O-CVP with Obinutuzumab maintenance

Indication

Adult patient with untreated advanced follicular lymphoma with Follicular Lymphoma International Prognostic Index (FLIPI) score of 2 or above.

(NICE TA513)

ICD-10 codes

Codes with prefix C82

Regimen details

Cycle 1

Day	Drug	Dose	Route
1	Obinutuzumab	1000mg	IV infusion
1	Cyclophosphamide	750mg/m^2	IV bolus
1	Vincristine	1.4mg/m^2 (maximum dose 2mg)	IV infusion
1-5	Prednisolone	60mg/m^2 (maximum dose 100mg)	PO
8	Obinutuzumab	1000mg	IV infusion
15	Obinutuzumab	1000mg	IV infusion

Cycles 2 onwards

Day	Drug	Dose	Route
1	Obinutuzumab	1000mg	IV infusion
1	Cyclophosphamide	750mg/m^2	IV bolus
1	Vincristine	1.4mg/m^2 (maximum dose 2mg)	IV infusion
1-5	Prednisolone	60mg/m^2 (maximum dose 100mg)	PO

Consider vincristine 1mg dose for patients > 70 years of age or > 60 years of age with pre-existing constipation or neurological problems.
Cyclophosphamide may be given orally as an alternative at a dose of 400mg/m^2 OD for 5 days.

Maintenance

Day	Drug	Dose	Route
1	Obinutuzumab	1000mg	IV infusion

Cycle frequency

Induction: Cycle repeats every 21 days for up to 6-8 cycles.

Maintenance: Obinutuzumab is given every 2 months for 2 years or until disease progression (whichever occurs first).

Administration

Obinutuzumab is administered in 250mL sodium chloride 0.9%.

The recommended starting infusion rates are below (presuming the patient has not experienced infusion related reactions in the prior infusion):

Cycle 1 day 1: Infuse at an initial rate of 50mg/hr; after the first hour this can be escalated in 50mg/hr increments every 30 minutes up to a maximum rate of 400mg/hr.

Subsequent infusions: If no or only Grade 1 infusion related reaction (IRR) occurred during the prior infusion when the final rate was ≥ 100mg/hr, infusions can be started at a rate of 100mg/hr and increased by 100mg/hr increments every 30 minutes up to a maximum rate of 400mg/hr.
If the patient experienced an IRR of ≥ Grade 2 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.

Hypotension may occur during obinutuzumab infusion. Therefore, antihypertensive treatments should be withheld for 12 hours prior to and throughout and 1 hour after each infusion. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medicine.

See below for guidance on infusion rates in the event of IRRs.

Cyclophosphamide is administered as an IV bolus in 250-500mL sodium chloride 0.9% over 30 minutes.

Vincristine is administered in 50mL sodium chloride 0.9% over 10 minutes, as per national guidance. Chemotherapy administrator to remain with patient throughout infusion.

Prednisolone is available as 5mg and 25mg tablets. The doses should be taken each morning for 5 days with or after food.

Pre-medication

Ensure that patients receive adequate hydration. In addition on cycle 1 day 1 administer 500mL sodium chloride 0.9% IV over 1 hour prior to obinutuzumab administration.

Cycle 1 day 1:
Obinutuzumab premedication:

- Paracetamol 500mg-1g PO at least 30 minutes prior to obinutuzumab infusion.
- Chloramphenamine 10mg IV bolus at least 30 minutes prior to obinutuzumab infusion.
- Dexamethasone* 20mg IV bolus at least 60 minutes prior to obinutuzumab infusion (consider omitting if patient has had 100mg prednisolone).

For subsequent cycles:
If no previous obinutuzumab IRR:

- Paracetamol 500mg-1g PO at least 30 minutes prior to obinutuzumab infusion.

If Grade 1-2 obinutuzumab IRR:

- Paracetamol 500mg-1g PO at least 30 minutes prior to obinutuzumab infusion.
- Chloramphenamine 10mg IV bolus at least 30 minutes prior to obinutuzumab infusion.

If Grade 3 obinutuzumab IRR OR lymphocyte count > 25 x 10^9/L prior to next treatment:

- Paracetamol 500mg-1g PO at least 30 minutes prior to obinutuzumab infusion.
- Chloramphenamine 10mg IV bolus at least 30 minutes prior to obinutuzumab infusion.
- Dexamethasone* 20mg IV bolus at least 60 minutes prior to obinutuzumab infusion.

* Hydrocortisone **should not** be used as an alternative to dexamethasone.

Emetogenicity

Induction: moderate-high emetic potential
Maintenance: low emetic potential

Additional supportive medication

Allopurinol 300mg (100mg if creatinine clearance <20mL/min) OD for the first cycle starting 12-24 hours prior to Cycle 1 Day 1.
H_2 antagonist or PPI if required.
Antiemetics as per local policy.
Antiviral and antifungal prophylaxis as per local policy

Extravasation

Vincristine is a vesicant (Group 5)
Cyclophosphamide and obinutuzumab are neutral (Group 1)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U&Es (including creatinine)	14 days
LFTs	14 days
Bone profile	14 days
HbA1c	14 days

Other pre-treatment investigations;
Hepatitis B serology (HBsAg & anti-HBc) & Hepatitis C antibody
HIV serology
HbA1c
Immunoglobulin levels
Direct antiglobulin test

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours
U&Es (including creatinine)	96 hours
LFTs	96 hours
Glucose	As clinically indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥1.5 x 10^9/L
Platelets	≥100 x 10^9/L
Creatinine Clearance (CrCl)	>30 mL/min
Bilirubin	≤ULN
AST/ALT	<2 x ULN

Dose modifications

- **Haematological toxicity**

If neutrophils <1.5 x 10^9/L and/or platelets <100 x 10^9/L delay 1 week or until recovery. Reduce cyclophosphamide dose to 80%.

