High Dose Carboplatin and Etoposide with autologous stem cell support

Indication

Second or third line treatment for relapsed germ cell cancer. Patients must have had an adequate peripheral blood stem cell collection before consideration for high dose chemotherapy.

GERM CELL CONSULTANT ONLY PRESCRIPTION – BEFORE PROCEEDING THE CHEMOTHERAPY PRESCRIPTION MUST BE COUNTERSIGNED BY THE SUPERVISING HAEMATOLOGY CONSULTANT

ICD-10 codes

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

Regimen details

Day	Drug	Dose	Route
-5, -4, -3	Carboplatin	AUC 8/ day (TOTAL = AUC 24)	IV infusion
-5, -4, -3	Etoposide	750 mg/m^2/day (TOTAL = 2250 mg/m^2)	IV infusion
0	Re-infusion of stem cells	At least 1 x 10^6 CD34+ cells / kg body weight	IV infusion

For heavily pre-treated patients (usually > 6 previous cycles of standard dose chemotherapy) or those with EDTA creatinine clearance < 80 ml/min consider reducing carboplatin to AUC 7/day (TOTAL = AUC 21) and etoposide to 600mg/m^2/day (Total = 1800 mg/m^2).

Cycle frequency

28 days

Number of cycles

Maximum of 2 cycles

Administration

Carboplatin is administered in 500mL 5% glucose over 60 minutes.

Etoposide is administered in sodium chloride 0.9% (concentration dependent) and infused over 2 hours. Consider using etoposide phosphate (Etopophos) due to high dose and therefore high volume of fluid required.

Pre-medication

Antiemetics as per local guidelines

Emetogenicity

This regimen has severe emetic potential.

Additional supportive medication

Allopurinol 300mg OD for patients with a high tumour burden
H_2 antagonist or proton pump inhibitor if required.
Mouthwashes as per local policy.
Anti-emetics as per local policy.
GCSF as per local policy
Antifungal and antiviral prophylaxis as per local policy

Prophylactic antibiotics as per local policy

Extravasation

Carboplatin and etoposide are irritant (Group 3)

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
Pulmonary Functions Tests (including transfer factor)	28 days
CXR	28 days
EDTA creatinine clearance	28 days
Echocardiogram	28 days

Where appropriate offer pre-treatment sperm storage.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours
U+E (including creatinine)	7 days
LFTS	7 days
Magnesium	7 days
AFP, HCG, LDH	7 days
CXR	7 days

Standard limits for administration to go ahead with first and second cycle

Investigation	Limit
WBC	$\geq 3.0 \times 10^9$/L*
Platelets	$\geq 100 \times 10^9$/L*
Neutrophils	$\geq 1.5 \times 10^9$/L*
Calculated CrCl	> 50 ml/min
Bilirubin	< 1.5 x ULN
AST/ALT	< 3.0 x ULN

Before proceeding with cycle one the supervising haematology consultant must be satisfied that the patient has adequate cardiac and pulmonary function.

It is recommended that the palliative and supportive care team are aware of the high dose chemotherapy treatment and review the patient to advise about symptom management.

Consider referral to a clinical psychologist prior to cycle one.

Consultant decision to proceed with cycle two – minimum interval between cycles is 28 days or until blood counts have recovered (* discuss with haematology consultant if blood counts have not recovered to these values at day 28 – it may be appropriate to proceed with the second cycle with lower counts than pre cycle one).

Dose modifications

- **Renal impairment**

This schedule is contra-indicated if EDTA CrCl is < 50mL/min

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Etoposide dose**
<1.5	and	< 2.5	100%
1.5-3.0	or	2.5-5.0	Consider reducing dose to 50 - 75% (consultant decision)
> 3.0	or	> 5.0	Consultant decision – high dose chemotherapy would not normally be appropriate for patients with significant hepatic impairment

No dose modification required for carboplatin

- **Other toxicities**

Do not continue with second cycle in the presence of any persisting grade 3-4 toxicity. Consultant decision to prescribe cycle 2.

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

- **Serious side effects**

Death
Myelosuppression
Nephrotoxicity
Ototoxicity
Neurotoxicity
Pulmonary toxicity
Infertility

- **Frequently occurring side effects**

Myelosuppression
Constipation, diarrhoea
Stomatitis, mucositis
Alopecia
Nausea and vomiting
Anorexia

- **Other side effects**

Electrolyte disturbances
Fatigue
Deranged LFTs

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.

Carboplatin:

Antibiotics: The renal toxicity of carboplatin 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.
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

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

Additional comments

The table below can be used to define a prognostic score for patients considered for high dose chemotherapy. This can help inform discussions with patients and their family/carers about likely survival benefits from high dose chemotherapy:

Table 4. Prognostic Score for Patients With Nonseminoma and Seminoma

	Score Points				
Parameter	0	1	2	3	Score
Primary site	Gonadal	Extragonadal	—	Mediastinal nonseminoma	
Prior response	CR/PRm−	PRm+/SD	PD	—	
PFI, months	> 3	≤ 3	—	—	
AFP salvage	Normal	≤ 1,000	> 1,000	—	
HCG salvage	≤ 1,000	> 1,000	—	—	
LBB	No	Yes	—	—	
Score sum (values from 0 to 10)					
Regroup score sum into categories: (0) = 0; (1 or 2) = 1; (3 or 4) = 2; (5 or more) = 3					
Add histology score points: pure seminoma = −1; nonseminoma or mixed tumors = 0					
Final prognostic score (−1 = very low risk; 0 = low risk; 1 = intermediate risk; 2 = high risk; 3 = very high risk)					

Abbreviations: CR, complete remission; PRm−, partial remission, negative markers; PRm+, partial remission, positive markers; SD, stable disease; PD, progressive disease; PFI, progression-free interval; AFP, alpha fetoprotein; HCG, human chorionic gonadotrophin; LBB, liver, bone, brain metastases.

(Reproduced from International prognostic factors study group JCO 2010 28;4906-11)

References

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- Summary of Product Characteristics Etoposide (Hospira) accessed 1 July 2015 via www.medicines.org.uk
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