PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

CHOP +/- Rituximab Non-Hodgkin Lymphoma

PROTOCOL REF: MPHACHORHA
(Version No. 2.0)

Approved for use in:

- R-CHOP: B cell non-Hodgkin lymphoma
- CHOP: Non-Hodgkin lymphoma not expressing CD20

Dosage:

Drug	Dose	Route	Frequency
Rituximab	375mg/m^2	IV	Once daily day 1
Cyclophosphamide	750mg/m^2	IV	Once daily day 1
Doxorubicin	50mg/m^2	IV	Once daily day 1
Vincristine	1.4mg/m^2 (Max 2mg/dose)	IV	Once daily day 1
Prednisolone	100mg	PO	Once daily days 1 to 5

Cycle frequency:

- R-CHOP: Every 21 days for 3-6 cycles, depending on the stage of disease
- CHOP: Every 21 days for 6-8 cycles

Administration:

- Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with rituximab.
- Doxorubicin may impart a red colour to the urine. Patients should be cautioned that this does not pose any health hazards.

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

Pre-infusion medication:

- Paracetamol tablet 1gram oral (PO)
- Chlorphenamine injection 10mg intravenous (IV)
- Ensure oral steroids have been taken at least 30 minutes prior to rituximab

Supportive medication:

- Ondansetron 8mg twice a day for 5 days.
- Metoclopramide 10mg three times a day when required.
- Allopurinol (dose based on renal function) for the first two cycles.
- Docusate sodium 200mg twice a day when required.
- Filgrastim (G-CSF, e.g. Zarzio) if required, as secondary prophylaxis. Consideration can be given to using as primary prophylaxis at clinician discretion. Dose is weight dependent. To start on day 5 and administer subcutaneously once daily for 5 days.
- Aciclovir 400mg twice a day and co-trimoxazole 480mg daily are not generally required but may be given at the discretion of the prescriber.

Extravasation risk (if applicable):

- Rituximab: non-vesicant
- Cyclophosphamide: non-vesicant
- Doxorubicin: vesicant
- Vincristine: vesicant

Refer to the CCC policy for the ‘Prevention and Management of Extravasation Injuries’

Dosing in renal and hepatic impairment:

Consideration can be given to full dose therapy if liver dysfunction is caused by lymphoma.

<table>
<tr><th colspan="5">Dose Modifications</th></tr>
<tr><th>Drug</th><th colspan="2">Renal Impairment</th><th colspan="2">Hepatic Impairment</th></tr>
<tr><td>Rituximab</td><td colspan="2">No dose adjustment necessary</td><td colspan="2">No dose adjustment necessary</td></tr>
<tr><td rowspan="4">Cyclophosphamide</td><td>CrCl (ml/min)</td><td>Modification</td><td colspan="2" rowspan="4">No dose adjustment necessary</td></tr>
<tr><td>>20</td><td>100%</td></tr>
<tr><td>10-20</td><td>75%</td></tr>
<tr><td><10</td><td>50%</td></tr>
<tr><td rowspan="4">Doxorubicin</td><td colspan="2" rowspan="4">No dose adjustment necessary</td><td>Parameter</td><td>Modification</td></tr>
<tr><td>AST 2-3 x ULN</td><td>75%</td></tr>
<tr><td>Bilirubin 21-50
or
AST >3 x ULN</td><td>50%</td></tr>
<tr><td>Bilirubin 51-85</td><td>25%</td></tr>
<tr><td rowspan="4">Vincristine</td><td colspan="2" rowspan="4">No dose adjustment necessary</td><td>Parameter</td><td>Modification</td></tr>
<tr><td>Bilirubin 26-51
or
AST/ALT 60-180</td><td>50%</td></tr>
<tr><td>Bilirubin >51
and
AST/ALT normal</td><td>50%</td></tr>
<tr><td>Bilirubin >51
and
AST/ALT >180</td><td>Omit</td></tr>
</table>

Interactions:

- Mould active azoles (e.g. posaconazole) should be avoided in combination with vincristine as there is an increased risk of neurotoxicity. Fluconazole can be given but signs of neurotoxicity should be monitored.
- Phenytoin given with vincristine and/or doxorubicin may reduce blood levels of the anticonvulsant and to increase seizure activity. Therapeutic drug monitoring (TDM) for phenytoin would be advised.
- Concomitant administration of inhibitors of CYP450 and/or P-glycoprotein might lead to increased plasma concentrations of doxorubicin and thereby increased toxicity.
- Clozapine may increase the risk/severity of the haematologic toxicity of doxorubicin
- Doxorubicin may reduce oral bioavailability of digoxin.

