Systemic Anti Cancer Treatment Protocol

Bleomycin Etoposide Cisplatin 3 Day (BEP3 Adjuvant)

PROTOCOL REF: MPHABECGC
(Version No: 1.2)

Approved for use in:

Non-seminomatous testicular Germ Cell Tumour
Stage 1
Vascular or lymphatic invasion

Dosage:

Drug	Dosage	Route	Frequency
Bleomycin	30,000 units days 1, 8 and 15	IV	One cycle only
Etoposide	165mg/m^2 day 1, 2 and 3	IV	One cycle only
Cisplatin	50mg/m^2 day 1 and 2	IV	One cycle only

Caution

Bleomycin advised up to 40 years (up to 45 years at clinician discretion)

Patients aged above 40 or with contraindications to bleomycin give EP for two cycles (doses as above)

Maximum total bleomycin dose 360,000 units

Supportive treatments:

Aprepitant 125mg day 1, 80mg days 2 and 3

Domperidone 10mg oral tablets, up to 3 times a day or as required

Dexamethasone tablets, 4mg twice daily for 3 days starting on day 4

Ondansetron 8mg nocte days 1 to 3

Filgrastim subcutaneous injection (300 or 480 micrograms) daily for 7 days, starting on day 4

Extravasation risk:

Bleomycin – non vesicant

Etoposide – Irritant

Cisplatin – Irritant

Administration:

Day	Drug	Dosage	Route	Diluent and Rate
1	Aprepitant 30 mins before chemotherapy	125mg	PO	
1	Dexamethasone 30 mins before chemotherapy	12mg	PO	
1	Ondansetron 30 mins before chemotherapy	24mg	PO	
1	Furosemide	20mg	PO	
1	Hydrocortisone	100mg	IV	
1	**Bleomycin**	**30,000 units**	IV	In 250mL sodium chloride 0.9% over 2 hours
1	**Etoposide**	**165mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 1 to 2 hours
1	Monitor urine output – see notes below			
1	**Cisplatin**	**50mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 90 minutes
1	20mmol potassium chloride in sodium chloride 0.9%	1000mL	IV	Over 90 minutes
2	Aprepitant	80mg	PO	24 hours after day one dose
2	Dexamethasone	12mg	PO	
2	Ondansetron	24mg	PO	
2	Furosemide	20mg	PO	
2	**Etoposide**	**165mg/m^2**	IV	In 1000mL 0.9% sodium chloride over 1 to 2 hours
2	**Cisplatin**	**50mg/m^2**	IV	In 1000mL 0.9% sodium chloride over 90 minutes
2	20mmol potassium chloride in sodium chloride 0.9%	1000mL	IV	Over 90 minutes
3	Aprepitant	80mg	PO	24 hours after day 2 dose
3	Dexamethasone	8mg	PO	
3	Ondansetron	16mg	PO	
3	**Etoposide**	**165mg/m^2**	IV	In 1000mL 0.9% sodium chloride over 1 to 2 hours

4	Filgrastim	30MU or 48MU	SC	Daily injection for 7 days (omitting on day 8)
8	Hydrocortisone	100mg	IV	
8	**Bleomycin**	**30,000 units**	IV	In 250mL sodium chloride 0.9% over 2 hours
15	Hydrocortisone	100mg	IV	
15	**Bleomycin**	**30,000 units**	IV	In 250mL sodium chloride 0.9% over 2 hours

Give for one cycle only

Notes:

Bleomycin

Ensure Hydrocortisone given prior to bleomycin

Pulmonary toxicity – unlikely at this total cumulative dose of bleomycin but be aware of any symptoms of lung toxicity – see toxicity management below

Proceed with day 8 and 15 bleomycin **irrespective of blood counts** if otherwise well however CrCl (Cockroft and Gault) must be checked before each administration of bleomycin – refer to renal toxicity criteria below.

Cisplatin

Encourage oral hydration throughout treatment e.g. one glass of water per hour.

Do not start cisplatin infusion unless urine output is at least 100mL/hour.

Check patient's weight before and after each cisplatin infusion, maintain a strict fluid balance chart, ensure urine output is adequate. If necessary, administer further 500ml 0.9% sodium chloride

The patient should be asked to drink 2 litres of fluid over 24 hours after the infusion and should contact the unit immediately if unable to do so for any reason.

