SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

High Dose **CARBOPLATIN & ETOPOSIDE Tandem Germ Cell BMT: AUTOGRAFT**

PROTOCOL REF: MPHABMTCE
(Version No. 1.0)

Approved for use in:

- Selected patients with relapsed Germ cell cancer (non-CNS involvement) - as conditioning prior to autologous stem cell transplant.

Blueteq not required

Dosage/Summary:

Day	Treatment
-7	Admit to ward. Complete pre-assessment and review. **Ensure EDTA creatinine clearance is sent to nuclear medicine**
-6	Insert Hickman line
-5	Carboplatin AUC 7 or 8 x (GFR + 25) IV infusion OD *1 Etoposide (Phosphate) 750 mg/m^2 IV infusion OD *2
-4	Carboplatin AUC 7 or 8 x (GFR + 25) IV infusion OD *1 Etoposide (Phosphate) 750 mg/m^2 IV infusion OD *2
-3	Carboplatin AUC 7 or 8 x (GFR + 25) IV infusion OD *1 Etoposide (Phosphate) 750 mg/m^2 IV infusion OD *2
-2	Rest day
-1	Rest day
0	Infuse stem cells (Minimum 1×10^8 nucleated cells/kg)
+3	GCSF (Filgrastim)

*1 Note total maximum AUC per cycle = 24
*2 Note total maximum dose per cycle = 2250mg/m^2

Cycle length 28 days

Maximum of 2 cycles

Use the Calvert Formula to Calculate the Carboplatin dose:

Carboplatin Dose in mg = Target AUC x (GFR +25)

Creatinine Clearance MUST be derived from EDTA clearance prior to transplant cycle. Estimations of creatinine clearance will not be accepted.

EDTA measured uncorrected GFR, maintain Carboplatin dose from initial EDTA and dose reduce as indicated below for toxicity

Pre-Assessment:

- Ensure results of the patient's pre-transplant investigations are reviewed – discuss with consultant if abnormal.
- Ensure the regimen specific fluid prescription proforma is completed prior to starting treatment, the chemotherapy regimen is prescribed in Meditech by a suitably trained doctor in the week before admission.
- Ensure that the patient has a dual lumen Hickman line or equivalent (PICC) inserted and working. If the patient does not have a line in situ, book a line to be inserted prior to start of conditioning regimen.
- Ensure that the patient receives irradiated blood products at least from the start of the conditioning regimen (this is usually done day before the start of the conditioning regime).
- Ensure a pregnancy test is carried out on all women of child-bearing potential 1-2 days before start of conditioning regimen (usually on day of admission).
- Request **EDTA** creatinine clearance (on ICE – usually done on Mondays and Wednesdays) on admission and send to nuclear medicine.

Administration / Counselling Points:

- Ensure that the patient has been provided with adequate verbal and written information and is happy to proceed.
- Answer any patient questions regarding the regimen.
- Ensure written consent has been obtained.

- Ensure that the patient has suitable intravenous access.
- Ensure that the patient has adequate daily fluid intake and supplement with IV fluids if necessary. Daily weight and urine output to be maintained at or below baseline with IV Furosemide
- Ensure blood products are irradiated

Emetogenic risk:

Severely emetogenic.

Supportive treatments:

Allopurinol	Oral 300mg ONCE daily (from admission until day 0). Note the requirement for a reduced dose in renal impairment
Antiemetics	• IV ondansetron in syringe driver (24mg/24 hours), prescribed on Meditech, to start evening before conditioning begins or the day conditioning starts (depending on admission) • IV dexamethasone (6.6mg OD), day -5 to day-3. Avoid prolonged use due to the increased risk of infection. • IV fosaprepitant 150mg STAT, 30minutes before chemotherapy on Day -5 • IV / oral cyclizine 50mg THREE times a day when required.
Anti-bacterial prophylaxis	• Oral ciprofloxacin 500mg TWICE daily, from day +3 until neutrophil count >0.5 x 10^9/L for 2 consecutive days • Prontoderm Foam, as per infection control. Use as directed ONCE daily throughout admission. Stop on discharge
Anti-viral prophylaxis	Oral aciclovir 400mg TWICE daily from the start of conditioning. It should be continued for approximately 3 months post-transplant then review stopping
Anti-fungal prophylaxis	Oral posaconazole from Day +3, (to avoid interaction with fosaprepitant). Loading: 300mg TWICE daily for ONE day then 300mg ONCE daily. Review to stop on discharge or until neutrophils >0.5 x 10^9/L for 2 consecutive days.
Anti-PCP Prophylaxis	Patients should receive the following immediately prior to admission (as scheduling and capacity allows). Otherwise patients should receive the following on admission prior to conditioning treatment starting: • 2.5mg nebulised salbutamol and then 300mg nebulised pentamidine immediately afterwards. The dose should be repeated after 28 days. • Pentamidine should be continued every 28 days if co-trimoxazole is unsuitable Atovaquone 750mg BD is an alternative agent if both co-trimoxazole and pentamidine are unsuitable • If the patient has adequate count recovery after the second cycle (neutrophil count ≥1.5x10^9/L and platelet count ≥50x10^9/L) then pentamidine can be switched to oral co-trimoxazole 480mg OD to start on the day pentamidine was due