Treatment schedule:

Day	Drug	Dosage	Route	Diluent and Rate
1	**Paracetamol**	**1g**	**PO**	At least 30 minutes before rituximab
	Chlorphenamine	**10mg**	**IV**	IV bolus at least 30 minutes before rituximab
	Prednisolone	**100mg**	**PO**	At least 30 minutes before rituximab
	Rituximab	**375mg/m^2**	**IV**	**≤450mg** in 250mL 0.9% sodium chloride **≥500mg** in 500mL 0.9% sodium chloride Rate as per rituximab infusion guideline
	Ondansetron	**8mg**	**IV**	100mL 0.9% sodium chloride Over 15 minutes
	Cyclophosphamide	**750mg/m^2**	**IV**	250mL 0.9% sodium chloride Over 30 minutes
	Doxorubicin	**50mg/m^2**	**IV**	Slow IV bolus
	Vincristine	**1.4mg/m^2**	**IV**	50mL 0.9% sodium chloride Over 5-10 minutes
2 to 5	**Prednisolone**	**100mg**	**PO**	Orally once a day in the morning

Main toxicities:

Infusion-related reactions, anaemia, myelosuppression, cardiotoxicity, neutropenia, fatigue, diarrhoea, nausea, pyrexia and neurotoxicity.

Haematological toxicities (no modifications required for cycle 1)	
Neutrophils (x10^9/L)	**Modification**
<1 on day of treatment	Delay cycle by 1 week. Discuss use of G-CSF or dose reductions for further cycles with consultant
Any febrile neutropenia following any cycle of CHOP	All subsequent cycles should be given with GCSF support. Consider dose reduction.
Febrile neutropenic episode despite G-CSF support	Consider reduction of cyclophosphamide and doxorubicin by 50% for all subsequent cycles
Platelets (x10^9/L)	**Modification**
<100 on day of treatment	Delay cycle by 1 week.
Second delay due to thrombocytopenia	Consider reducing dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles

Non-Haematological toxicities:	
Rituximab	
Infusion-related Reactions	Severe infusion-related reactions with fatal outcome can have an onset ranging within 30 minutes to 2 hours after starting the first rituximab infusion. They can be characterised by pulmonary events and in some cases included rapid tumour lysis and features of tumour lysis syndrome (TLS) in addition to fever, chills, rigors, hypotension, urticaria, and angioedema. Severe cytokine release syndrome may occur. Monitor patients closely. Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm or hypoxia should have infusion interrupted immediately. The patient should then be evaluated for evidence of TLS including appropriate laboratory tests and, for pulmonary infiltration, with a chest x-ray. The infusion should not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest x-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same adverse reaction occurs for a second time, the decision to stop the treatment should be seriously considered on a case-by-case basis. Anaphylactic and other hypersensitivity reactions may occur. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Mild or moderate infusion-related reactions usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms

Vincristine		
	Grade	**Modification**
Neurotoxicity	Grade 2 motor weakness or grade 3 sensory toxicity	Give 50% vincristine
	Higher grades of neurological toxicity	Omit vincristine
Elderly Population	Consider reducing the dose to 1mg for patients >70years old.	

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2 onwards	Ongoing
Informed Consent	X			
Clinical Assessment	X	X	X	
SACT Assessment (to include PS and toxicities)	X	X	X	
Blood pressure	X	X	X	Continuous monitoring required if on rituximab
Temperature, respiratory rate, pulse		X	X	Continuous monitoring required if on rituximab
FBC	X	X	X	
U&E, LFTs and bone profile	X	X	X	
CrCl (Cockcroft and gault)	X			
HbA1C	X			Repeat as clinically indicated
Serum immunoglobulins	X			Repeat as clinically indicated
CT or PET CT Scan	X			Interim and end of treatment scans as indicated
Bone Marrow	X			If clinically indicated
ECHO or MUGA Scan	X			Before treatment in patients over 60 or with pre-existing cardiac disease
Viral screening (Hepatitis B cAb and SAg, Hep C & HIV)	X			
Pregnancy test	X			Where appropriate
Height	X			
Weight	X	X	X	

References:

1. NHSE Cheshire & Merseyside Strategic Clinical Networks Protocol. R-CHOP, Haematology CNG, 2015
2. Summary of Product Characteristics, Truxima 500mg Concentrate for Solution for Infusion, Napp Pharmaceuticals Ltd. July 2019. Monograph available from: http://www.medicines.org.uk [accessed on 06th August 2019].
3. Summary of Product Characteristics, Cyclophosphamide 500mg Powder for Solution for Injection or Infusion, Sandoz Limited. June 2017. Monograph available from: http://www.medicines.org.uk [accessed on 06th August 2019].
4. Summary of Product Characteristics, Doxorubicin 2mg/ml Concentrate for Solution for Infusion, Accord Healthcare Ltd. June 2016. Monograph available from: http://www.medicines.org.uk [accessed on 06th August 2019].
5. Summary of Product Characteristics, Vincristine Sulphate 1mg/1ml Injection, Hospira UK Ltd. October 2018. Monograph available from: http://www.medicines.org.uk [accessed on 06th August 2019].
6. NICE Guideline NG52: *''Non-Hodgkin's lymphoma: diagnosis and management''*, National Institute for Health and Clinical Excellence, July 2016

Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
Date document posted on the Intranet	For completion by DCM

Version History

Date	Version	Author name and designation	Summary of main changes
23/09/2019	1	**Niamh McLaughlin - Advanced Pharmacist**	V1.0 New CCC protocol created
23/01/2023	1.1	**Daniel Dutton – Advanced Pharmacist**	V2.0 Protocol updated to current CCC Format Protocol updated to remove rituximab rate information – signposted to approved rituximab infusion protocol