Thames Valley
Strategic Clinical Network

R-CHOP-21 / CHOP-21

INDICATION

Lymphoma
Histiocytosis

Omit rituximab if CD20-negative.

TREATMENT INTENT

Disease modification or curative 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, magnesium, creatinine, LFTs, glucose, Igs, β_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 *if clinically indicated*.
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.

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^2 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^2 IV bolus.

VINCRISTINE 1.4 mg/m^2 (maximum 2 mg*) IV infusion in 50 mL sodium chloride 0.9% over 10 minutes.
CYCLOPHOSPHAMIDE 750 mg/m^2 IV bolus or IV infusion over 20 mins in 250 mL sodium chloride 0.9%.

Days 1 to 5 **PREDNISOLONE** 40 mg/m^2 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 if patient is over 70 years of age or is immunosuppressed prior to chemotherapy.

CYCLE FREQUENCY

Cycle repeats every three weeks, support with G-CSF when necessary.
(Patients with low grade NHL may need 4 weekly cycles).

Low IPI patients: 6 cycles of R-CHOP/ CHOP.

High IPI patients: 6 cycles of R-CHOP/ CHOP, followed by 2 rituximab 375mg/m^2 infusion every 3 weeks which can be scheduled to the day before intravenous high-dose methotrexate infusion if CNS prophylaxis is indicated.

RESTAGING

Give 4 courses and restage with CT. If progressive or stable disease, consider other treatment.
If partial or complete remission, continue to 6 courses of R-CHOP.

DOSE MODIFICATIONS

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

Neutrophils ≥1 x 10^9/L	100% dose
Neutrophils 0.5 - <1 x 10^9/L	If patient is fit and well, proceed with chemo and give G-CSF from Day 6. If patient is unwell, delay for 1 week.
Neutrophils <0.5 x 10^9/L	Delay by one week
Platelets ≥75 x 10^9/L	100% doe
Platelets 50 – 74 x 10^9/L	Give 75% of cyclophosphamide and doxorubicin dose
Platelets <50 x 10^9/L	Delay by one week

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

Doxorubicin:

Renal impairment	Hepatic impairment	
Discuss with consultant if renal impairment severe	**Bilirubin micromole/L**	**Dose**
	20-51	50%
	51-85	25%
	>85	omit
	If AST 2-3 x normal, give 75% dose If AST >3 x ULN, give 50% dose	

Doxorubicin maximum cumulative dose (additive to other anthracyclines):
450-550 mg/m^2 (in normal cardiac function)
400 mg/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
	Bilirubin 26-51 micromol/L or ALT/AST 60-180 u/L 50% dose Bilirubin >51 micromol/L & normal ALT/AST 50% dose Bilirubin >51 micromol/L & ALT/ AST >180 u/L omit

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

Cyclophosphamide:

Renal impairment		Hepatic impairment
GFR (mL/min)	**Dose**	Clinical decision. Exposure to active metabolites may not be increased, suggesting dose reduction may not be necessary.
>20	100%	
10-20	75%	
<10	50%	
Clinical decision – consider whether patient is being treated with high dose treatment.		

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)
Ranitidine (or PPI - discuss with consultant)	150mg twice daily 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^2 (40% of IV cyclophosphamide dose), starting at 2 hours before cyclophosphamide injection, every 4 hours for 3 doses. Regimen 2: Mesna IV 150mg/m^2 (20% of IV cyclophosphamide dose), immediately before cyclophosphamide injection, followed by Mesna PO 300mg/m^2 (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 if required. See “Drug Regimen” and “Dose Modification”.

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

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 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

1. Chaganti S et al. BSH Guidelines for the management of diffuse large B- cell Lymphoma. BJH 2016; 174(1):43-56
2. Feugier P et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol. 2005; 23(18):4117-26.
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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.
7. UCLH - Dosage Adjustment for Cytotoxics in Hepatic Impairment (Version 3 - updated January 2009).
8. UCLH - Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3 - updated January 2009).

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