(R) ICE – Ifosfamide, Carboplatin, Etoposide +/- Rituximab (Lymphoma)

Indication

Salvage chemotherapy for relapsed/refractory Hodgkin's or Non-Hodgkin's Lymphoma
Can be used in combination with MATRix for high grade lymphoma with synchronous CNS involvement as part of MARIETTA protocol (IELSG 42 trial)

ICD-10 codes

Codes with prefix C81-85

Regimen details

Day	Drug	Dose	Route
1	Rituximab*	375mg/m^2	IV infusion
1, 2 and 3	Etoposide	100mg/m^2	IV infusion
2	Carboplatin	AUC5	IV infusion
2	Mesna	1000mg/m^2	IV bolus/IV infusion
2	Ifosfamide and Mesna	5000mg/m^2 5000mg/m^2	IV infusion
3	Mesna	3000mg/m^2	IV infusion

*if indicated
Carboplatin dose calculated using the Calvert equation: Carboplatin dose (mg) = AUC (5) x (CrCl +25)
The creatinine clearance (CrCl) is calculated using the Cockcroft and Gault equation, however for patients where the creatinine level may not truly reflect renal function (e.g. in extremes of BSA or debilitated patients) a measured GFR should be performed. CrCl should be capped at 125mL/min

Cycle frequency

21 days or on count recovery

Number of cycles

3-4 cycles
Aim to assess disease response after cycle 2 with CT or PET-CT scan, and for consideration of consolidation with stem cell transplant

Administration

Rituximab is administered in 500mL sodium chloride 0.9%. The first infusion should be initiated at 50mg/hour and if tolerated the rate can be increased at 50mg/hour every 30 minutes to a maximum of 400mg/hour.
Subsequent infusions should be initiated at 100 mg/hour and if tolerated increased at 100mg/hour increments every 30 minutes to a maximum of 400 mg/hour

Etoposide is administered as an IV infusion in 500-1000mL sodium chloride 0.9% over 60 minutes

Carboplatin is administered as an IV infusion in 500 mL glucose 5% over 60 minutes

Prior to administering ifosfamide, check urine output:
If >100 mL/hr, administer Ifosfamide.
If <60-100 mL/hr, administer 200 mL mannitol 20% over 30 minutes
Mesna may be administered as an IV bolus or IV infusion over 15 min prior to Ifosfamide infusion on day 1.

Ifosfamide and Mesna are administered together as an IV infusion in 1000ml sodium chloride 0.9% over 24 hours on day 2. An additional 1000ml sodium chloride 0.9% is run concurrently as hydration.

Mesna is administered as an IV infusion in 1000ml sodium chloride 0.9% over 12 hours on day 3. For fluid restricted patients this 12 hour infusion could be substituted for 3 x Mesna 1000mg/m2 in sodium chloride 0.9% at 28 hours, 32 hours and 36 hours post start of ifosfamide infusion.

Pre-medication

Antiemetics as per local policy.
Rituximab premedication:

- Paracetamol 1g PO 60 minutes prior to rituximab infusion
- Chlorphenamine 10mg IV bolus 15 minutes prior to rituximab infusion
- Dexamethasone 8mg IV bolus or hydrocortisone 100mg IV bolus 15 minutes prior to rituximab infusion

Emetogenicity

Day 1 has low emetic potential
Day 2 has high emetic potential. NB. NK-1 inhibitors can increase exposure to ifosfamide.
Day 3 has moderate emetic potential

Additional supportive medication

Allopurinol 300mg OD (100mg OD if CrCl < 20mL/min) for the first 2 weeks.
Antiemetics as per local policy
Antiviral, antifungal and PCP prophylaxis as per local policy.
Prophylactic antibiotics may be required e.g. ciprofloxacin (or as per local policy) when neutrophil count <0.5 x 10^9/L.
Mouthwashes as per local policy.
H2 antagonist or proton-pump inhibitor if required.
If magnesium/potassium levels < normal reference range, replace as per local policy.
GCSF dosing:

- If used for priming stem cell mobilisation GCSF should be administered on days 6 to 13 with planned stem cell collection on days 13-14
- If used for primary prophylaxis only then GCSF should be administered on days 5 to 11 or as per local policy.

