PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

CVP +/- Rituximab Non-Hodgkin's Lymphoma

PROTOCOL REF: MPHACVPRHA
(Version No. 2.0)

Approved for use in:

Non-Hodgkin lymphoma (NHL). Rituximab should only be added to CVP if CD20+ disease

Blueteq is <u>not</u> required

Dosage:

Drug	Dose	Route	Frequency
+/- Rituximab	**375mg/m^2**	IV infusion	Day 1
Cyclophosphamide	**750mg/m^2**	IV infusion	Day 1
Vincristine	***1.4mg/m^2 (max 2mg)**	IV infusion	Day 1
Prednisolone	**40mg/m^2**	Oral	Days 1 to 5

*Consider reducing the dose to 1mg for patients >70years old.

Cycle frequency is every 21 days for up to 8 cycles.

Administration:

- Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential must employ effective contraceptive methods during and for 12 months after treatment with rituximab. For further contraceptive guidance for the drugs in this regime please consultant the individual SPCs
- Prednisolone needs to be taken at least 30 minutes prior to rituximab so patient should be counselled to take it prior to admission to the day ward on day one.
- Since hypotension may occur during rituximab administration, consideration should be given to withholding anti-hypertensive medicines 12 hours prior to the rituximab infusion.

- Reactivation of Hepatitis B can occur if rituximab is administered to people previously exposed to Hepatitis B. Virology screening including Hepatitis B Core Antibody and Surface Antigen should be carried out and confirmed as negative prior to administration of rituximab. Any positive or equivocal result should be discussed with Consultant.
- Cyclophosphamide may irritate the bladder mucosa. Patients should be encouraged to drink plenty of fluids before and after their cyclophosphamide infusion, to reduce the risk of urinary tract toxicity.

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

Pre-infusion medicines:

- Paracetamol oral 1g (prior to rituximab)
- Chlorphenamine IV bolus 10mg (prior to rituximab)
- Prednisolone (dose as above) should be taken at least 30 minutes prior to rituximab
- Ondansetron oral 8mg (prior to chemotherapy)

Supportive medicines:

- Allopurinol once daily for first one or two cycles
- Ondansetron oral 8mg twice daily for 5 days
- Metoclopramide oral 10mg three times daily when required
- Docusate oral 100mg twice daily when required
- Filgrastim S/C 30 or 48 million units once daily from day 5 for 5 days if required for secondary prophylaxis of neutropenia. Primary prophylaxis can be considered in cases of bone marrow infiltration or if deemed clinically appropriate for any other reason (30million units if <70kgs and 48 million units >70kgs).
- Aciclovir 400mg twice daily and co-trimoxazole 480mg once daily are not generally required but may be given at the discretion of the prescriber.

Extravasation risk:

Rituximab: non-vesicant

Cyclophosphamide: non-vesicant

Vincristine: vesicant

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

Dosing in renal and hepatic impairment:

Renal Dose Modifications		
Drug	**Creatinine Clearance (mL/min)**	**Dose Adjustment**
Cyclophosphamide	10 - 29	75% dose
	< 10 or haemodialysis	Not recommended. If unavoidable consider 50% dose
Vincristine	No dose adjustment required	

Hepatic Dose Modifications		
Drug	**Bilirubin (micromol/L)**	**Dose Adjustment**
Cyclophosphamide	Severe liver dysfunction	Not recommended.
Vincristine	>51	50% dose

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.
- Vincristine may reduce levels of phenytoin – monitor phenytoin levels.
- The neurotoxicity of vincristine may be additive with that of isoniazid and other drugs acting on the nervous system.
- Caution should be exercised when administering vincristine in patients also taking drugs known to inhibit/induce CYP450, or in patients with hepatic dysfunction.
- Cyclophosphamide is inactive until it is metabolised in the liver, mainly by CYP2A6, 2B6, 2C9, 2C19 and 3A4, into two active metabolites. There are therefore a number of drug

that have the potential to interact with cyclophosphamide, please refer to the cyclophosphamide SPC for full details.

For full details of potential drug interactions please refer to the individual drug SPCs

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Prednisolone**	**40mg/m^2**	**PO**	30 minutes before rituximab
	Paracetamol	**1g**	**PO**	30 minutes before rituximab
	Chlorphenamine	**10mg**	**IV**	Bolus bolus over 3-5 minutes
	+/- Rituximab*	**375mg/m^2**	**IV infusion**	500ml** sodium chloride 0.9%
	Ondansetron	**8mg**	**PO**	30 minutes before vincristine
	Vincristine	**1.4mg/m^2 (max dose 2mg)**	**IV infusion**	50ml sodium chloride 0.9% over 15 minutes.
	Cyclophosphamide	**750mg/m^2**	**IV infusion**	250ml sodium chloride 0.9% over 30 minutes.
2 to 5	**Prednisolone**	**40mg/m^2**	**PO**	Give as TTO on day 1

If lymphocytes ≥25x10^9/L then consider splitting the first dose of rituximab (100mg in 100mL sodium chloride 0.9% over 2 hours on day 1 and then the remainder of the dose in 250mL or 500mL sodium chloride 0.9% as per standard infusion rates on day 2). If no IRR then subsequent doses can be given in one infusion.

