Obinutuzumab and CHOP Therapy – 21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Obinutuzumab in combination with CHOP chemotherapy is indicated for the treatment of patients with previously untreated advanced follicular lymphoma.	C82	00549a	Obinutuzumab – ODMS 01/05/19 Cyclophosphamide and vinCRIStine – Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

- Treatment is administered every 21 days as detail below or until disease progression or unacceptable toxicity develops
    - Cycles 1-6 consist of obinutuzumab in combination with CHOP
    - Cycles 7-8 consist of obinutuzumab **alone**
- Obinutuzumab is administered at a dose of 1000mg on Day 1, 8 and Day 15 of the first 21 day treatment cycle. This is given in combination with CHOP on day 1.
- For cycles 2-8 obinutuzumab is administered at a dose of 1,000mg on day one of each 21 day treatment cycle
- Patients who respond to induction treatment should continue to receive obinutuzumab 1,000 mg as single agent maintenance therapy once every 2 months for two years or until disease progression (whichever occurs first) (Reference NCCP Protocol 00425 Obinutuzumab Maintenance Therapy-56 day)

Facilities to treat anaphylaxis MUST be present when obinutuzumab is administered.

Treatment cycles 1-6

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Obinutuzumab[1,2]	1000mg	IV infusion	250ml 0.9% NaCl 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.	1
1	Cyclophosphamide[3]	750mg/m^2	IV infusion[2]	250 mL 0.9% NaCl over 30 minutes	1-6
1	DOXOrubicin[4]	50mg/m^2	IV Bolus over 15 mins	Into the side arm of a fast running 0.9% NaCl infusion	1-6
1	VinCRIStine[5]	1.4mg/m^2 (Max 2mg)	IV infusion	50ml minibag 0.9% NaCl over 15minutes	1-6
1,2,3,4,5	Prednisolone	100mg[6]	PO		1-6
8 and 15	Obinutuzumab[1,2]	1000mg	IV infusion	250ml 0.9% NaCl at a maximum rate of 400mg/hr[7,8]	1
1	Obinutuzumab[1,2]	1000mg	IV infusion	250ml 0.9% NaCl at a maximum rate of 400mg/hr[7,8]	2-6

[1] If a planned dose of obinutuzumab is missed, it should be administered as soon as possible; do not wait until the next planned dose. The planned treatment interval for obinutuzumab should be maintained between doses

[2] Obinutuzumab infusions should NOT be administered as an intravenous push or bolus.

[3]Cyclophosphamide may also be administered as an IV bolus over 5-10mins

[4]Lifetime cumulative dose of DOXOrubicin is 450mg/m^2
In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors below[i] and to the age of the patient

[5]Vincristine is a neurotoxic chemotherapeutic agent.
Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer. Here

[6]Alternative steroid regimens may be used at consultant discretion

[7] If no infusion related reaction or if an IRR Grade 1 occurred during the prior infusion when the final infusion rate was 100 mg/hr or faster, 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.

[8] 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.

Treatment cycles 7 and 8

Day	Drug	Dose	Route of Administration	Diluent & Rate	Cycle
1	Obinutuzumab[1,2]	1000mg	IV infusion	250ml 0.9% NaCL at a maximum rate of 400mg/hr[3,4]	7-8

[1] If a planned dose of obinutuzumab is missed, it should be administered as soon as possible; do not wait until the next planned dose. The planned treatment interval for obinutuzumab should be maintained between doses

[2] Obinutuzumab infusions should NOT be administered as an intravenous push or bolus.

[3]If no infusion related reaction or if an IRR Grade 1 occurred during the prior infusion when the final infusion rate was 100 mg/hr or faster, 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.

[4] 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.

ELIGIBILITY:

- Indications as above

- Previously untreated, CD20-positive follicular lymphoma (grade 1 to 3a) with advanced disease (stage III or IV, or stage II with bulk disease [tumor of ≥7 cm in the greatest dimension])
- ECOG status 0-2
- Adequate haematological, renal and liver status

EXCLUSIONS:

- Hypersensitivity to obintuzumab, cyclophosphamide, DOXOrubicin, vinCRIStine, prednisolone or to any of the excipients
- LVEF <50% (MUGA or echocardiogram)
- A cumulative life-long dose of 450mg/m^2 of DOXOrubicin should only be exceeded with extreme caution as there is as risk of irreversible congestive heart failure

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Oncologist or Haematologist working in the area of haematological malignancies

TESTS:

Baseline tests:

- FBC, renal and liver profile
- LDH, Uric acid
- ECG
- MUGA or ECHO should be considered prior to the administration of DOXOrubicin
- Virology screen -Hepatitis B (HBsAg, HBcoreAb)
  *See Adverse Effects/Regimen Specific Complications

Regular tests:

- FBC, renal and liver profile and LDH prior to each cycle
- Evaluate for peripheral neuropathy prior to each cycle
- ECG as clinically indicated
- MUGA or ECHO as clinically indicated (doxorubicin)

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- No dose reductions of obinutuzumab are recommended.
- Consider vinCRIStine dose reduction in elderly patients

Haematological:

Table 1: Recommended dose modification for CHOP haematological toxicity

ANC (x 10^9/L)		Platelets(x 10^9/L)	Dose
<1	and/or	<75	Dose modification not generally indicated. Consider treatment delay and/or add G-CSF.

