Obinutuzumab and Chlorambucil

Indication

Previously untreated chronic lymphocytic leukaemia (CLL) in patients who are unsuitable for full-dose fludarabine or bendamustine-based therapies.

NICE TA343

ICD-10 codes

Code with a prefix C 91

Regimen details

Cycle 1

Day	Drug	Dose	Route
1	Obinutuzumab	100mg	IV infusion
	Chlorambucil	0.5mg/kg*	PO (single dose)
2	Obinutuzumab	900mg	IV infusion
8	Obinutuzumab	1000mg	IV infusion
15	Obinutuzumab	1000mg	IV infusion
	Chlorambucil	0.5mg/kg*	PO (single dose)

Cycles 2-6

Day	Drug	Dose	Route
1	Obinutuzumab	1000mg	IV infusion
	Chlorambucil	0.5mg/kg*	PO (single dose)
15	Chlorambucil	0.5mg/kg*	PO (single dose)

*For elderly patients or those with poor performance status consider starting at 50% dose and escalating or reducing as tolerated.

Cycle frequency

28 days

Number of cycles

Maximum 6 cycles.

Administration

Obinutuzumab is administered in 100mL sodium chloride on cycle 1 day 1 and in 250mL sodium chloride 0.9% for all subsequent doses.

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

Cycle 1 day 1: Infuse at a rate of 25mg/hr over 4 hours. DO NOT increase the infusion rate.

If no infusion related reactions:
Cycle 1 day 2: Infuse at a rate of 50mg/hr; after the first 60 minutes, this can be escalated in 50mg/hr increments every 30 minutes to a maximum rate of 400mg/hr.

If no infusion related reactions:
Subsequent infusions: Infuse at an initial rate of 100mg/hr, and increase by 100mg/hr increments at 30-minute intervals, to a maximum of 400mg/hr.

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

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.

Chlorambucil is available as 2mg tablets. Tablets should be taken on an empty stomach, at least 1 hour before or 3 hours after a meal.

Pre-medication

Ensure the patient receives adequate hydration. In addition on days 1 and 2 administer 500mL sodium chloride 0.9% over 1 hour prior to administering obinutuzumab.

For cycle 1 days 1 and 2:
Obinutuzumab premedication:

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

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

If no previous obinutuzumab reaction:

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

If Grade 1-2 obinutuzumab infusion related reaction:

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

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

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

This regimen has low emetic potential.

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. Patients should also be adequately hydrated. Not usually required for subsequent cycles.
H_2 antagonist or PPI if required.
Anti-emetic, such as metoclopramide, for 3-4 days with each chlorambucil treatment.

Antiviral and antifungal 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)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+Es (including creatinine)	14 days
LFTs	14 days
Glucose	14 days
FISH to assess for 17p/TP53 deletion	Baseline

HIV serology, hepatitis B core antibody and hepatitis BsAg, hepatitis C antibody, CMV serology prior to commencing treatment.

Investigations – pre subsequent cycles

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

* before start of each cycle

Patients at high risk of tumour lysis syndrome (TLS) (lymphocytes > 25 x 10^9/L and or CrCl <70mL/min) should be monitored closely for the initial days of treatment, including creatinine and electrolytes and uric acid)

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	> 45mL/min
ALT/AST	< ULN

Dose modifications

- ### Haematological toxicity

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

- ### Renal impairment

Obinutuzumab:
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.

Chlorambucil:
If CrCl <45mL/min monitor closely for myelosuppression.

- **Hepatic impairment**

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

Chlorambucil:
Chlorambucil should be dose reduced in severe hepatic impairment and the dose further modified based on response and degree of myelosuppression.

- **Other toxicities**

Any Grade 2-3 non-haematological toxicity: withhold treatment until ≤ grade 1 (except alopecia)

Discontinue treatment if any of the following:
- ≥ Grade 2 non-haematological toxicity requiring treatment delay > 4 weeks
- Any Grade 4 non-haematological toxicity
- Severe haemorrhage
- Pneumonitis
- Severe cardiovascular events
- Severe skin reaction
- Viral hepatitis or other serious infections.

Patients with underlying cardiac disease should be closely monitored as arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred.

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 angiooedema) 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 there is a doctor and experienced nurse available during administration of all doses on cycle 1 and subsequent doses if the patient previously reacted.
Monitor the patient closely during the infusion.
Have symptomatic rescue medication readily available for administration in case of occurrence of IRRs.
Have emergency resuscitation facilities 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	Recommendation
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 restarted at no more than half the previous rate. 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. On cycle 1 day 1 the infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further. If the patient experiences a second occurrence of a Grade 3 IRR, the infusion must be stopped and therapy permanently discontinued.
Grades 1 and 2 (mild)	The infusion rate must be reduced and symptoms treated. Upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate. 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. On cycle 1 day 1 the infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.

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
Worsening of cardiac conditions
Hepatitis B reactivation

- **Frequently occurring side effects**

Myelosuppression
Nausea or vomiting
Anorexia, weight loss
Constipation, diarrhoea
Stomatitis/mucositis
Nasopharyngitis
Alopecia
Hypotension (during infusion)

- **Other side effects**

Rash
Transient elevation in liver enzymes
Arthralgia

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

Coumarin-derived anticoagulants such as warfarin: patients established on warfarin should either be changed to low molecular weight heparin or have weekly monitoring of INR. Patients who are initiated on anti-coagulation should remain on low molecular weight heparin until completion of the course of chemotherapy.

Additional comments

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

- National Institute for Health and Clinical Excellence TA343. Accessed 27 November 2019 via www.nice.org.uk
- Summary of Product Characteristics Chlorambucil (Medac). Accessed 27 November 2019 via www.medicines.org.uk
- Summary of Product Characteristics Obinutuzumab (Roche). Accessed 27 November 2019 via www.medicines.org.uk
- Valentin Goede, M.D.,et al. Obinutuzumab plus Chlorambucil in Patients with CLL and Coexisting Conditions. N Engl J Med 2014; 370:1101-1110

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