PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

GDP +/- Rituximab Relapsed or Refractory Hodgkin's or Non-Hodgkin's Lymphoma

PROTOCOL REF: MPHARRHL
(Version No.2.0)

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 can be given on day prior to GDP.** *Omit rituximab for Hodgkin's lymphoma or high grade T cell non-Hodgkin lymphoma patients
Gemcitabine	**1000mg/m^2**	IV infusion	Days 1 and 8
Cisplatin	**75mg/m^2**	IV infusion	Day 1 only
Dexamethasone	**40mg**	Oral	Days 1 to 4

Maximum of 6 cycles (21 day cycle)

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.
- Dexamethasone needs to be taken at least 30 minutes prior to rituximab so patient should be counseled to take it prior to admission to the day ward on day one.
- Furosemide 20-40mg may be added if weight gain >2kgs during infusion on day 1.
- Liaise with the BMT team if applicable concerning timing of bone marrow harvest
- Ensure urine output is >100mL/hour before starting cisplatin. Patients should drink 3L of fluid in the 24 hours after their cisplatin infusion.

Anti-emetic risk:

Severely emetogenic.

Supportive treatments:

Rituximab pre-infusion medicines:

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

GDP pre-infusion medicines:

- Ondansetron IV 8mg

Supportive medicines:

- 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
- Chlorhexidine 0.2% mouthwash 10mls four times daily
- Co-trimoxazole PO 480mg once daily
- Ondansetron PO 8mg BD days 1-3 and days 8-10
- Metoclopramide PO 10mg three times daily when required

- Filgrastim S/C 30 or 48 million units OD from day 9 for 5 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

Gemcitabine: non-vesicant

Cisplatin: irritant

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

Interactions:

Gemcitabine

Gemcitabine is a radiosensitiser therefore extreme care is required is a patient is receiving concurrent radiotherapy.

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.

Please see SPC of individual drugs for a full list of interactions.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Dexamethasone**	**40mg**	**PO**	30 minutes before rituximab
	Paracetamol	**1000mg**	**PO**	30 minutes before rituximab
	Chlorphenamine	**10mg**	**IV**	30 minutes before rituximab
	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 **NB if chemo to be given in a day ward setting then rituximab can be given on the day prior to GDP**
	Ondansetron	**8mg**	**IV**	100mL Sodium chloride 0.9% Over 15 minutes
	Gemcitabine	**1000mg/m^2**	**IV**	250mL Sodium chloride 0.9% Over 30 minutes
	Pre-hydration			
	1000mL Sodium chloride 0.9%		**IV**	Over 1 hour
	Mannitol 10%	**200mls**	**IV**	Over 30 minutes (immediately before cisplatin)
	Cisplatin	**75mg/m^2**	**IV**	In 1000mls sodium chloride 0.9% over 2 hours. Cisplatin *must* be started after the gemcitabine. Ensure urine output >100ml/he before starting cisplatin
	Post-hydration			
	1000mL Sodium chloride 0.9% with 20mmol potassium and 10mmol magnesium sulfate		**IV**	Over 2 hours
8	**Gemcitabine**	**1000mg/m^2**	**IV**	250mL Sodium chloride 0.9% Over 30 minutes
9	**Filgrastim (GCSF)**	**<70kg:** 30 million units **≥70kg:** 48 million units	**SC**	**Non-mobilisation** Once daily for 5 days **Mobilisation** Once daily until harvesting complete

- Vein discomfort throughout infusion of gemcitabine may be eased using heat pack.
- Gemcitabine is a radiation sensitizer: be aware if patients are also receiving radiotherapy**.**

Haematopoietic Stem Cell Mobilisation:

The GDP component of R-GDP 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 14.

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 (Day 15 if GDP given on day 2)

- 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:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea, infusion related reactions, cytokine release syndrome, ototoxicity, nephrotoxicity, hepatitis B reactivation.

Investigations and treatment plan:

	Pre	Cycle 1 D1	Cycle 1 D8	Cycle 2 D1	Cycle 2 D8	Ongoing
Informed consent	x					
Clinical Assessment	x	x		x		As clinically indicated or at the end of treatment
SACT Assessment (including PS and toxicity assessment)	x	x	x	x	x	
FBC	x	x	x	x	x	
U&E & LFTs & Magnesium	x	x		x		
CrCl (Cockcroft and Gault)	x	x		x		
HbA1C	x					Repeat as clinically indicated
Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2	x					
CT or PET CT scan	x					Interim and end of treatment scans as indicated
Blood pressure measurement	x	x	x	x	x	Continuous monitoring required if on rituximab
Temperature, respiratory rate and pulse		x	x	x	x	Continuous monitoring required if on rituximab
Pregnancy test	x					If indicated
Height	x					
Weight	x	x		x		
Bone Marrow						If indicated
Blood glucose	x					Repeat if clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Day of cycle	ANC (x 10^9/L)	Platelets (x 10^9/L)	Action
1	ANC ≥ 1.0 and platelets ≥ 75		100% all drugs
	ANC ≥ 1.0 and platelets < 75		Delay 1 week. If plt then ≥ 50, give 100%. Support with platelet transfusions as necessary.
	ANC < 1.0 and platelets ≥ 75		Delay 1 week. If ANC then ≥ 0.5, proceed with 100% and support with GCSF
	ANC < 1.0 and platelets < 75		Delay 1 week. If ANC then ≥ 0.5 and plt ≥ 50, give 100% dosing. Support with GCSF and/or transfusions as necessary OR If ANC <0.5 and/or plts <50 defer and check counts every 3 days. Resume when ANC ≥ 0.5 and plts ≥50
8	ANC ≥ 1.0 and platelets ≥ 75		Give 100% gemcitabine
	ANC 0.5-1.0 and platelets ≥ 75		Give 100% gemcitabine and support with GCSF, or give 75% of original dose
	ANC ≥ 1.0 and platelets 50 to 75		Give 75% of original dose
	ANC < 0.5 and platelets < 50		Omit gemcitabine

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.

Dosing in renal and hepatic impairment:

Gemcitabine		
Renal Function	No dose adjustment required but for haemodialysis patients start dialysis 6 to 12 hours after gemcitabine	
Liver Function	**Bilirubin (micromol/L)**	**Dose**
	>27	Consider starting at 80% dose and increase as tolerated. Alternatively start at usual dose and monitor closely.

Cisplatin	
Renal Function	
CrCl (ml/min)	**Dose**
50-59	75%
40-49	50%
<40	Not recommended; consider carboplatin
Haemodialysis	Consider 50%

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 rituximab (accessed July 2020)
2. https://www.medicines.org.uk/emc cisplatin (accessed July 2020)
3. https://www.medicines.org.uk/emc gemcitabine (accessed July 2020)
4. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.
5. Thames Valley Strategic Clinical Network RGDP Protocol

Circulation/Dissemination

Date added into Q-Pulse	26th May 2022
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
April 2022	1.0	**Aileen McCaughey, Advanced Pharmacist**	New protocol
April 2023	2.0	**Daniel Dutton - Pharmacist**	Protocol updated to new format and harvesting info added. Rituximab IRR table added