SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

DHAP +/- Rituximab
Relapsed or Refractory Lymphoma

PROTOCOL REF: MPHADRRRL
(Version No. 1.0)

Approved for use in:

- Relapsed / refractory Hodgkin and non-Hodgkin lymphoma
- First line treatment for mantle cell lymphoma (alternate with RCHOP)

Dosage:

Drug	Dose	Route	Frequency
Dexamethasone	**40 mg**	Oral	Days 1 to 4
Rituximab*	**375 mg/m^2**	IV infusion	Day 1
Cisplatin	**100 mg/m^2**	IV infusion	Day 1 (or carboplatin in renal impairment)
Cytarabine	**2000mg/m^2**	IV infusion	Day 2 BD (morning and evening)

*Omit rituximab for CD20 negative lymphoma.

Every 21 days. Re-assess after 2 cycles for suitability of stem cell transplant. Maximum 4 cycles if not transplant eligible.

Drug	Dose	Route	Frequency
Carboplatin	**AUC5 (max. 800mg)**	IV infusion	Days 1 Dose (mg) = AUC5 x creatinine clearance (Wright formula) +25

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 stem cell transplant team prior to initiation if considering transplant
- An inpatient stay of at least 3 days is required for this regimen
- A dual lumen PICC line is required
- Urine output must be greater than 100mls/hour prior to administration of cisplatin
- IV hydration is required pre and post cisplatin administration
- Patient should report any changes in hearing or balance

Emetogenic risk:

Severely emetogenic

Supportive treatments:

Rituximab pre-infusion medication:

- Paracetamol tablet PO 1gram oral
- Chlorphenamine injection IV bolus 10mg
- Dexamethasone should be given at least 30 minutes before the rituximab

Supportive medication:

- Allopurinol PO 300mg daily for the first cycle (reduce in renal impairment)
- Aciclovir 400mg twice daily
- Chlorhexidine 0.2% mouthwash 10mls QDS
- Co-trimoxazole PO 480mg OD
- Fluconazole 50mg once daily
- Fosaprepitant 150mg IV once only day 1 pre-med prior to cisplatin/carboplatin
- Metoclopramide PO 10mg three times a day when required
- Omeprazole PO 20mg OD
- Ondansetron PO 8mg BD (IV on days 1 and 2)
- Prednisolone 0.5% eye drops 1 drop into both eyes QDS for 10 days starting on day 2
- IV hydration pre and post cisplatin (for details see below)
- Filgrastim S/C 30 or 48 million units OD on days 9 to 15 (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

Carboplatin – irritant

Cytarabine – non-vesicant

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

Dosing in renal and hepatic impairment:

		CrCl (mL/min)	Dose
Renal	**Cisplatin**	45 – 59	75%
		<45	Switch to carboplatin
	Carboplatin	<20	Contraindicated – discuss with consultant
	Cytarabine	45 – 59	60%
		30 – 44	50%
		<30	Omit

Hepatic	**Cisplatin**	No dose adjustment required
	Cytarabine	Bilirubin 34 µmol/L - reduce to 50%. Escalate in subsequent cycles in the absence of toxicity

Interactions:

Cisplatin:

- Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity when given within 2 weeks of cisplatin.
- Nephrotoxic drugs: increased nephrotoxicity; not recommended
- Ototoxic drugs: increased risk of ototoxicity
- Phenytoin: cisplatin reduces absorption and efficacy of phenytoin, monitor levels and adjust dose as necessary.
- Anti-gout agents: cisplatin may increase plasma concentration of uric acid therefore dose adjustments may be required to control hyperuricaemia and gout.
- Lithium: cisplatin may affect lithium plasma levels – monitor.

Cytarabine:

- Digoxin: cytarabine may affect plasma digoxin levels – consider monitoring

See SPCs for full information regarding interactions.

