O-Bendamustine with maintenance Obinutuzumab

INDICATION:
Follicular Lymphoma:

- 1st line treatment in advanced symptomatic patients (NICE TA513 for FLIPI score 2 or higher - BLUETEQ required)
- Rituximab refractory (progression on R-chemo, R-maintenance or within 6 months of last maintenance rituximab infusion) (NICE TA472 – BLUETEQ required)

Prior to a course of treatment

- Document the histological diagnosis including the staging CT Scan with Marrow report
- Blood tests - FBC, DAT, U&Es, LDH, ESR, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, β2 microglobulin, hepatitis B core antibody and hepatitis BsAg, hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent, group and save (irradiated blood products required for all future transfusions).
- Urine pregnancy test - before cycle 1 of each new chemotherapy course for women of childbearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy.
- Obtain written consent.
- Fertility – if appropriate make sure the patient understands the potential risk of infertility, all patients should be offered fertility advice.
- Withhold antihypertensive treatment 12 hours before, during and 1 hour after Obinutuzamb infusion.
- Consider dental assessment / Advise dental check is carried out by patient's own dental practice.

Prior to each dose

- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function
- Check FBC, U&Es, creat, LFTs - neuts must be >1.0 and plats > 100 – *see dose modifications*

Make sure that the patient receives adequate hydration. For cycle 1 day 1 administer 500mL normal saline 0.9% over 1 hour before administering Obinutuzumab.

DRUG	DOSE	ROUTE	FREQUENCY
Dexamethasone*	**20mg** (as pre-med 60mins prior to obinutuzumab)**	IV	Cycle 1 – Days 1, 8 & 15 (with obinutuzumab) Cycle 2+ – Day 1 only (with obinutuzumab)
Sodium Chloride 0.9% 500mL		IV infusion over 1hr pre obinutuzumab	Cycle 1 only
Paracetamol	**1000mg** (pre-med 30mins prior to obinutuzumab)	PO	Cycle 1 – Days 1, 8 & 15 (with obinutuzumab) Cycle 2+ – Day 1 only (with obinutuzumab)
Chlorphenamine***	**10mg** (pre-med 30mins prior to obinutuzumab)	IV bolus	Cycle 1 – Days 1, 8 & 15 (with obinutuzumab) Cycle 2+ – Day 1 only (with obinutuzumab)
Obinutuzumab	**1000mg**	IV in 250mL NaCl 0.9%§	Cycle 1 - Days 1, 8 & 15 Cycle 2 onwards – Day 1 only
Bendamustine	**90mg/m^2**	IV infusion in 500mL NaCl 0.9%	Day 1 & 2

Repeat every 28 days for 6 cycles followed by maintenance (see below)

*****Once WBC < 25 x 109/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.
****** Hydrocortisone should not be used for pre-medication as it is not effective in reducing infusion related reactions
******* If the patient tolerated the previous obinutuzumab dose without any adverse reactions, the chlorphenamine dose may be omitted for the remaining infusions.
§ See infusion rate below

MAINTENANCE:

Dexamethasone*	**20mg** (as pre-med 60mins prior to obinutuzumab)**	IV	Day 1 (with obinutuzumab)
Paracetamol	**1000mg** (pre-med 30mins prior to obinutuzumab)	PO	Day 1 (with obinutuzumab)
Chlorphenamine***	**10mg** (pre-med 30mins prior to obinutuzumab)	IV bolus	Day 1 (with obinutuzumab)
Obinutuzumab	**1000mg**	IV in 250mL NaCl 0.9%§	Day 1

Repeat cycle every 8 weeks for 2 years

***Once WBC < 25 x 109/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.
**** Hydrocortisone should not be used for pre-medication as it is not effective in reducing infusion related reactions
***** If the patient tolerated the previous obinutuzumab dose without any adverse reactions, the chlorphenamine dose may be omitted for the remaining infusions.
§ See infusion rate below

§INFUSION RATE

These are the recommended starting infusion rates assuming the patient has not experience infusion related reactions in the prior infusion; otherwise the infusion rate should be no more than half the previous rate.

