PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

ESHAP +/- Rituximab Relapsed or Refractory Hodgkin or Non-Hodgkin Lymphoma

PROTOCOL REF: MPHAERRRH
(Version No. 1.0)

Approved for use in:

- Relapsed or refractory Lymphoma or myeloma (Omit rituximab if CD20 negative)
- ECOG 0-2.
- Patients suitable for a bone marrow transplant (BMT).

Dosage:

Drug	Dose	Route	Frequency
Methylprednisolone	**500mg**	IV infusion	Days 1 to 5
Rituximab	**375mg/m^2**	IV infusion	Day 1 only (omit if CD20 negative)
Etoposide	**40mg/m^2**	IV infusion	Days 1 to 4
Cisplatin	**25mg/m^2**	IV infusion	Days 1 to 4
Cytarabine	**2000mg/m^2**	IV infusion	Day 5

Maximum of 4 cycles, usually 21 day cycle but may be extended to 28 days to allow for count recovery. Usual maximum of 3 cycles if given as priming regimen prior to BMT, suitability for a BMT must be made after 2 cycles.

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 if using as a priming regimen.
- This regimen requires an inpatient stay of at least 5 days.
- If CD20 positive and rituximab is prescribed – methylprednisolone should be given 30 minutes prior to rituximab.
- Dual lumen central line required

Emetogenic risk:

Severely emetogenic.

Supportive treatments:

Rituximab pre-infusion medicines:

- Paracetamol PO 1g
- Chlorphenamine IV bolus 10mg
- Methylprednisolone should be administered at least 30 minutes prior to rituximab

Supportive medicines:

- Aciclovir 400mg twice daily
- Allopurinol PO 100mg or 300mg daily (depending on renal function) for first cycle
- Aprepitant 125mg once daily day 1 then 80mg once daily on days 2 and 3
- Co-trimoxazole PO 480mg once daily
- Omeprazole 20mg once daily
- Ondansetron PO 8mg twice daily when required (ondansetron is given as IV prior to treatment on days 1 to 5)
- Prednisolone 0.5% or 1% eye drops, one drop four times a day for 7 days starting on day 5.

- Filgrastim S/C 30 or 48 million units once daily from day 6 for 7 days (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

Extravasation risk:

Rituximab: non-vesicant

Cisplatin: exfoliant

Etoposide: irritant

Cytarabine: Non-vesicant

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

Dosing in renal and hepatic impairment:

Renal	Rituximab	No adjustment required in renal impairment	
	Cisplatin	**CrCL (mL/min)**	**Recommendation**
		50-59	75% of original dose
		40-49	50% of original dose
		<40	Not recommended
	Etoposide	**CrCL (mL/min)**	**Recommendation**
		10-50	75% of original dose – can increase if tolerated
		<10	No safety data available – consultant decision
	Cytarabine	**CrCL (mL/min)**	**Recommendation**
		45-59	60% of original dose
		30-44	50% of original dose
		<30	Not recommended

Hepatic	Rituximab	No adjustment required in hepatic impairment
	Cisplatin	No adjustment required in hepatic impairment
	Etoposide	Bilirubin >50µmol/L **or** decreased albumin levels: consider 50% of original dose and increase as tolerated
	Cytarabine	Mild to moderate: no dose adjustment recommended Severe: consider 25-50% of original dose and increase as tolerated

Interactions:

Cisplatin

Concomitant administration of nephrotoxic (e.g. cephalosporins, aminoglycosides, Amphotericin B or contrast media) or ototoxic (e.g. aminoglycosides, loop diuretics) medicinal products will potentiate the toxic effect of cisplatin on the kidneys and auditory function.

Cisplatin may reduce the absorption of phenytoin resulting in reduced epilepsy control when phenytoin is given as current treatment. During cisplatin therapy starting new anticonvulsant treatment with phenytoin is strictly contraindicated.

Cytarabine:

Digoxin: cytarabine may affect plasma digoxin levels – consider monitoring

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.