Treatment schedule:

Day	Time	Drug	Dose	Route	Diluent and rate
1	08:00	**Dexamethasone**	**40mg**	**PO**	
		Paracetamol	**1g**	**PO**	
		Chlorphenamine	**10mg**	**IV**	Bolus over 3 to 5 minutes
		Ondansetron	**8mg**	**IV**	100mL Sodium chloride 0.9% Over 15 minutes
	08:30	**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
	13:00	**Fosaprepitant**	**150mg**	**IV**	100mL Sodium chloride 0.9% Over 20 minutes
		PRE-HYDRATION			
		Potassium 0.15% + Magnesium	**20mmol 10mmol**	**IV**	1000mL Sodium chloride 0.9% Over 2 hours
	15:00	**Mannitol 10%**	**-**	**IV**	200mL over 30 minutes (immediately before cisplatin)
	15:30	**Cisplatin**	**100 mg/m^2**	**IV**	1000mL Sodium Chloride 0.9% Over 2 hours. **Only proceed if urine output is >100mls/hour.**
	17:30	**POST-HYDRATION**			
		Potassium 0.15% + Magnesium	**20mmol 10mmol**	**IV**	1000mL Sodium chloride 0.9% Over 2 hours
2	08:00	**Ondansetron**	**8mg**	**IV**	100mls Sodium Chloride 0.9% over 15 minutes
		Dexamethasone	**40mg**	**PO**	
	09:00	**Cytarabine**	**2000mg/m^2**	**IV**	1000mls Sodium Chloride 0.9% over 3 hours
	20:00	**Ondansetron**	**8mg**	**IV**	100mL Sodium chloride 0.9% Over 15 minutes
	21:00	**Cytarabine**	**2000mg/m^2**	**IV**	1000mls Sodium Chloride 0.9% over 3 hours (12 hours after first dose)
3 & 4	08:00	**Dexamethasone**	**40mg**	**PO**	Once daily (mane)
9		**Filgrastim (GCSF)** **<70kg:** 30 million units **≥70kg:** 48 million units		**SC**	**Non-mobilisation** Once daily for 7 days **Mobilisation** Once daily until harvesting complete

Replace cisplatin with carboplatin as below if creatinine clearance <45mL/min:

Day	Day	Drug	Dose	Route	Diluent and rate
1	13:30	**Carboplatin**	**AUC5 (max 800mg)**	**IV**	500mL glucose 5% Over 60 minutes

Haematopoietic Stem Cell Mobilisation:

R-DHAP 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:

Diarrhoea, mucositis, steroid side effects, nausea or vomiting.

SACT 1	
Rituximab	Cytokine release syndrome, infusion related reactions, hepatitis B reactivation.
SACT 2	
Cisplatin / Carboplatin	Nephrotoxicity - ensure adequate pre and post hydration is prescribed. Ototoxicity - assess patient for tinnitus or hearing abnormalities Bone marrow suppression
SACT 3	
Cytarabine	Rash, conjunctivitis, flu-like syndrome, oral ulceration, hepatic dysfunction and rarely cerebellar toxicity Bone marrow suppression

Investigations and treatment plan:

	Pre	Every cycle				Ongoing
		Day 1	Day 2	Day 3	Day 4	
Informed Consent	X					
Clinical Assessment	X					Prior to each cycle, as clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	X	X	X	X		Every day of treatment within each cycle
Viral Screening (Hep B core antibody & Surface antigen hepatitis C antibody, EBV, CMV, VZV, HI)	X					
FBC	X	X	X	X	X	Prior to each cycle, daily during admission and at the end of treatment
U&E & LFTs & Magnesium	X	X	X	X	X	
CrCl (Cockcroft and Gault)	X	X	X	X	X	
CT scan**	X					At the end of treatment and if clinically indicated
ECG						If clinically indicated
Blood pressure measurement	X	X	X	X	X	Repeat if clinically indicated
Urine output		X				Prior to and during platinum administration and afterwards if clinically indicated.
Height & Weight recorded	X	X	X	X		Every cycle
Blood glucose	X					Repeat if clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity (if required):

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.

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 Cisplatin
2. https://www.medicines.org.uk/emc Cytarabine
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4. Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009 UCLH - Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3 - updated January 2009)
5. BNF available via: https://bnf.nice.org.uk/
6. Velasquez WS, Cabanillas F, Salvador P et al. Effective salvage therapy for lymphoma with cisplatin in combination with high dose Ara-C and Dexamethasone (DHAP). Blood 1988;71(1):117-122
7. Delarue R et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation (ASCT) in mantle cell lymphoma (MCL): a phase II study from the GELA. Blood 2013 121:48-53

Circulation/Dissemination

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Version History

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