Bleomycin, Etoposide and CISplatin (BEP) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Adjuvant treatment of high risk (vascular invasion carcinoma) stage 1 nonseminoma germ cell tumour	C62	00300a	Hospital
Metastatic germ cell tumours of the testis	C62	00300b	Hospital
Advanced stage or metastatic germ cell tumours (dysgerminoma) of the ovaries	C56	00300c	Hospital
Extra-gonadal germ cell tumours	C56/C62	00300d	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Treatment with etoposide and CISplatin is administered on days 1-5, and treatment with bleomycin is administered on days 1, 8 and 15 of a 21 day cycle.

For good risk patients - 3 cycles are administered,
For intermediate to poor risk patients - 4 cycles are administered

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Admin Order	Day	Drug	Dose	Route	Diluent & Rate
1	1, 8 and 15	Bleomycin	[a]30,000 International Units (30mg)	IV Bolus or IM[b]	
2	1-5	Etoposide	100mg/m^2	IV infusion	1000ml 0.9% NaCl over 60 minutes[c]
3	1-5	CISplatin	20mg/m^2	IV infusion	1000ml 0.9% NaCl over 1 hour (Pre hydration therapy required) [d]
Bleomycin dosing may be referred to in international units (IU) or in mg. 1,000 international units = 1mg					
[a]The total cumulative dose of bleomycin should NOT exceed 400,000 international units (400mg). The risk of pulmonary toxicity increases beyond a cumulative dose of 300,000 international units (300mg).					
[b]For IM injection dose is dissolved in up to 5ml 0.9% NaCl. If pain occurs at the site of injection a 1% solution of lignocaine may be used as a solvent (6)					
[c]Hypotension following rapid IV administration has been reported. Longer infusion times may be required based on the patient's tolerance					
[d] **Prehydration therapy required for CISplatin** See local hospital policy recommendations. Suggested prehydration for CISplatin therapy: 1. Administer 10mmol magnesium sulphate ($MgSO_4$) ((+/-KCl 20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 minutes. Administer CISplatin as described above					

ELIGIBILITY:

- Indications as above
- ECOG status 0-3

EXCLUSIONS:

- Hypersensitivity to bleomycin, etoposide, CISplatin or any of the excipients.
- Bleomycin is contraindicated in patients with acute pulmonary infection or chest X rays suggesting diffuse fibrotic changes or greatly reduced lung function
- CISplatin
    - Pre existing neuropathies ≥ grade 2
    - Creatinine clearance < 40 mL/min
    - Significant hearing impairment/tinnitus
- Severe liver impairment (etoposide)

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile, creatinine
- Pulmonary function tests (PFTs) and Chest X-ray prior to bleomycin
- Consider sperm banking for appropriate patients prior to initiation of therapy
- Consider Audiometry testing

Regular tests:

- FBC weekly during treatment
- Renal and liver profile, creatinine prior to each treatment cycle
- Chest X-ray prior to each cycle
- PFTs as clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant

Haematological:

- Delay and dose reductions are not recommended as the efficacy of this treatment may be greatly compromised
- All delays to treatment must be approved by prescribing consultant.
- Prophylactic use of G-CSF is not recommended.
- G-CSF is indicated in patients receiving their second or subsequent cycle of BEP who have had an episode of neutropenic fever or who have not recovered their neutrophil count by Day 5.

Renal and Hepatic Impairment:

Table 2: Dose modification in renal and hepatic impairment

Drug	Renal impairment		Hepatic Impairment			
Bleomycin	**CrCl (ml/min)**	**Dose**	No dose recommendations available in SmPC, clinical decision			
	>50	100%				
	10-50	75%				
	<10	50%				
Etoposide	**CrCl (ml/min)**	**Dose**	**Bilirubin (micromol/L)**		**AST (Units/L)**	**Dose**
	>50	100%				
	15-50	75%	26-51	or	60-180	50%
	<15	50%	>51	or	>180	Clinical decision
	Subsequent dosing should be based on patient tolerance and clinical effect.					
CISplatin	**CrCl (ml/min)**	**Dose**	No dose reduction necessary			
	≥ 60	100%				
	*45-59	75%				
	<45	Hold CISplatin or delay with additional IV fluids				

**Due to the curative intent of this chemotherapy regimen , in cases where CrCl falls between 45-59ml/min it may be appropriate to maintain dose of CISplatin but with extra hydration, longer infusion time and daily Creatinine measurements at the discretion of the prescribing consultant.*

Bleomycin Induced Lung Toxicity:

- Bleomycin can be associated with the development of life-threatening pulmonary toxicity.
- Bleomycin should be discontinued in patients demonstrating clinical or radiographic evidence of pulmonary injury or significant deterioration of pulmonary diffusion capacity.
- Do not reintroduce bleomycin to patients with any bleomycin-induced lung injury.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Days 1-5 High
Days, 8 15 Minimal (**Refer to local policy).**

PREMEDICATIONS:

Hydration prior to CISplatin administration **(Reference local policy or see recommendations above).**

OTHER SUPPORTIVE CARE:

No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Pulmonary toxicity**: Bleomycin: may cause severe and life threatening pulmonary toxicity. Pulmonary toxicity of bleomycin is both dose-related and age-related. It may also occur when lower doses are administered, especially in elderly patients, patients with reduced kidney function, pre-existing lung disease, previous or concurrent radiotherapy to the chest and in patients who need administration of oxygen. It is significantly enhanced by thoracic radiation and by hyperoxia used during surgical anaesthesia.
- **Hypersensitivity:** Hypersensitivity reactions have been reported with etoposide and CISplatin. Monitor infusion of etoposide for the first 15 minutes for signs of hypotension.
- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately. Avoid aminoglycoside antibiotics.
- **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Strongly encourage oral hydration. If oral hydration is not possible (e.g. excessive nausea), IV hydration is indicated. Avoid nephrotoxic drugs such as aminoglycoside antibiotics where possible. Where treatment with nephrotoxic drugs must be used, monitor renal function.
- **Ototoxicity and sensory neural damage**: These are associated with CISplatin therapy. They should be assessed by history prior to each cycle.

DRUG INTERACTIONS:

- Bleomycin causes sensitization of lung tissue to oxygen. If oxygen is required the use of low concentration (e.g. 25%) is recommended. Fluid replacement should be carefully monitored with emphasis on administration of colloid rather than crystalloid to avoid interstitial pulmonary oedema.
- CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- Concomitant CISplatin therapy is associated with reduced total body clearance of etoposide.
- CYP3A4 inducers may increase the clearance of etoposide.
- CYP3A4 and p-gp inhibitors may decrease the clearance of etoposide
- Current drug interaction databases should be consulted for more information

ATC CODE:

Bleomycin	L01DC01
CISplatin	L01XA01
Etoposide	L01CB01

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Version	Date	Amendment	Approved By
1	08/04/2016		Dr Maccon Keane
2	27/09/2017	Updated with new NCCP regimen template	Prof Maccon Keane
3	06/12/2017	Updated with revised CISplatin hydration regimen recommendations	Prof Maccon Keane
4	20/11/2019	Reviewed. Standardised treatment table and renal dose modifications.	Prof Maccon Keane
5	11/11/2020	Updated baseline tests	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.