R–BENDAMUSTINE-90 FOR LYMPHOMA

For first-line or relapsed treatment of low grade NHL
First-line treatment of mantle cell lymphoma

Blueteq registration is required before treatment may start

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)

Drug/Dosage:	**Rituximab**	375mg/m^2	IV	Day 1
		(dose 'banded' according to dosing table below)		
	Bendamustine	90mg/m^2	IV	once daily on Day 1 and Day 2

Premedication:	Paracetamol 1000mg	po	60 minutes pre rituximab
	Chlorphenamine 10mg	IV	15 minutes pre rituximab
	Dexamethasone 8mg	IV	15 minutes pre rituximab

Other Drugs: Allopurinol 300mg po daily, ideally starting 24 hours before first dose - review after 4 weeks
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

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.

Rituximab should be given before bendamustine, diluted in 500ml 0.9% sodium chloride & administered according to following instructions:

First infusion#: start at 50mg/hr, according to infusion table below; escalate in 50mg/hr increments every 30 minutes to a maximum of 400mg/hr.
Monitor patient's vital signs (blood pressure, pulse, temp and O_2 saturation) at baseline and then every 30 minutes (before each increase in infusion rate) until end of infusion.

	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**							
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

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

Subsequent Infusions:

Patients who tolerated their first infusion at the standard recommended rate
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.
Monitor patient's vital signs at baseline, then every 30 minutes until end of infusion.

*** Patients who did not tolerate their first infusion at the standard rate ***
Administer and monitor as per first infusion, or at a slower rate if required.

#**If WBC ≥ 25 x 10^9/l,** there is an increased risk of severe cytokine release syndrome with rituximab administration. Options include omitting the rituximab for this cycle, or splitting rituximab dosing over two 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.

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

If reactions occur at any time, stop the infusion. If symptoms improve, restart at half the previous infusion rate, and escalate as tolerated.

Frequency: every 4 weeks for up to 6 cycles

Main Toxicities: severe cytokine release syndrome – usually occurs within 1–2 hours of the first rituximab infusion (see Comments); myelosuppression; alopecia; hypersensitivity reactions to bendamustine (e.g. rash, urticaria); ovarian failure; infertility; tumour lysis syndrome (ensure pre-medicated with allopurinol and good hydration)

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

Extravasation: non-vesicants

Regular Investigations:

FBC	Day 1
U&Es & LFTs	Day 1
LDH	Day 1

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, monitor fluid and electrolyte balance, paying particular attention to potassium.

Dose Modifications

Haematological Toxicity: If neutrophil count is < 1.0 x 10^9/L or platelet count is < 75 x 10^9/L, defer treatment until FBC recovered, then proceed with dose reductions as follows:
Patients with neutrophils < 0.5 x 10^9/l or platelets < 25 x 10^9/l to continue treatment once recovered, but reduce the bendamustine dose to 60mg/m^2 on Day 1 and Day 2; patients with counts above these levels can proceed with full dose.

Non-haematological Toxicities: For any Grade 3 non-haematological toxicity, defer treatment until resolved to Grade 1 – 0, and then give bendamustine 60mg/m^2 for further cycles.

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

Hepatic Impairment:

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

Patient Information: Macmillan leaflets available for Rituximab and Bendamustine

References:
Rummel, M et al; Lancet 2013; 381 (9873): 1203 – 1210 (1st line)
Flinn, I et al; Blood 2014; 123 (19): 2944 – 2952 (1st line)
Cheson, BD et al; Clinical Lymphoma, Myeloma & Leuk 2010; 10 (1): 21 - 27
Robinson, K et al; JCO 2008; 26: 4473 – 4479 (relapsed)