PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

ICE +/- Rituximab (OUTPATIENT) Relapsed or Refractory Lymphoma

PROTOCOL REF: MPHAIROUTP
(Version No. 1.0)

Approved for use in:

- Relapsed or refractory lymphoma
- Primary or secondary CNS lymphoma
- ECOG 0-2.
- Patients suitable for a bone marrow transplant (BMT).
- Omit rituximab for Hodgkin's lymphoma or high grade T cell non-Hodgkin lymphoma patients.

Blueteq application is not required

Dosage:

Drug	Dose	Route	Frequency
Rituximab	**375mg/m^2**	IV infusion	Day 1 *Omit rituximab for Hodgkin's lymphoma or high grade T cell non-Hodgkin lymphoma patients
Carboplatin	**AUC 5* Max dose = 800mg**	IV infusion	Day 1
Etoposide	**100mg/m^2**	IV infusion	Days 1, 2 and 3
Mesna	**333mg/m^2**	IV infusion	Day 1, 2 and 3 prior to ifosfamide infusion
Ifosfamide and Mesna	**1667mg/m^2 and 1667mg/m^2**	IV infusion	Day 1, 2 and 3
Mesna	**1600mg****	Oral	Day 1, 2 and 3 (2 hours and 6 hours after the end of each ifosfamide infusion)

***Dose (mg)(AUC 5) = 5 x (Wright's CrCl + 25)**
****Dose based on 40% of ifosfamide dose with average body surface area 2m^2 rounded to the nearest 400mg tablet

Maximum of 6 cycles of 21 day duration (suitability for BMT should be made after cycle 2).

Administration:

- Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential must employ effective contraceptive methods during and for 12 months after treatment with rituximab.
- Liaise with BMT team prior to initiation.
- This regimen requires an inpatient stay of at least 5 days
- Ifosfamide can irritate the bladder mucosa. Patients should be encouraged to drink 3L of fluid per 24 hours. Test urine for microscopic haematuria every morning during each cycle as per urine testing protocol (see toxicity management)
- Administration of ifosfamide can cause CNS toxicity and other neurotoxic effects. Ifosfamide neurotoxicity may manifest within a few hours to a few days after first administration and in most cases resolves within 48 to 72 hours of ifosfamide discontinuation. Symptoms may persist for longer periods of time. Occasionally, recovery has been incomplete. Fatal outcome of CNS toxicity has been reported. Recurrence of CNS toxicity after several uneventful treatment courses has been reported. Methylene blue can be used to treat ifosfamide related encephalopathy. Observe for insidious signs of encephalopathy, initially somnolence and confusion (see toxicity management)

Emetogenic risk:

Moderate to severely emetogenic.

Supportive treatments:

Rituximab pre-infusion medication:

- Paracetamol tablet PO 1gram oral
- Chlorphenamine injection IV bolus 10mg
- Hydrocortisone sodium succinate IV bolus 100mg (should be given at least 30 minutes before the rituximab)

Supportive medication:

- Allopurinol PO 300mg once daily for the first cycle
- Aciclovir PO 400mg twice daily

- Aprepitant PO 125mg day 1 and 80mg days 2 and 3
- Chlorhexidine 0.2% mouthwash 10mls four times daily
- Fluconazole PO 50mg once daily
- Filgrastim S/C 30 or 48 million units once daily on days 6 to 12 (30million units if <70kgs and 48 million units >70kgs) when NOT used for priming. See below for information when used for mobilisation prior to haematopoietic stem cell harvesting
- Mesna 1600mg 2 hours and 4 hours after end of ifosfamide infusion on days 1, 2 and 3
- Metoclopramide PO 10mg three times daily when required
- Ondansetron PO 8mg twice daily when required
- Anti-seizure prophylaxis should be considered for patients receiving ifosfamide who have a high risk of seizures or CNS disease. Levetiracetam 500-750mg twice daily can be used used and continued until discharge or at clinician discretion. For patients who have had seizures there should be a discussion with the Neurology team. Alternative anti-epileptics can be used on discussion with Neurology. Please consider drug interactions.

