PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Dose Adjusted (DA) EPOCH +/- Rituximab High Grade Non-Hodgkin Lymphoma

PROTOCOL REF: MPHADAEPOC
(Version No. 1.0)

Approved for use in:

- DA-EPOCH-R: High grade non-Hodgkin lymphoma
- DA-EPOCH: High grade non-Hodgkin lymphoma not expressing CD20

Dosage:

Drug	Dose level -2	Dose level -1	Dose level 1	Dose level 2	Dose level 3	Route	Frequency
Prednisolone	60 mg/m^2	60 mg/m^2	60 mg/m^2	60 mg/m^2	60 mg/m^2	PO	Twice daily* Days 1 to 5
Rituximab	375 mg/m^2	375 mg/m^2	375 mg/m^2	375 mg/m^2	375 mg/m^2	IV	Once daily Day 1
Etoposide	50 mg/m^2/day	50 mg/m^2/day	50 mg/m^2/day	60 mg/m^2/day	72 mg/m^2/day	IV	Once daily Days 1 to 4
Doxorubicin	10 mg/m^2/day	10 mg/m^2/day	10 mg/m^2/day	12 mg/m^2/day	14.4 mg/m^2/day	IV	Once daily Days 1 to 4
Vincristine	0.4 mg/m^2/day	0.4 mg/m^2/day	0.4 mg/m^2/day	0.4 mg/m^2/day	0.4 mg/m^2/day	IV	Once daily Days 1 to 4
Cyclophosphamide	480 mg/m^2	600 mg/m^2	750 mg/m^2	900 mg/m^2	1080 mg/m^2	IV	Once daily Day 5
*Although prednisolone dose was given as 60mg/m^2 twice daily in reference studies, some centres have reduced prednisolone to 60mg/m^2 once daily due to patient tolerability							

Cycle frequency:

- Every 21 days for 6-8 cycles, depending on the stage of disease

Administration:

- Patients will require central venous access with at least two lumens, a dual lumen PICC is sufficient for this protocol.
- 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.
- Etoposide, doxorubicin and vincristine will be given as continuous infusions on days 1 to 4. These will be supplied as 24 hourly infusion bags as below:
    - Etoposide in 500mL 0.9% sodium chloride
    - Doxorubicin and vincristine in 500mL 0.9% sodium chloride

Emetogenic risk:

Moderate to highly emetogenic.

Supportive treatments:

Rituximab pre-infusion medication:

- Paracetamol tablet 1000mg oral (PO)
- Chlorphenamine injection 10mg intravenous (IV)
- Ensure oral steroids have been taken at least 30 minutes prior to rituximab

Supportive medication:

- Allopurinol - (dose based on renal function) for cycle 1 only
- Co-trimoxazole - 480mg daily
- Docusate sodium - 200mg twice a day when required.
- Metoclopramide - 10mg three times a day when required.
- Ondansetron - 8mg twice a day for 5 days.

- Filgrastim (G-CSF, e.g. Zarzio) - Dose is weight dependent. To start on day 5 and administer subcutaneously once daily for 7 days until ANC has recovered (>1.0x10^9/L).
- Mesna PO 800mg for 3 doses at 4 hourly intervals starting 2 hours prior to cyclophosphamide infusion. This is for patients at high risk of cyclophosphamide induced haemorrhagic cystitis (in particularly with dose level 2 and 3). The dose may be increased to four dosed at 3 hourly intervals in patients at higher risk of urothelial toxicity.
- Sodium Chloride 0.9% 500mL over 30mins to be prescribed for those patients at high risk of cyclophosphamide induced haemorrhagic cystitis / urothelial toxicity.
- Antiviral and antifungal prophylaxis is not generally required but may be added at the discretion of the treating clinician.
- For patients with a higher risk of infection, e.g. HIV positive patients, please prescribe prophylactic azithromycin 250mg-500mg OD until neutrophils >1x10^9/L

Extravasation risk:

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

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

Dosing in renal and hepatic impairment:

Dose Modifications		
Drug	**Renal Impairment**	**Hepatic Impairment**
Rituximab	No dose adjustment necessary	No dose adjustment necessary
Cyclophosphamide	CrCl ≥30 mL/min: 100% CrCl 10-29: 75% Not recommended in CrCl <10mL/min. If absolutely necessary consider 50% dosing	Mild and moderate: no need for dose adjustment is expected. Severe: not recommended, due to risk of reduced efficacy
Etoposide	CrCl 10-50mL/min: 75% dose CrCl <10mL/min: consider 50% dose. Subsequent doses should be based on clinical response	Bilirubin <50micromol/L and normal albumin and normal renal function: no need for dose adjustment is expected Bilirubin ≥50micromol/L or decreased albumin levels: consider 50% of the dose, increase if tolerated
Doxorubicin	No dose adjustment necessary	Bilirubin 20-50 micromol/L: 50% of the original dose Bilirubin 51 micromol/L – 86 micromol/: 25% of the original dose Bilirubin > 86 micromol/L or Child-Pugh C: not recommended
Vincristine	No dose adjustment necessary	Bilirubin > 51 microimol/l: 50% of original dose
Consideration can be given to full dose therapy in the presence of hepatic impairment, if this is caused by lymphoma.		

Interactions:

Main interactions listed below – refer to product SmPC for full list of drug 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 to 5	**Prednisolone**	**60mg/m^2**	**PO**	Twice daily. Ensure day 1 dose is taken bolus at least 30 minutes before rituximab
1	**Paracetamol**	**1g**	**PO**	At least 30 minutes before rituximab
	Chlorphenamine	**10mg**	**IV**	IV bolus 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
1 to 4	**Etoposide**	**See above**	**IV**	500mL 0.9% sodium chloride Over 24 hours
	Doxorubicin	**See above**	**IV**	Doxorubicin and vincristine combined in 500mL 0.9% sodium chloride Over 24 hours
	Vincristine	**See above**	**IV**	
5	**Cyclophosphamide**	**See above**	**IV**	250mL 0.9% sodium chloride Over 30 minutes

Main toxicities:

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

Haematological toxicities
Cyclophosphamide, Doxorubicin and Etoposide dose adjustment paradigm: Cycle one should always be dosed at dose level one (prior to dose modifications for renal/hepatic impairment) The doses in cycle 2 onwards may be adjusted as below based on results of TWICE-WEEKLY complete FBC obtained 3 days apart, e.g. days 9, 12, 15, 18. Dose adjustments apply to a whole treatment cycle and are based on neutrophil count at nadir of previous cycle. • If nadir ANC ≥ 0.5 x 10^9/L, increase by 1 dose level. • If nadir ANC < 0.5 x 10^9/L on 1 OR 2 measurements, maintain the same dose level. • If nadir ANC < 0.5 x 10^9/L on AT LEAST 3 measurements, decrease by 1 dose level. • If platelet nadir < 25 x 10^9/L, reduce by 1 dose level regardless of ANC. Note: Dose adjustments above starting dose level (level 1) apply to etoposide, doxorubicin and cyclophosphamide. Dose adjustments below starting dose level (level 1) apply to cyclophosphamide only

Non-Haematological toxicities:
Vincristine
In the presence of motor weakness or severe sensory symptoms, discuss reducing or withholding vincristine with a consultant. Consider the following dose adjustments: • Reduce dose 25% if grade 2 motor neuropathy develops • Reduce dose 50% if grade 3 motor or sensory neuropathy develops • Patients should remain on the reduced dose for the duration of the course unless there is significant clinical reason to increase the dose. In this case it should be increase by one dose level per cycle.

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 **Twice weekly**	X **Twice Weekly**	FBC should be done twice weekly as above to support the dose adjustment paradigm
U&E, LFTs and bone profile	X	X	X	
CrCl (Cockcroft and gault)	X			
Serum immunoglobulins	X			Repeat as clinically indicated
CT or PET CT Scan	X			Interim and end of treatment scans as indicated
Bone Marrow	If clinically indicated			Repeat as 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	

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Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
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Version History

		Author name and designation	Summary of main changes
		Daniel Dutton **Advanced HO Pharmacist**	V1.0 New regimen protocol