Renal and Hepatic Impairment:

Table 2: Recommended dose modifications in patients with renal or hepatic impairment

Drug	Renal impairment		Hepatic impairment			
Obinutuzumab	**CrCl (ml/min)**	**Dose**	Safety and efficacy not established in patients with impaired hepatic function. No specific dose recommendations can be made.			
	30-89	100%				
	<30	Safety and efficacy not established				
Cyclophosphamide	**CrCl (ml/min)**	**Dose**	Dose reduction may need to be considered in severe hepatic impairment. Clinical Decision			
	>20	100%				
	10-20	75%				
	<10	50%				
DOXOrubicin	Dose reduce in severe renal impairment		**Total Bilirubin (micromol/L)**			**Dose**
			20-50			50%
			51-85			25%
			>85			Omit
			If AST 2-3 x normal, give 75% dose.			
			If AST >3x ULN, give 50% dose			
VinCRIStine	No dose reduction required		**Bilirubin (micromol/L)**		**AST/ALT**	**Dose**
			26-51	or	60-180	50%
			>51	and	Normal	50%
			>51	and	>180	Omit

Management of adverse events:

Table 3: Dose modification schedule of obinutuzumab based on adverse events

Adverse reactions	Recommended dose modification
Infusion Related Reactions (IRR)	
Grade 1-2 Symptom resolution	Reduce infusion rate. Treat symptoms Infusion can be continued upon resolution of symptoms and 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.
Grade 3 • First occurrence ○ Symptom resolution	Temporarily stop the infusion. Treat the symptoms Upon resolution of symptoms Restart infusion at no more than half the previous rate and, 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.
• Second occurrence	Stop infusion and discontinue treatment.

Grade 4	Stop infusion and discontinue treatment.
PML	Discontinue treatment
Hypersensitivity reaction	Discontinue treatment

Table 4: Dose modification of vinCRIStine based on neurotoxicity

Symptom*	Dose of VinCRIStine
Grade 1	100%
Grade 2	Hold until recovery then reduce dose by 50%
Grade 3 and 4	Omit

*Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Obinutuzumab: Minimal **(Refer to local policy).**
DOXOrubicin cyclophosphamide cycles: Moderate **(Refer to local policy).**

PREMEDICATIONS:

Table 5 describes the recommended premedication to be administered before obinutuzumab infusion to reduce the risk of infusion related reactions (IRRs)**.**

Table 5: Premedication to be administered before obinutuzumab infusion to reduce the risk of IRRs

Day of treatment cycle	Patients requiring premedication	Premedication	Administration
Cycle 1: Day 1	All patients	Intravenous corticosteroid[1,4] (recommended)	Completed at least 1 hour prior to obinutuzumab infusion
		Oral anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion
		Anti-histamine [3]	
All subsequent infusions	Patients with no IRR during the previous infusion	Oral anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion
	Patients with an IRR (Grade 1 or 2) with the previous infusion	Oral anti-pyretic[2] Anti-histamine[3]	
	Patients with a Grade 3 IRR with the previous infusion OR Patients with lymphocyte counts >25 x 10^9/L prior to next treatment	Intravenous corticosteroid[1,4]	Completed at least 1 hour prior to obinutuzumab infusion
		Oral anti-pyretic[3] Anti-histamine	At least 30 minutes before obinutuzumab infusion

[1] *100 mg prednisone/prednisolone or 20 mg dexamethasone or 80 mg methylprednisolone*
Hydrocortisone should <u>not</u> be used as it has not been effective in reducing rates of IRR.
[2] e.g. *1,000 mg paracetamol*
[3] e.g. *10mg chlorpheniramine*
[4] If a corticosteroid-containing chemotherapy regimen is administered on the same day as obinutuzumab, the corticosteroid can be administered as an oral medication if given at least 60 minutes prior to obinutuzumab, in which case additional IV corticosteroid as premedication is not required.