Extravasation risk:

Rituximab – non-vesicant

Etoposide – irritant

Carboplatin – irritant

Ifosfamide – irritant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

	Drug	Creatinine Clearance (mL/min)	Dose adjustment
Renal	Ifosfamide	40 – 59	70% dose
		<40	Clinical decision
		Haemodialysis	Not recommended
	Etoposide	15 – 50	75% dose (can increase if tolerated)
		<15	Consider 50% dose
		Haemodialysis	Not dialysed (consider 75% dose)
	Carboplatin	<20	Contraindicated – clinical decision

		Haemodialysis	Dose according to above formula with CrCl equals 0. Perform HD between 12 and 24 hours after administration.
Hepatic	Ifosfamide	Severe impairment	Not recommended due to risk of impaired efficacy
	Etoposide	Bilirubin >50micromol/L or albumin <35g/L	Consider 50% dose reduction; increase if tolerated
	Carboplatin	No dose adjustment	

Interactions:

Etoposide

Concomitant phenytoin therapy is associated with increased etoposide clearance and reduced efficacy, and other enzyme-inducing antiepileptic therapy may be associated with increased etoposide clearance and reduced efficacy.

As etoposide phosphate is converted *in vivo* to etoposide by phosphorylation, caution should be exercised when administering etoposide phosphate with drugs that are known to inhibit phosphatase activity as such combination may reduce efficacy of etoposide phosphate.

In vitro plasma protein binding is 97%. Phenylbutazone, sodium salicylate, and aspirin may displace etoposide from plasma protein binding.

Co-administration of antiepileptic drugs and etoposide can lead to decreased seizure control due to pharmacokinetic interactions between the drugs.

Carboplatin

Carboplatin may interact with aluminium to form a black precipitate. Needles, syringes, catheters or IV administration sets that contain aluminium parts which may come into contact with carboplatin, should not be used for the preparation or administration of the drug.

Concomitant use not recommended:-

- Phenytoin, fosphenytoin: Risk of exacerbation of convulsions (resulting from the decrease of phenytoin digestive absorption by the cytotoxic drug), risk of toxicity enhancement or loss of efficacy of the cytotoxic drug (due to increased hepatic metabolism by phenytoin).
- Concomitant use to take into consideration

- Concurrent therapy with nephrotoxic drugs or ototoxic drugs such as amino glycosides, vancomycin, capreomycin and diuretics, may increase or exacerbate toxicity, particularly in renal failure patients, due to carboplatin induced changes in renal clearance.
- Loop diuretics: The concomitant use of carboplatin with loop diuretic should be approached with caution due to the cumulative nephrotoxicity and ototoxicity

Ifosfamide

The potential for increased formation of metabolites responsible for cytotoxicity and other toxicities (depending on the enzymes induced) must be considered in case of prior or concomitant treatment with, for example:

- Carbamazepine
- Corticosteroids
- Rifampin
- Phenobarbital
- Phenytoin
- St. John's Wort

Inhibitors of CYP 3A4: Reduced activation and metabolism of ifosfamide may alter the effectiveness of ifosfamide treatment. Inhibition of CYP 3A4 can also lead to increased formation of an ifosfamide metabolite associated with CNS and nephrotoxicity. CYP 3A4 inhibitors include:

- Ketoconazole
- Fluconazole
- Itraconazole
- Sorafenib

For more detailed interactions please refer to the SPC and add a link to the appropriate SPC

Treatment schedule:

Day	Time	Drug	Dose	Route	Diluent and rate
1	08:30	**Aprepitant**	**125mg**	**PO**	
		Chlorphenamine	**10mg**	**IV**	Bolus over 3 to 5 minutes (30 minutes prior to rituximab)
		Paracetamol	**1g**	**PO**	(30 minutes prior to rituximab)

