CHLORAMBUCIL +/- RITUXIMAB FOR CLL

Treatment of CLL in elderly patients for whom treatment with fludarabine and cyclophosphamide is not considered appropriate, due to co-morbidities or performance status

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

Drugs/Dosage:

Chlorambucil	10mg/m^2/day	PO	once daily for 7 days, on Days 1 – 7
+/-			
Rituximab	375mg/m^2	IV	fractionated over Day 1 and Day 2 of Cycle 1 (see Administration section)
then			
Rituximab (dose 'banded' as table below)	500mg/m^2	IV	Day 1 +/- Day 2 of subsequent cycles (see Administration section)

Rituximab Premedication (to be administered before **all** rituximab 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.

Frequency: 4 weekly cycle for up to 6 cycles, then a further 6 cycles of chlorambucil alone may be considered for patients with a continuing response

Administration: Chlorambucil available as 2mg tablets, which need to be stored in the fridge.
The daily dose may be divided to reduce the incidence of nausea.

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 in line with current RMH practice:

Cycle 1: Give rituximab over 2 days as follows:
Day 1: **rituximab 50mg/m^2** in 50ml sodium chloride 0.9% IV infusion at 50mg/hr fixed rate throughout.

Day 2: **rituximab 325mg/m^2** 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.

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

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

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:

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

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;	mucositis;	ovarian failure;	infertility
Anti - emetics:	mildly emetogenic			

Extravasation: rituximab is a non-vesicant

Regular Investigations:	FBC	Day 1
	LFTs	Day 1
	U&Es	Day 1
	LDH	every other cycle

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.

Dose Modifications

Haematological Toxicity:

Cycle 1:
For any low initial counts thought to be disease-related, proceed with full dose treatment.

Subsequent Cycles:
Treatment should be deferred if neutrophil count is < 1.0 x 10^9/L and/or if platelet count is < 100 x 10^9/L, unless secondary to bone marrow infiltration or autoimmune.
Consider reducing the number of days of chlorambucil treatment per cycle if significant thrombocytopenia or neutropenia occurs, that is thought to be due to the treatment rather than the disease.

Renal Impairment: Patients with impaired renal function may be more prone to myelosuppression with chlorambucil.

Hepatic Impairment: Dose reduction of chlorambucil is only recommended with gross hepatic dysfunction, with dose adjustment according to response.

Patient Information: Macmillan leaflets for Rituximab and Chlorambucil

References:
Hillmen, P et al; JCO; published online March 17, 2014
CLL4 trial; MRC Adult Leukaemia Working Party, 2001
Catovsky D, Else M, Richards S; Clin Lymphoma Myeloma Leuk 2011; 11 Suppl 1: S2-6