Obinutuzumab & Venetoclax

Indication

Venetoclax plus obinutuzumab is recommended as an option for untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) in adults, only if:

- there is a 17p deletion or *TP53* mutation, or
- there is no chr17p deletion or *TP53* mutation, and fludarabine pulse cyclophosphamide and rituximab (FCR), or bendamustine plus rituximab (BR), is unsuitable

(NICE TA663)

Additionally, venetoclax plus obinutuzumab is recommended as an option for untreated CLL or SLL if there is no 17p deletion or TP53 mutation, and FCR or BR is suitable

(CDF)

ICD-10 codes

Codes with a prefix C91

Regimen details

Cycle 1

Day	Drug	Dose	Route
1	Obinutuzumab	100mg	IV infusion
2	Obinutuzumab	900mg	IV infusion
8 & 15	Obinutuzumab	1000mg	IV infusion
22-28	Venetoclax	20mg OD	PO

Cycle 2

Day	Drug	Dose	Route
1	Obinutuzumab	1000mg	IV infusion
1-7	Venetoclax	50mg OD	PO
8-14	Venetoclax	100mg OD	PO
15-21	Venetoclax	200mg OD	PO
22-28	Venetoclax	400mg OD	PO

Cycles 3-6

Day	Drug	Dose	Route
1	Obinutuzumab	1000mg	IV infusion
1-28	Venetoclax	400mg OD	PO

Cycles 7-12

Day	Drug	Dose	Route
1-28	Venetoclax	400mg OD	PO

Cycle frequency

28 days

Number of cycles

6 cycles of Obinutuzumab
Total duration of Venetoclax is 45 weeks, starting with 1 week on cycle 1, day 22 then followed by 11 x 4 weekly cycles.

Administration

Obinutuzumab
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):

Dose cycle/day	Starting rate	Rate increment	Maximum rate
Cycle 1 D1	25mg/h	Do not increase rate	Do not increase rate
Cycle 1 D2	50mg/h	Increase by a further 50mg/h every 30 minutes If the patient experienced an infusion related reaction (IRR) during the previous infusion, start with administration at 25 mg/hr. The rate of infusion can be escalated in increments up to 50 mg/hr every 30 minutes	400mg/h
All subsequent infusions	100mg/h	After 30 minutes increase by 100mg/h Increase by a further 100mg/h every 30 minutes If the patient experienced an IRR during the previous infusion administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes	400mg/h

Hypotension may occur during obinutuzumab infusion. Therefore, antihypertensive treatments should be withheld for 12 hours prior to, 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.

Venetoclax
Venetoclax is available as 10mg, 50mg and 100mg tablets. The tablets should be swallowed whole with water at approximately the same time each day. Tablets should be taken with a meal, ideally breakfast.

Grapefruit products, Seville oranges and starfruit should be avoided during treatment with venetoclax.

If a patient misses a dose within 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible on the same day. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose and should resume the usual dosing schedule the following day.

If a patient vomits following a dose, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time on the following day.

Some patients especially those at greater risk of tumour lysis syndrome (TLS) may require hospitalisation on the day of the first dose of venetoclax for more intensive prophylaxis and monitoring during the first 24 hours.

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 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 as it has not been effective in reducing rates of IRR.
The need for ongoing pre-medication with dexamethasone and chlorphenamine is based on the incidence of infusion related reactions (IRR) during previous Obinutuzumab infusions:

Premedication	**Cycle 1 D1 and D2**	**All subsequent obinutuzumab infusions (i.e. Cycle 1 D8 and D15 and cycle 2-6)**		
	All patients	***No IRR***	***Grade 1-2 IRR***	***Grade 3 IRR***
Dexamethasone 20mg IV bolus	✓			✓
Chlorphenamine 10mg IV bolus	✓		✓	✓
Paracetamol 1g PO	✓	✓	✓	✓

Emetogenicity

This regimen has low emetic potential

Additional supportive medication

Allopurinol until established on venetoclax 400mg for at least 7 days
Antiviral prophylaxis as per local policy

