SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

GCVP +/- Rituximab
Non Hodgkins Lymphoma

PROTOCOL REF: MPHAGRNL
(Version No. 1.0)

Approved for use in:

- R-GCVP – B Cell Non-Hodgkin's Lymphoma
- GCVP – Non-Hodgkin's Lymphoma not expressing CD20
- Recommended for NHL patients who are not suitable for RCHOP due to cardiac problems or other co-morbidities.

Dosage:

Drug	Dose	Route	Frequency
+/- Rituximab	**375mg/m^2**	IV infusion	Day 1
Cyclophosphamide	**750mg/m^2**	IV infusion	Day 1
Vincristine	**1.4mg/m^2 (max 2mg)**	IV infusion	Day 1
Gemcitabine	**1000mg/m^2 ***	IV infusion	Day 1 and 8** *dose can be reduced to 750mg/m^2 for cycle 1 and then titrated to 875mg/m^2 for cycle 2 and 1000mg/m^2 for cycle 3 if required. **Day 8 dose can be omitted if concerns regarding fitness or toxicity
Prednisolone	**100mg**	PO	Days 1 to 5

Cycle frequency is every 21 days for up to 6 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.

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

Rituximab pre-infusion medicines:

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

GCVP and G pre-infusion medicines:

- Ondansetron IV 8mg

Supportive medicines:

- Allopurinol PO 100mg or 300mg OD (depending on renal function) for the first cycle/two cycles
    - Consider prophylactic rasburicase for patients at high risk of tumour lysis syndrome
- Ondansetron PO 8mg BD for 5 days
- Metoclopramide PO 10mg TDS prn
- Docusate PO 200mg BD prn
- Filgrastim S/C 30 or 48 million units OD from day 9 for 5 days (30million units if <70kgs or 48 million units if >70kgs).

- Aciclovir 400mg BD and co-trimoxazole 480mg OD are not generally required but may be given at the discretion of the prescriber if the patient is expected to experience profound prolonged neutropenia (>7days)

Extravasation risk:

Rituximab: non-vesicant

Cyclophosphamide: non-vesicant

Vincristine: vesicant

Gemcitabine: non-vesicant

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

Interactions:

The main interactions are detailed below however, for a full list and more detailed interaction information please refer to the appropriate SPC

Rituximab

No significant interactions

Cyclophosphamide

- Substances that reduce the efficacy of cyclophosphamide include:
    - Aprepitant, bupropion, busulfan,ciprofloxacin, chloramphenicol, azole-antimycotics (e.g, fluconazole and itraconazole), CYP2B6 and CYP3A4 inhibitors (e.g. nevirapin and ritonavir), prasugrel, sulfonamides, e.g. sulfadiazine, sulfamethoxazole and sulfapyridine, thiotepa, grapefruit (fruit or juice), rifampicin, St. John's wort.
- An increased risk of side-effects may occur with:
    - Azathioprine: increased risk of hepatotoxicity (liver necrosis), chloral hydrate, cimetidine, disulfiram, glyceraldehyde, protease inhibitors, saquinavir, rifampin,

phenobarbital, carbamazepine, phenytoin, St. John's wort, benzodiazepines, corticosteroids and dabrafenib.

- There is an increased risk of cardiotoxicity when cyclophosphamide is co-administered with:
    - Anthracyclines, mitomycin, cytarabine, pentostatin and radiation therapy.

Vincristine

- Care is needed with concurrent drugs that can also cause neurotoxicity.
- Vincristine may reduce plasma levels of phenytoin therefore dose adjustment of phenytoin based on levels may be required.
- Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily, or in patients with hepatic dysfunction.
- When chemotherapy is being given in conjunction with radiation therapy through portals which include the liver, the use of vincristine should be delayed until radiation therapy has been completed.

Gemcitabine

Gemcitabine is a radiosensitiser, therefore extreme care is required is a patient is receiving concurrent radiotherapy (given together or ≤ 7 days apart).

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Prednisolone**	**100mg**	**PO**	To be taken at least 30 minutes before rituximab
	Paracetamol	**1g**	**PO**	
	Chlorphenamine	**10mg**	**IV**	Bolus dose over 3-5 minutes
	Rituximab	**375mg/m^2**	**IV infusion**	In 500ml 0.9% NaCl. (See rituximab infusion rate policy)
	Ondansetron	**8mg**	**IV infusion**	In 100ml 0.9% NaCl over 15 minutes.