OTHER SUPPORTIVE CARE:

G-CSF prophylaxis may be required **(Refer to local policy)**
Tumour lysis syndrome prophylaxis **(Refer to local policy)**
PJP prophylaxis **(Refer to local policy)**
Proton pump inhibitor **(Refer to local policy)**
Anti-viral prophylaxis **(Refer to local policy)**
Anti-fungal prophylaxis **(Refer to local policy)**
Mouth care **(Refer to local policy)**
Patients should have an increased fluid intake of 2-3 litres on day 1 and 2 to prevent haemorrhagic cystitis associated with cyclophosphamide.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Obinutuzumab is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Obinutuzumab

- **Infusion Related Reactions**: Most reactions are mild or moderate and are further reduced by slowing or temporarily stopping the infusion. Risks for IRRs include high tumour burden, renal impairment and Cumulative Illness Rating Scale (CIRS) >6. If the patient experiences an IRR, the infusion should be managed according to the grade of the reaction (see Table 3).
- **Hypotension**, as a symptom of IRRs, may occur during obinutuzumab intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration
- **Tumour lysis syndrome**: There is an increased risk with high tumour burden or a high circulating lymphocyte count >25x10^9/L
- **Neutropenia:** Severe and life threatening neutropenia including febrile neutropenia has been reported during treatment with obinutuzumab. Consider G-CSF, if severe and associated with infection; consider anti-microbial prophylaxis if severe and prolonged (>1 week), including anti-viral and anti-fungal prophylaxis. Cases of late onset neutropenia (occurring 28 days after the end of treatment) or prolonged neutropenia (lasting more than 28 days after treatment has been completed/stopped) have also been reported. Patients with renal impairment (CrCl < 50 mL/min) are more at risk of neutropenia.
- **Thrombocytopenia**: This can be severe and life-threatening, including acute onset within 24 hours post infusion; monitor closely and treat bleeding according to local policy. Renal impairment increases risk of thrombocytopenia. Dose delays may be required. Use of all concomitant therapies that could possibly worsen thrombocytopenia-related events, such as platelet inhibitors and anticoagulants, should also be taken into consideration, especially during the first cycle. Patients with renal impairment (CrCl < 50 mL/min) are more at risk of thrombocytopaenia
- **Worsening of pre-existing cardiac conditions**: Atrial fibrillation, angina, acute coronary syndrome, myocardial infarction, hypertension and heart failure can occur in patients with underlying cardiac disease. Monitor closely and hydrate cautiously to prevent fluid overload.

- **Infections**: Do not administer if active infection; fatal infections may occur. Caution should be exercised when considering the use of obinutuzumab in patients with a history of recurring or chronic infections. Risk is increased if CIRS > 6 or renal impairment present.
- **Progressive multifocal leucoencephalopathy (PML)**: New or worsening neurological, cognitive or behavioural symptoms or signs due to PML have occurred with obinutuzumab.
- **Hepatitis B Reactivation**: All patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with lamivudine 100 mg/day orally, for the entire duration of chemotherapy and for six months afterwards. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to stopping chemotherapy.

DOXOrubicin

- **Cardiotoxicity**: DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction
- **Extravasation:** DOXOrubicin causes pain and tissue necrosis if extravasated (Refer to local policy).

VinCRIStine

- **Neuropathy:** VinCRIStine may cause peripheral neuropathy which is dose related and cumulative, requiring monitoring before each dose is administered. The presence of pre-existing neuropathies or previous treatment with other neurotoxic drugs may increase risk of peripheral neuropathy. Patients with mild peripheral neuropathy can usually continue to receive full doses of vinCRIStine, but when symptoms increase in severity and interfere with neurologic function, dose reduction or discontinuation of the drug may be necessary. The natural history following discontinuation of treatment is gradual improvement, which may take up to several months. A routine prophylactic regimen against constipation is recommended for all patients receiving vinCRIStine sulphate. Paralytic ileus may occur. The ileus will reverse itself upon temporary discontinuance of vinCRIStine and with symptomatic care.
- **Extravasation:** VinCRIStine causes pain if extravasated. **(Refer to local policy**).

DRUG INTERACTIONS:

- No interaction studies have been performed with obinutuzumab.
- Vaccinations with live organism vaccines are not recommended.
- DOXOrubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines, or other potentially cardiotoxic drugs (e.g. 5-Fluorouracil, cyclophosphamide or paclitaxel) or with products affecting cardiac function (e.g. calcium antagonists).
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Obinutuzumab	L01XC15
DOXOrubicin	L01DB01
Cyclophosphamide	L01AA01
VinCRIStine	L01CA02

REFERENCES:

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Version	Date	Amendment	Approved By
1	26/04/2019		Dr Brian Bird

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[ii]Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.

Risk factors for developing anthracycline-induced cardiotoxicity include:
- high cumulative dose, previous therapy with other anthracyclines or anthracenediones
- prior or concomitant radiotherapy to the mediastinal/pericardial area
- pre-existing heart disease
- concomitant use of other potentially cardiotoxic drugs

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient.