PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

IVE +/- Rituximab
Relapsed or Refractory Lymphoma

PROTOCOL REF: MPHAIVER
(Version No. 1.0)

Approved for use in:

- Relapsed or refractory CD20 positive Non-Hodgkin's 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 **NB if chemo to be given in a day ward setting then rituximab should be given on day prior to rest of chemotherapy.** *Omit rituximab for Hodgkin's lymphoma or high grade T cell non-Hodgkin lymphoma patients
Epirubicin	**50mg/m^2**	IV infusion	Day 2
Mesna	**1800mg/m^2**	IV infusion	Day 2
Etoposide	**200mg/m^2**	IV infusion	Days 2 to 4
Ifosfamide & Mesna	**3000mg/m^2 & 3000mg/m^2**	IV infusion	Days 2 to 4. Total daily dose divided into 3 equal doses and each dose infused over 8 hours
Mesna	**5400mg/m^2**	IV infusion	Day 5

Maximum of 4 cycles of 21 day duration (suitability for a BMT should be made after cycle 2).

Administration:

- Liaise with the BMT team prior to starting treatment
- 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.
- Aggressive hydration is required the day before epirubicin
- 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. Regularly dip the urine for blood (see non-haematology toxicity section)
- 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 neuropathy (see trust protocol)
- There is a maximum lifetime cumulative dose of anthracyclines. Ensure the patient hasn't breached this before prescribing epirubicin.

Emetogenic risk:

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 OD on days 7 to 11 (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
- Metoclopramide PO 10mg three times daily when required
- Ondansetron PO 8mg twice daily when required (IV twice daily day 2, 3 and 4)
- 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

Epirubicin – vesicant

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)
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
	Epirubicin	**Bilirubin (µmol/L) or ALT (units/L)**	**Dose adjustment**
		Bilirubin 21 to 51 or ALT 70 to 140	50% of original dose
		Bilirubin 51 to 85 or ALT > 140 units/L	25% of original dose
		Bilirubin > 85 or Child-Pugh score C	Not recommended

Interactions:

Rituximab

No significant 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.

Epirubicin

The potential risk of cardiotoxicity may increase in patients who have received concomitant cardiotoxic agents (e.g. 5-fluorouracil, cyclophosphamide, cisplatin, taxanes), or concomitant (or prior) radiotherapy to the mediastinal area. The use of epirubicin in combination chemotherapy with other potentially cardiotoxic medicinal products, as well as the concomitant use of other

cardioactive compounds (e.g. calcium channel blockers), requires monitoring of cardiac function throughout treatment.

Cimetidine increased the AUC of epirubicin by 50 % and should be discontinued during treatment with epirubicin.

Verapamil may alter the pharmacokinetics of epirubicin.

Medicinal products which delay uric acid excretion (e.g. sulphonamides, certain diuretics) can lead to increased hyperuricaemia when epirubicin is used simultaneously.

Epirubicin binds to heparin; precipitation and loss of efficacy of both agents may occur.

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 or 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 and sorafenib.

For more detailed interactions please refer to the SPC.

Treatment schedule:

Day	Time	Drug	Dose	Route	Diluent and rate
1	08:30	**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**	**Non-Hodgkin patients ONLY.** **≤450mg** 250mL sodium chloride 0.9% **≥500mg** 500mL sodium chloride 0.9% Rate as per rituximab infusion guideline

