Systemic Anti Cancer Therapy Protocol

Rituximab, Fludarabine and Cyclophosphamide (R-FC) Chronic Lymphocytic Leukaemia

PROTOCOL REF: MPHARFCHA
(Version No: 1.0)

Approved for use in:

- First line treatment of Chronic Lymphocytic leukaemia/ Small lymphocytic lymphoma
- ECOG 0-2

Blueteq registration is not required

Dosage Cycle One:

Drug	Dose	Route	Frequency
Rituximab	**375mg/m^2**	IV infusion	Day 1 only of a 28 day cycle. NB if WCC >25 x 10^9/L then dose can be split into day 1: 100mg; day 2: remainder of 375mg/m^2 dose
Fludarabine	**24mg/m^2**	oral	Days 1 to 5 of a 28 day cycle To be taken at lunchtime Round to the nearest 10mg
Cyclophosphamide	**150mg/m^2**	Oral	Days 1 to 5 of a 28 days cycle. Once daily Round to the nearest 50mg tablet

Dosage Subsequent Cycles:

Drug	Dose	Route	Frequency
Rituximab	**500mg/m^2**	IV infusion	Day 1 only of a 28 day cycle
Fludarabine	**24mg/m^2**	oral	Days 1 to 5 of a 28 day cycle To be taken at lunchtime Round to the nearest 10mg
Cyclophosphamide	**150mg/m^2**	Oral	Days 1 to 5 of a 28 days cycle. Once daily Round to the nearest 50mg tablet

Maximum of 6 cycles (28 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.
- Irradiated blood products are required after administration of fludarabine. It is the responsibility of the medical team when consenting the patient for treatment to inform the transfusion lab that the patient requires irradiated blood.

Anti-emetic risk:

Severely emetogenic.

Supportive treatments:

Rituximab pre-infusion medicines:

- Paracetamol PO 1g
- Chlorphenamine IV bolus 10mg
- Hydrocortisone sodium succinate IV bolus 100mg

Supportive medicines:

- Allopurinol PO 100mg or 300mg daily (depending on renal function) for first cycle
- Aciclovir 400mg twice daily depending on clinical circumstances (e.g. previous history of shingles)
- Co-trimoxazole PO 480mg daily (to continue for 6 months after last cycle)
- Metoclopramide PO 10mg three times a day when required
- Ondansetron PO 8mg twice a day for 5 days
- Filgrastim S/C 30 or 48 million units daily from day 8 for 5 days if required for secondary prophylaxis of neutropenia (30million units if <70kgs and 48 million units >70kgs).

Extravasation risk:

Rituximab – non-vesicant

Refer to the Trust guidance for the prevention and management of extravasation

Interactions:

Rituximab

No significant interaction

Fludarabine

Dipyridamole and other inhibitors of adenosine uptake may reduce the therapeutic efficacy of fludarabine.

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): co-administration may reduce the efficacy of cyclophosphamide, prasugrel, sulfonamides, e.g. sulfadiazine, sulfamethoxazoel 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.

Cycle One Treatment Schedule (split dose rituximab):

Day	Drug	Dose	Route	Diluent and rate
1	**Paracetamol**	**1g**	**PO**	
	Chlorphenamine	**10mg**	**IV**	Bolus dose over 3-5 minutes
	Hydrocortisone sodium succinate	**100mg**	**IV**	Bolus dose over 3-5 minutes
	Rituximab	**100mg**	**IV**	In 500mls of NaCl 0.9% For infusion rate see rituximab infusion rate policy
	Cyclophosphamide	**150mg/m^2**	**PO**	Mane
	Fludarabine	**24mg/m^2**	**PO**	Lunchtime

2	**Paracetamol**	**1g**	**PO**	
	Chlorphenamine	**10mg**	**IV**	Bolus dose over 3-5 minutes
	Hydrocortisone sodium succinate	**100mg**	**IV**	Bolus dose over 3-5 minutes
	Rituximab	**275mg/m^2**	**IV**	In 500mls of NaCl 0.9% For infusion rate see rituximab infusion rate policy
	Cyclophosphamide	**150mg/m^2**	**PO**	Mane
	Fludarabine	**24mg/m^2**	**PO**	Lunchtime
3 to 5	**Cyclophosphamide**	**150mg/m^2**	**PO**	Mane
	Fludarabine	**24mg/m^2**	**PO**	Lunchtime