- **Renal impairment**

CrCl (mL/min)	**Cyclophosphamide dose**
> 20	100%
10-20	75%
<10	50%

No dose adjustments for obinutuzumab required if CrCl >30mL/min. There is no experience of this regimen for patients with CrCl <30mL/min therefore not recommended. Patients with CrCl < 50 mL/min are more at risk of IRRs, neutropenia and thrombocytopenia.

- **Hepatic impairment**

Cyclophosphamide is not recommended if bilirubin > 1.5 x ULN or AST/ALT > 3 x ULN (consultant decision).

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Vincristine dose**
< ULN	and	≤ 2	100%
1 – 2.5	Or	> 3	50%
> 2.5	and	< ULN	50%
> 2.5	and	> 3	Omit

The safety and efficacy of obinutuzumab has not been established in patients with severe hepatic impairment.

- **Other toxicities**

Neurotoxicity

Monitor for signs of peripheral sensory loss or constipation. Consider reducing vincristine dose. If grade 3-4 discontinue vincristine. Discuss with consultant.

Infusion-related toxicity:

Obinutuzumab should be administered as above.

Infusion-related side effects such as rashes, allergic and anaphylactic reactions or cytokine release syndrome (dyspnoea, bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria and angioedema) should be treated promptly.

It is recommended that the infusion should be temporarily interrupted or slowed until the adverse event has subsided and then re-started at 50% of the previous rate.

Ensure a doctor and experienced nurse are available during administration of all doses in cycle 1 and subsequent doses if the patient previously reacted. Monitor the patient closely during the infusion.

Symptomatic rescue medication must be readily available for administration in case of occurrence of IRRs.

Emergency resuscitation facilities must be available during infusion.

Management of infusion related reactions (IRR) may require temporary interruption, reduction in the rate of infusion or treatment discontinuations as outlined below:

Toxicity Grade	Recommendations
Grade 4 (life threatening)	Infusion must be stopped and therapy must be permanently discontinued.
Grade 3 (severe)	Infusion must be temporarily stopped and symptoms treated. Upon resolution of symptoms, the infusion can be started at no more than half the previous rate (i.e. the rate being used at the time that the IRR occurred). If the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose. If the patient experiences a second occurrence of Grade 3 IRR, the infusion must be stopped and therapy permanently discontinued.
Grade 1 and 2 (mild)	The infusion rate must be reduced and symptoms treated. Upon resolution of symptoms, the infusion can be started at no more than half the previous rate (i.e. the rate being used at the time that the IRR occurred). If the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Secondary malignancy
Myelosuppression
Infertility/Early menopause
Tumour lysis syndrome
Neurotoxicity
Hepatitis B reactivation
Infusion related reactions
Arrhythmia & cardiac failure
Progressive multifocal leukoencephalopathy

- **Frequently occurring side effects**

Constipation
Fatigue
Nausea and vomiting
Mucositis/Stomatitis
Myelosuppression
Alopecia
Hypotension (during infusion)
Arthralgia
Pruritus
Headache

- **Other side effects**

Fluid retention
Haemorrhagic cystitis

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly. Patients who are initiated on anti-coagulation should remain on low molecular weight heparin until completion of the course of chemotherapy.

Co-trimoxazole/trimethoprim: enhances antifolate effect. Avoid if possible, if essential, monitor FBC regularly.

Vincristine:
Itraconazole, voriconazole, posaconazole: increase severity of neuromuscular side effects. Avoid for 72 hours either side of vincristine dose if concurrent use cannot be avoided.

Cyclophosphamide:
Amiodarone: increased risk of pulmonary fibrosis – avoid if possible
Clozapine: increased risk of agranulocytosis – avoid concomitant use
Digoxin tablets: reduced absorption – give as liquid form
Indapamide: prolonged leucopenia is possible - avoid
Itraconazole: may increase adverse effects of cyclophosphamide
Phenytoin: reduced absorption - may need to increase dose of phenytoin
Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

Additional comments

Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose. Discuss the need for contraception with both male and female patients if appropriate.

Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients receiving CD20-directed cytolytic antibodies, including obinutuzumab. Screen all patients for HBV infection before treatment initiation. Monitor HBV-positive patients during and after treatment with Obinutuzumab, and give prophylaxis as per local guidelines. Discontinue obinutuzumab and concomitant medications in the event of HBV reactivation.

Progressive Multifocal Leukoencephalopathy (PML), including fatal PML can occur in patients receiving obinutuzumab.

Hypotension may occur during obinutuzumab infusion. Therefore anti-hypertensive medications should be withheld from 12 hours pre to 1 hour post each infusion. Patients at risk of acute risk of hypertensive crisis should be evaluated for the risks and benefits of withholding their anti-hypertensives.

References

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