2	08:00	**Aprepitant**	**125mg**	**PO**	
		Ondansetron	**8mg**	**IV**	100mL sodium chloride 0.9% over 15 minutes
	08:30	**Epirubicin**	**50mg/m^2**	**IV**	100mL Sodium chloride 0.9% Over 30 minutes
	09:00	**Etoposide**	**200mg/m^2**	**IV**	In sodium chloride 0.9%* over 2 hours **(Lumen 1)**
	09:00	**Mesna**	**1800mg/m^2**	**IV**	100mL Sodium chloride 0.9% Over 15 minutes **(Lumen 2)**
	09:30	**Ifosfamide & Mesna**	****1000mg/m^2 & 1000mg/m^2**	**IV**	1000mL Sodium chloride 0.9% Over 8 hours **(Lumen 2)**
	17:30	**Ifosfamide & Mesna**	****1000mg/m^2 & 1000mg/m^2**	**IV**	1000mL Sodium chloride 0.9% Over 8 hours **(Lumen 2)**
3	01:30	**Ifosfamide & Mesna**	****1000mg/m^2 & 1000mg/m^2**	**IV**	1000mL Sodium chloride 0.9% Over 8 hours **(Lumen 2)**
	08:00	**Aprepitant**	**80mg**	**PO**	
		Ondansetron	**8mg**	**IV**	100mL sodium chloride 0.9% over 15 minutes
	09:00	**Etoposide**	**200mg/m^2**	**IV**	In sodium chloride 0.9%* over 2 hours **(Lumen 1)**
	09:30	**Ifosfamide & Mesna**	****1000mg/m^2 & 1000mg/m^2**	**IV**	1000mL Sodium chloride 0.9% Over 8 hours **(Lumen 2)**
	17:30	**Ifosfamide & Mesna**	****1000mg/m^2 & 1000mg/m^2**	**IV**	1000mL Sodium chloride 0.9% Over 8 hours **(Lumen 2)**
4	01:30	**Ifosfamide & Mesna**	****1000mg/m^2 & 1000mg/m^2**	**IV**	1000mL Sodium chloride 0.9% Over 8 hours **(Lumen 2)**
	08:00	**Aprepitant**	**80mg**	**PO**	
		Ondansetron	**8mg**	**IV**	100mL sodium chloride 0.9% over 15 minutes
	09:00	**Etoposide**	**200mg/m^2**	**IV**	In sodium chloride 0.9%* over 2 hours **(Lumen 1)**
	09:30	**Ifosfamide & Mesna**	****1000mg/m^2 & 1000mg/m^2**	**IV**	1000mL Sodium chloride 0.9% Over 8 hours **(Lumen 2)**
	17:30	**Ifosfamide & Mesna**	****1000mg/m^2 & 1000mg/m^2**	**IV**	1000mL Sodium chloride 0.9% Over 8 hours **(Lumen 2)**
5	01:30	**Ifosfamide & Mesna**	****1000mg/m^2 & 1000mg/m^2**	**IV**	1000mL Sodium chloride 0.9% Over 8 hours **(Lumen 2)**
	09:30	**Mesna**	**5400mg/m^2**	**IV**	1000mL Sodium chloride 0.9% Over 12 hours
7		**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

**3000mg/m^2 of ifosfamide and mesna administered over 24 hours (split into 3 x 8 hour infusions)

Haematopoietic Stem Cell Mobilisation:

The IVE component of R-IVE should be administered on a Tuesday to facilitate apheresis starting on a Monday (day 14)

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 14

- 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
Epiribucin	Bone marrow suppression, nausea, vomiting, alopecia, ototoxicity, cardiac toxicity, mucositis, stomatitis, conjunctivitis, diarrhoea, red colouration of the urine, deranged LFTs
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	Cycle 3	Ongoing
Clinical Assessment	X	X	X	X	As clinically indicated or at the end of treatment
SACT Assessment	X	X	X	X	Every cycle
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 screen (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:

Complete this guidance in line with SPC/ other protocols or trial protocols

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Platelet ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Platelet ≤ 99 x 10^9/L

Restart treatment when ANC ≥ 1.0 x 10^9/L and platelets ≥ 100 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:

1. https://www.medicines.org.uk/emc Ifosfamide (accessed 23/2/23)
2. https://www.medicines.org.uk/emc Epirubicin (accessed 23/2/23)
3. https://www.medicines.org.uk/emc Etoposide (accessed 23/2/23)
4. https://www.medicines.org.uk/emc Mesna (accessed 23/2/23)
5. McQuaker IG et al.; Stem cell mobilization in resistant or relapsed lymphoma: superior yield of progenitor cells following a salvage regimen comprising ifosfamide, etoposide and epirubicin compared to intermediate-dose cyclophosphamide; Br J Haematol.; 1997; 98:228-233
6. Menzel H et al: Ifosfamide, epirubicin and etoposide rituximab in refractory or relapsed B-cell lymphoma: analysis of remission induction and stem cell mobilization. Leuk Lymphoma. 2008 Jul;49(7):1337
7. The Lancet Oncology. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20:e201-08.

Circulation/Dissemination

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Version History

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