PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Escalated BEACOPDac High Grade Hodgkin Lymphoma

PROTOCOL REF: MPHAEHGHL
(Version No. 1.0)

Approved for use in:

- Early stage unfavourable classical Hodgkin lymphoma
- Advanced classical Hodgkin lymphoma
- After a positive interim PET-CT scan post 2 cycles of ABVD

Blueteq registration is not required

Dosage:

Drug	Dose	Route	Frequency
Doxorubicin	**35mg/m^2**	IV infusion	Day 1
Cyclophosphamide	**1250mg/m^2**	IV infusion	Day 1
Etoposide	**200mg/m^2**	IV infusion	Days 1 to 3
Dacarbazine	**250mg/m^2**	IV infusion	Days 2 to 3
Prednisolone	**40mg/m^2**	Oral once a day	Days 1 to 14
Bleomycin	**10,000unit/m^2**	IV infusion	Day 8
Vincristine	**1.4mg/m^2** (max dose 2mg)	IV infusion	Day 8
Filgrastim	**300 or 480 micrograms**	Once a day S/C	Days 9 to 13

Maximum of 6 cycles (21 day cycle)

Administration:

- Doxorubicin may impart a red colour to the urine. Patients should be cautioned that this does not pose any health hazards.
- Hydrocortisone 100mg IV can be added as pre-medication for any patient experiencing infusion reactions with bleomycin
- **Patients will required irradiated blood products (lifelong) –the patients receive information booklets about irradiated blood when counselled by the specialist nurses. It contains an alert car that the patient carries around with them. The specialist nurses then contacts the lab.**

Emetogenic risk:

Severely emetogenic.

Supportive treatments:

- Allopurinol – PO 300mg daily for cycle 1 only
- Aprepitant – PO 125mg D1, 80mg days 2 and 3
- Co-trimoxazole – PO 480mg daily
- Docusate sodium – PO 100mg twice a day when required.
- Metoclopramide – PO 10mg three times a day when required.
- Nystatin – Topical 1mL four times a day
- Omeprazole – PO 20mg daily
- Ondansetron – PO 8mg twice a day for days 1 to 5 and 8 to 10.
- Filgrastim (G-CSF, e.g. Zarzio) - Dose is weight dependent (weight < 70kg: 300 micrograms, weight ≥ 70kg: 480 micrograms). To be given on days 9 to 13.
- Mesna – As per consultant discretion. 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. The dose may be increased to four dosed at 3 hourly intervals in patients at higher risk of urothelial toxicity.

- Antiviral and antifungal prophylaxis is not generally required but may be added at the discretion of the treating clinician.

Extravasation risk:

- Doxorubicin: vesicant
- Cyclophosphamide: non-vesicant
- Etoposide: irritant
- Bleomycin: non-vesicant
- Vincristine: vesicant
- Dacarbazine: 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**
Bleomycin	10-50mL/min: 75% <10mL/min: 50% Haemodialysis: Consider 50%	No recommendations for hepatic impairment – clinician decision
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
Dacarbazine	≥30 mL/min with no hepatic impairment (in patients with combined renal and hepatic dysfunction elimination is impaired): 100% <30mL/min: consider 70% Haemodialysis: consider 70%	Mild and moderate impairment without renal dysfunction (in patients with combined renal and hepatic dysfunction elimination is impaired): no dose adjustment required Severe: Not recommended
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

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
Vincristine	No dose adjustment necessary	Bilirubin > 51 micromol/L: 50% of original dose
Consideration can be given to full dose therapy in the presence of hepatic impairment, if his suspicion this is caused by lymphoma.		

Interactions: Main interactions listed below – refer to product SPC for full list of drug interactions

Doxorubicin

Doxorubicin undergoes metabolism via CYP450 so concomitant use of inhibitors may increase toxicity and inducers may reduce efficacy. Ciclosporin and cimetidine increase the AUC of doxorubicin; dose adjustments may be required. Barbiturates may lead to an accelerated plasma clearance of doxorubicin, while the concomitant administration of phenytoin may result in lower plasma phenytoin levels. Doxorubicin is a potent, radio sensitizing agent.

Cyclophosphamide

Substances that reduce the efficacy of cyclophosphamide include:

Aprepitant, bupropion, busulfan, ciprofloxacin, chloramphenicol, azole-antimycotics (e.g. fluconazole and itraconazole), CYP2B6 and CYP3A4 inhibitors (e.g. nevirapin and ritonavir), prasugrel, sulfonamides (e.g. sulfadiazine, sulfamethoxazoel and sulfapyridine), thiotepa, grapefruit (fruit or juice), rifampicin, St. John's wort.

An increased risk of side-effects may occur with:

Azathioprine: increased risk of hepatotoxicity (liver necrosis), chloral hydrate, cimetidine, disulfiram, glyceraldehyde, protease inhibitors, saquinavir, rifampin, phenobarbital, carbamazepine, phenytoin, St. John's wort, benzodiazepines, corticosteroids and dabrafenib.