		Hydrocortisone	**100mg**	**IV**	Bolus over 3 to 5 minutes (30 minutes prior to rituximab)
	09:00	**Rituximab**	**375mg/m^2**	**IV**	**CD20+ lymphoma patients only** **≤450mg** 250mL sodium chloride 0.9% **≥500mg** 500mL sodium chloride 0.9% Rate as per rituximab infusion guideline
	12:30	**Ondansetron**	**8mg**	**IV**	100mL sodium chloride 0.9% Over 15 minutes
	13:00	**Carboplatin**	**AUC 5** **Max 800mg**	**IV**	500mls Glucose 5% Over 30 minutes
		Check urine output. If <100mL/hr administer mannitol 20% 200mL over 30 minutes. If >100mL/hr administer ifosfamide and mesna			
	13:30	**Etoposide**	**100mg/m^2**	**IV**	in Sodium chloride 0.9%* over 1 hour
	14:30	**Mesna**	**333mg/m^2**	**IV**	100mL sodium chloride 0.9% over 15 minutes prior to ifosfamide and mesna
	14:30	**Ifosfamide** & Mesna**	**1667mg/m^2 & 1667mg/m^2**	**IV**	1000mL Sodium chloride 0.9% Over 2 hours
		Mesna	**1600mg**	**PO**	**TTO:** 2 hours and 6 hours after the end of ifosfamide infusion
2	08:30	**Aprepitant**	**80mg**	**PO**	
		Ondansetron	**8mg**	**IV**	100mL sodium chloride 0.9% Over 15 minutes
	09:00	**Etoposide**	**100mg/m^2**	**IV**	in Sodium chloride 0.9%* over 1 hour
	10:00	**Mesna**	**333mg/m^2**	**IV**	100mL sodium chloride 0.9% over 15 minutes prior to ifosfamide and mesna
	10:00	**Ifosfamide** & Mesna**	**1667mg/m^2 & 1667mg/m^2**	**IV**	1000mL Sodium chloride 0.9% Over 2 hours
		Mesna	**1600mg**	**PO**	**TTO:** 2 hours and 6 hours after the end of ifosfamide infusion
3	08:30	**Aprepitant**	**80mg**	**PO**	
	08:00	**Ondansetron**	**8mg**	**IV**	100mL sodium chloride 0.9% Over 15 minutes
	09:00	**Etoposide**	**100mg/m^2**	**IV**	In Sodium chloride 0.9%* over 1 hour
	10:00	**Mesna**	**333mg/m^2**	**IV**	100mL sodium chloride 0.9% over 15 minutes prior to ifosfamide and mesna
	10:00	**Ifosfamide** & Mesna**	**1667mg/m^2 & 1667mg/m^2**	**IV**	1000mL Sodium chloride 0.9% Over 2 hours
		Mesna	**1600mg**	**PO**	**TTO:** 2 hours and 6 hours after the end of ifosfamide infusion
6		**Filgrastim (GCSF)**	**<70kg:** 30 million units **≥70kg:** 48 million units	**SC**	**Non-mobilisation:** Once daily for 7 days **Mobilisation:** Once daily until harvesting complete

*Diluent volume 500mL or 1000mL is dependent on final concentration

**5000mg/m^2 of ifosfamide and mesna administered over 3 days (split into 3 x 2 hour infusions)

Haematopoietic Stem Cell Mobilisation:

R-ICE day 1 should be administered on a Wednesday to facilitate apheresis starting on a Monday (day 13)

Clinical Interventions Prior to Admission

- Arrange for insertion of central venous catheter if insufficient peripheral venous access – apheresis team to assess veins if clinical suspicion that inadequate. Patient may require inpatient admission (ideally ward 4 CCC) if requiring temporary central venous access (femoral vein) and not local to CCC (within 1 hour drive) or if patient is living alone.
- Ensure adequate renal, lung and cardiac function, additional investigations may be required if clinically indicated.
- Discuss with Consultant/HPCT coordinator should any of these results fall out of normal limits
- Book apheresis session in apheresis diary from Day 13.

Patient Preparation

- Complete appropriate documentation for Stem Cell Therapeutics laboratory to request cryopreservation of HPCs.
- Ensure all blood products are irradiated for a minimum of 7 days pre-harvest.
- Explain procedures of mobilisation chemotherapy and HPC-A collection to patient and discuss potential complications.
- Offer relevant written information available.
- Obtain written informed consent from patient.

Filgrastim

- Patients should be given the opportunity to be taught how to self-administer filgrastim. A district nurse referral for G-CSF administration should be completes if the patient is unsuitable for self-administration.

Day(s) of Harvesting – From Day 13

- A peripheral blood CD34 count should be checked.
  - If <5 x10^6/L not for apheresis and discus with the transplant team about return following day

- if 5-10 x10^6/L not for apheresis but transplant team to consider plerixafor before returning the following morning
- if >10 x10^6/L for attempt at apheresis.

