Systemic Anti Cancer Therapy Protocol

Escalated BEACOPP Hodgkin's Lymphoma

PROTOCOL REF: MPHAEBEAHA
(Version No: 1.1)

Approved for use in:

Patients with Hodgkin's Lymphoma and positive interim PET (Deauville 4 or more) after four doses (two full cycles) of ABVD

Blueteq registration 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, 2 and 3
Procarbazine	**100mg/m^2**	Oral once a day	Days 1 to 7
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 4 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.
- Dietary information must be provided to patients taking procarbazine

- Procarbazine dosing may require a different dose in the morning to evening dose given the capsule strength
- 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.**

Anti-emetic risk:

Severely emetogenic.

Supportive treatments:

- Allopurinol 300mg daily (first cycle only)
- Co-trimoxazole PO 480mg daily
- Ondansetron PO 8mg BD twice a day days 1 to 5 and 8 to 10
- Metoclopramide PO 10mg three times a day when required
- Omeprazole 20mg daily
- Nystatin 1ml four times a day
- Aciclovir 400mg twice daily (if history of shingles)
- Aprepitant 125mg D1, 80mg days 2 and 3

Extravasation risk:

Doxorubicin: vesicant

Cyclophosphamide: non-vesicant

Etoposide: irritant

Bleomycin: non-vesicant

Vincristine: vesicant

Refer to the Trust guidance for the prevention and management of extravasation

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): co-administration may reduce the efficacy of cyclophosphamide, 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.

Procarbazine

Procarbazine is a weak MAO inhibitor and therefore interactions with certain foodstuffs and drugs, although very rare, must be borne in mind. Thus, owing to possible potentiation of the effect of barbiturates, narcotic analgesics (especially Pethidine), drugs with anticholinergic effects (including phenothiazine derivatives and tricyclic antidepressants), other central nervous system depressants (including anaesthetic agents) and anti-hypertensive agents, these drugs should be given concurrently with caution and in low doses.

With enzyme-inducing antiepileptics is associated with an increased risk of hypersensitivity reactions to procarbazine.

Intolerance to alcohol (Disulfiram-like reaction) may occur.

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, amikacin and ticarcillin 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	**Prednisolone**	40mg/m^2	PO	
	Procarbazine	100mg/m^2	PO	Round to nearest 50mg tablet
	Ondansetron	8mg	PO	
	Doxorubicin	35mg/m^2	IV	In 100ml Sodium Chloride 0.9% over 30 minutes
	Cyclophosphamide	1250mg/m^2	IV	In 500mL Sodium Chloride 0.9% over 60 minutes
	Etoposide	200mg/m^2	IV	In 1000ml Sodium Chloride 0.9% over 60 minutes
2	**Prednisolone**	40mg/m^2	PO	
	Procarbazine	100mg/m^2	PO	Round to nearest 50mg tablet
	Etoposide	200mg/m^2	IV	In 1000ml Sodium Chloride 0.9% over 60 minutes
3	**Prednisolone**	40mg/m^2	PO	
	Procarbazine	100mg/m^2	PO	Round to nearest 50mg tablet
	Etoposide	200mg/m^2	IV	In 1000ml Sodium Chloride 0.9% over 60 minutes
4 to 7	**Prednisolone**	40mg/m^2	PO	
	Procarbazine	100mg/m^2	PO	Round to nearest 50mg tablet
8	**Prednisolone**	40mg/m^2	PO	
	Vincristine	1.4mg/m^2 (max 2mg dose)	IV	In 50mls NaCl 0.9% over 10 minutes
	Bleomycin	10000units/m^2	IV	In 250ml NaCl over 30 minutes
9 to 13	**Prednisolone**	40mg/m^2	PO	
	Filgrastim	300 or 480 micrograms	S/C	Weight < 70kg then 300 micrograms Weight ≥ 70kg then 480 micrograms
14	**Prednisolone**	40mg/m^2	PO	

SACT to be administration on Days 4-7 and 9-14 to be taken at home.

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea, peripheral neuropathy, constipation, mucositis and pulmonary toxicity.

Investigations and treatment plan:

	Pre	Cycle 1+ D1	Cycle 1+ D2	Cycle 1+ D3	Cycle 1+ D8	Cycle 1+ D15	Ongoing
Informed consent	X						
Clinical Assessment	X	X					
SACT Assessment (including performance status and toxicity assessment)		X	X	X	X		
FBC	X	X			X	X	No need to wait for day 8 bloods before giving treatment
U&E & LFTs & Calcium profile	X	X			X	X	
LDH	X						
CrCl (Cockcroft and Gault)	X						
PET CT scan	X						Repeat after 3 cycles
Pulmonary function tests	X						If clinically indicated
Hepatitis B core antibody and surface antigens & Hep C antibody & HIV 1+2 antibody and antigen	X						
Height	X						
Weight recorded	X	X					
Blood glucose	X						Repeat if clinically indicated
ECG/ECHO							If over 60 or pre-existing cardiac risk factors

Dose Modifications and Toxicity Management:

Haematological toxicity:

Cycle one should go ahead regardless of cytopenias.

Subsequent cycles should go ahead on day one if:-

WCC > 2.5 x 10^9/L	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

Dosing in renal and hepatic impairment:

Doxorubicin

Renal Function	
Haemodialysis	Consider 75% of dose
Liver Function	
Bilirubin (micromole/L)	Dose
20-50	50%
51-86	25%
>86 or Child Pugh C	Omit

Bleomycin

Renal Function	
CrCl (ml/min)	Dose
10-50	75%
<10	50%
Haemodialysis	Consider 50%

Vincristine

Liver Function	
Bilirubin (micromole/L)	Dose
>51	50% of dose

Procarbazine

Renal Function	
CrCl (ml/min)	Dose
≥30 with no hepatic impairment (in patients with combined renal and hepatic dysfunction elimination is impaired)	No dose adjustment required
<30	Consider 70%
Haemodialysis	Consider 70%
Liver Function	
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

Cyclophosphamide

Renal Function	
CrCl (ml/min)	Dose
10-29	Consider 75% of dose
<10 or haemodialysis	Not recommended. If unavoidable consider 50% of dose.
Liver Function	
Severe liver dysfunction	Not recommended

Neurotoxicity

If the patient complains of significant constipation or sensory loss in fingers and/or toes, consider possible dose reduction of Vincristine. For patients who develop ≥ Grade 3 ileus, treatment should be delayed until recovery and discuss dose reductions with consultant. If ≥ Grade 3 ileus recurs, Vincristine should be discontinued.

References:

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5. https://www.medicines.org.uk/emc bleomycin (accessed Feb 2020)
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