Etoposide

Concomitant phenytoin therapy is associated with increased etoposide clearance and reduced efficacy, and other enzyme-inducing antiepileptic therapy may be associated with increased etoposide clearance and reduced efficacy. As etoposide phosphate is converted *in vivo* to etoposide by phosphorylation, caution should be exercised when administering etoposide phosphate with drugs that are known to inhibit phosphatase activity as such combination may reduce efficacy of etoposide phosphate. *In vitro* plasma protein binding is 97%. Phenylbutazone, sodium salicylate, and aspirin may displace etoposide from plasma protein binding. Co-administration of antiepileptic drugs and etoposide can lead to decreased seizure control due to pharmacokinetic interactions between the drugs.

Dacarbazine

Dacarbazine is metabolised by cytochrome P450 (CYP1A1, CYP1A2, and CYP2E1). Review if used alongside other drugs that effect CYP enzymes. Phenytoin: absorption of phenytoin is reduced from the gastrointestinal tract and may predispose the patient to convulsions.

Bleomycin

Previous or concurrent thoracic radiotherapy contributes significantly to increased frequency and severity of pulmonary toxicity. These are case reports of a reduced effect of digoxin as a result of a reduced oral bioavailability when combined with bleomycin. There are case reports of reduced levels of phenytoin when combined with bleomycin. Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic medicinal products or risk of toxicity enhancement or loss of efficacy of the cytotoxic medicinal product due to increased hepatic metabolism by phenytoin. Concomitant use is not recommended. The bacteriostatic efficacy of gentamicin and amikacin may be reduced

Vincristine

Care needed with drugs that also cause neurotoxicity. Vincristine may reduce plasma levels of phenytoin therefore dose adjustment of phenytoin based on levels may be required. Caution

should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily, or in patients with hepatic dysfunction.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1 to 14	**Prednisolone**	40mg/m^2	PO	
1	**Mesna (at clinical discretion)**	800mg	PO	
	Ondansetron	8mg	PO	
	Doxorubicin	35mg/m^2	IV	100mls sodium chloride 0.9% 30 mins
	Cyclophosphamide	1250mg/m^2	IV	500mL sodium chloride 0.9% 60 minutes
	Etoposide	200mg/m^2	IV	1000mL sodium chloride 0.9% 60 minutes
2 to 3	**Dacarbazine**	250mg/m^2	IV	500mL sodium chloride 0.9% 60 minutes
	Etoposide	200mg/m^2	IV	1000mL sodium chloride 0.9% 60 minutes
8	**Bleomycin**	10,000units/m^2	IV	100mL sodium chloride 0.9% 60 minutes
	Vincristine	1.4mg/m^2 (max 2mg dose)	IV	50mL sodium chloride 0.9% 10 minutes

Main toxicities:

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

Haematological toxicities

Cycle one should go ahead regardless of cytopenias

Subsequent cycles should go ahead if: WCC >2.5 x 10^9/L and Plt >80 x 10^9/L

If WCC <1.0 x 10^9/L for more than four days or platelets are <25 x 10^9/L for any length of time, then cyclophosphamide and etoposide should be dose reduced in subsequent cycles by one level as per table below. If toxic effects occur in two successive cycles, level 5 ('standard dose') should be used for all subsequent cycles.

Doses should also be reduced by one level in response to episodes of infection or mucositis. Discuss with consultant.

Level 1 – escalated dose	Level 2	Level 3	Level 4	Level 5 – standard dose
Cyclophosphamide 1250mg/m^2	1100mg/m^2	950mg/m^2	800mg/m^2	650mg/m^2
Etoposide 200mg/m^2	175mg/m^2	150mg/m^2	125mg/m^2	100mg/m^2

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.

Non-Haematological toxicities: Bleomycin

All patients complaining of shortness of breath should have a CXR (also consider HRCT chest) and pulmonary function tests prior to further administration of Bleomycin. Bleomycin should be discontinued if any clinical signs or CXR evidence of pulmonary infiltration/fibrosis develop, or if the transfer factor is <50% of the predicted value.

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	
FBC	X	**Twice Weekly**	**Twice Weekly**	FBC should be done twice weekly, especially while on the escalated doses, due to the risk of cytopenias
U&E, LFTs and bone profile	X	X	X	
CrCl (Cockcroft and gault)	X			
CT or PET CT Scan	X			Interim and end of treatment scans as indicated
Bone Marrow	If Clinically Indicated			Repeat as clinically indicated
Pulmonary function test	X (if clinically indicated)			
ECG / ECHO	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:

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Circulation/Dissemination

Date added into Q-Pulse	21st December 2022
Date document posted on the Intranet	N/A

Version History

		Author name and designation	Summary of main changes
		Daniel Dutton – Advanced Pharmacist	V1.0 New CCC protocol created