Extravasation

Rituximab, Ifosfamide and Mesna are neutral (Group 1)
Etoposide & Carboplatin are irritants (Group 3)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U&Es (including creatinine)*	14 days
LFTs	14 days
Magnesium	14 days
Calcium	14 days
LDH	14 days

* Any hyponatraemia or hypokalaemia should be corrected prior to treatment as these are risk factors for ifosfamide related encephalopathy

Other pre-treatment investigations:
Hepatitis B sAg & core antibody, hepatitis C antibody, HIV viral screen
Immunoglobulin levels (IgG, A, M)
HbA1c

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	72 hours
U&Es (including creatinine)*	72 hours
LFTs	72 hours
Magnesium	72 hours
LDH	If clinically indicated

* Any hyponatraemia or hypokalaemia should be corrected prior to treatment as these are risk factors for ifosfamide related encephalopathy

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L*
Platelets	≥ 50 x 10^9/L*
Creatinine Clearance (CrCl)	≥ 60mL/min
Bilirubin	<1.5 x ULN

*Unless cytopenias are disease related.

Dose modifications

- **Haematological toxicity**

There are no dose adjustments for haematological toxicity.
If neutrophils < 1.0 x 10^9/L and/or platelets (unsupported) < 100 x 10^9/L delay treatment until recovery (unless cytopenias are disease related).

- **Renal impairment**

CrCl (mL/min)	Etoposide dose
>50	100%
15-50	75%
<15	50%

CrCl (mL/min)	Ifosfamide dose
> 60	100%
40-59	70%
<40	Clinical decision (discuss with consultant)

CrCl (mL/min)	Carboplatin dose
>30	100%
20-30	Discuss with consultant – consider formal GFR measurement
<20	Omit

- **Hepatic impairment**

Etoposide: if bilirubin <2.5 x ULN with normal albumin and renal function, no dose reduction indicated. If bilirubin >2.5 x ULN **or albumin**<35g/L, consider dose reduction to 50% dose and increase if tolerated.

Ifosfamide: No need for dose reduction is expected in mild to moderate hepatic impairment (Child Pugh A or B), discuss with consultant. Ifosfamide is not recommended in severe hepatic impairment (Child Pugh C) due to the risk of reduced efficacy.
NB. Ifosfamide is protein bound therefore in patients with significant hypoalbuminaemia there may be a higher risk of neurotoxicity.

Carboplatin: no need for dose adjustment is expected

- **Other toxicities**

Any Grade 3-4 toxicity (except mucositis and alopecia) – delay until ≤ grade 1 toxicity and reduce doses of Carboplatin and Etoposide to 75%

Management of Ifosfamide specific toxicities

Haemorrhagic cystitis

Patients should be encouraged to drink at least 3L per day of fluid. Urine dipstick should be monitored every 4 hours during treatment. If positive (and other causes of haematuria have been excluded) additional mesna should be prescribed as per table below:

Dipstick blood result	Action
Trace	Re-test
+	Re-test, if positive on more than one consecutive test, give additional bolus Mesna 1000mg/m^2
++	Give bolus Mesna and double Mesna infusion dose – discuss with consultant
+++	Give bolus Mesna and double Mesna infusion dose – discuss with consultant

If a patient suffers haemorrhagic cystitis, consider increasing Mesna dose for next cycle.

Encephalopathy

Ifosfamide can cause encephalopathy. This should be actively monitored for and treated as per the grade of severity.

Assess risk factors for neurotoxicity pre-ifosfamide administration:

- Albumin <30 or fluid overload
- Creatinine >150µmol/L
- Large pelvic tumour
- Previous Ifosfamide-induced encephalitis
- Hyponatraemia (<130mmol/L) /hypokalaemia (<3mmol/L)

If any risk factors present prescribe methylene blue* 50 mg IV bolus (over 5 mins) TDS for the duration of ifosfamide infusions.

If no risk factors present, prescribe methylene blue* 50 mg IV bolus (over 5 mins) PRN on the drug chart

Nurse to alert Doctor IMMEDIATELY if patient develops confusion, drowsiness, hallucinations, incontinence, clumsiness, agitation, change in speech, vision or hearing OR any other deviation from neurological baseline