Cycle 1 Day 1
Administer at 50mg/hr. The rate of infusion can be escalated in 50mg/hr increments every 30 minutes to a maximum of 400mg/hr.

Subsequent infusions
If no infusion related reactions (IRR) or if an IRR Grade 1 occurred during the prior infusion when the final infusion rate was 100mg/hr or faster, infusions can be started at a rate of 100mg/hr and increased by 100mg/hr increments every 30 minutes to a maximum of 400mg/hr.

If the patient experienced an IRR of Grade 2 or higher during the previous infusion administer at 50 mg/hr. The rate of infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.

Prophylaxis for acute emesis	5HT Antagonist (not required with obinutuzumab only)
Prophylaxis for delayed emesis	Metoclopramide 3-4days (not required with obinutuzumab only)
Other medications	Allopurinol 300mg daily for cycle 1 days starting on the day following bendamustine (day 3) - first course / cycle 1 only *[There have been rare skin reactions and other toxicities associated with the administration of allopurinol and bendamustine when given together. For those patients at intermediate risk (low grade NHL with disease bulk) of tumour lysis should receive allopurinol for 3 days prior to the administration of Bendamustine and for 5-7 days following Bendamustine]*
	Aciclovir 400mg twice a day for duration of treatment and for 3 months after completion
	Co-trimoxazole 480mg daily throughout treatment and until lymphocyte count is $>1x10^9$/L
	Consider Fluconazole 50mg od as antifungal prophylaxis

Dose modifications

Haematological toxicity (unless due to disease)	
• Neuts > 1.0 and PLT > 75	Proceed with Bendamustine 100% dose
• Neuts < 1.0 and/or PLT < 75 when cycle due	Delay for up to 2 weeks and proceed if parameters met – if not met reconsider suitability for bendamustine
• If treatment delayed due to neutropenia	Proceed at 100% dose with GCSF support
• If treatment delayed due to neutropenia despite G-CSF	Proceed with 75% dose Bendamustine for first delay, 50% for second delay
• If treatment delayed due to neutropenia despite G-CSF and dose reduction	Proceed with 50% bendamustine at 100% dose with GCSF support
• If treatment delayed due to PLT < 75 when treatment due	Proceed with 75% dose bendamustine for first delay, 50% for second delay
• Treatment delay due to thrombocytopenia despite dose reduction to 50%	Reconsider suitability for bendamustine

There are no dose reductions for obinutuzumab

Renal/Hepatic impairement

Bendamustine:

Renal impairement		**Hepatic impairement**	
CrCl< 40mL/min	use of bendamustine has not been studied in this group (clinical decision)	Moderate dysfunction – AST > 2.5 X ULN and bili >50 X ULN	Bendamustine has not been studied in this group of patients – clinical decision. Use with caution.
CrCl 40 – 60 mL/min –	imited information (clinical decision – use with caution)	Mild dysfunction – AST 1 – 2.5 X ULN, bili 20-50	Reduce Bendamustine by 30%

Obinutuzumab:

Renal impairement	**Hepatic impairement**
No dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance [CrCl] 30-89 mL/min) The safety and efficacy of Obinutuzumab has not been established in patients with severe renal impairment (CrCl < 30 mL/min) Patients with renal impairment (CrCl < 50 mL/min) are more at risk of IRRs, neutropenia and thrombocytopenia.	The safety and efficacy of Obinutuzumab in patients with impaired hepatic function has not been established. No specific dose recommendations can be made.

Toxicities

Obinutuzumab Infusion-related Toxicity:

- Rashes, allergic and anaphylactic reactions or cytokine release syndrome(dyspnoea, bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria and angiooedema) should be treated promptly. It is recommended, that the infusion should be temporarily interrupted or slowed until the adverse ebvent has subsided and then re-started at 50% of the previous dose.

Bedamustine Toxicities

Tumour lysis syndrome with 1st cycle	Nausea & vomiting
Neutropenic sepsis & thrombocytopenia	Constipation
Amenorrhoea & infertility (offer semen cryopreservation)	Fatigue
Diarrhoea	Rash
Mucositis	Transient elevation of serum creatinine
Infusion reactions including fever, rigours, hypotension & pruritis	

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