	Vincristine	**1.4mg/m^2 (max dose 2mg)**	**IV infusion**	In 50ml 0.9% NaCl over 15 minutes.
	Gemcitabine	**1000mg/m^2 ***	**IV infusion**	In 250mls NaCl 0.9% over 30 minutes
	Cyclophosphamide	**750mg/m^2**	**IV infusion**	In 250ml 0.9% NaCl over 30 minutes.
2 to 5	**Prednisolone**	**100mg**	**PO**	
8**	**Gemcitabine**	**1000mg/m^2 ***	**IV infusion**	In 250mls NaCl 0.9% over 30 minutes
9	**Filgrastim**	**30 million units (if <70kg) or 48 million units (if ≥70kg)**	**S/C**	For 5 days starting on day 9

*Or reduced doses as detailed on page 1 if clinically appropriate
**Day 8 dose can be omitted if concerns regarding fitness or toxicity

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea, constipation, bladder irritation, high blood sugars, raised ALT, rash, hepatitis B reactivation and peripheral neuropathy

Investigations and treatment plan:

	Pre	Prior to cycle 1	Cycle 1 D8	Prior to each cycle	D8 at every cycle	Ongoing
Informed Consent	X					Prior to treatment initiation
Clinical Assessment	X	X		X		Every cycle
SACT Assessment (to include PS and toxicities)	X	X		X		Every cycle
Viral screening	X					Hepatitis B core antibody, hepatitis B surface antigen, HIV 1+2.
FBC	X	X	X	X	X	Every cycle
U&E, LFTs, Magnesium and bone profile	X	X		X		Every Cycle
CrCl (Cockcroft and Gault)	X	X		X		Every cycle
HbA1c and blood glucose	X					Repeat if clinically indicated
PET/CT scan (CT scan usually used for interim assessment)	X					After 3 cycles and at the end of treatment. Or sooner if clinically indicated
ECG	X					If clinically indicated
Blood pressure measurement	X			X		During each infusion of rituximab
Temperature, respiratory rate, pulse	X			X		During each infusion of rituximab
Height and weight recorded	X	X		X		Every cycle
Pregnancy test (if indicated)	X					Women of childbearing potential

Dose Modifications and Toxicity Management:

Haematological toxicity:

Day 1

Proceed with full doses on **day 1** if:-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 75 x 10^9/L

Dose reduce gemcitabine, cyclophosphamide and vincristine to 75% on day 1 if:-

ANC 0.5 to 0.9 x 10^9/L	Plt 50 to 74 x 10^9/L

Delay **day 1** and repeat FBC after one week if:-

ANC <0.5 x 10^9/L	Plt <50 x 10^9/L

Delay until ANC ≥1 x 10^9/L and platelets ≥75 x 10^9/L then 100% dose

Day 8

Proceed with full dose of gemcitabine on **day 8** if:-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 75 x 10^9/L

Dose reduce gemcitabine to 75% on **day 8** if:-

ANC 0.5 to 0.9 x 10^9/L	Plt 50 to 74 x 10^9/L

Omit **day 8** if:-

ANC <0.5 x 10^9/L	Plt <50 x 10^9/L

NB if the gemcitabine dose is reduced then it should remain at the lower dose for the remainder of the course.

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:

Renal	Cyclophosphamide	**CrCl (mL/min)**	**Dose adjustment**
		≥30	No dose adjustment required
		10-29	Consider 75% of dose
		<10 or haemodialysis	Not recommended. If unavoidable consider 50% of dose
	Gemcitabine	No adjustment required for renal impairment however, if receiving haemodialysis the gemcitabine should be given 6 to 12 hours prior to haemodialysis.	

Hepatic	Cyclophosphamide	**Hepatic impairment**	**Dose adjustment**
		Mild to moderate hepatic impairment	No dose adjustment necessary
		Severe hepatic dysfunction	Not recommended due to risk of reduced efficacy
	Gemcitabine	**Bilirubin (micromol/L)**	**Dose adjustment**
		≥27	Consider starting at 80% dose and increase as tolerated or alternatively start at standard dosing and monitor closely
	Vincristine	**Bilirubin (micromol/L)**	**Dose adjustment**
		>51	50% of dose

References:

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Version History

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