Other

Ensure that primary prophylaxis with filgrastim on day 4 is prescribed and administered. This should be 24 hours after the last chemotherapy

Do NOT administer filgrastim concurrently with bleomycin

Ensure antiemetics are prescribed and given

Filgrastim dose:

For patients under 70kg: 300 micrograms subcutaneous injection daily

For patients 70kg and above: 480 micrograms subcutaneous injection daily

Main Toxicities:

Myelosuppression, nephrotoxicity, ototoxicity, mucositis, neurotoxicity, alopecia, skin changes, infertility, pulmonary toxicity, rigors (during bleomycin – see notes)

Investigations and treatment plan

	Pre	Day 1	Day 8	Day 15	Comments
Medical Assessment	X				
Nursing Assessment	X	X	X	X	
FBC		X	X	X	
U&E & LFT		X	X	X	
CrCl (Cockroft and Gault)	X	X	X	X	Day 1 of each cycle and before every bleomycin
LDH	X				Pre and post treatment
AFP, βHCG	X				Pre and post treatment
Chest X-Ray	X				Review Radiology Report prior to bleomycin, to exclude signs of bleomycin lung toxicity. Repeat only if deteriorating symptoms
Pulmonary function tests	X				Repeat only if clinically indicated
Informed Consent	X				
PS recorded	X	X	X	X	
Toxicities documented	X	X	X	X	
Weight recorded	X				

Dose Modifications and Toxicity Management:

Any delay in chemotherapy may be detrimental to outcomes

Do not delay chemotherapy or modify any doses without consultant approval

Haematological toxicity

Proceed on day 1 if:-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

Do not delay patient without discussing with the consultant first

As bleomycin is non myelosuppressive treatment may proceed on days 8 and 15 irrespective of blood count provided the patient is well in all other respects.

Non-haematological toxicity

Renal

Cisplatin is eliminated primarily (>90%) in the urine and is itself nephrotoxic. If there is any significant renal toxicity discuss with consultant before proceeding.
Calculate CrCl before the start of treatment using Serum Creatinine and Cockroft and Gault. If the result is borderline consider EDTA clearance. Recalculate CrCl using Cockroft and Gault every cycle and consider EDTA if serum creatinine varies by >30% from baseline.

CrCl (mL/min)	**Cisplatin dose**
Above 60	100% dose
45 to 60	75% dose
Below 45	Do not give, discuss with consultant consider carboplatin
	Bleomycin dose
Above 50	100% dose
10 to 50	75% dose
	Etoposide dose
Above 50	100% dose
15 to 50	75% dose
Below 15	50% dose

Hepatic

Creatinine clearance is the strongest predictor of etoposide clearance. There is conflicting advice about the need for dose adjustment with hepatic impairment. Use table below but discuss with consultant need for any adjustment

Bilirubin (micromol/L)	**AST (units/L)**	**Etoposide Dose**
26 to 51 OR	60 to 180	50% dose
Above 51 OR	Above 180	Clinical decision

Pulmonary	Bleomycin may cause severe and life threatening pulmonary toxicity. Toxicity is associated with cumulative doses over 300,000 units and patients of older age as well as poor renal function, advanced disease, smoking history. Bleomycin must be discontinued permanently if signs of pulmonary toxicity occur but this is a consultant decision only. Auscultate chest before each administration. Discuss with consultant if symptoms occur e.g. dyspnea, abnormal chest X-Ray or decreased pulmonary function. Note that concomitant oxygen or radiation therapy can influence the risk of developing pulmonary toxicity. Use room air for pulmonary function tests. Avoid oxygen concentrations above 30-40%.
GI toxicity	Cisplatin induced nausea and vomiting may be severe. Uncontrolled vomiting may exacerbate cisplatin induced fluid and electrolyte imbalance. Follow antiemetic policy rigorously and monitor fluids and electrolytes closely if severe vomiting occurs. Note that electrolyte disturbance due to cisplatin may be a long term manifestation due to renal tubular dysfunction. Check electrolytes, longer term supplementation with magnesium, potassium or calcium may be required.
Acute reactions and fever	**Bleomycin** Hypersensitivity is rare but not unknown and severe when it occurs. Stop infusion and follow trust anaphylaxis policy. Half of patients will have a febrile reaction to bleomycin within 48 hours. Hydrocortisone should prevent this and paracetamol can be used to treat. **Cisplatin and Etoposide** Anaphylactic like reactions have been reported. These commonly include facial oedema, bronchoconstriction, tachycardia, hypotension. Follow trust anaphylactic policy. Discuss next cycle with consultant before proceeding
Skin	50% of patients will develop a rash with bleomycin – this is normal. Severe skin lesions may also occur. Discuss with consultant. **Decision to stop is consultant only.**
Mucositis	Discuss – delay until recovery, note that concomitant radiotherapy and high cumulative doses are risk factors
Neurotoxicity	Seek advice if patient displays symptoms of neuro- or ototoxicity

References:

Surveillance or adjuvant treatments in stage 1 testis germ cell tumours
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