	It should be continued for approximately 3 months post-transplant then review stopping
Mouthcare	• Nystatin 1mL FOUR times a day • Sodium chloride 0.9% 10mL plastic ampoules, as a mouthwash, FOUR times a day • Benzydamine 0.15%, as a mouthwash, 15mLs FOUR times a day • Ascorbic Acid and Zinc effervescent tablets, Use ¼ tablet as a mouthwash FOUR times a day. Review to stop mouthcare on discharge
Gastric-protection	Oral omeprazole 40mg ONCE daily from admission. Review before discharge or when platelets >50 x 10^9/L.
Renal protection	Oral sodium bicarbonate,1gram FOUR times a day, Day -2 to day 0
Norethisterone	(*Menstruating women):* 5-10mg THREE times a day from admission until platelets >50 x 10^9/L
Filgrastim	GCSF (e.g. Zarzio®) by subcutaneous injection, to start on day +3 until neutrophils >1.5 x 10^9/L for 3 consecutive days.
Other	• IV Hydrocortisone Sodium Succinate 100mg, ONCE daily PRN • IV Chlorphenamine 10mg in 1mL injection, ONCE daily PRN • IV Paracetamol 500-1000mg, FOUR times a day PRN (review in hepatic impairment or reduce dose if weight <50Kg)

Extravasation risk:

Carboplatin- Irritant

Etoposide phosphate – non vesicant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment and pre-treatment:

Heavily pre-treated patients (usually >6 cycles of standard dose chemotherapy)	**Carboplatin**	AUC 7 (Total = AUC 21 per cycle**)**
	Etoposide (phosphate)	600mg/m^2/day (Total = 1800mg/m^2 per cycle).

Renal	Carboplatin	**Creatinine Clearance (mL/min - EDTA)**		**Carboplatin Dose**	
		>80		AUC 8	
		50 - 80		AUC 7	
		<50		Contra-indicated and to be confirmed at the pre-transplant MDT.	
	Etoposide	**Creatinine Clearance (mL/min - EDTA)**		**Etoposide Dose**	
		>80		750 mg/m^2	
		50 - 80		600 mg/m^2	
		<50		Contra-indicated and to be confirmed at the pre-transplant MDT.	
Hepatic	Carboplatin	No dose reduction necessary in hepatic impairment.			
	Etoposide	**Bilirubin (microl/L)**		**AST/ALT (ULN)**	**Etoposide dose**
		<31.5	And	<2.5	100%
		31.5-63	Or	2.5-5.0	Consider reducing dose to 50-75%(consultant decision)
		>63	Or	>5.0	Consultant decision

Interactions:

Review other medication prior to treatment and stop any other nephrotoxic drugs where possible e.g. NSAIDs.

Please refer to each agent's SPC for further information. See reference section.

Treatment schedule:

Prior to starting treatment, please ensure the following is prescribed:

- Hydration is prescribed on regimen specific hydration chart
- IV furosemide (if required), supportive medications and chemotherapy are prescribed in Meditech and visible on the MAR as per protocol

Monitor fluid balance closely; liaise with the medical team to ensure adequate fluid balance.

Day	Time	Drug	Dose	Route	Diluent and rate
-5	9:30	**Fosaprepitant**	**150mg**	**IV**	IV Infusion over 30 minutes. Give 30minutes before chemotherapy
	10:00	**Carboplatin**	**AUC 7 or 8**	**IV**	Glucose 5% 500mLs over 60 minutes
	11:00	**Etoposide (Phosphate)**	**750 mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mLs over 120 minutes
-4	10:00	**Carboplatin**	**AUC 7 or 8**	**IV**	Glucose 5% 500mLs over 60 minutes
	11:00	**Etoposide (Phosphate)**	**750 mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mLs over 120 minutes
-3	10:00	**Carboplatin**	**AUC 7 or 8**	**IV**	Glucose 5% 500mLs over 60 minutes
	11:00	**Etoposide (Phosphate)**	**750 mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mLs over 120 minutes
-2	**REST DAY**				
-1	**REST DAY**				
0		**Chlorphenamine**	**10mg**	**IV**	Bolus over 3-5 minutes. **Give 15 minutes before stem cell re-infusion.**
		Hydrocortisone	**100mg**	**IV**	Bolus over 3-5 minutes. **Give 15 minutes before stem cell re-infusion.**
		Stem Cell Re-infusion	**-**	**IV**	
+3		**Filgrastim**	**30 or 48 million units**	**SC**	Daily until neutrophils >1.5 x10^9/L for 3 consecutive days

Main toxicities:

Main toxicities	Nausea, vomiting, diarrhoea, anorexia, mucositis, stomatitis Alopecia, rash. Severe myelosuppression, severe infections, bleeding, anaemia. Electrolyte disturbances (hypokalaemia may complicate persistent vomiting and diarrhoea), Renal failure. Transient hepatic dysfunction, neuropathy, secondary malignancies. Infertility. Treatment-related mortality.
Carboplatin	Infections, blood and lymphatic disorders (thrombocytopenia, neutropenia, leukopenia, anaemia), Haemorrhage, hypersensitivity, anaphylactoid-type reactions, visual disturbances, ototoxicity, cardiac issues, respiratory issues including interstitial lung disease, bronchospasm. Nausea, vomiting, abdominal pain, alopecia, skin issues, musculoskeletal disorders, urogenital disorders. Asthenia, renal dysfunction, liver function test abnormalities, electrolyte dysfunction.
Etoposide	Infections, acute leukaemia, anaemia, leucopenia, myelosuppression, neutropenia, thrombocytopenia Anaphylactic reactions, dizziness, arrhythmia, myocardial infarction, hypertension, transient systolic hypotension Interstitial pneumonitis, pulmonary fibrosis. Abdominal pain, anorexia, constipation, nausea and vomiting Liver function test abnormalities, alopecia, pigmentation, pruritus, rashes, urticarial, asthenia, malaise.

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Investigations and treatment plan:

Repeat for each cycle

Investigation	Pre-/day of admission	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Additional Information
Ensure informed and written consent	X								
Clinical Assessment	X	X				X		X	
SACT Assessment, (includes PS and toxicities)	X	X	X	X	X			X	
Weight and Fluid Balance	X	X	X	X	X	X	X	X	Report positive fluid balance of > 2 litres
Height	X								
FBC	X		X		X		X		Monitored on a Mon, Wed and Fri
U&E & LFTs & Magnesium	X		X		X		X		Monitored on a Mon, Wed and Fri
Glucose	X								Repeat as clinically indicated
Bone Profile (vitamin D level)	X								Requested on admission
CRP	X	X	X	X	X	X	X	X	Monitored on a Mon, Wed and Fri thereafter
Chest X-Ray	X								Repeat as clinically indicated
B12 and folate	X								
Respiratory swabs	X								
EDTA CREATININE CLEARANCE	X								Estimations will not be accepted. Re-check and adjust doses as indicated.
Specimens for virology and microbiology (including **Covid-19** swabs)	X								Repeat as clinically indicated
Vital signs (includes TPR, O_2 saturation and BP)	X	X	X	X	X	X	X	X	Monitor vital signs four times a day or adjust as clinically indicated
Serum pregnancy test (if applicable)	X								
Tumour Markers	X								Weekly if appropriate Tumour specific markers
CT Scan	X								Repeat as clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

For cycle 1 no dose modifications required for haematological parameters.

Cycle 2 can commence following haematopoietic recovery from cycle 1, or at the discretion of the cellular therapies consultant:

ANC > 1.5 x 10^9 /L	Platelets > 75 x 10^9 /L

Non- Haematological toxicity:

See specific BMT guidelines for toxicity management.

References:

1. Summary of Product Characteristics, Carboplatin 10mg/ml intravenous infusion, Hospira. Available via www.medicines.org.uk [accessed 16th December 2022]
2. Summary of Product Characteristics Etopophos 100mg Powder for Solution for Injection –Last updated on eMC 12-Dec-2021. Available via www.medicines.org.uk. [accessed 9th June 2023]
3. South West Clinical Network, High Dose Carboplatin and Etoposide with Autologous Stem Cell Support Protocol, December 2018
4. Renal Drug Database, available via www.renaldrugdatabase.com [accessed 16th December 2022]
5. Krens S D, Lassche, Jansman G F G A, *et al*. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.
6. Adra N, et al. High-Dose Chemotherapy and Autologous Peripheral blood stem-cell transplantation for relapsed metastatic germ cell tumours: The Indiana University Experience. Journal of Clinical Oncology 2017; 35(10): 1096-1102.
7. National Cancer Control Programme, Carboplatin (AUC7) and Etoposide-Autologous Conditioning Germ Cell Tumour Regimen. December 2017.

8. A randomised phase III trial comparing conventional dose chemotherapy using Paclitaxel, Ifosfamide and Cisplatin (TIP) with high dose chemotherapy using mobilising Paclitaxel plus Ifosfamide followed by high dose Carboplatin and Etoposide (TI-CE) as first salvage treatment in relapsed or refractory germ cell tumours.

Circulation/Dissemination

Date added into Q-Pulse	12th October 2023
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Version History

Date	Version	Author name and designation	Summary of main changes
June 23	1.0	**SCT Team**	**New protocol**