Extravasation

Obinutuzumab is neutral (Group 1)

Investigations – pre first cycle

Investigation	**Validity period**
FBC	7 days
U&Es (including creatinine)	7 days
LFTs	7 days
Magnesium	7 days
Calcium	7 days
Phosphate	7 days
Uric acid	7 days
LDH	7 days
Glucose	7 days

Other investigations:
Hepatitis B core antibody and hepatitis BsAg, Hepatitis C antibody
HIV 1+2 serology
EBV/CMV/VZV serology
Direct antibody test (DAT)
Immunoglobulins, β2 microglobulin
Urine pregnancy test (women of child bearing potential)
CT scan (neck, chest, abdomen, pelvis) – must be performed prior to commencing treatment to confirm disease bulk and TLS risk factor category.
Baseline ECG +/- ECHO as clinically indicated

Investigations – during venetoclax dose titration phase

Monitoring for electrolyte changes indicative of TLS should be done before and after starting venetoclax and with each dose increase. Bloods including FBC, U&E, creatinine, calcium, phosphate, uric acid and LCH should be taken as per schedule below:

- Within 24 hours prior to the first dose of venetoclax, or an increase in dose of venetoclax
- 6-8 hours after the first dose of venetoclax, or an increase in dose of venetoclax
- 24 hours after the first dose of venetoclax, or an increase in dose of venetoclax

Investigations – following venetoclax dose titration phase

Investigation	**Validity period**
FBC	7 days
U&E (including creatinine)	7 days
Calcium	7 days
Phosphate	7 days
Uric acid	7 days
LDH	7 days
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	$\geq 1 \times 10^9$/L
Platelets	$\geq 25 \times 10^9$/L
Creatinine Clearance (CrCl)	≥ 80 mL/min
Potassium	Within normal limits
Calcium	Within normal limits
Phosphate	Within normal limits
Bilirubin	See hepatic impairment section
ALT/AST	See hepatic impairment section

Dose modifications

No dose modifications of Obinutuzumab are recommended

Venetoclax dose reductions should be managed as follows:

Dose at interruption	**Dose to restart**
400mg	300mg
300mg	200mg
200mg	100mg
100mg	50mg
50mg	20mg
20mg	10mg

Consider discontinuing venetoclax in patients who require dose reductions to less than 100mg for more than 4 weeks.

- **Haematological toxicity**

Venetoclax

Haematological toxicity	Occurrence	Action
Neutrophils <0.5 x 10^9/L or <1 x 10^9/L with infection or fever *Or* Platelets <25	1st occurrence	Interrupt venetoclax Consider GCSF as per local policy Once toxicity resolved to Grade 1 (Neutrophils ≥1.5 x 10^9/L, Platelets ≥75 x 10^9/L or Hb ≥10g/dL) or to baseline if pre-existing cytopenias, resume venetoclax at same dose.
Or Haemoglobin <80g/L which is not appropriate to be managed supportively	2nd and subsequent occurrence	Interrupt venetoclax Consider GCSF as per local policy Once toxicity resolved to Grade 1 (Neutrophils ≥1.5 x 10^9/L, Platelets ≥75 x 10^9/L or Hb ≥10g/dL) or to baseline if pre-existing cytopenias, resume venetoclax at dose reduction as per above table. A larger dose reduction may be implemented if required at consultant discretion.

Obinutuzumab
If neutrophils <1 x 10^9/L or platelets <25 x 10^9/L delay until recovery. Discuss with consultant if cytopenias due to bone marrow infiltration. No dose modification of obinutuzumab is recommended.

- **Renal impairment**

Patients with CrCl 30 – 80 mL/min do not require a dose reduction. They are, however, at increased risk of TLS (venetoclax), IRRs (obinutuzmab) and cytopaenias (both). They may require more intensive prophylaxis and monitoring to reduce the risk during initiation and titration phases.

CrCl <30 mL/min or on renal replacement therapy: There is very little information available. Treatment of these patients requires a careful balancing of expected risks and benefits. Patients should be monitored closely for signs of toxicity.

