TICE - Autologous Conditioning Germ Cell Tumour Regimen

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of metastatic relapsed/refractory germ cell tumours	C62	00437a	Hospital

TREATMENT:

The complete treatment course consists of:

- Two cycles of PACLitaxel plus ifosfamide (cycle 1 & 2) administered 14 days apart followed by
- Three cycles of CARBOplatin and etoposide (cycle 3,4 & 5) with autologous stem-cell support every 21 days

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

Cycles 1-2

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	PACLitaxel	200mg/m^2	IV Infusion	500ml 0.9% NaCl over 3hr[a,b]	Every 14 days for 2 cycles
2-4	Mesna	400mg/m^2	IV Bolus	IV bolus 15 minutes before and 4 and 8 hours after administration of each dose of ifosfamide.	Every 14 days for 2 cycles
2-4	Ifosfamide	2000mg/m^2	IV Infusion	1000ml 0.9% NaCl over 3 hours	Every 14 days for 2 cycles
5	G-CSF (Round to nearest whole syringe)	[c]5mcg/kg twice daily	SC	N/A	Continue daily until CD34+ cells harvested
[a]PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22 µm filter with a microporous membrane.					
[b]PACLitaxel should be diluted to a concentration of 0.3-1.2mg/ml.					
[c]G-CSF may be administered as 10mcg/kg once daily at the discretion of the prescribing Consultant					
Maintain strict fluid balance during therapy, by (1) monitoring fluid balance and (2) daily weights. If fluid balance becomes positive by >1000mls or weight increases by >1 Kg, the patient should be reviewed and consideration given to diuresing with furosemide					

Cycle 3-5

Admin Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	-5, -4, -3	CARBOplatin	[a]AUC 7 or 8	IV Infusion	500ml 5% glucose over 60mins	Repeat every 21 days for 3 cycles
2	-5, -4, -3	Etoposide	[b]200mg/m^2	IV Infusion	1000ml of 0.9% NaCl over 2 hours	Repeat every 21 days for 3 cycles
3	-5, -4, -3	Etoposide	[b]200mg/m^2	IV Infusion	1000ml of 0.9% NaCl over 2 hours *(start immediately after first etoposide infusion finishes)*	Repeat every 21 days for 3 cycles
	0	Stem cell infusion		Minimum 48 hours post end of last etoposide infusion		
	Start day +1	G-CSF (Round to nearest whole syringe)	5mcg/kg twice daily	sc	N/A	Continue until ANC > 1 x 10^9/L for two consecutive days

[a]Use AUC 8 for patients who have received ≤6 cycles of prior CISplatin therapy.
Use AUC 7 for patients who have received > 6 cycles of prior CISplatin therapy

[b]The etoposide 200mg/m^2 dose may need to be split into two 1000ml bags for stability reasons. These should be administered sequentially.

[c]G-CSF may be administered as 10mcg/kg once daily at the discretion of the prescribing Consultant

Maintain strict fluid balance during therapy, by (1) monitoring fluid balance and (2) daily weights.
If fluid balance becomes positive by >1000mls or weight increases by >1 Kg, the patient should be reviewed and consideration given to diuresing with furosemide

The dose in mg of CARBOplatin to be administered is calculated as follows:

(mg) = target AUC (mg/ml x min) X GFR ml/min +25

Reference NCCP Protocol 00261 CARBOplatin Monotherapy for information on calculation of CARBOplatin dose.

ELIGIBILTY:

- Indication as above

EXCLUSIONS:

- Hypersensitivity to PACLitaxel, ifosfamide, etoposide, CARBOplatin or any of the excipients.
- Severe liver impairment (etoposide)
- Pregnancy
- Breast Feeding

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Assess neurological function daily while on ifosfamide
- Check urinalysis for haematuria prior to ifosfamide and daily during treatment with ifosfamide
- LDH, Uric acid
- Creatinine Clearance
- Audiology if clinically indicated
- Virology screen -Hepatitis B* (HBsAg, HBcoreAb) & C, HIV I and II, CMV and HSV.
  *Hepatitis B reactivation: See Adverse events/ Regimen specific complications

Regular tests:

- Blood, renal and liver profile required daily during therapy

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

Renal and Hepatic Impairment:

Table 1: Dose modification in renal and hepatic impairment

Drug	Renal impairment		Hepatic Impairment			
PACLitaxel	No dose modifications necessary		**Category**	**Dose modification**		
			Mild	Reduce PACLitaxel by 25%		
			Moderate	Reduce PACLitaxel by 50%		
			Severe	Omit PACLitaxel		
Ifosfamide	**CrCl (ml/min)**	**Dose**	Dose reductions are probably not necessary for patients with altered liver function. However ifosfamide is extensively hepatically metabolised and some clinicians recommend a 25% dose reduction for patients with significant hepatic dysfunction (serum AST > 300IU/L or bilirubin > 51.3 micromol/L) (5) The SPC states that it is not recommended in patients with a bilirubin >17 micromol/L or AST/ALT/ALP >2.5xULN			
	>60	100%				
	40-59	70%				
	<40	Clinical decision				
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.					
CARBOplatin	**CrCl (ml/min)**	**Dose**	No dose reduction necessary			
	<60	Greater risk of developing myelosuppression				
	<20	Contra-indicated				

Non-Haematological Toxicity:

Table 2: Dose modification of PACLItaxel for peripheral neuropathy

Adverse reactions	Discontinue	Recommended dose modification
Motor or sensory neuropathy Grade 2 Grade ≥ 3		 Reduce PACLitaxel by 25% Omit PACLitaxel

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate-High **(Refer to local policy)**

PREMEDICATIONS:

All patients must be premedicated with corticosteroids, antihistamines, and H_2-antagonists prior to PACLitaxel treatment. Table 3 outlines **suggested** premedications prior to treatment with PACLitaxel.

