Obinutuzumab and Bendamustine (with Obinutuzumab maintenance)

Indication

First line treatment of adult patients with advanced follicular lymphoma with Follicular Lymphoma International Prognostic Index (FLIPI) score of 2 or more.

(NICE TA513)

Treatment of adult patients with follicular lymphoma that did not respond or progressed during or up to 6 months after treatment with rituximab or a rituximab containing regimen.

(NICE TA472)

ICD-10 codes

Codes with a prefix C82.4, C82.9

Regimen details

Cycle 1

Day	Drug	Dose	Route
1	Bendamustine	90mg/m^2	IV infusion
1	Obinutuzumab	1000mg	IV infusion
2	Bendamustine	90mg/m^2	IV infusion
8 and 15	Obinutuzumab	1000mg	IV infusion

Cycles 2-6

Day	Drug	Dose	Route
1	Bendamustine	90mg/m^2	IV infusion
1	Obinutuzumab	1000mg	IV infusion
2	Bendamustine	90mg/m^2	IV infusion

Maintenance

Day	Drug	Dose	Route
1	Obinutuzumab	1000mg	IV infusion

Cycle frequency

Induction: 28 days with bendamustine
Maintenance: Obinutuzumab is given every 2 months for 2 years or until disease progression (whichever occurs first).

Number of cycles

Maximum 6 cycles.

Maintenance:
Maintenance Obinutuzumab is included in NICE guidance and is given following Obinutuzumab and Bendamustine according to local practice as per consultant decision. It is given every 2 months for 2 years or until disease progression (whichever occurs first).

Administration

Bendamustine is administered in 500mL sodium chloride 0.9% over 30-60 minutes.

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 infusion related reactions.

Pre-medication

Ensure the patient receives adequate hydration. In addition on day 1 administer 500mL sodium chloride 0.9% over 1 hour prior to administering obinutuzumab.
Anti-emetics as per local policy.

For cycle 1 day 1:
Obinutuzumab premedication:

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

For subsequent infusions on days 8 and 15 and for cycles 2-6 premedication depends on grade of infusion related reaction (if any) and/or lymphocyte count:

If no previous obinutuzumab reaction:

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

If Grade 1-2 obinutuzumab infusion related reaction:

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

If Grade 3 obinutuzumab infusion related reaction or lymphocytes > 25 x 10^9/L:

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

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

Emetogenicity

This regimen has moderate emetic potential during induction treatment and low emetic potential during maintenance.

Additional supportive medication

Allopurinol 300mg (100mg if creatinine clearance <20mL/min) OD for the first cycle. To start 12-24 hours before the first cycle and to continue for 7 days. Not usually required for subsequent cycles. (**Omit allopurinol on days of bendamustine administration** – see interactions section).
Antiviral and PCP prophylaxis as per local policy.
Withhold antihypertensive treatment 12 hours before, during and 1 hour after infusion.
Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medicine.

Extravasation

Obinutuzumab is neutral (Group 1)
Bendamustine is an irritant (Group 3)

Investigations – pre first cycle

Investigation	**Validity period**
FBC	14 days
U+Es (including creatinine)	14 days
LFTs	14 days
Glucose	14 days

Other pre-treatment investigations;
Hepatitis B serology (HBsAg & anti-HBc) & Hepatitis C antibody
HIV serology

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+Es (including creatinine)	96 hours
LFTs	96 hours
Potassium	96 hours
Glucose	As clinically indicated

*Serum potassium must be monitored in all patients with cardiac disorders. If serum potassium <3.5mml/L start potassium supplementation and perform an ECG.

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	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
CrCl	≥ 30mL/min
Bilirubin	≤ ULN

Dose modifications

- **Haematological toxicity**

If neutrophils <1.0x10^9/L and/or platelets < 100x10^9/L delay treatment until recovery. Discuss with consultant if due to bone marrow infiltration. No dose modification of obinutuzumab is recommended. Consider bendamustine dose reduction – discuss with consultant.

- **Renal impairment**

Obinutuzumab:
No dose adjustments required if CrCl >30mL/min. There is no experience of this regimen for patients with CrCl <30mL/min therefore not recommended.

There is no information regarding use of bendamustine if CrCl ≤ 10mL/min. Discuss with consultant.

- **Hepatic impairment**

Bilirubin (xULN)	Bendamustine Dose	Obinutuzumab Dose
≤ ULN	100%	100%
> ULN - 3 x ULN	70%	100%
> 3 x ULN	No information – Discuss with consultant	

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

- **Other toxicities**

For any grade 3-4 toxicity (except alopecia) delay treatment until toxicity ≤ grade 1 and consider reducing subsequent bendamustine doses to 50% - 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**

Myelosuppression
Stevens-Johnson syndrome
Hypersensitivity and allergic reactions
Infertility
Infusion related reactions
Tumour lysis syndrome
Cardiotoxicity
Progressive Multifocal Leukoencephalopathy (PML)

Hepatitis B Virus (HBV) reactivation

- **Frequently occurring side effects**

Myelosuppression
Nausea or vomiting
Anorexia, weight loss
Constipation, diarrhoea
Stomatitis/mucositis
Hypokalaemia
Renal impairment
Hypotension (during infusion)

- **Other side effects**

Rash, Urticaria
Transient elevation in liver enzymes
Arthralgia
Fatigue
Alopecia
Insomnia

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

Coumarin-derived anticoagulants/Warfarin: 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.

Bendamustine
Allopurinol: reports of Stevens-Johnson syndrome and toxic epidermal necrolysis – avoid concurrent administration.

CYP 1A2 inhibitors: metabolism of bendamustine by cytochrome P450 (CYP) 1A2 isoenzyme is a significant route of hepatic clearance so interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, aciclovir and cimetidine is possible. May increase toxicity – avoid concomitant use.

Additional comments

Patients must receive irradiated blood products for all future transfusions.

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. Discontinue Obinutuzumab and concomitant medications in the event of HBV reactivation

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

References

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