R-BENDAMUSTINE FOR CLL

For first-line use in the treatment of CLL - NICE approved 2011
(Note that this regimen has shown only limited benefit in patients with p53 deletion)

All patients should be screened for hepatitis B virus before starting treatment, and patients should be monitored throughout treatment for opportunistic infections, in line with MHRA alert July 2017
(https://www.gov.uk/drug-safety-update/bendamustine-levact-increased-mortality-observed-in-recent-clinical-studies-in-off-label-use-monitor-for-opportunistic-infections-hepatitis-b-reactivation

Drugs/Dosage:	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)
1st line use:	Bendamustine	**90mg/m^2**	IV	once daily on Day 1 and Day 2 of each cycle
(Relapsed setting: (no current funding for NHS patients)	Bendamustine	**70mg/m^2**	IV	once daily on Day 1 and Day 2 of each cycle)

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 sodium chloride 0.9% is administered before starting treatment.
Co-trimoxazole 480mg od throughout treatment and until lymphocyte count > 1 x 10^9/l
Aciclovir 400mg bd throughout treatment
Consider fluconazole as antifungal prophylaxis

Frequency: every 28 days for up to 6 cycles

Administration: Bendamustine in 500ml sodium chloride 0.9% and infused over 30 – 60 minutes.
IV antihistamine and steroid cover should be considered with subsequent doses of bendamustine for patients who experience even a mild hypersensitivity reaction on Cycle 1.
It is suggested that bendamustine-related reactions ≥ Grade 3 should not be rechallenged.

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.

Reason for Update: supportive meds reviewed / MHRA alert added	Approved by Chair of Alliance TSSG: Dr A Laurie
Version: 5	Date: 9.8.17
Supersedes: Version 4	Review date: September 2019
Prepared by: S Taylor	Checked by: C Tucker

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 rituximab 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.

Full resuscitation equipment must be available, with immediate access to clinical staff trained in resuscitation for the first hour of the first rituximab infusion.

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:

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); myelosuppression; hypersensitivity reactions to bendamustine (e.g. rash, urticaria); alopecia; tumour lysis syndrome (ensure pre-medicated with allopurinol and good hydration); ovarian failure; infertility

Anti - emetics: highly emetogenic on Day 1 and Day 2

Extravasation: non-vesicants

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

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

Due to previous reports of bendamustine-related cardiac side-effects (e.g. heart failure, arrhythmias, hypotension), use with caution if patient has pre-existing heart disease (e.g. MI, severe cardiac arrhythmias). In such cases the heart disease should be monitored more closely and an ECG recorded. In addition, the fluid and electrolyte balance should be monitored, paying particular attention to potassium.

Dose Modifications If a dose reduction is considered, note that doses below 50mg/m^2/day are considered sub-therapeutic.

Haematological Toxicity: If neutrophil count is < 1.0 x 10^9/L or if platelet count is < 100 x 10^9/L, defer treatment until recovered.

Non-haematological Toxicities: For any Grade 3 non-haematological toxicity, defer treatment until resolved to Grade 1 – 0.

Renal Impairment: No bendamustine dose adjustment required if CrCl > 10ml/min.

Hepatic Impairment:

Bilirubin (µmol/l)	Bendamustine dose
< 21	Give 100% dose
21 – 51	Give 70% dose
> 51	No data available

Patient Information: Macmillan leaflets for Rituximab and Bendamustine

References:
Fischer, K et al; JCO 2012; 30 (26): 3209 – 3216 (1st line)
Fischer, K et al; JCO 2011; 29 (26): 3559 – 3566 (relapsed)
Cheson, BD et al; Clinical Lymphoma, Myeloma & Leuk 2010; 10 (1): 21 – 27