Table 3: Suggested premedications prior to treatment with PACLitaxel

Drug	Dose	Administration prior to PACLitaxel
Dexamethasone	20mg oral or IV[a]	For oral administration: approximately 6 and 12 hours or for IV administration: 30 minutes prior to PACLitaxel administration
Chlorphenamine	10mg IV	30 minutes prior to PACLitaxel administration
Ranitidine[b]	50mg IV	30 minutes prior to PACLitaxel administration
[a]Dose of dexamethasone may be reduced or omitted in the absence of hypersensitivity reaction according to consultant guidance.		
[b]Or equivalent e.g. Cimetidine		

Prior to stem cell infusion administer premedications as per local policy.

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis (**Refer to local policy**)
- Proton pump Inhibitor**(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**
- Mouthcare **(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy)** *Do not give Co-trimoxazole until engraftment achieved* and continue until day 100 or CD4 count> 200/microlitre.
- All patients must receive irradiated cellular blood components starting one week prior to TICE conditioning and until 12 months after stem cell infusion to prevent transfusion associated graft versus host disease.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

- **Ifosfamide-induced encephalopathy:** This may occur in patients treated with high doses of ifosfamide.
  - Consider risk factors for ifosfamide induced encephalopathy (renal insufficiency, low serum albumin, large pelvic mass).
  - Methylene blue is used to manage ifosfamide-associated encephalopathy **(Refer to local policy)**
- **Renal and urothelial toxicity:** Ifosfamide is both nephrotoxic and urotoxic. For prophylaxis of hemorrhagic cystitis, ifosfamide should be used in combination with mesna.
- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately. Avoid aminoglycoside antibiotics.
- **Neurotoxicity and ototoxicity:** Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose CARBOplatin. Neurotoxicity, such as parasthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with cisplatin, other platinum treatments and other ototoxic agents. Frequency of neurologic toxicity is also increased in patients older than 65 years.
- **Hepatitis B Reactivation**: Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy. **(Refer to local infectious disease policy**). These patients should be considered for assessment by hepatology.

DRUG INTERACTIONS:

- Avoid concurrent use of CARBOplatin and ifosfamide with nephrotoxic drugs (e.g. aminoglycosides, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.

- Avoid concurrent use of CARBOplatin with ototoxic drugs (e.g. aminoglycosides, NSAIDS). When necessary perform regular audiometric testing.
- Consider increased risk of ifosfamide-induced neurotoxicity due to inhibition of CYP3A4 by aprepitant.
- Current drug interaction databases should be consulted for more information e.g interaction potential with CYP3A4 inhibitors/ inducers.

ATC CODE:

Ifosfamide	L01AA06
PACLitaxel	L01CD01
CARBOplatin	L01XA02
Etoposide	L01CB01

REFERENCES:

1. Feldman DR, Sheinfeld J et al. TI-CE High-Dose Chemotherapy for Patients With Previously Treated Germ Cell Tumors: Results and Prognostic Factor Analysis. J Clin Oncol 2010; 28: (10) 1706-13.
2. Lorch A, Bascoul-Mollevi C, Kramar A, et al. Conventional dose versus high dose chemotherapy as first salvage treatment in male patients with metastatic germ cell tumors: Evidence from a large international database. J Clin Oncol 2011; 29:2178-2184 .
3. Kondagunta GV, Bacik J, Sheinfeld J et al. Paclitaxel plus Ifosfamide followed by high-dose carboplatin plus etoposide in previously treated germ cell tumors. J Clin Oncol. 2007;25(1):85-90.
4. Motzer RJ, Mazumdar M, Sheinfeld J et al. Sequential dose-intensive paclitaxel, ifosfamide, carboplatin, and etoposide salvage therapy for germ cell tumor patients. J Clin Oncol. 2000;18(6):1173-80.
5. Floyd J and Kerr TA. Chemotherapy hepatotoxicity and dose modification in patients with liver disease UptoDate https://www.uptodate.com/contents/chemotherapy-hepatotoxicity-and-dose-modification-in-patients-with-liver-disease#H14
6. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network. Available at http://www.londoncancer.org/media/65600/renal-impairment-dosage-adjustment-for-cytotoxics.pdf
7. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009;North London Cancer Network. Available at http://londoncancer.org/media/65594/hepatic-impairment-dosage-adjustment-for-cytotoxics.pdf
8. PACLitaxel. Summary of Product Characteristics. Last updated: 02/08/2019. Accessed Nov 2019. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-050-001_02082019150408.pdf
9. Ifosfamide (Mitoxana®) Summary of Product Characteristics. Last updated: 15/11/2019. Accessed Nov 2019. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-028-001_15102019093147.pdf
10. CARBOplatin Summary of Product Characteristics. Last updated: 10/11/2019. Accessed Dec 2019. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-032-001_10112019092721.pdf
11. Etoposide 20 mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics. Last updated: 29/07/2019. Accessed Dec 2019. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-036-001_29072019103821.pdf
12. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V1 2018. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp%20antiemetic%20classification%20document%20v1%202018.pdf

Version	Date	Amendment	Approved By
1	18/12/2017		Prof Maccon Keane
2	07/02/2018	Updated suggested premedications	Prof Maccon Keane
3	05/12/2018	Amended dosing recommendations for G-CSF, standardization of pre-medication for NCIS	Dr Dearbhaile O'Donnell
4	10/07/2019	Standardisation of PACLitaxel hepatic dose modifications.	Prof Maccon Keane
5	15/01/2020	Reviewed. Standardisation of treatment table. Updated exclusions, renal and hepatic dose modifications, premedications table and hepatitis B reactivation recommendations.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.