Systemic Anti Cancer Treatment Protocol

Bleomycin Etoposide Cisplatin (BEP5 + EP5)

PROTOCOL REF: MPHABEP5GC
(Version No: 1.2)

Approved for use in:

First line treatment for testicular germ cell tumours and all other germ cell tumours

Intermediate to high risk

Curative intent

Dosage:

Schedule

BEP5 x 3 cycles -> EP5 x 1 cycles

BEP5

Drug	Dosage	Route	Frequency
Bleomycin	30,000 units days 1, 5 and 15	IV	Every 21 days
Etoposide	100mg/m^2 days 1,2,3,4 and 5	IV	Every 21 days
Cisplatin	20mg/m^2 days 1,2,3,4 and 5	IV	Every 21 days

EP5

Drug	Dosage	Route	Frequency
Etoposide	100mg/m^2 days 1,2,3,4 and 5	IV	Every 21 days
Cisplatin	20mg/m^2 days 1,2,3,4 and 5	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 to five 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 6

Ondansetron 8mg nocte days 1 to 5

Filgrastim subcutaneous injection (300 or 480 micrograms) daily for 7 days, starting on day 6

Extravasation risk:

Bleomycin – non vesicant

Etoposide – Irritant

Cisplatin – Irritant

Administration:

Day	Drug	Dosage	Route	Diluent and Rate
1	Dexamethasone 30 mins before chemotherapy	8mg	PO	
1	Ondansetron 30 mins before chemotherapy	8mg	PO	
1	Aprepitant 30 mins before chemotherapy	125mg	PO	
1	Hydrocortisone	100mg	IV	Slow IV bolus
1	**Bleomycin**	**30,000 units**	IV	In 250mL sodium chloride 0.9% over 2 hours
1	**Etoposide**	**100mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 60 minutes
1	**Cisplatin**	**20mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 60 minutes
1	Sodium chloride 0.9% 1000mL With 20mmol Potassium Chloride		IV infusion over 6 hours	
2	Dexamethasone	8mg	PO	
2	Ondansetron	8mg	PO	
2	Aprepitant 30 mins before chemotherapy	80mg	PO	
2	**Etoposide**	**100mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 60 minutes

2	**Cisplatin**	**20mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 60 minutes
2	Sodium chloride 0.9% 1000mL With 20mmol Potassium Chloride		IV infusion over 6 hours	
3	Dexamethasone	8mg	PO	
3	Ondansetron	8mg	PO	
3	Aprepitant 30 mins before chemotherapy	80mg	PO	
3	**Etoposide**	**100mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 60 minutes
3	**Cisplatin**	**20mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 60 minutes
3	Sodium chloride 0.9% 1000mL With 20mmol Potassium Chloride		IV infusion over 6 hours	
4	Dexamethasone	8mg	PO	
4	Ondansetron	8mg	PO	
4	**Etoposide**	**100mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 60 minutes
4	**Cisplatin**	**20mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 60 minutes
4	Sodium chloride 0.9% 1000mL With 20mmol Potassium Chloride		IV infusion over 6 hours	
5	Dexamethasone	8mg	PO	
5	Ondansetron	8mg	PO	
5	Hydrocortisone	100mg	IV	Slow IV bolus
5	**Bleomycin**	**30,000 units**	IV	In 250mL sodium chloride 0.9% over 2 hours
5	**Etoposide**	**100mg/m^2**	IV	In 1000mL 0.9% sodium chloride over 1 hour
5	**Cisplatin**	**20mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 60 minutes
5	Sodium chloride 0.9% 1000mL With 20mmol Potassium Chloride		IV infusion over 6 hours	
15	Hydrocortisone	100mg	IV	Slow IV bolus
15	**Bleomycin**	**30,000 units**	IV	In 250mL sodium chloride 0.9% over 2 hours

Give 3 every 21 days for 3 cycles followed by 1 cycle of EP5 (see below)

EP5

Day	Drug	Dosage	Route	Diluent and Rate
1	Dexamethasone 30 mins before chemotherapy	8mg	PO	
1	Ondansetron 30 mins before chemotherapy	8mg	PO	
1	**Etoposide**	**100mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 60 minutes
1	**Cisplatin**	**20mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 60 minutes
1	Sodium chloride 0.9% 1000mL With 20mmol Potassium Chloride		IV infusion over 6 hours	
2	Dexamethasone	8mg	PO	
2	Ondansetron	8mg	PO	
2	**Etoposide**	**100mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 60 minutes
2	**Cisplatin**	**20mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 60 minutes
2	Sodium chloride 0.9% 1000mL With 20mmol Potassium Chloride		IV infusion over 6 hours	
3	Dexamethasone	8mg	PO	
3	Ondansetron	8mg	PO	
3	**Etoposide**	**100mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 60 minutes
3	**Cisplatin**	**20mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 60 minutes
3	Sodium chloride 0.9% 1000mL With 20mmol Potassium Chloride		IV infusion over 6 hours	
4	Dexamethasone	8mg	PO	
4	Ondansetron	8mg	PO	
4	**Etoposide**	**100mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 60 minutes
4	**Cisplatin**	**20mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 60 minutes
4	Sodium chloride 0.9% 1000mL With 20mmol Potassium Chloride		IV infusion over 6 hours	
5	Dexamethasone	8mg	PO	
5	Ondansetron	8mg	PO	
5	**Etoposide**	**100mg/m^2**	IV	In 1000ml 0.9% sodium chloride over 1 hour
5	**Cisplatin**	**20mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 60 minutes
5	Sodium chloride 0.9% 1000mL With 20mmol Potassium Chloride		IV infusion over 6 hours	

