R-FC

First-line treatment of CLL in patients for whom treatment with fludarabine and cyclophosphamide is considered appropriate - NICE approved 2009
An option for relapsed/refractory CLL, *except* for patients who have already received R-FC or who have disease refractory (not responded or relapsed within 6 months) to fludarabine - NICE approved 2010

All patients should be screened for hepatitis B virus before starting treatment

Drugs/Dosage:

Rituximab	375mg/m^2	IV Infusion	fractionated over Day 1 and Day 2 of Cycle 1 (see Administration below)
then			
Rituximab (dose 'banded' as table below)	500mg/m^2	IV Infusion	Day 1 +/- Day 2 of subsequent cycles (see Administration below)

Cyclophosphamide	150mg/m^2 PO once daily for 5 days*, starting on the day after rituximab completed (rounded to nearest 50mg and taken at breakfast)
Fludarabine	24mg/m^2 PO once daily for 5 days*, starting on the day after rituximab completed (rounded to nearest 10mg and taken at lunchtime)

*For patients aged > 65 years, consider reducing to a 3 or 4 day course with the first cycle, adjusting in subsequent cycles according to response.

Or, if the oral route is not tolerated, the following schedule may be used:

Cyclophosphamide	250mg/m^2	IV daily	Days 1, 2 and 3
Fludarabine	25mg/m^2	IV daily	Days 1, 2 and 3

Rituximab Premedication (to be administered before **all** infusions):

Paracetamol 1000mg	po	60 minutes before rituximab
Chlorphenamine 10mg	IV	15 minutes before rituximab
Dexamethasone 8mg	IV	15 minutes before rituximab

Other Drugs: Allopurinol 300mg po daily, ideally starting 24 hours before treatment - review after 4 weeks.
For patients with high initial counts (WBC > 100) or bulky disease, it is suggested that at least 1 litre of IV N/saline is administered before starting treatment.
PCP prophylaxis - prescribe according to unit practice/protocol (generally until 6 months after completion of treatment, or according to CD_4 counts)
Consider aciclovir prophylaxis (400mg bd) if history of VZV or HSV reactivation

Administration: It is assumed that the majority of patients will present with WBC > 25 x 10^9/L, which requires rituximab to be administered with caution at a reduced rate, and with careful monitoring, as there is an increased risk of severe cytokine release syndrome. Ensure all patients are well hydrated before starting treatment. The following fractionated schedule over 2 days complies with the UK CLL advisory board advice, and is line with current RMH practice:

Cycle 1: Give rituximab over 2 days as follows:
Day 1: **rituximab 50mg/m²** in 50ml sodium chloride 0.9% IV infusion at 50mg/hr fixed rate throughout.
Day 2: **rituximab 325mg/m²** in 250-500ml sodium chloride 0.9% IV infusion, start at 50mg/hr, escalate in 50mg/hr increments every 30 mins to max 400mg/hr.

Cycle 2: If WBC < 25 x 10^9/L;
Give rituximab 500mg/m^2 in 500ml sodium chloride 0.9% total dose on Day 1.
If no problems with Cycle 1 infusions, start at 100mg/hr; escalate in 100mg/hr increments every 30 minutes to a maximum of 400mg/hr.
If reactions occurred with Cycle 1, give as for Day 2 of Cycle 1.

If WBC > 25 x 10^9/L, consider fractionating again as follows:
Day 1: rituximab 125mg/m^2 in 100-250ml sodium chloride 0.9%
Day 2: rituximab 375mg/m^2 in 500ml sodium chloride 0.9%
If no problems with Cycle 1 infusions, start both fractions at 100mg/hr; escalate in 100mg/hr increments every 30 minutes to a maximum of 400mg/hr.
If reactions occurred with Cycle 1, give both fractions as for Day 2 of Cycle 1.

Cycle 3 onwards: ***Assuming tolerated all previous infusions at standard rates, and WBC < 25***
Give rituximab 500mg/m^2 in 500ml N/saline as a single dose on Day 1 of the cycle.
Give 20% of dose (i.e. 100ml) over 30 minutes, then the remaining 80% (i.e. 400ml) over 1 hour, to give a total infusion time of 90 minutes.

*** Patients who did not tolerate their previous infusion at the standard rate ***
Administer as per Day 2 of first infusion, or at a slower rate if required.

Monitoring: For all infusions, monitor and record patient's vital signs (blood pressure, pulse, temperature and O_2 saturation) at baseline and then every 30 minutes (before each increase in infusion rate for escalating infusions) until the end of the infusion.
If reactions occur at any time, stop the infusion. If symptoms improve, restart at half the previous infusion rate, and escalate as tolerated.

Calculating infusion rates: For rituximab doses **in 500ml volume only**, you may use the table below, *or* a locally approved method of calculating infusion rates.