- **Hepatic impairment**

No dose adjustment is required in mild or moderate hepatic impairment. Patients with moderate hepatic impairment should be monitored more closely for toxicity during initiation and dose titration of venetoclax.

It is not recommended to administer obinutuzumab or venetoclax to patients with severe hepatic impairment as there is not sufficient information available.

- **Other toxicities**

Venetoclax

Biochemistry results:
If any of the following occur withhold venetoclax until resolved:
- Potassium > 0.5mmol/L increase from prior value or >ULN
- Urate > 476 umol/l (8.0mg/dL)
- Corrected Calcium <1.75 mmol/L
- Phosphate > 1.615 mmol/l
- Creatinine >25% increase from baseline

Tumour Lysis Syndrome (TLS):
Venetoclax can cause rapid reduction in tumour load and there is a risk of TLS, particularly during the titration period. Fatal cases of TLS have been observed even in patients receiving the lowest dose of venetoclax so dose escalation and TLS risk minimisation measures must be strictly adhered to and all patients should receive a patient alert card. Changes in electrolytes consistent with TLS can occur as early as 6 – 8 hours following the first dose of venetoclax and at each dose increase. Prompt management is required.

Concomitant use of venetoclax with strong or moderate CYP3A inhibitors is contraindicated as this may increase venetoclax exposure and may increase the risk for TLS at initiation and during the dose-titration phase and for other toxicities.

Risk Assessment for TLS
The risk of TLS is based on multiple factors, including comorbidities. Patients with high/medium tumour burden (e.g., any lymph node with a diameter > 5 cm or high absolute lymphocyte count [ALC > 25 × 10^9/L]) have a greater risk of TLS. Reduced renal function (creatinine clearance CrCl < 80 mL/min) further increases the risk. The risk may decrease as tumour burden decreases with venetoclax treatment. Prior to initiating venetoclax, tumour burden assessment, including radiographic evaluation (e.g., CT scan) should be performed for all patients.
In addition, blood chemistry (creatinine, uric acid, potassium, phosphate, magnesium and calcium) should be carried out for all patients prior to starting treatment with correction of pre-existing abnormalities corrected.

Prevention of TLS
Hydration: Patients should be adequately hydrated, as described below.
For patients at risk of volume overload consider admission to hospital.

Recommended prophylaxis based on tumour burden (consider all patient co-morbidities and creatinine clearance before final determination of prophylaxis and monitoring schedule):

Tumour Burden		**Prophylaxis**		**Setting and Biochemistry Monitoring**
		Hydration	***Anti-hyperuricaemics (started 2-3 days prior to initiation of venetoclax)***	
Low	All lymph nodes < 5cm **and** ALC <25 x 10^9/L	Oral (1.5-2L)	Allopurinol	*Outpatient* *For first dose of 20 mg and 50 mg:* Pre-dose, 6 to 8 hrs, 24 hrs *For subsequent dose increases*: Pre-dose
Medium	Any lymph node 5 - <10cm **or** ALC >25 x 10^9/L	Oral (1.5-2L) Consider additional IV if required.	Allopurinol	*Outpatient* *For first dose of 20 mg and 50 mg*: Pre-dose, 6 to 8 hours, 24 hours *For subsequent dose increases:* Pre-dose *For first dose of 20 mg and 50 mg **in patients with CrCl <80ml/min**:* Consider hospitalisation for patients; see below for monitoring in hospital

High	Any lymph node >10cm **or** ALC >25 x 10^9/L **and** any lymph node > 5 cm **or** ALC >100 x10^9/L	Oral (1.5-2L) and IV (150-200mL/hr as tolerated)	Allopurinol Consider rasburicase if baseline uric acid is elevated	*Inpatient* *For first dose of 20 mg and 50 mg* Pre-dose and 4, 8,12 and 24 hours post dose *Outpatient* *For subsequent dose increases*: Pre-dose, 6 to 8 hours, 24 hours

Management of venetoclax if TLS develops:
During treatment if biochemistry changes or symptoms suggestive of TLS:
- Withhold venetoclax.
- If resolved within 24-48 hours of last dose, resume at the same dose
- If takes more than 48 hours to resolve, resume at reduced dose. Discuss with consultant. If rapid dose escalation required due to progressive disease consider admission for IV hydration.