For more detailed interactions please refer to the SPCs of each drug

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**1000mL Sodium chloride 0.9% and potassium 0.15% (20mmol)**		**IV**	Over 6 hours Starting 6 hours prior to cisplatin
	Aprepitant	**125mg**	**PO**	60 minutes before chemotherapy
	Paracetamol	**1000mg**	**PO**	60 minutes before chemotherapy
	Chlorphenamine	**10mg**	**IV**	Bolus over 3-5 minutes
	Methylprednisolone	**500mg**	**IV**	100mL sodium chloride 0.9% Over 15 minutes 30 minutes prior to rituximab
	Ondansetron	**8mg**	**IV**	100mL sodium chloride 0.9% Over 15 minutes
	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 **(Lumen 2)**
	Cisplatin*	**25mg/m^2**	**IV**	1000mL sodium chloride 0.9% Over 23 hours **(Lumen 1)**
	Etoposide	**40mg/m^2**	**IV**	Sodium chloride 0.9%** Over 60 minutes **(Lumen 2)**
2	**1000mL Sodium chloride 0.9% and potassium 0.15% (20mmol)**		**IV**	Over 6 hours Starting 6 hours prior to cisplatin
	Aprepitant	**80mg**	**PO**	60 minutes before chemotherapy
	Ondansetron	**8mg**	**IV**	100mL sodium chloride 0.9% Over 15 minutes
	Methylprednisolone	**500mg**	**IV**	100mL sodium chloride 0.9% Over 15 minutes
	Cisplatin*	**25mg/m^2**	**IV**	1000mL sodium chloride 0.9% Over 23 hours **(Lumen 1)**
	Etoposide	**40mg/m^2**	**IV**	Sodium chloride 0.9%** Over 60 minutes **(Lumen 2)**
3	**1000mL Sodium chloride 0.9% and potassium 0.15% (20mmol)**		**IV**	Over 6 hours Starting 6 hours prior to cisplatin
	Aprepitant	**80mg**	**PO**	60 minutes before chemotherapy
	Ondansetron	**8mg**	**IV**	100mL sodium chloride 0.9% Over 15 minutes
	Methylprednisolone	**500mg**	**IV**	100mL sodium chloride 0.9% Over 15 minutes

Day	Drug	Dose	Route	Diluent and rate
3	**Cisplatin***	**25mg/m^2**	**IV**	1000mL sodium chloride 0.9% Over 23 hours **(Lumen 1)**
	Etoposide	**40mg/m^2**	**IV**	Sodium chloride 0.9%** Over 60 minutes **(Lumen 2)**
4	**1000mL Sodium chloride 0.9% and potassium 0.15% (20mmol)**		**IV**	Over 6 hours Starting 6 hours prior to cisplatin
	Ondansetron	**8mg**	**IV**	100mL sodium chloride 0.9% Over 15 minutes
	Methylprednisolone	**500mg**	**IV**	100mL sodium chloride 0.9% Over 15 minutes
	Cisplatin*	**25mg/m^2**	**IV**	1000mL sodium chloride 0.9% Over 23 hours **(Lumen 1)**
	Etoposide	**40mg/m^2**	**IV**	Sodium chloride 0.9%** Over 60 minutes **(Lumen 2)**
5	**Ondansetron**	**8mg**	**IV**	100mL sodium chloride 0.9% Over 15 minutes
	Methylprednisolone	**500mg**	**IV**	100mL sodium chloride 0.9% Over 15 minutes
	Cytarabine	**2000mg/m^2**	**IV**	500mL sodium chloride 0.9% Over 3 hours **(Lumen 2)**
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
***Strict Fluid Balance should be kept. Maintain a urine output of at least 100mL/hour. If urine output <100mL/hour consider giving give IV Furosemide 20-40mg**				
**Etoposide diluent volume (100mL, 250mL or 500mL) is dose dependent.				

Haematopoietic Stem Cell Mobilisation:

R-ESHAP day 1 should be administered on a Monday to facilitate apheresis starting on a Monday (day 15)

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 15.

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 15

- 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:

RITUXIMAB
Infusion related reactions, cytokine release syndrome, reactivation of hepatitis B
CISPLATIN
Bone marrow suppression (thrombocytopenia, anaemia, neutropenia), infection, nausea and vomiting, hyponatraemia, ototoxicity, arrythmias, VTE, renal impairment.
ETOPOSIDE
Bone marrow suppression (thrombocytopenia, anaemia, neutropenia), infection, nausea and vomiting, diarrhoea, anaphylactoid reaction, dizziness, arrythmias, hypertension, alopecia, rash, fatigue
CYTARABINE
Bone marrow suppression (thrombocytopenia, anaemia, neutropenia), infection, nausea and vomiting, hemorrhagic conjunctivitis, hyperuricaemia, CNS deterioration (nystagmus, loss of consciousness), fever, urinary retention, renal impairment, immunoallergic effect.

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
Height and Weight recorded	X	X	X	X	Every cycle
Blood glucose	X	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 ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

ANC <1.0 x 10^9/L	Platelets < 100 x 10^9/L

Delay until ANC ≥ 1.0 x 10^9/L and platelets ≥ 100 x 10^9/L. If cytopenias are presumed to be due to bone marrow involvement 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:

Renal and Hepatic Impairment

See previous section regarding dose adjustment in renal and hepatic impairment.

Neurotoxicity / Ototoxicity

Grade 2 or above should be discussed with consultant as dose reduction may be required. Consider omitting cisplatin.

Infusion Related Reactions

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

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Circulation/Dissemination

Date added into Q-Pulse	31st August 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
21/3/23	1	**Daniel Dutton**	New protocol created