Cycle one treatment schedule (no split dose rituximab):

Day	Drug	Dose	Route	Diluent and rate
1	**Paracetamol**	**1g**	**PO**	
	Chlorphenamine	**10mg**	**IV**	Bolus dose over 3-5 minutes
	Hydrocortisone sodium succinate	**100mg**	**IV**	Bolus dose over 3-5 minutes
	Rituximab	**375mg/m^2**	**IV**	In 500mls of NaCl 0.9% For infusion rate see rituximab infusion rate policy
	Cyclophosphamide	**150mg/m^2**	**PO**	Mane
	Fludarabine	**24mg/m^2**	**PO**	Lunchtime
2 to 5	**Cyclophosphamide**	**150mg/m^2**	**PO**	Mane
	Fludarabine	**24mg/m^2**	**PO**	Lunchtime

Subsequent Cycles Treatment Schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Paracetamol**	**1g**	**PO**	
	Chlorphenamine	**10mg**	**IV**	Bolus dose over 3-5 minutes
	Hydrocortisone sodium succinate	**100mg**	**IV**	Bolus dose over 3-5 minutes
	Rituximab	**500mg/m^2**	**IV**	In 500mls of NaCl 0.9% For infusion rate see rituximab infusion rate policy
	Cyclophosphamide	**150mg/m^2**	**PO**	Mane
	Fludarabine	**24mg/m^2**	**PO**	Lunchtime

	Cyclophosphamide	**150mg/m^2**	**PO**	Nocte
2 to 5	**Cyclophosphamide**	**150mg/m^2**	**PO**	Mane
	Fludarabine	**24mg/m^2**	**PO**	Lunchtime
	Cyclophosphamide	**150mg/m^2**	**PO**	Nocte

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea

Investigations and treatment plan:

	Pre	Cycle 1 D1	Cycle 1 D2 (if spilt dose rituximab)	Cycle 2+ D1	Ongoing
Informed Consent	X				
Clinical Assessment	X				
SACT Assessment (including performance status and toxicity assessment)		X	X	X	
FBC	X	X		X	Every cycle
U&E & LFTs & Calcium profile	X	X		X	Every Cycle
DAT	X				
CrCl (Cockcroft and Gault)	X				Every cycle
Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2	X				
Radiological Imaging	X				If clinically indicated, repeat scans at the discretion of MDT
Bone marrow assessment	X				Where clinically indicated
ECG/ ECHO	X				If clinically indicated
Blood pressure measurement	X	X	X	X	Continuous monitoring required if on rituximab
Temperature, respiratory rate, pulse		X	X	X	Continuous monitoring required if on rituximab
Weight	X	X		X	Every cycle
Height	X				Repeat if clinically indicated
Pregnancy test	X				If clinically appropriate

Dose Modifications and Toxicity Management:

Haematological toxicity:

Cycle 1 to proceed despite cytopenia

Subsequent cycles should proceed 1 if: -

ANC ≥ 1.0 x 10^9/L	Plt ≥ 75 x 10^9/L

Delay 1 or 2 weeks on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

If counts have not recovered by week two then proceed with chemo with a 50% dose reduction for the fludarabine and cyclophosphamide.

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:

Fludarabine

Renal	
CrCl (ml/min)	Dose
30 – 70	80% of original dose
<30	Not recommended
Hemodialysis	80% of original dose. Start dialysis 12 hours after dose.

Cyclophosphamide

Renal Function	
CrCl (ml/min)	Dose
10-29	Consider 75% of dose
<10 or haemodialysis	Not recommended. If unavoidable consider 50% of dose.
Liver Function	
Severe liver dysfunction	Not recommended

References:

1. https://www.medicines.org.uk/emc Rituximab (accessed April 2020)
2. https://www.medicines.org.uk/emc_Fludarabine (accessed April 2020)
3. https://www.medicines.org.uk/emc Cyclophosphamide (accessed April 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. Cheshire and Merseyside Strategic Clinical Network R-Chlorambucil Protocol