Grade	Action
Grade 1 - mild somnolence or agitation	• Document mental state each shift in nursing notes. • Ensure ifosfamide infusion runs no faster than 1g/m2 per hour
Grade 2 – moderate somnolence or agitation	• Ensure ifosfamide infusion is running no faster than 1g/m^2/hour • Start methylene blue* 50mg 4 hourly • Continue methylene blue until encephalopathy has resolved to Grade 0 • If neurotoxicity deteriorates to >grade 2, **stop ifosfamide** but continue MESNA infusion • If recurs consider switching to cyclophosphamide
Grade 3 – severe somnolence or agitation or onset of confusion, disorientation or hallucinations	• **Stop ifosfamide infusion** • Ensure MESNA continues to run to completion of planned infusion. • Start methylene blue* 50mg 4 hrly, continue until resolution of symptoms. • Other supportive measures may be considered • Monitor neurological status • Outreach review • **Do not give further ifosfamide instead substitute for cyclophosphamide.**
Grade 4 – coma, seizure or toxic psychosis	

*Contraindications for methylene blue: known G6PD deficiency. Side effects: rare but serious; hypotension, cardiac arrhythmias. Common; nausea, abdominal pain, blue discoloration of urine, stools and saliva.

Methylene blue administration information:

Intravenous (IV) administration	Treatment of moderate symptoms or prophylactic use: 50mg IV TDS (8 hourly) in 50 – 100mL glucose 5% as slow IV bolus over a minimum of 5 minutes. Treatment of moderate-severe symptoms: Increase frequency to 4 hourly
Oral (PO) administration	For prophylactic use only (due to variable absorption): Methylene blue 50mg TDS (6-8 hourly) PO Use injection for oral administration. Dilute one ampoule in 100mL water before administration to minimise GI effects. Drink through a straw to avoid staining teeth. NB. 53-97% oral absorption.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Neuropathy
Hypersensitivity reactions
Nephrotoxicity
Neurotoxicity
Ototoxicity
Nephrotoxicity

- **Frequently occurring side effects**

Myelosuppression
Alopecia
Constipation, diarrhoea
Stomatitis, mucositis
Nausea and vomiting
Anorexia
Electrolyte disturbances
Fatigue

- **Other side effects**

Rash
Flu like illness

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid, and consider switch patient to an alternate suitable anticoagulant.

Etoposide:
Ciclosporin: increases exposure to etoposide, monitor closely and consider dose adjustment
Phenylbutazone, sodium salicylate and salicylic acid: can affect protein binding of etoposide.
Phenytoin, phenobarbital, carbamazepine: increased etoposide clearance and potential for reduced efficacy

Carboplatin :
Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity
Clozapine: increased risk of agranulocytosis, avoid concomitant use
Diuretics: increased risk of nephrotoxicity and ototoxicity

Nephrotoxic drugs: increased nephrotoxicity; not recommended
Phenytoin: carboplatin reduces absorption and efficacy of phenytoin

Ifosfamide:
Amiodarone: increased risk of pulmonary toxicity – avoid if possible
Aprepitant, Fosaprepitant, Netupitant: increases exposure of ifosfamide, avoid or use with caution.
Nephrotoxic agents: increased risk of nephrotoxicity, avoid where possible.

Additional Information

Nil

References

- Summary of Product Characteristics – Ifosfamide (Baxter Healthcare Ltd). Accessed 1 September 2022 via www.medicines.org.uk
- Summary of Product Characteristics – Carboplatin (Accord) Accessed 1 September 2022 via www.medicines.org.uk
- Summary of Product Characteristics – Rituximab (Rixathon - Sandoz) Accessed 1 September 2022 via www.medicines.org.uk
- Summary of Product Characteristics – Etoposide (Accord) Accessed 1 September 2022 via www.medicines.org.uk
- Summary of Product Characteristics – Mesna (Baxter) Accessed 1 September 2022 via www.medicines.org.uk
- Kewalramani T., Zelenetz A.D., Nimer S.D., et al (2004). Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood. 2004 May 15;103(10):3684-8
- Küpfer A., Aeschlimann C., Wermuth B., et al (1994). Prophylaxis and reversal of ifosfamide encephalopathy with methylene blue. Lancet. Mar 26;343(8900):763-4.
- Moskowitz C.H., Bertino J.R., Glassman J.R., et al (1999). Ifosfamide, carboplatin, and etoposide: A highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma. J Clin Oncol. Dec;17(12):3776-85.
- Krens, SD. *et al.* Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019:20:e201-208
- Ferreri, AJM. *et al.* MATRix-RICE therapy and autologous haematopoietic stem-cell transplantation in diffuse large B-cell lymphoma with secondary CNS involvement (MARIETTA): an international, single-arm, phase 2 trial. *Lancet Haematology* 2021:8(2):E110-E121

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