ICE (Ifosfamide, CARBOplatin and Etoposide) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of relapsed/refractory Non Hodgkin's Lymphoma	C85	00842a	N/A
Treatment of relapsed/refractory Hodgkin's Lymphoma	C81	00842b	N/A

* This is for post 2012 indications only

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 60 minutes	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[c,d]	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.
[c]G-CSF support is required with this regimen (**Refer to local policy or see Suggested support above**).
[d] Standard mobilization dose of g-CSF post ICE mobilisation is 5 mcg/Kg; however this must be verified on an individual basis with local harvesting centre (**Refer to local policy).**

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

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

GFR (mL/min) = S x (140 - age in years) x wt (kg)
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 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[b]	**CrCL (ml/min)**	**Dose**	**Total Bilirubin (micromol/L)**	**Dose**
	>60	No dose adjustment is needed	< 50 and normal albumin and normal renal function	No need for dose adjustment is expected
	10-50	75% of the original dose, increase if tolerated	>50 or decreased albumin levels	Consider 50% of the dose, increase if tolerated
	Haemodialysis	Not dialysed, consider 75% of the original dose		
Ifosfamide[c]	**CrCl (mL/min)**	**Dose**	**Total Bilirubin (micromol/L)**	**Dose**
	≥ 50	No dose adjustment is needed	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.	
	< 50	Not recommended		
	Haemodialysis	Not recommended		

[b]Etoposide (renal and hepatic - Giraud et al);
[c]Ifosfamide (renal - Giraud et al, hepatic -based on Giraud et al 2023 and as agreed with clinical reviewer)

[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 hours 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:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting - Available on the NCCP website

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.

For information:

Within NCIS regimens, antiemetics have been standardised by Medical Oncologists Haemato-oncologists and information is available in the following document:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

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)**
  Note: When this regimen is being used for stem cell mobilisation, do not give co-trimoxazole for 2 weeks prior to collection. Recommence when collection completed
- Mouth care **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**

ADVERSE EFFECTS

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS:

- **Hepatitis B Reactivation**: 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:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

1. Moskowitz CH, Bertino JB, Glassman JR, Hedrick EE, Hunte S, Coady-Lyons N. Ifosfamide, Carboplatin, and Etoposide: A Highly Effective Cytoreduction and Peripheral-Blood Progenitor-Cell Mobilization Regimen for Transplant-Eligible Patients With Non-Hodgkin's Lymphoma. Journal of Clinical Oncology. 1999; 17(12):3776-3785.
2. Hertzberg, MS. Crombie C, Benson W. et al. Outpatient fractionated ifosfamide, carboplatin and etoposide as salvage therapy in relapsed and refractory non-Hodgkin's and Hodgkin's lymphoma. Ann Oncol 2006; 17 (4):iv25-30.
3. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2012; 30 (13): 1553-1561.
4. Ekhart C, Rodenhuis S et al. Carboplatin dosing in overweight and obese patients with normal renal function, does weight matter? Cancer Chemother Pharmacol 2009; 64:115-122.
5. Wright JG, Boddy AV, et al, Estimation of glomerular filtration rate in cancer patients. British Journal of Cancer 2001; 84(4):452-459
6. 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
7. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
8. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf.
9. CARBOplatin Summary of Product Characteristics. Last updated 08/08/2024. Accessed August 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-080-001_08082024145541.pdf

10. Etoposide Summary of Product Characteristics. Last updated 13/02/2024. Accessed August 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-036-001_13022024104803.pdf
11. Ifosfamide (Mitoxana®) Summary of Product Characteristics. Last updated 11/09/2023. Accessed August 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-028-001_11092023124600.pdf

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
3	18/11/2024	Updated treatment table footnotes regarding G-CSF and stem cell mobilisation. Updated exclusions section. Updated renal and hepatic dose modifications in line with Giraud recommendations, 2023 except ifosfamide hepatic dose modification which is in line with NCCP standardisation. Updated Other Supportive Care section for PJP prophylaxis. Regimen updated in line with NCCP standardisation.	Prof Elisabeth Vandenberghe

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.