RITUXIMAB + HIGH DOSE METHYLPREDNISOLONE

A treatment option in CLL for patients with limited myeloid reserve, pre-treatment cytopenias or adverse cytogenetics

Drug/Dosage:	**Rituximab**	375mg/m^2	IV	Day 1
	Methylprednisolone	1000mg/m^2	IV or PO	once daily on Days 1 to 5 (5 doses in total)

Premedication: (before **all** infusions)	Paracetamol 1000mg po	60 minutes pre rituximab
	Chlorphenamine 10mg IV	15 minutes pre rituximab
	Dexamethasone 8mg or Hydrocortisone 100mg IV	15 minutes pre rituximab

(IV steroid may be omitted if Day 1 methylprednisolone given at least 30 minutes before start of rituximab infusion)

Other drugs:
Allopurinol (dose according to renal function) – review after 4 weeks
Omeprazole 20mg od (or ranitidine) is recommended whilst treating with steroids
Fluconazole 100mg od for antifungal prophylaxis
Aciclovir prophylaxis (400mg bd) if history of VZV or HSV reactivation
PCP prophylaxis – prescribe according to unit practice

Anti-emetics: none required

Frequency: every 28 days for 6 cycles

Administration: Methylprednisolone intravenous doses to be reconstituted as directed, then diluted in 250 ml of 0.9% sodium chloride and infused over 30 minutes; ideally administered in the mornings. Methylprednisolone oral doses to be taken with or after breakfast.

Rituximab should be administered according to the following instructions:

Ensure all patients are well hydrated before starting treatment.
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. The following fractionated schedule over 2 days complies with the UK CLL advisory board advice:

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 onwards: **Assuming tolerated the previous infusions at standard rate, and WBC < 25**
Give rituximab 375mg/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.

Reason for Update: Other Drugs reviewed; don't need to be ritux-naive	Approved by Chair of Alliance TSSG: Dr A Laurie
Version: 4	Date: 2.3.16
Supersedes: Version 3	Review Date: April 2018
Prepared by: S Taylor	Checked by: C Tucker

Monitoring:	For all infusions, monitor patient's vital signs (blood pressure, pulse, temperature and O_2 saturation) at baseline and then every 30 minutes (before any increase in infusion rate) until end of infusion. If reactions occur at any time, stop the infusion. If symptoms improve, restart at half previous infusion rate and escalate as tolerated.
Calculating infusion rates:	For rituximab doses **in 500ml volume only**, refer to the table included in other rituximab-containing protocols such as R-FC. For rituximab in smaller volumes (50ml, 100ml or 250ml), do **not** refer to the table; you may use a locally approved method, or the following equation: 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); steroid side effects; tumour lysis syndrome (ensure pre-medicated with allopurinol and good hydration)

Regular Investigations:	
FBC	before each cycle
U&Es and LFTs	before each cycle
LDH	before each cycle
Blood glucose monitoring	see Comments
Urine testing for glucose	see Comments
Blood pressure monitoring	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 glucose and blood pressure monitoring to be tailored according to individual patient needs, but with all patients monitored, as practical, during the first 5 days of Cycle 1. Oral hypoglycaemic agents will be required if blood glucose is sustained above 12 mmol/l. Patients should also be advised to report any increase in thirst or increase in need to urinate.

Dose Modifications

Haematological Toxicity:	No dose adjustment necessary
Renal or Hepatic Impairment:	No dose adjustment necessary
Other:	If severe steroid-related side effects develop, consider reducing dose and/or duration.
Patient Information:	Macmillan leaflet for rituximab. Macmillan also produces a Steroid leaflet, which may be used as required.

References:

1st line: Castro et al; Leukaemia 2009; 23 (10): 1779 – 1789

Refractory: Castro et al; Leukaemia 2008; 22 (11): 2048 – 2053
Dungarwalla et al; Haematologica 2008; 93(3): 475–476 (chosen schedule)
Pileckyte et al; Leuk Lymphoma 2011; 52 (6): 1055–1065