CBOP/BEP

Indication
Curative intent for poor prognosis metastatic non-seminomatous and combined germ cell cancers.

ICD-10 codes
Codes pre-fixed with C38, C48, C56, C62, C63, C75.3.

Regimen details
CBOP

Day	Drug	Dose	Route
1 and 8	Vincristine	2mg	IV infusion
1 and 2 **OR** 1-5	Cisplatin Cisplatin	50mg/m^2 (total 100mg/m^2) 20mg/m^2(total 100mg/m^2)*	IV infusion IV infusion
1	Bleomycin	15,000 iu	IV infusion
8	Carboplatin	AUC 3	IV infusion
8	Cisplatin	40mg/m^2	IV infusion
8-12	Bleomycin	75,000 iu	IV infusion over 5 days

*Cisplatin administered over 5 days is the preferred schedule

BO

Day	Drug	Dose	Route
1 and 8	Vincristine	2mg	IV infusion
1 and 8	Bleomycin	15,000 iu	IV infusion

BEP 500

Day	Drug	Dose	Route
1 – 5	Etoposide	100 mg/m^2	IV infusion
1 – 5	Cisplatin	20mg/m^2	IV infusion
2, 8 and 15	Bleomycin	**15,000 iu**	IV infusion

Cycle frequency
CBOP (cycles 1 and 2) - 14 days each
BO (cycle 3) - 14 days
BEP (cycles 4, 5 and 6) – 21 days each

Number of cycles
As above

Administration
CBOP
Vincristine is administered as an intravenous infusion in 50mL sodium chloride 0.9% over 10 minutes, as per national guidance. The nurse should remain with patient throughout infusion.

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.

Bleomycin is administered in 50mL sodium chloride 0.9% over 15 minutes on day 1.

Day 8:
Vincristine is administered as an intravenous infusion in 50mL sodium chloride 0.9% over 10 minutes, as per national guidance. The nurse should remain with patient throughout infusion.

Carboplatin is administered in 500mL glucose 5% over 30-60 minutes. This is administered immediately before the cisplatin infusion.

Cisplatin is administered as above.

Bleomycin is administered as a 5 day infusion (15,000 units per day), starting on day 8 via an ambulatory device as per local practice.

BO
Vincristine is administered as an intravenous infusion in 50mL sodium chloride 0.9% over 10 minutes, as per national guidance. The nurse should remain with patient throughout infusion.

Bleomycin is administered in 50mL sodium chloride 0.9% over 15 minutes on days 1 and 8.

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

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.

Bleomycin is administered in 50mL sodium chloride 0.9% over 15 minutes. **Please note the bleomycin dose is 15,000iu on days 2, 8 and 15**

Pre-medication

Hydrocortisone 100mg IV prior to each bleomycin dose. If patients are discharged and bleomycin is administered via an ambulatory device, they should be prescribed prednisolone 10mg BD for the duration of the infusion (total of 5 days).

Emetogenicity

CBOP and BEP regimens have severe emetic potential.
BO has moderate emetic potential.

Additional supportive medication

Allopurinol 300mg OD (100mg OD if CrCl< 20mL/min) for patients with a high tumour burden
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.
Pegylated GCSF on day 1 of week 5 (day 1 of BO cycle) and on day 6 of each BEP cycle (or as per local policy using daily GCSF for 7 days)
Antibiotic prophylaxis as per local policy

Extravasation

Cisplatin and carboplatin are exfoliant (Group 4)
Etoposide is an irritant (Group 3)
Bleomycin is neutral (Group 1)
Vincristine is vesicant (Group 5)

Investigations – pre first cycle

Investigation	Validity period
FBC	7 days
U+E (including creatinine)	7 days
LFTS	7 days
Magnesium	7 days
AFP, HCG, LDH	7 days
LH, FSH and testosterone	28 days
Pulmonary Functions Tests (including transfer factor)	28 days
CXR and chest auscultation	28 days
Audiology	28 days

Discuss with consultant about bleomycin schedule if:

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

Where possible formal EDTA measurement of creatinine clearance is recommended

Where appropriate offer pre-treatment sperm storage.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	48 hours for CBOP and BO. 96 hours for BEP (repeat weekly, prior to bleomycin during BEP)
U+E	7 days
LFTS	7 days
Magnesium	7 days
AFP, HCG, LDH	7 days (repeat at least weekly during treatment)
At pre-assessment ask the patient about symptoms of cough	7 days

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

CBOP/BO

Investigation	Limit
WBC	$\geq 1.0 \times 10^9$/L*
Neutrophils	$\geq 0.5 \times 10^9$/L*
Platelets	$\geq 50 \times 10^9$/L*
Calculated CrCl	> 60 ml/min
Bilirubin	< 1.5 x ULN
AST/ALT	< 2.5 x ULN

BEP

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 doses based on the FBC alone. If patient is unwell, e.g. neutropenic sepsis, discuss with consultant.

Dose modifications

- **Haematological toxicity**

CBOP/BO

If on day 1 or day 8 WBC < 1.0 x 10^9/L or platelets < 50 x 10^9/L omit that dose of chemotherapy. FBC should be monitored and treatment should resume with the next scheduled treatment when counts have recovered.

BEP

If patients suffer repeated or severe (grade 4) neutropenia (despite GCSF which should be given as standard primary prophylaxis) or thrombocytopenia, etoposide should be given for 3 days only (100mg/m^2).

- **Renal impairment**

Full dose cisplatin should be administered if calculated CrCl is ≥ 60ml/min. An EDTA creatinine clearance should be arranged if CrCl falls below this value.

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

Carboplatin is contraindicated if CrCl is < 20ml/min.

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

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

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Etoposide dose**	**Vincristine dose**
<1.5	and	< 2.5	100%	100%
1.5-3.0	or	2.5-5.0	50%	50%
>3.0	or	> 5.0	25% or omit (consultant decision)	Usually omit (consultant decision)

No dose modification required for cisplatin or carboplatin.

No information regarding use of bleomycin in hepatic impairment (consultant decision)

- **Other toxicities**

Pulmonary toxicity:
Discuss with consultant if patient develops dry cough or dyspnoea. PFT's 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.

Neurotoxicity:
If persistent grade 2 neuropathy reduce vincristine dose to 50%, if grade ≥ 3 neuropathy discontinue.

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 (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: can affect protein binding of etoposide.

Carboplatin:
Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity
Clozapine: increased risk of agranulocytosis, avoid concomitant use

Diuretics: increased risk of nephrotoxicity and ototoxicity
Nephrotoxic drugs: increased nephrotoxicity ; not recommended
Phenytoin: carboplatin reduces absorption and efficacy of phenytoin

Additional comments

References

- Summary of Product Characteristics Cisplatin (Hospira) accessed 10 February 2016 via www.medicines.org.uk
- Summary of Product Characteristics Etoposide (Hospira) accessed 10 February 2016 via www.medicines.org.uk
- Summary of Product Characteristics Bleomycin (ProStraken) accessed 10 February 2016 via www.medicines.org.uk
- Summary of Product Characteristics Vincristine (Hospira) accessed 10 February 2016 via www.medicines.org.uk
- Summary of Product Characteristics Carboplatin (Hospira) accessed 10 February 2016 via www.medicines.org.uk
- MRC TE23 trial protocol
- Huddart RA, Gabe R, Cafferty FH, et al. A randomised phase 2 trial of intensive induction chemotherapy (CBOP/BEP) and standard BEP in poor-prognosis germ cell tumours (MRC TE23, CRUK 05/014, ISRCTN 53643604). Eur Urol 2015; 67:534-43

Written/reviewed by: Dr Jeremy Braybrooke (Consultant Oncologist, UHBristol NHS Trust)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Clinical Network), Dr Addeo, Dr Farrugia, Dr Hong and Dr Highley

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Clinical Network)

Date: April 2016 v2 December 2018