BEACOPP-14

An option for early salvage in advanced classical Hodgkin's lymphoma Stage IIB - IV

Drugs / Dosage:	**Doxorubicin**	25mg/m^2	IV	Day 1
	Cyclophosphamide	650mg/m^2	IV	Day 1
	Etoposide	100mg/m^2	IV	Day 1, Day 2 & Day 3
	Prednisolone	80mg/m2	PO	Day 1 to Day 7 (7 doses)
	Procarbazine	100mg/m^2	PO	Day 1 to Day 7 (7 doses)
	Vincristine	1.4mg/m^2 (cap at 2mg)	IV	Day 8
	Bleomycin	10,000iu/m^2	IV	Day 8

Other drugs: Allopurinol 300mg po daily, ideally starting 24 hours before chemotherapy starts - review at 4 weeks
Omeprazole 20mg po od while on prednisolone (or ranitidine 150mg bd)
Co-trimoxazole 480mg po od as PCP prophylaxis
Fluconazole 50mg po od as antifungal prophylaxis
Hydrocortisone 100mg IV before bleomycin, to prevent rigors
G-CSF primary prophylaxis for 5 days, starting on Day 9

Administration: Doxorubicin injection via fast running infusion of 0.9% sodium chloride
Cyclophosphamide slow IV bolus (and encourage 2 – 3 litres oral fluid intake over the 24 hours after each dose)
Etoposide in 1000ml sodium chloride 0.9% over 60 minutes
Procarbazine available as 50mg capsules; procarbazine daily dose may be divided evenly during the day
Prednisolone (5mg, 20mg or 25mg tablets), to be taken in the morning with or after food
Vincristine diluted in 50ml 0.9% sodium chloride and infused over 5-10 minutes
Bleomycin in 100ml 0.9% sodium chloride over 15-30 minutes

Frequency: 14 day cycle
When used after a +ve interim PET with ABVD, further PET recommended after 4 cycles of BEACOPP. If PET negative, administer 2 further cycles.

Main Toxicities: tumour lysis syndrome (ensure pre-medicated with allopurinol and good hydration); myelosuppression; alopecia; mucositis; cardiomyopathy; peripheral neuropathy; constipation; haemorrhagic cystitis; pulmonary toxicity; skin reactions to bleomycin; rigors during bleomycin infusion (ensure steroid given before bleomycin); steroid side effects; ovarian failure; infertility

Anti-emetics:
Day 1: highly emetogenic
Days 2 & 3: moderately emetogenic
Day 8: mildly emetogenic

Extravasation: doxorubicin and vincristine are vesicants

Regular Investigations:	FBC	Day 1 and Day 8
	LFTs & U&Es	Day 1
	LDH	Day 1
	MUGA/echo	see Comments
	Lung function tests	according to local practice (see Comments)

Reason for Update: N/A	Approved by Chair of Alliance TSSG: Dr A Laurie
Version: 1	Date: 18.1.16
Supersedes: None	Review Date: Feb 2018
Prepared by: S Taylor	Checked by: C Tucker

Comments: Procarbazine is a mild MAOI – alcohol should be avoided whilst taking it. Dietary restrictions are not required, although patients should be advised of the foods that have the rare potential to cause an unpleasant reaction (as listed in the procarbazine PIL).

Maximum cumulative dose of doxorubicin = 450 - 550mg/m^2
A baseline MUGA scan/echocardiogram should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, obese, smoker, ≥ 70 years old, previous exposure to anthracyclines, previous thoracic radiotherapy. MUGA scan/echo should be repeated if there is suspicion of cardiac toxicity at any point during treatment.

Bleomycin pulmonary toxicity is age-dependent, with an increase in frequency and associated mortality as patient age rises above 40 years. Dose modifications for bleomycin should be made according to table below. Bleomycin should be used with caution if approaching max cumulative dose.
Lung function may be monitored throughout treatment, according to local practice.
If patient reports new respiratory symptoms, inform consultant for advice on required investigations prior to any further administration of bleomycin.
There should be a low threshold for omitting further bleomycin if clinical concerns develop.

Age (years)	Maximum Bleomycin dose/week (IU)	Max Cumulative Dose (IU)
< 60	30,000 – 60,000	500,000
60 – 69	30,000 – 60,000	200,000 – 300,000
70 – 79	30,000	150,000 – 200,000
80 and over	15,000	100,000

Dose Modifications

Haematological Toxicity:

Day 1:
Proceed with the cycle if WBC > 2.5 x 10^9/l and platelets > 80 x 10^9/l.
If counts below this cut-off, delay the next cycle until recovered. Then proceed with dose modifications according to the table below:

Delay in WBC or platelet recovery	Dose Modification
< 1 week	None
1-2 weeks	75% doses of cyclophosphamide, doxorubicin, etoposide and procarbazine
> 2 weeks	50% doses of cyclophosphamide, doxorubicin, etoposide and procarbazine

Day 8:
Day 8 chemotherapy is not significantly myelosuppressive and may be given in the presence of neutropenia or thrombocytopenia. However, FBC should be noted and managed accordingly.

Renal Impairment: Cockcroft and Gault may be used to predict CrCl. If borderline, an EDTA may be requested.

CrCl (ml/min)	Cyclophosphamide Dose
> 20	Give 100%
10 – 20	Give 75%
< 10	Give 50%

CrCl (ml/min)	Bleomycin Dose
> 50	Give 100%
10 – 50	Give 75%
< 10	Give 50%

CrCl (ml/min)	Etoposide Dose
> 50	Give 100%
15 – 50	Give 75%
< 15	Give 50%

Procarbazine may accumulate with renal impairment, but there is a lack of specific information. A dose reduction could be considered, and it should be avoided in severe renal impairment.

Hepatic Impairment:

Bilirubin (µmol/l)	Doxorubicin Dose
20 – 50	Give 50%
51 – 85	Give 25%
> 85	Omit

Bilirubin (µmol/l)		ALT / AST (units/l)	Vincristine Dose
26 – 51	**or**	60 – 180	Give 50%
> 51	**and**	≤ 180	Give 50%
> 51	**and**	> 180	Omit

Creatinine clearance is the strongest predictor of etoposide clearance. There is conflicting information about dose reduction with hepatic impairment. Use the table below but, if in doubt, discuss with Consultant.

Bilirubin (µmol/l)		AST (units/l)	Etoposide Dose
26 – 51	**or**	60 - 180	Give 50% dose
> 51	**or**	> 180	Clinical decision

Bilirubin (µmol/L)		AST (units)	Procarbazine Dose
> 50		N/A	Consider 50% dose reduction
> 85	**or**	> 180	Contra-indicated

Neuropathy: If the patient complains of significant constipation or sensory loss in fingers and/or toes, consider a vincristine dose reduction. Stop vincristine if patient experiences Grade 3 – 4 neurotoxicity.

Lung Toxicity: Discontinue bleomycin permanently if any symptoms of pulmonary infiltration / fibrosis.

Skin Toxicity: Severe skin lesions e.g. desquamation may require discontinuation of bleomycin.

Patient Information: Macmillan leaflets for Cyclophosphamide, Doxorubicin, Etoposide, Procarbazine, Bleomycin and Vincristine

References:
Sieber, M et al; JCO 2003; 21 (9): 1734 – 1739
Johnson, P et al; abstract presented at ICML, 2015 (not yet published, but obtained access to RATHL trial protocol)