SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

R-CEOP

Non-Hodgkins Lymphoma

PROTOCOL REF: MPHARCEOP
(Version No. 1.0)

Approved for use in:

Treatment of Non Hodgkin CD20 positive lymphoma for patients not suitable for anthracycline therapy

Dosage:

Drug	Dose	Route	Frequency
Rituximab	**375mg/m^2**	IV infusion	Day 1 only
Cyclophosphamide	**750mg/m^2**	IV infusion	Day 1 only
Etoposide	**50mg/m^2**	IV infusion	Day 1 only
Vincristine	**1.4mg/m^2**	IV bolus	Day 1 only
Etoposide	**100mg/m^2 ***	PO	Days 2 and 3
Prednisolone	**100mg**	PO	Days 1 to 5

*Dose rounded to the nearest 50mg

21 day cycle, for 6 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.
- Etoposide (oral) should be taken an hour before food or on an empty stomach

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

Rituximab pre-infusion medicines:

- Paracetamol PO 1g
- Chlorphenamine IV bolus 10mg
- Prednisolone dose as per schedule should be taken at least 30 minutes prior to rituximab (utilised as a pre-medication, whilst also being part of the regime)

Supportive medicines:

- Allopurinol PO 100mg or 300mg OD (depending on renal function) for first cycle
    - Consider prophylactic rasburicase for patients at high risk of tumour lysis syndrome
- Ondansetron PO 8mg BD for 5 days
- Metoclopramide PO 10mg TDS PRN
- Docusate PO 100mg BD PRN
- Whilst GCSF prophylaxis is not usually required this can be added at the discretion of the consultant if clinically indicated

Extravasation risk:

Rituximab: Non-vesicant

Cyclophosphamide: Non-vesicant

Etoposide: Irritant

Vincristine: Vesicant

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

Interactions:

The main interactions are detailed below however, for a full list and more detailed interaction information please refer to the appropriate SPC

- 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.
- Cyclophosphamide is inactive, but is metabolised in the liver, mainly by CYP2A6, 2B6, 2C9, 2C19 and 3A4, into two active metabolites. Care should be taken when using cyclophosphamide with known inducers/inhibitors of these metabolic pathways
- High dose ciclosporin results in increased exposure to etoposide
- Concomitant phenytoin or phenobarbital therapy is associated with increased etoposide clearance and reduced efficacy
- Co-administration of antiepileptic drugs and etoposide can lead to decreased seizure control due to pharmacokinetic interactions between the drugs.
- Co-administration of warfarin and etoposide may result in elevated international normalized ratio (INR). Close monitoring of INR is recommended (or switching to a LMWH)

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	Paracetamol	1g	PO	At least 30 minutes before rituximab
	Chlorphenamine	10mg	IV	
	Prednisolone	100mg	PO	Orally once a day in the morning **(give at least 30 minutes before rituximab on D1 of cycle)**
	Rituximab	375mg/m^2	IV	In 500ml sodium chloride 0.9% (See rituximab infusion rate policy)
	Ondansetron	8mg	IV	
	Vincristine	1.4mg/m^2 Max dose 2mg)	IV	In 50mL sodium chloride 0.9% over 5-10 minutes **Intravenous Use only. Fatal if given by any other route**

	Etoposide	50mg/m^2	IV	500ml 0.9% sodium chloride over 60 minutes
	Cyclophosphamide	750mg/m^2	IV	In 250mL sodium chloride 0.9% over 30 minutes
2 and 3	Etoposide	100mg/m^2	PO	Dose rounded to the nearest 50mg
2 to 5	Prednisolone	100mg	PO	

Main toxicities:

Infusion-related reactions, anaemia, myelosuppression, cardiotoxicity, neutropenia, fatigue, diarrhea or constipation, nausea, alopecia, pyrexia, cystitis, and neurotoxicity.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2 onwards	Ongoing
Informed Consent	X			
Clinical Assessment	X	X	X	As clinically indicated or at the end of treatment
SACT Assessment	X	X	X	Every cycle
FBC	X	X	X	Every cycle
U&E & LFTs and bone profile	X	X	X	Every Cycle
CrCl (Cockcroft and Gault)	X	X	X	Every cycle
HbA1c	X			
Serum Immunoglobulins	X			Repeat as clinically indicated
CT or PET CT scan	X			At the end of treatment and if clinically indicated
Bone marrow	X			Repeat as clinically indicated
ECG	X			If clinically indicated
Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2	X			
PS recorded	X			
Pregnancy test (if indicated)	X			Where appropriate
Blood pressure measurement	X	X	X	Continuous monitoring required if on rituximab
Temperature, respiratory rate and pulse	X	X	X	Continuous monitoring required if on rituximab
Height and weight recorded	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

Haematological toxicity:

Neutrophils (x 10^9/L)	Dose modifications (cyclophosphamide and etoposide)
≥ 1	100%
0.5 – 0.9	**1st occurrence:** If patient has not previously been given growth factors and the intent is curative, give 100% of the dose with G-CSF **2nd occurrence:** Delay until neutrophils are ≥ 1 x 10^9/L and then give 50% of original dose and prophylactic growth factors
< 0.5 or febrile neutropenia	**1st occurrence:** Delay until neutrophils ≥ 1 x 10^9/L and then give 75% of the original dose plus G-CSF **2nd occurrence:** Delay until neutrophils are ≥ 1 x 10^9/L and then give 50% of the original dose plus G-CSF
Platelets (x 10^9/L)	Dose modifications (cyclophosphamide and etoposide)
≥ 75	100%
50 – 74	**1st occurrence:** Give 75% of the original dose **2nd occurrence:** Give 50% of the original dose
< 50 or signs of active haemorrhage	**1st occurrence** Delay until the platelets are ≥ 75 and then give 75% of the original dose **2nd occurrence** Delay until the platelets are ≥ 75 and then give 50% of the original dose

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:

Dosing in renal and hepatic impairment:

Renal	Cyclophosphamide	CrCl ≥ 30mL/min: no dose adjustment is necessary CrCl 10-29 mL/min: consider 75% of the original dose CrCl < 10mL/min or haemodialysis: not recommended, is unavoidable consider 50% of the original dose
	Etoposide (IV)	CrCl ≥ 50 ml/min: no dose adjustment is needed CrCl 10-50 ml/min: 75% of the original dose, increase if tolerated HD: not dialysed, consider 75% of the original dose

Hepatic	Consideration can be given to full dose therapy if liver dysfunction is caused by lymphoma				
	Cyclophosphamide	<u>Mild and moderate impairment:</u> no need for dose adjustment <u>Severe impairment:</u> not recommended due to risk of reduced efficacy			
	Etoposide (IV)	Bilirubin < 50 micromol/L	AND	Normal albumin and renal function	No dose adjustment needed
		Bilirubin ≥ 50 micromol/L	OR	Decreased albumin levels	Consider 50% of the original dose (increase if tolerated)
	Vincristine	Bilirubin < 51micromol/L		No dose adjustment	
		Bilirubin ≥ 51 micromol/L		50% of the original dose	

Rituximab	
Infusion related reactions (IRRs)	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		
Neurotoxicity	**Grade**	**Modification**
	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 > 70 years old	

References:

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Circulation/Dissemination

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Version History

Date	Version	Author name and designation	Summary of main changes
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