***Rituximab Infusion Rates**

Refer to CCC Rituximab Administration Guideline.

**Doses of 400mg and 450mg will be in 250mL sodium chloride 0.9%

Main toxicities:

Rituximab
Infusion related reactions, cytokine release syndrome. 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
Cyclophosphamide
Haematuria. Bladder irritation. Bone marrow suppression (anaemia, thrombocytopenia, neutropenia), nausea, vomiting, diarrhoea, constipation
Vincristine
Peripheral neuropathy, jaw pain. Bone marrow suppression (anaemia, thrombocytopenia, neutropenia), nausea, vomiting, diarrhoea, constipation

For full details on toxicities please refer to the individual drug SPCs

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2+	Ongoing
Informed consent	X			
Clinical Assessment	X	X	X	As clinically indicated or at the end of treatment
SACT Assessment (including performance status and toxicity assessment)	X	X	X	Every cycle
FBC	X	X	X	Every cycle
U&E & LFTs & Magnesium	X	X	X	Every Cycle
CrCl (Cockcroft and Gault)	X	X	X	Every cycle
PET CT scan (follicular lymphoma only)	X			Interim CT scan after 3 to 4 cycles and PET CT scan at end of treatment. Or if obvious palpable clinical response, end of treatment PET CT scan only, may be sufficient
CT scan (other low grade lymphomas)	X			Interim CT scan after 3 to 4 cycles and CT scan at end of treatment. Or if obvious palpable clinical response, end of treatment CT scan only, may be sufficient
Blood pressure		X	X	Continuous monitoring required if on Rituximab
Temperature, respiratory rate, pulse		X	X	Continuous monitoring required if on Rituximab
Height	X			
Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2	X			
Pregnancy test	X			Where appropriate
Weight recorded	X	X	X	Every cycle
Blood glucose	X			Repeat if clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Cycle 1 can go ahead despite cytopenias if thought to be due to lymphoma infiltration of the bone marrow.

Proceed on day 1 if:

ANC ≥ 1.0 $x10^9$/L	Platelets ≥ 100 $x10^9$/L

Delay cycle by 1 week if:

ANC < 1.0 $x10^9$/L	Platelets < 100 $x10^9$/L

Consider addition of GCSF for subsequent cycles if delayed due to neutropenia. GCSF should be considered following any instance of febrile neutropenia.

In the event of subsequent delays due to cytopenias consider dose reductions below:

Neutrophils ($x10^9$/L)	And/or	Platelets ($x10^9$/L)	Dose Modification Cyclophosphamide
0.5 – 0.9	And	>100	Consider 75% dose
0.5 – 0.9	And	50 - 100	Consider 50% dose
<0.5	And / or	<50	Omit cyclophosphamide

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

See ‘Dosing in Renal and Hepatic Impairment’.

Infusion Related Reactions

Rituximab

Infusion-related Reactions	Severe infusion-related reactions with fatal outcome can have an onset ranging from 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 no 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

Neuropathy (Vincristine)

Vincristine		
	Grade	**Modification**
Neurotoxicity	Grade 2 motor weakness or grade 3 sensory toxicity	Give 50% vincristine
	Higher grades of neurological toxicity	Omit vincristine

References:

1. Clatterbridge Cancer Centre Rituximab Administration Guideline (V1.0)

2. Truxima 100 mg concentrate for solution for infusion (Rituximab). Celltrion Healthcare UK Limited. Summary of Product Characteristics. Last updated 13/12/22. Avaialble Truxima 100 mg concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Last accessed 01/08/23
3. Cyclophosphamide 1000 mg Powder for Solution for Injection or Infusion. Sandoz Limited. Summary of Product Characteristics. Last updated 06/04/21. Available: Cyclophosphamide 1000 mg Powder for Solution for Injection or Infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk). Last accessed 01/08/23
4. Vincristine Sulphate 1 mg/ml Injection. Hospira UK Ltd. Summary of Product Characteristics. Last updated 14/03/23. Avaialble: Vincristine Sulphate 1 mg/ml Injection - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk). Last accessed 01/08/23
5. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.
6. Thames Valley Strategic Clinical Network RCVP Protocol

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
May 2020	1.0	**Aileen McCaughey – Advanced Pharmacist HO**	**New protocol**
Sept 2023	2.0	**Jade Marsh – Advanced Pharmacist HO**	**3 yearly review. Transferred to new template. Toxicity information added. Administration information added. Dose modifications updated.**