# ICE (Ifosfamide, CARBOplatin and Etoposide) Therapy

## INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | Reimbursement Status |
|---|---|---|---|
| Treatment of relapsed/refractory Non Hodgkin's Lymphoma | C85 | 00842a | Hospital |
| Treatment of relapsed/refractory Hodgkin's Lymphoma | C81 | 00842b | 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 is administered on Day 1-3 as described in table every 21 days until remission induction or up to a maximum of 6 cycles.

Facilities to treat anaphylaxis MUST be present when systemic anti cancer therapy (SACT) is administered.

**Note: Specific Hydration therapy is required for the safe administration of [a]ifosfamide (See Table below)**

| Day | Drug | Dose | Route and Method of Administration | Diluent & Rate | Cycle |
|---|---|---|---|---|---|
| 1, 2, 3 | Etoposide | 100mg/m$^2$ | IV infusion | 1000mls 0.9% NaCl over 60minutes | 1-6 |
| 2 | CARBOplatin | AUC 5 | IV infusion | 500ml glucose 5% over 30 minutes | 1-6 |
| 2 | Mesna | 1000mg/m$^2$ | IV Bolus | Into the side arm of a fast-flowing 0.9% NaCl drip immediately before ifosfamide infusion starts | 1-6 |
| 2 | [a]Ifosfamide | 5000mg/ m$^2$ | IV infusion | In 1000ml 0.9% NaCl over 24 hours[b] | 1-6 |
| 2 | Mesna | 5000mg/ m$^2$ | IV infusion | In 1000ml 0.9% NaCl over 24 hours Y-sited with the ifosfamide | 1-6 |
| 3 | Mesna | 1000mg/m$^2$ | IV bolus | Into the side arm of a fast-flowing 0.9% NaCl drip 3 hours post end ifosfamide infusion | 1-6 |
| 3 | Mesna | 1000mg/m$^2$ | IV bolus | Into the side arm of a fast-flowing 0.9% NaCl drip 6 hours post end ifosfamide infusion | 1-6 |
| 3 | Mesna | 1000mg/m$^2$ | IV bolus | Into the side arm of a fast-flowing 0.9% NaCl drip 9 hours post end ifosfamide infusion | 1-6 |
| From day 6 | G-CSF | 5mcg/kg | SC (Round to nearest whole syringe) | Continued until ANC >1x10$^{9}$/L for 2 consecutive days | 1-6 |

[a] **Ifosfamide Hydration: (Refer to local policy or see suggested hydration below).**
Ensure IV hydration (1L NaCL 0.9% IV every 6 hours) is given, commencing prior to first dose of ifosfamide and continuing for 24 hours after completion.
Furosemide should also be administered if required to ensure a urinary output of at least 100ml/hour.
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.

[b] In order to facilitate the infusion of ifosfamide over 24 hours consideration may be given to splitting the dose of ifosfamide over multiple infusion bags for stability reasons.

**CARBOplatin dose:**

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

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

- Measured GFR (e.g. nuclear renogram) is preferred whenever feasible.
- Estimation of GFR may be performed using the Wright formula to estimate GFR or the Cockcroft and Gault formula to estimate creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.
- For obese patients and those with a low serum creatinine, for example, due to low body weight or post-operative asthenia, estimation using formulae may not give accurate results; measured GFR is recommended.
    - where obesity (body mass index [BMI] ≥ 30 kg/m$^2$) or overweight (BMI 25-29.9) is likely to lead to an overestimate of GFR and isotope GFR is not available the use of the adjusted ideal body weight in the Cockcroft and Gault formula may be considered.
    - where serum creatinine is less than 63 µmol/L, the use of a creatinine value of 62 µmol/L or a steady pre-operative creatinine value may be considered.
- These comments do not substitute for the clinical judgement of a physician experienced in prescription of CARBOplatin.

WRIGHT FORMULA

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method. The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

1. SCr measured using enzymatic assay.

$$\text{GFR (ml/min)} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr (micromol/min)}}$$

2. SCr measured using Jaffe assay

$$\text{GFR (ml/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \text{Sex})}{\text{SCr (micromol/min)}}$$

Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

COCKCROFT-GAULT FORMULA

$$\text{GFR (ml/min)} = \frac{S \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

S= 1.04 for females and 1.23 for males

## ELIGIBILITY:

- Indications as above

## EXCLUSIONS:

- Hypersensitivity to CARBOplatin*, etoposide, ifosfamide, or any of the excipients.

  *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

## PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Oncologist or Haematologist working in the area of haematological malignancies.

