Systemic Anti Cancer Treatment Protocol

Bleomycin Etoposide Cisplatin 3 Day (BEP3) for Intermittent / Low Risk

PROTOCOL REF: MPHABEP3GC
(Version No: 1.2)

Approved for use in:

Low to intermediate risk germ cell tumours

Metastatic seminoma

Dosage:

Drug	Dosage	Route	Frequency
Bleomycin	30,000 units days 1, 8 and 15	IV	Every 21 days
Etoposide	165mg/m^2 day 1, 2 and 3	IV	Every 21 days
Cisplatin	50mg/m^2 day 1 and 2	IV	Every 21 days

Caution

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

Patients aged above 40 or with contraindications to bleomycin give EP5 for four cycles

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 60 to 120 minutes
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 60 to 120 minutes
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
2	**Etoposide**	**165mg/m^2**	IV	In 1000mL 0.9% sodium chloride over 60 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 60 to 120 minutes
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

Cycle is repeated every 21 days for 3 cycles

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:

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

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

<table>
<tr><td>Hepatic</td><td>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
<table>
<tr><th>Bilirubin (micromol/L)</th><th>AST (units/L)</th><th>Etoposide Dose</th></tr>
<tr><td>26 to 51
OR</td><td>60 to 180</td><td>50% dose</td></tr>
<tr><td>Above 51
OR</td><td>Above 180</td><td>Clinical decision</td></tr>
</table></td></tr>
<tr><td>Pulmonary</td><td>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%.</td></tr>
<tr><td>GI toxicity</td><td>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.</td></tr>
<tr><td>Acute reactions and fever</td><td>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</td></tr>
<tr><td>Skin</td><td>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.</td></tr>
<tr><td>Mucositis</td><td>Discuss – delay until recovery, note that concomitant radiotherapy and high cumulative doses are risk factors</td></tr>
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Neurotoxicity	Seek advice if patient displays symptoms of neuro- or ototoxicity

References:

Equivalence of Three or Four Cycles of Bleomycin, Etoposide, and Cisplatin Chemotherapy and of a 3- or 5-Day Schedule in Good-Prognosis Germ Cell Cancer: A Randomized Study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council

R de Wit, et al, Journal of Clinical Oncology 2001 19:6, 1629-1640