BEP 360 3 day (Bleomycin, Etoposide and Cisplatin)

Indication
Adjuvant treatment of non-seminoma or combined germ cell cancers (pT2 or pT3).

ICD-10 codes
Codes pre-fixed with C38, C48, C56, C62, C63, C75.

Regimen details

Day	Drug	Dose	Route
1 and 2	Cisplatin	50mg/m^2	IV infusion
1, 2 and 3	Etoposide	120 mg/m^2	IV infusion
2, 9 and 16	Bleomycin	30,000 iu	IV infusion

Cycle frequency
21 days

Number of cycles
2

Administration
Cisplatin is administered in 500mL sodium chloride 0.9% over 60 minutes following the pre and post hydration protocol below.

Infusion Fluid & Additives	Volume	Infusion Time
Sodium Chloride 0.9%	1000mL	1 hour
Mannitol 20% **OR** Mannitol 10%	200mL 400mL	30 minutes 30 minutes
Ensure urine output > 100mL / hour prior to giving cisplatin. If a patient develops fluid retention i.e. weight gain >2.5kg or urine output < 100ml/ hour during treatment give a single dose of 20mg furosemide or mannitol (200mL mannitol 20% OR 400mL mannitol 10%). Do not give more than a single dose of either furosemide or mannitol without discussing with consultant.		
Cisplatin	500mL	1 hour
Sodium Chloride 0.9% + 2g $MgSO_4$ + 20mmol KCl	1000mL	2 hours
TOTAL	**2700mL or 2900mL**	**4 hours 30 minutes**

Note: Patients with magnesium or potassium below the normal range should have 2g $MgSO_4$ and 20mmol KCl added to the pre-hydration bag and the duration of the infusion increased to 2 hours.
All patients must be advised to drink at least 2 litres of fluid over the following 24 hours.

Etoposide is administered in 1000-2000mL sodium chloride 0.9% (concentration dependent) and infused over a minimum of 1 hour.

Bleomycin is administered in 100-250mL sodium chloride 0.9% over 15 minutes.

Pre-medication

Hydrocortisone 100mg IV prior to each bleomycin dose (days 2, 9 and 16)

Emetogenicity

This regimen has severe emetic potential on days 1 to 3 and mild emetic potential on days 9 and 16.

Additional supportive medication

H_2 antagonist or proton pump inhibitor if required.
Mouthwashes as per local policy.
Oral magnesium supplementation between cycles in addition to the intravenous magnesium administered at the time of chemotherapy if required as per local magnesium replacement guidelines.
Anti-emetics as per local policy.
GCSF from day 4 as per local policy.

Extravasation

Cisplatin is an exfoliant (Group 4)
Etoposide is an irritant (Group 3)
Bleomycin is neutral (Group 1)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTS	14 days
Magnesium	14 days
AFP, HCG, LDH	14 days (repeat on day 1)
LH, FSH and testosterone	28 days
Pulmonary Functions Tests (including transfer factor)	28 days
CXR	28 days
Audiology	28 days

Discuss with consultant about omitting bleomycin if:

- >50 years of age,
- Impaired renal function (creatinine clearance < 60ml/min)
- Pre-existing lung disease and/or significant smoking history

Consider formal EDTA measurement of creatinine clearance in patients with a low body surface area or poor renal function.

Where appropriate offer pre-treatment sperm storage.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours (repeat weekly, prior to bleomycin)
U+E (including creatinine)	7 days
LFTS	7 days
Magnesium	7 days
AFP, HCG, LDH	7 days

At pre-assessment ask the patient about symptoms of cough. Repeat PFTs if patient describes dyspnoea or persistent dry cough.

Repeat audiology if patient reports hearing loss or persistent tinnitus.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
WBC	≥ 1.5 x 10^9/L*
Neutrophils	≥ 0.5 x 10^9/L*
Platelets	≥ 75 x 10^9/L*
Calculated CrCl	> 60 ml/min
Bilirubin	< 1.5 x ULN
AST/ALT	< 2.5 x ULN

*Prior to day one only. As bleomycin is not significantly myelosuppressive do not omit day 9 or 16 based on the FBC alone. If patient is unwell eg with neutropenic sepsis discuss with consultant.