## TESTS:

**Baseline tests**:

- FBC, renal and liver profile
- LDH, Uric acid
- Isotope GFR measurement (preferred) or GFR / Cr Clearance estimation
- Virology screen - Hepatitis B (HBsAg, HBcoreAb) & C, HIV
  *See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

**Regular tests**:

- FBC, renal profile and LDH daily during therapy and twice weekly until count recovery
- Assess neurological function daily while on ifosfamide
- Check urinalysis for haematuria prior to ifosfamide and daily during treatment with ifosfamide

**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:**

**Table 1. Recommended dose modification for haematological toxicity**

| ANC ( x $10^9$/L) | | Platelets( x $10^9$/L) | Dose |
|---|---|---|---|
| <1 | and/or | <50 | Discuss with consultant before proceeding |

**Renal and Hepatic Impairment:**

**Table 2. Recommended dose modifications in patients with renal or hepatic impairment**

| Drug | Renal impairment | | Hepatic impairment | | | |
|---|---|---|---|---|---|---|
| **CARBOplatin** | See note below[a] | | No dose modification required | | | |
| **Etoposide** | **Cr Cl (ml/min)** | **Dose** | **Total Bilirubin (micromol/L)** | | **AST** | **Dose** |
| | >50 | 100% | 26-51 | or | 60-180 | 50% |
| | 15-50 | 75% | >51 | or | >180 | Clinical decision |
| | <15 | 50% | | | | |
| | Subsequent doses should be based on clinical response | | | | | |
| **Ifosfamide** | **CrCl (ml/min)** | **Dose** | **Total Bilirubin (micromol/L)** | | | **Dose** |
| | >60 | 100% | Mild and moderate: no need for dose adjustment is expected. Severe: not recommended, due to risk of reduced efficacy. 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 > 300units/L or bilirubin > 51.3 micromol/L. Clinical decision. | | | |
| | 40-59 | 70% | | | | |
| | <40 | Clinical decision | | | | |

**[a]Renal dysfunction and CARBOplatin:**

- Patients with creatinine clearance values of <60ml/min are at greater risk of developing myelosuppression.
- If GFR between 20 to ≤ 30ml/min, CARBOplatin should be administered with extreme caution.
- If GFR ≤ 20ml/min, CARBOplatin should not be administered at all.
- If Cockcroft & Gault or Wright formula are used, the dose should be calculated as required per cycle based on a serum creatinine obtained within 48 hrs of drug administration.
- If isotope GFR is used, the dose can remain the same provided the serum creatinine is ≤ 110% of its value at the time of the isotope measurement. If the serum creatinine increases, consideration should be given to remeasuring the GFR or to estimating it using Cockcroft & Gault or Wright formulae.

## SUPPORTIVE CARE:

### EMETOGENIC POTENTIAL:

**Etoposide** Low **(Refer to local policy)**
**CARBOplatin** High **(Refer to local policy)**
**Ifosfamide** High **(Refer to local policy)**

Consider increased risk of ifosfamide-induced neurotoxicity due to inhibition of CYP3A4 by aprepitant.

**PREMEDICATIONS:** Not usually required

### OTHER SUPPORTIVE CARE:

- Proton pump inhibitor **(Refer to local policy)**
- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy)**
- Mouth care **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**

## ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Hypersensitivity:** High risk with etoposide and CARBOplatin. Hypersensitivity risk increases with number of cycles of CARBOplatin. Reactions to CARBOplatin may develop in patients who have been previously exposed to platinum therapy. However, allergic reactions have been observed upon initial exposure to CARBOplatin.

**CARBOplatin:**

- **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.

**Ifosfamide:**

- **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, dexmedetomidine (a sympathetic blocker) or thiamine may be a treatment option for the prevention and management of 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. Ifosfamide should be used with caution, if at all, in patients with active urinary tract infections.

- **Hepatitis B Reactivation:** All lymphoma 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.
- Consider increased risk of ifosfamide-induced neurotoxicity due to inhibition of CYP3A4 by aprepitant.
- Avoid concurrent use of CARBOplatin with ototoxic drugs (e.g. aminoglycosides, NSAIDS). When necessary perform regular audiometric testing.
- 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 e.g. interaction potential with CYP3A4 inhibitors / inducers.

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| Version | Date | Amendment | Approved By |
|---|---|---|---|
| 1 | 1/12/2020 | | Based on NCCP 00397 (R*)-ICE ((RiTUXimab), Ifosfamide, CARBOplatin and Etoposide) Therapy V2 26/07/2019 |
| 2 | 18/01/2023 | Reviewed. Updated CARBOplatin infusion time. Updated CARBOplatin dose wording in line with NCCP standardisation. Amendment of dose modification in renal impairment for CARBOplatin and in hepatic impairment for ifosfamide in line with NCCP standardisation. Amended emetogenic potential. Amended adverse events. Updated drug interactions. Update of Hep B reactivation wording. | Prof Maccon Keane |

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.