# 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 |

**If the reimbursement status is not defined [1], the indication has yet to be assessed through the formal HSE reimbursement process.*

## 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 | 500-1000ml 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 etoposide, [b]CARBOplatin or any of the excipients.
- Severe liver impairment (etoposide)
- Pregnancy
- Breast Feeding

[b]If it is felt that the patient may have a major clinical benefit from CARBOplatin, it may in exceptional circumstances be feasible to rechallenge a patient with a prior mild hypersensitivity reaction e.g using a desensitisation protocol, but only with immunology advice, premedication as advised, and a desensitisation protocol under carefully controlled conditions with resuscitation facilities available and medical and/or ITU/ HDU supervision (1).

## 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 (4)<br>The SPC states that it is not recommended in patients with a bilirubin >17 micromol/L or transaminases >2-3xULN | | | |
| | >60 | 100% | | | | |
| | 40-59 | 70% | | | | |
| | <40 | Clinical decision | | | | |
| **Etoposide** | **CrCl (ml/min)** | **Dose** | **Bilirubin (micromol/L)** | | **AST (Units/L)** | **Dose Etoposide** |
| | >50 | 100% | | | | |
| | 15-50 | 75% | 26-51 | or | 60-180 | 50% |
| | Subsequent dosing should be based on patient tolerance and clinical effect. Data are not available in patients with CrCl < 15ml/min and further dose reductions should be considered in these patients. | | >51 | or | >180 | Clinical decision |
| **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**<br>Grade 2<br><br>Grade ≥ 3 | | <br>Reduce PACLitaxel by 25%<br><br>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 predmedications 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 min |
| Chlorphenamine [b] | 10mg IV | 30 minutes |
| Ranitidine | 50mg IV | 30 minutes |
| [a]Dose of dexamethasone may be reduced or omitted in the absence of hypersensitivity reaction according to consultant guidance. | | |
| [b] or an equivalent antihistamine e.g. diphenhydramine | | |

- 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 Hepatitis B test is positive, patients should be treated with lamivudine 100 mg/day orally during transplantation and for six months afterwards and should be monitored with at least monthly liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis

## 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. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network. Available at http://londoncancer.org/media/65600/renal-impairment-dosage-adjustment-for-cytotoxics.pdf
6. 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
7. PACLitaxel. Summary of Product Characteristics. Accessed Sept 2017. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1426-002-001_01072015115039.pdf

8. Mitoxana Summary of Product Characteristics. Accessed Sept 2017. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0167-135-001_29092016170101.pdf
9. CARBOplatin Summary of Product Characteristics. Accessed Sept 2017Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1422-008-001_15102013103044.pdf
10. Etoposide 20 mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics. Accessed Sept 2017Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1809-020-001_07102015115038.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 |

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[1] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/