O-CVP with maintenance Obinutuzumab

INDICATION: Follicular Lymphoma: 1st line treatment in advanced symptomatic patients (NICE TA513 for FLIPI score 2 or higher - 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.
- 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.

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.

Prednisolone	**100mg** (Day 1 as pre-med 60mins prior to obinutuzumab) *	PO	Cycle 1 – Days 1-5, Day 8 & Day 15 Cycle 2 onwards – Days 1-5
Paracetamol	**1000mg** (pre-med 30mins prior to obinutuzumab)	PO	Days 1, 8 &15 (with obinutuzumab)
Chlorphenamine	**10mg** (pre-med 30mins prior to obinutuzumab)	IV bolus	Days 1, 8 &15 (with obinutuzumab)
Obinutuzumab	**1000mg**	IV in 250mL NaCl 0.9%§	Cycle 1 - Days 1, 8 & 15 Cycle 2 onwards – Day 1 only
Cyclophosphamide	**750mg/m^2**	IV bolus	Day 1
Vincristine	**1.4mg/m^2 (max dose 2mg)** **	IV in 50ml NaCl 0.9% over 5 minutes	Day 1
Repeat every 21 days for up to 6-8 cycles			
MAINTENANCE:			
Prednisolone	**100mg** (Day 1 as pre-med 60mins prior to obinutuzumab) *	PO	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			

***** Hydrocortisone should not be used for pre-medication as it is not effective in reducing infusion related reactions
****** Patients >70 years use 1 mg vincristine.
§ 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 7 days starting 24-48 hours prior to chemotherapy (first course / cycle 1 only) Aciclovir 200mg three times a day for duration of treatment and for 3 months after completion Ranitidine (or PPI if indicated) daily for the duration of steroid treatment

Dose modifications

Haematological Toxicity

Neutrophils x 10^9/L	Platelets x 10^9/L	Cyclophosphamide	Vincristine	Prednisolone
>1.5 and	≥100	100%	100%	100%
1.0-1.49 and	≥100	75%	100%	100%
0.5-1.0 and/or	50-100	50%	100%	100%
<0.5 and/or	<50	0%	100%	100%

Renal/Hepatic impairement

Vincristine:

Renal impairement	Hepatic impairement
No dose reduction necessary	Bilirubin 26-51 micromol/L or ALT/AST 60-180 u/L 50% dose Bilirubin >51 micromol/L & normal ALT/AST 50% dose Bilirubin >51 micromol/L & ALT/ AST >180 u/L omit
Vincristine In the presence of motor weakness or severe sensory symptoms, discuss reducing or withholding vincristine with a consultant.	

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.

Cyclophosphamide:

Renal impairement		Hepatic impairement
GFR (mL/min)	Dose	Clinical decision. Exposure to active metabolites may not be increased, suggesting dose reduction may not be necessary.
>20	100%	
10-20	75%	
<10	50%	
Clinical decision – consider whether patient is being treated with high dose treatment.		

Toxicities

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.

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