Notes:

Bleomycin (see also toxicity management)

Ensure Hydrocortisone given prior to bleomycin to prevent rigors and any acute hypersensitivity reactions

Pulmonary toxicity is much more common at cumulative doses > 300,000 units. If for any reason a fourth cycle is given then only the day 1 bleomycin should be administered.

Proceed with day 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

Ensure adequate hydration pre and post cisplatin

Pre-hydration only needed for day one as the fluid in the etoposide will suffice

Check and correct electrolytes, Mg^{2+}, Ca^{2+}, K^{+} before starting cisplatin and check them regularly throughout treatment.

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 +/- furosemide 20 or 40mg po.

Give 20 or 40mg furosemide po if there is a positive fluid balance of 1.5 litres, weight gain of 2kg or symptoms of fluid overload.

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 6 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:

For clarity day 15 only shown for cycle 1

Investigations and assessments for cycle 1 apply to cycles 2 and 3.

	Pre	Cycle 1	(Every) Day 15	Cycle 2	Cycle 3	Comments
Medical Assessment	X				X	
Nursing Assessment		X	X	X	X	
FBC		X	X	X	X	Do not delay or omit D15 bleomycin due to low counts.
U&E & LFT		X	X	X	X	Check electrolytes regularly throughout treatment
Serum Creatinine	X	X	X	X	X	
CrCl (Cockroft and Gault)		X	X	X	X	Day 1 of each cycle and before every bleomycin
Ca2+, Mg2+		X		X	X	Repeat within the cycle if needed
LDH	X			X	X	
AFP, βHCG	X			X	X	
Chest X-Ray	X			X	X	Before each cycle, Review Radiology Report prior to bleomycin, to exclude signs of bleomycin lung toxicity.
CT scan	X					Also at end of treatment
Pulmonary function tests	X					If clinically indicated
Informed Consent	X					

Blood pressure measurement	X					If clinically indicated
PS recorded	X	X	X	X	X	Every administration
Toxicities documented		X	X	X	X	Every administration
Weight recorded	X	X		X	X	Every 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

Delay 3 days on day 1 if:-

ANC ≤ 0.9 x 10^9/L	Platelets ≤ 99 x 10^9/L

Recheck FBC on day 3 and if counts recovered proceed with full dose treatment

If FBC still low after 3 days check that filgrastim was administered and seek advice from consultant.

Use day 15 FBC to monitor patients and pre-empt any possible delays to subsequent cycles.

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

Do not lower doses in subsequent cycles for single episodes of neutropenic fever or sepsis provided haematologic recovery has occurred by day 21

Non-haematological toxicity

Do not routinely carry dose adjustments from one cycle to the next without discussing with consultant first

<table>
<tr><td>Renal</td><td>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.
<table>
<tr><th>CrCl (mL/min)</th><th>Cisplatin dose</th></tr>
<tr><td>Above 60</td><td>100% dose</td></tr>
<tr><td>45 to 60</td><td>75% dose</td></tr>
<tr><td>Below 45</td><td>Do not give, discuss with consultant consider carboplatin</td></tr>
<tr><td></td><td>Bleomycin dose</td></tr>
<tr><td>Above 50</td><td>100% dose</td></tr>
<tr><td>10 to 50</td><td>75% dose</td></tr>
<tr><td></td><td>Etoposide dose</td></tr>
<tr><td>Above 50</td><td>100% dose</td></tr>
<tr><td>15 to 50</td><td>75% dose</td></tr>
<tr><td>Below 15</td><td>50% dose</td></tr>
</table></td></tr>
<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 - 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</td></tr>
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	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 Hypersensitivity 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 of bleomycin are risk factors
Neurotoxicity	Seek advice if patient displays symptoms of neuro- or ototoxicity

References:

Treatment of disseminated germ cell tumors with cisplatin, bleomycin and either vinblastine or etoposide

Williams, S et al

NEJM 1987 316(23):1435

Are 3 cycles of BEP or 4 cycles of EP equivalent optimal regimens for patients with good risk metastatic germ cell tumours of the testis? The need for a randomised trial

Culine S et al

J Urol 1997 175(3):855-8