- One or more harvest procedures may be required to achieve minimal requirement of 2.5 x10^6 $CD34^+$/kg, usually target 4–8x10^6 $CD34^+$/kg. If results are not within target range clarify with consultant in charge.

Main toxicities:

Drug	Toxicity
Ifosfamide	Bone marrow suppression, nausea and vomiting, haemorrhagic cystitis, ifosfamide induced encephalopathy
Carboplatin	Bone marrow suppression, nausea, vomiting, nephrotoxicity, ototoxicity, visual disturbance
Etoposide	Bone marrow suppression, nausea, vomiting, fatigue
Rituximab	Infusion reactions, cytokine release syndrome, hepatitis B reactivation

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Prior to cycle 3	Cycle 3	Ongoing
Clinical Assessment	X				X**	As clinically indicated or at the end of treatment
SACT Assessment	X	X	X		X	Every cycle
On treatment review*				X		
FBC	X	X	X		X	Every cycle
U&E & LFTs & Magnesium	X	X	X		X	Every Cycle
CrCl (Cockcroft and Gault)	X	X	X		X	Every cycle
Virology screening (including Hepatitis B)	X					
CT scan**	X					At the end of treatment and if clinically indicated
Informed Consent	X					
Urine Dip		X	X		X	Daily while having ifosfamide
Neurological assessment		X	X		X	Daily while having ifosfamide
Blood pressure measurement	X					Repeat if clinically indicated
PS recorded	X	X	X		X	Every Cycle
Toxicities documented	X	X	X		X	Every Cycle
Weight recorded	X	X	X		X	Every cycle
Blood glucose	X					Repeat if clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 if-

ANC > 1.0 x 10^9/L	Platelets > 50 x 10^9/L

If neutrophils and platelets below the levels above then discuss with Consultant.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non-Haematological toxicity:

Ifosfamide Induced Encephalopathy

Observe closely for signs of encephalopathy. This may present insidiously in a variety of ways but usually includes somnolence and confusion initially. Report any early signs to medical staff immediately. Three risk factors may predispose to encephalopathy: renal impairment, low albumin, and large pelvic tumour mass. Refer to Methylthioninium Chloride (Methylene Blue) for Ifosfamide Induced Encephalopathy Clinical Guideline for more information.

Ifosfamide Induced Haemorrhagic Cystitis

Monitor closely for haematuria following ifosfamide and inform consultant if this occurs.

Managing positive urine dip for blood

Test result	Action
Trace	Re-test
+	Re-test. If positive on more than one consecutive test give additional IV bolus mesna. Check fluids and any concurrent mesna is running correctly or oral dose has been taken.
++ / +++	Double dose of any concurrently running IV mesna. Repeated ++ / +++ result, or evidence of macroscopic haematuria should prompt pause and review of current treatment

Recommended bolus dose: Mesna intravenous 600mg/m^2 or a fixed dose of 1g in 250ml sodium chloride 0.9% over 30 minutes or oral mesna 1800mg. Patients needing bolus mesna should have their infusional mesna or oral doses doubled for all subsequent chemotherapy treatments.

Infusion Related Reactions:

Non-Haematological toxicities:	
Rituximab	
Infusion-related Reactions	Severe infusion-related reactions with fatal outcome can have an onset ranging within 30 minutes to 2 hours after starting the first rituximab infusion. They can be characterised by pulmonary events and in some cases included rapid tumour lysis and features of tumour lysis syndrome (TLS) in addition to fever, chills, rigors, hypotension, urticaria, and angioedema. Severe cytokine release syndrome may occur. Monitor patients closely. Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm or hypoxia should have infusion interrupted immediately. The patient should then be evaluated for evidence of TLS including appropriate laboratory tests and, for pulmonary infiltration, with a chest x-ray. The infusion should not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest x-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same adverse reaction occurs for a second time, the decision to stop the treatment should be seriously considered on a case-by-case basis. Anaphylactic and other hypersensitivity reactions may occur. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Mild or moderate infusion-related reactions usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms

References:

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Version History

Date	Version	Author name and designation	Summary of main changes
Version 1.0	March 2023	**Daniel Dutton – Pharmacist** **Jennifer Gibson – Principal HO Pharmacist**	New protocol