OBINUTUZUMAB + CHLORAMBUCIL

An option for untreated CLL in patients who have co-morbidities that make full-dose fludarabine-based therapy unsuitable for them, and bendamustine-based therapy is also unsuitable
NICE approved June 2015

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

Drugs/Dosage:

Cycle 1:

Obinutuzumab	100 mg in 100ml	IV	Day 1
	900 mg in 250ml	IV	Day 2
	1000mg in 250ml	IV	Day 8 and Day 15

Cycle 2 onwards:

Obinutuzumab	1000 mg in 250ml	IV	Day 1 only of each cycle

Chlorambucil	10mg/m^2/day	PO	once daily for 7 days, on Days 1 – 7 of each cycle

Pre-medication for obinutuzumab:

Paracetamol	1000 mg	po	at least 30 minutes before infusion starts
Chlorphenamine**	10 mg	IV	at least 30 minutes before infusion starts
Dexamethasone*	20 mg	IV	at least 60 minutes before infusion starts

*Once WBC < 25 x 10^9/l **and** if the previous obinutuzumab dose was administered without a serious reaction, the dexamethasone dose may be reduced or omitted for the remaining infusions, according to clinician preference.
** If the patient tolerated the previous obinutuzumab dose without any adverse reactions, the chlorphenamine dose may be omitted for the remaining infusions.

Other Drugs:

Allopurinol 300mg po od, 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.
Consider advising patient to omit any antihypertensive medicines on the morning of treatment, particularly on the first cycle.
It is recommended that patients with severe and long lasting (>1 week) neutropenia receive antimicrobial prophylaxis throughout the treatment period until resolution to Grade 1 or 2, plus antiviral and antifungal prophylaxis should be considered.

Administration:

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

Obinutuzumab Cycle 1, Day 1 dose prepared in 100ml sodium chloride 0.9%.
All other obinutuzumab doses are prepared in 250ml sodium chloride 0.9%.

For Day 1 and Day 2 of Cycle 1, monitor patient's vital signs at baseline and then every 15 minutes (including before each increase in infusion rate).

For all subsequent doses, monitor patient's vital signs at baseline and then every 30 minutes (including before each increase in infusion rate).

Reason for Update: dex pre-med increased to 20mg	Approved by Chair of Haem Tumour Group: Dr A Laurie
Version: 2	Date: 7.6.16
Supersedes: Version 1	Review date: July 2018
Prepared by: S Taylor	Checked by: C Tucker

Obinutuzumab is infused as follows, in the absence of any infusion related reactions:

Cycle & Day of treatment	Rate of infusion
Cycle 1, Day 1 (100mg in 100ml)	Administer 100ml infusion at 25ml/hour over 4 hours. Do not increase the infusion rate.
Cycle 1, Day 2	Administer at 50 **mg**/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr. **For 900mg in 250ml volume only,** this means that the infusion may be administered as follows: Give 7ml at 14ml/hour; then 14ml at 28ml/hour; then 21ml at 42ml/hour; then 28ml at 56ml/hour; then 35ml at 70ml/hour; then 42ml at 84ml/hour; then remainder (approx 105ml) at 100ml/hour. Total time approx 4 hours
Cycle 1, Days 8 & 15 and Cycle 2 – 6, Day 1	Infusions can be started at a rate of 100 **mg**/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. **For 1000mg in 250ml volume only,** this means that the infusion may be administered as follows: Give 12.5ml at 25ml/hour; then 25ml at 50ml/hour; then 37.5ml at 75ml/hour; then remainder (approx 175ml) at 100ml/hour Total time approx 3 hours

Infusion-related reactions:

In the event of a Grade 1-2 (mild or moderate) infusion-related reaction, the infusion rate must be slowed down and symptoms treated. Once the symptoms have resolved, the infusion rate can be escalated according to standard procedure for the dose.
(For the Cycle 1, Day 1 dose, increase up to 25ml/hr only after 60 minutes at a slower rate)

In the event of a Grade 3 (severe) infusion-related reaction, the infusion should be interrupted and, when the patient is stable, re-started at no more than half the previous rate at the time the reaction occurred. The infusion rate can then be increased according to standard procedure for that dose.
(For the Cycle 1, Day 1 dose, re-start at 12.5ml/hour for 60 minutes, then increase up to 25ml/hour)

In the event of a Grade 4 (life-threatening) infusion-related reaction, or a second occurrence of a Grade 3 (severe) infusion-related reaction, the infusion must be stopped and obinutuzumab permanently discontinued.

Frequency: 28 day cycle for 6 cycles

Main Toxicities: infusion-related reactions (in majority of patients during the 1st and 2nd infusions); myelosuppression; diarrhoea; ovarian failure; infertility

Anti- emetics:	mildly emetogenic	
Extravasation:	obinutuzumab is a non-vesicant	
Regular Investigations:	FBC	Day 1 of each cycle, plus Day 8 and Day 15 of Cycle 1
	U&Es and LFTs	Day 1 of each cycle
	LDH	every other cycle
Comments:	Patients should not receive live vaccines during treatment, and until B cell counts have normalised. The shingles vaccine is also contra-indicated in CLL patients at any time, even if not on treatment.	

Dose Modifications

Haematological Toxicity:	Treatment should be deferred if neutrophil count is < 1.0 x 10^9/L and/or if platelet count is < 50 x 10^9/L, unless secondary to bone marrow infiltration or autoimmune causes. When counts have recovered, continue treatment with chlorambucil at 7.5mg/m^2/day.* (There are no dose reductions for obinutuzumab) *If a second occurrence of low counts, a further chlorambucil dose reduction can be made to 5mg/m^2/day.
Renal Impairment:	If CrCl < 50ml/minute, the patient is more at risk of myelosuppression. No obinutuzumab dose adjustment is required if CrCl > 30ml/min. There is no data for CrCl < 30ml/min.
Hepatic Impairment:	Dose reduction of chlorambucil is only recommended with gross hepatic dysfunction, with dose adjustment according to response. Obinutuzumab in hepatic impairment has not been studied. No specific dose recommendations can be made.
Patient Information:	Macmillan leaflet for Chlorambucil; no Macmillan leaflet currently available for obinutuzumab. Patients may be guided to website http://www.gazyva.com/ for patient information
Reference:	Goede, V et al; NEJM 2014; 370: 1101 – 1110 (CLL11) Dose modifications advice for haematological toxicity adapted from the CLL11 protocol