If on day one WBC < 1.5 x 10^9/L, neutrophils < 0.5 x 10^9/L or platelets < 75 x 10^9/L delay for 3 days and if recovered resume at full doses. If not repeat FBC every 3 days and start treatment when counts have recovered. If more than 3 days delay discuss with consultant about modifying etoposide to 75% dose. Modifications of cisplatin or bleomycin dose are not usually required for myelosuppression

If doses are reduced for one cycle, the second cycle should be assessed independently based on the FBC on day 1 of that cycle. Dose modifications for myelosuppression are not usually carried forward to the next cycle.

Dose modifications

- **Renal impairment**

Full dose cisplatin should be administered if calculated CrCl is > 60ml/min. An EDTA creatinine clearance should be arranged if calculated CrCl falls below this value. Discuss with consultant about modifying dose of cisplatin as below or substituting with carboplatin.

CrCl (mL/min)	**Cisplatin dose**
>60	100%
51 – 60	75%
40 – 50	50%
<40	Discuss with consultant – consider carboplatin

Carboplatin is contraindicated if CrCl < 20mL/min

CrCl (mL/min)	**Bleomycin dose**
>50	100%
10-50	75%
<10	50% - discuss with consultant

CrCl (mL/min)	**Etoposide dose**
>50	100%
15-50	75%
<15	50% - discuss with consultant

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Etoposide dose**
<1.5	And	≤2.5	100%
1.5-3.0	Or	2.5-4.0	Discuss with consultant – consider 50 - 75%
>3.0	Or	> 4.0	Discuss with consultant – consider 25% or omit

No dose modification required for cisplatin.
No information regarding use of bleomycin in hepatic impairment (consultant decision)

- **Other toxicities**

Discuss with consultant if patient develops dry cough or dyspnoea. PFTs should be repeated and consider organising a high resolution CT scan of the chest. If there is a > 25% drop in transfer factor or radiological changes consistent with bleomycin then discuss with consultant about omitting further doses of bleomycin. High concentrations of oxygen (>30%) should be avoided unless absolutely necessary. Patients should be warned that if they have future general anaesthetics they must inform the anaesthetist that they have received bleomycin. They should be advised against scuba diving

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Nephrotoxicity
Ototoxicity
Neurotoxicity
Pulmonary toxicity
Infertility
Long term risk of cardiovascular disease and metabolic syndrome
Osteonecrosis of the hip

- **Frequently occurring side effects**

Myelosuppression
Constipation, diarrhoea
Stomatitis, mucositis
Alopecia
Nausea and vomiting
Anorexia
Fever, rigors, malaise, skin rash (bleomycin)

- **Other side effects**

Electrolyte disturbances
Fatigue

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.

Antibiotics: The renal toxicity of cisplatin is potentiated by aminoglycoside antibacterials (e.g. gentamicin) and amphotericin. Aminoglycosides should be avoided. If aminoglycosides are prescribed, close monitoring of renal function and serum antibiotic levels is required.

Avoid all nephrotoxic drugs where possible

Phenylbutazone, sodium salicylate and salicylic acid: may displace etoposide from plasma protein binding thereby increasing systemic exposure.

Additional comments

Encourage patients who smoke to stop – offer referral to smoking cessation services.
This regimen may be given as an inpatient or day case as per local practice.

References

- Summary of Product Characteristics Cisplatin (Hospira) accessed 29 July 2015 via www.medicines.org.uk
- Summary of Product Characteristics Etoposide (Hospira) accessed 29 July 2015 via www.medicines.org.uk
- Summary of Product Characteristics Bleomycin (ProStraken) accessed 29 July 2015 via www.medicines.org.uk
- Cullen MH, et al. Short-course adjuvant chemotherapy in high-risk stage I non-seminomatous germ cell tumours of the testis: a Medical Research Council report. Journal Clin. Oncol. Apr 1 1996: 14: 1106–1113.

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