For any other Grade 3 or 4 non-haematological toxicity thought to be related to venetoclax:

Occurrence	**Action**
1st occurrence	Interrupt venetoclax Once toxicity has reduced to Grade 1 or baseline, resume venetoclax at same dose. No dose modification is required.
2nd and subsequent occurrences	Interrupt venetoclax Reduce dose according to dose levels outline in table above. A larger dose reduction may be implemented if required at consultant discretion.

Obinutuzumab

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 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. 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. For patients receiving the Day 1 (Cycle 1) dose split over the two days, the Day 1 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
Hypersensitivity and allergic reactions
Infusion related reactions
Tumour lysis syndrome
Hepatitis B reactivation
Bacterial/fungal Infections
Progressive multifocal leukoencephalopathy
Squamous cell carcinomas of skin, basal cell carcinoma

- **Frequently occurring side effects**

Myelosuppression
Diarrhoea, constipation
Hypotension (during infusion)
Nausea, vomiting
Pyrexia
Fatigue
Cough
Headache

- **Other side effects**

Rash

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

Obinutuzumab – no formal drug interaction studies have been performed but Obinutuzumab is not a substrate, inhibitor or inducer of cytochrome P450, UGT enzymes or transporters such as P-gp so no pharmacokinetic interaction is expected via these mechanisms.

Venetoclax

Strong CYP3A inhibitors: (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, ritonavir)
Concomitant use is contraindicated during initiation and the dose-titration phase. If the patient requires use of these medications after titration phase, use with caution and reduce the venetoclax dose by at least 75% during co-administration. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.

Patients must not consume grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within the 3-day period prior to the first venetoclax administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction.

Moderate CYP3A inhibitors and P-gp and BCRP inhibitors:
Avoid concomitant use of venetoclax with moderate CYP3A inhibitors (e.g., ciprofloxacin, diltiazem, erythromycin, fluconazole, verapamil) and P-gp and BCRP inhibitors at initiation and during the dose-titration phase. Consider alternative treatments. If a moderate CYP3A inhibitor or P-gp inhibitor must be used, reduce the initiation and titration doses of venetoclax by at least 50%. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.

CYP3A inducers:
Avoid concomitant use of venetoclax with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's Wort) or moderate CYP3A inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin) as efficacy of venetoclax may be reduced. Consider alternative treatments with less CYP3A induction.

Bile acid sequestrants:
Co-administration of bile acid sequestrants with venetoclax is not recommended as this may reduce the absorption of venetoclax. If a bile acid sequestrant is to be co-administered with venetoclax, the summary of product characteristics for the bile acid sequestrant should be followed to reduce the risk for an interaction, and venetoclax should be administered at least 4-6 hours after the sequestrant.

Warfarin:
If concomitant use is necessary the INR should be closely monitored.

Substrates of P-gp, BCRP, and OATP1B1:
Venetoclax is a P-gp, BCRP and OATP1B1 inhibitor *in vitro*. Co-administration of narrow therapeutic index P-gp, or BCRP substrates (e.g. digoxin, dabigatran, everolimus, sirolimus) with venetoclax should be avoided.

If a narrow therapeutic index P-gp or BCRP substrate must be used, it should be used with caution. For an orally administered P-gp or BCRP substrate sensitive to inhibition in the gastrointestinal tract (e.g., dabigatran exetilate), its administration should be separated from venetoclax administration as much as possible to minimise a potential interaction.

If a statin (OATP substrate) is used concomitantly with venetoclax, close monitoring of statin-related toxicity is recommended.

Additional comments

Women of childbearing potential must use effective contraception during and for 18 months after treatment with Obinutuzumab.

References

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