as IV bolus on day 1.

**Classification of extravasation:** neutral.

**Emetic risk:** high (when used in combination with doxorubicin).

**Side effects:** nasal stuffiness (can be reduced by slowing rate of administration), dizziness, nausea and vomiting, diarrhoea, anorexia, taste changes neutropenia, bone marrow suppression, alopecia, risk of haemorrhagic cystitis in patients with pre-existing bladder conditions.

**H = DOXORUBICIN (Hydroxydoxorubicin):** Anthracycline antibiotic.

Administered as IV bolus on day 1.

**Classification of extravasation:** vesicant.

**Emetic risk:** high (when used in combination with cyclophosphamide).

**Side effects:** anthracycline flare (red flare along vein), vein pain, nausea and vomiting, alopecia, mucositis, red urine, cardiotoxicity (may be severe), palmer/planter, bone marrow depression, nail and skin pigmentation.

**O = VINCRISTINE (Oncovin):** Vinca Alkaloid.

Administered as 10 minute IV infusion on day 1.

**Classification of extravasation:** vesicant.

**Emetic risk:** low.

**Side effects:** cold sensation along vein, jaw pain, constipation, peripheral neuropathy, alopecia.

**P = PREDNISOLONE:** Steroid.

Administered orally on Days 1-5.

**Side effects:** increased appetite, GI disturbance, mood swings, restlessness, insomnia, hyperglycaemia, increased susceptibility to infection.

**RITUXIMAB:** Monoclonal antibody for CD 20.

Administered as IV infusion.

**Classification of extravasation:** neutral.

**Emetic risk:** low.

**Side effects:** risk of anaphylaxis, severe dyspnoea, bronchospasm and hypoxia

- Infusion reactions (Most common during first infusion - PREMED 30 MINS PRIOR TO INFUSION): fever, chills, rigors, urticaria, nausea, hypotension, dizziness, cough, chest tightness, back pain.
- Rituximab can cause hypotension. Consider withholding anti-hypertensives 12 hours prior to Rituximab (especially first dose).
- Risk of tumour-lysis syndrome, especially with bulky disease.
- Post infusion side effects: flu-like symptoms, fever, diarrhoea
- **For first Rituximab:**
  - Ensure patient is treated on a bed.

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- In DTU setting (where the patient is visually in front of the nursing station with very close observation): Record baseline vital observations and then if patient reacts. On the ward setting: record vital observations every 30 minutes for the first two hours and then hourly. To have close observation.
- Have anaphylaxis box nearby.
- Increment drug infusion rate as per protocol. *Note there are different rates for first and subsequent treatments and for different doses.*
- Educate patients re possible reactions and the importance of reporting any symptoms immediately.
- **If patient reacts to Rituximab:**
  - Stop infusion.
  - Record observations.
  - Seek an immediate medical review.
  - Consider administration of Hydrocortisone, Chlorphenamine, Oxygen, Salbutamol nebuliser depending on type and severity of reaction.
  - Restart infusion at same or previous rate after 30 minutes if symptoms resolved.

**Regime Specific Considerations**

- Patients over 70 years old routinely receive a 50% dose reduction of Vincristine.
- Check if your patient needs GCSF. This is sometimes given in patients over 70 years old, those with immunosuppression, and those who have had a previous episode of neutropenic sepsis. Ensure patient/carer are taught to self-administer GCSF. Arrange a district nursing referral and prescription if this is not possible.
- Suggested order of administration Doxorubicin, Cyclophosphamide, Vincristine, Rituximab.
- When given peripherally, Vincristine must be administered via a gravity drip, never through a pump. The nurse must remain with the patient throughout the infusion in order to detect any signs of extravasation.
- Advise patients that it is important to maintain fluid intake of at least 3 litres a day for next few days. Cyclophosphamide may irritate bladder mucosa.

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