	Infusion Rate (mg/hour)							
	50	100	150	200	250	300	350	400
Rituximab 'banded' dose	**Infusion Rate (ml/hour) for rituximab in 500ml volume only**							
400mg	62	125	187	250	312	375	437	500
450mg	55	111	166	222	277	333	388	444
500mg	50	100	150	200	250	300	350	400
600mg	42	83	125	167	208	250	292	333
700mg	36	71	107	143	178	214	250	286
800mg	31	62	94	125	156	187	219	250
900mg	28	56	83	111	139	167	194	222
1000mg	25	50	75	100	125	150	175	200
1100mg	23	45	68	90	114	136	159	182
1200mg	21	42	63	83	104	125	146	167
1300mg	19	38	58	77	96	115	134	154

Reason for Update: ritux infusion table updated in line with new dose banding	Approved by Chair of Alliance TSSG: Dr A Laurie
Version: 5	Date: 2.3.16
Supersedes: Version 4	Review date: April 2018
Prepared by: S Taylor	Checked by: C Tucker

For rituximab in smaller volumes (50ml, 100ml or 250ml), do **not** refer to the table; you may again use a locally approved method, or the following equation:

$$\text{Infusion rate in ml/hr} = \frac{\text{required infusion rate in mg/hr} \times \text{total volume (ml)}}{\text{dose of rituximab (mg)}}$$

Cyclophosphamide tablets to be taken at breakfast time. They should be swallowed whole with plenty of water. Encourage the patient to drink plenty of fluids during the five days of oral cyclophosphamide, and for 24 hours after completed.
Fludarabine tablets to be taken at lunchtime, swallowed whole with water.

IV cyclophosphamide should be given immediately before IV fludarabine, and after rituximab. Both may be given as a bolus.

Frequency: 4 weekly cycle for up to 6 cycles

Main Toxicities: severe cytokine release syndrome – usually occurs within 1–2 hours of the first rituximab infusion (see Comments) and consists of fever, headache, rigors, flushing, nausea, rash, URTI symptoms;
transient hypotension and bronchospasm are usually infusion rate related, manage as above;

tumour lysis syndrome (ensure pre-medicated with allopurinol and good hydration); myelosuppression; alopecia: opportunistic infections; haemorrhagic cystitis; GI upset, chiefly diarrhoea (more common with oral option); autoimmune haemolytic anaemia (fludarabine – see Comments); ovarian failure; infertility

Anti - emetics: oral route for FC – mildly emetogenic, but have low threshold to use ondansetron and so avoid switching to IV route for FC
IV route - moderately emetogenic

Extravasation: non-vesicants

Regular Investigations:	FBC		Day 1
	LFTs and U&Es		Day 1
	LDH		every other cycle **only** if elevated prior to treatment baseline, and
	DAT	}	repeat if disproportionate anaemia or any history of autoimmune
	Reticulocytes	}	haemolytic anaemia (AHA)
	Bilirubin	}	(see Comments)

Comments: Full resuscitation equipment must be available, with immediate access to clinical staff trained in resuscitation for the first hour of the first rituximab infusion. Blood pressure, pulse, temperature and O_2 saturation must be measured and recorded at regular intervals as specified above.

Oral treatment with fludarabine and cyclophosphamide is preferred, if tolerated, but may produce more GI side effects (in up to 50% patients)

All patients must receive irradiated blood products for all future transfusions - inform patient and blood bank.

Patients undergoing treatment with fludarabine should be closely monitored for signs of AHA. Fludarabine should be used with caution if DAT positive in the absence of haemolysis.

In patients presenting with both leukaemia and haemolysis, the patient should usually first be treated to control haemolysis before commencing fludarabine. If the haemolysis subsequently re-occurs / worsens, then discontinuation of fludarabine is recommended.

Dose Modifications

Haematological Toxicity:

Cycle 1:
If low counts thought to be disease-related (marrow infiltration or autoimmune causes), proceed with full dose treatment.

Subsequent Cycles:
If a fall in counts is thought to be due to treatment, proceed as follows:

If neutrophils < 1.0 x 10^9/l or platelets < 75 x 10^9/l, defer treatment for 1 week.
Repeat FBC and, if counts have recovered, proceed with full dose treatment.
If the counts have not recovered after 2 weeks delay, consider continuing treatment with a 50% dose reduction of both cyclophosphamide and fludarabine.

Renal Impairment:

CrCl (ml/min)	Fludarabine Dose
> 70	Give 100%
30 – 70	Give 50%
< 30	Contra-Indicated

CrCl (ml/min)	Cyclophosphamide Dose
> 20	Give 100%
10 – 20	Give 75%
< 10	Give 50%

Patient Information: Macmillan leaflet for FCR

References:

Hallek, M et al; Lancet 2010; 376 (9747): 1164 - 1174
Robak, T et al; JCO 2010; 28 (10): 1756 - 1765
Fabbri, A et al; Br J Haem 2007; 139; 90 – 93 (dosing in the elderly)