Rituximab-Venetoclax

Indication

Treatment of chronic lymphocytic leukaemia (CLL) in patients who have had at least one previous therapy.

(NICE TA561)

ICD-10 codes

Codes with a prefix C91.10

Regimen details

Venetoclax:

Venetoclax dose is titrated weekly as below to reduce tumour burden and decrease the risk of tumour lysis syndrome (TLS):

Day	Drug	Dose	Route
1-7	Venetoclax	20mg OD	PO
8-14	Venetoclax	50mg OD	PO
15-21	Venetoclax	100mg OD	PO
22-28	Venetoclax	200mg OD	PO
29 onwards	Venetoclax	400mg OD	PO

Rituximab:

Rituximab should be administered after the patient has completed the dose-titration schedule and has received the recommended daily dose of 400 mg venetoclax for 7 days. Each cycle is 28 days.

Cycle 1

Day	Drug	Dose	Route
1 (see dose intervals below)	Rituximab	375mg/m^2	IV infusion

Cycle 2 onwards

Day	Drug	Dose	Route
1 (see dose intervals below)	Rituximab	500mg/m^2	IV infusion

Cycle frequency

See above

Number of cycles

Venetoclax can be taken for a maximum of 2 years from day 1 of cycle 1 of rituximab, or until disease progression or unacceptable toxicity.

Rituximab may be given for a maximum of 6 cycles.

Administration

Rituximab is administered in 500mL sodium chloride 0.9%. The first infusion should be initiated at 50mg/hour and if tolerated the rate can be increased by 50mg/hour every 30 minutes to a maximum of 400mg/hour. Subsequent infusions should be initiated at 100 mg/hour and if tolerated increased by 100mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

Venetoclax is available as 10mg, 50mg and 100mg tablets. The tablets should be swallowed whole with water at approximately the same time each day. It is preferable that the dose is taken in the morning to allow for laboratory monitoring. 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 TLS, may require hospitalisation on the day of the first dose of venetoclax for more intensive prophylaxis and monitoring during the first 24 hours (see TLS assessment below).

Pre-medication

Rituximab premedication:

- Paracetamol 1g PO 60 minutes prior to rituximab
- Chlorphenamine 10mg IV bolus (or 4mg PO) 15 minutes prior to rituximab
- Dexamethasone 8mg IV bolus or hydrocortisone 100mg IV bolus (or prednisolone 25mg PO) 15 minutes prior to rituximab

Patients should be adequately hydrated during the dose-titration phase to reduce the risk of TLS. Patients should drink at least 1.5 to 2.0 L of water daily starting 2 days before the first dose and throughout the dose-titration phase. Intravenous fluids should be administered as indicated based on overall risk of TLS or for those who cannot maintain an adequate level of oral hydration.

Anti-hyperuricaemic agents should be administered 2 to 3 days prior to starting treatment with venetoclax and may be continued through the titration phase.

Emetogenicity

This regimen has low emetic potential.

Additional supportive medication

Anti-emetics if required.
Anti-viral and PCP prophylaxis as per local policy.
Anti-hyperuricaemic agents – see below

Extravasation

Rituximab is neutral (Group 1)

Investigations – prior to commencing venetoclax and before each dose increase

Investigation	Validity period
FBC	24 hours
U+Es (including creatinine)	24 hours
Urate	24 hours
LFTs	24 hours
LDH	24 hours
Calcium	24 hours
Magnesium	24 hours
Phosphate	24 hours

Other investigations:
Hepatitis B core antibody and hepatitis BsAg, Hepatitis C antibody
HIV 1+2 serology
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.

Investigations – during dose titration phase

(see below for management plan)
The following should be assessed within 24 hour prior to the first dose and 6-8 hours and 24 hours post first dose. The second dose should not be administered until these results are reviewed. The same monitoring schedule should be followed at the start of the 50 mg dose and then, for patients who continue to be at risk, at subsequent dose increases during titration period. All patients should have blood monitoring within 24 hours of each dose increase as per recommendations below.

See sections below for action required in the event of abnormal results.

Investigation	Validity period
FBC	As above
U+Es (including creatinine)	As above
Urate	As above
LFTs	As above
Calcium	As above
Magnesium	As above
Phosphate	As above

Any electrolyte abnormalities should be corrected prior to commencing treatment. The next dose of venetoclax should not be administered until the 24-hour blood chemistry results have been evaluated.

Investigations – following dose titration phase

Investigation	Validity period
FBC	Monthly or as clinically indicated
U+Es (including creatinine)	Monthly or as clinically indicated
Urate	Monthly or as clinically indicated
LFTs	Monthly or as clinically indicated
Calcium	Monthly or as clinically indicated
Magnesium	Monthly or as clinically indicated
Phosphate	Monthly or as clinically indicated

Standard limits for 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	> 25 x 10^9/L
CrCl	> 80 mL/min
Potassium	Within normal limits
Calcium	Within normal limits
Phosphate	Within normal limits
Bilirubin	See below
AST/ALT	See below

Dose modifications

Any venetoclax dose reductions should be as follows:

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

Once a dose has been reduced it should be continued for 1 week before increasing.

- **Haematological toxicity**

If grade 3 or 4 neutropenia (neutrophils < 1.0 x10^9/L) with infection or fever or any grade 4 haematological toxicity (except lymphopenia) (neutrophils < 1.0 x10^9/L and/or platelets < 25 x10^9/L):

Withhold venetoclax. Consider GCSF as per local policy. Once resolved to ≤ Grade 1 (or baseline) resume at the same dose.

Rituximab should be given with caution if neutrophils < 1.5 x 10^9/L and/or platelets < 75 x 10^9/L.

If second or subsequent occurrence, withhold venetoclax. Consider GCSF as per local policy. Once resolved to ≤ Grade 1 (or baseline) resume at reduced dose (as per table above).

- **Renal impairment**

Renal function should be evaluated prior to commencing treatment.

Patients with CrCl <80 mL/min are at increased risk of TLS and may require more intensive prophylaxis and monitoring to reduce the risk of TLS during the initiation and titration phase.

CrCl ≥30 mL/min- No venetoclax dose modification required.

CrCl <30 mL/min or dialysis- No information for venetoclax available. Administer only if the benefit outweighs the risk. Patients should be monitored closely for signs of toxicity.

There is no data regarding rituximab in renal impairment.

- **Hepatic impairment**

No dose adjustment required for venetoclax in mild or moderate hepatic impairment.

Severe hepatic impairment- No information available. It is not recommended to administer venetoclax to patients with severe hepatic impairment.

There is no data regarding rituximab in hepatic impairment.

- **Other toxicities**

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 (hyperkalaemia, hyperuricaemia, hyperphosphataemia, hypocalcaemia) 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.

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

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 and requirement for inpatient or outpatient monitoring should be assessed prior to each dose increase. 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 above.
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	
Low	All lymph nodes < 5cm **and** ALC <25 x 10^9/L	Oral (1.5-2L)	Allopurinol	Outpatient Monitoring as below.
Medium	Any lymph node 5 - <10cm **or** ALC >25 x 10^9/L	Oral (1.5-2L) Consider additional IV if required.	Allopurinol	Outpatient Monitoring as below.
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 or CrCl<50ml/min	Inpatient for commencement and/or each dose escalation (to be reassessed weekly): Monitoring as below at 6-8 hours and 24 hours post dose

Inpatient management:
Day 0: (day prior to commencement or dose escalation)

- Admit patient to the ward and check bloods as above.
- Ensure anti hyperuricaemics have been started.
- Start IV hydration e.g. sodium chloride 0.9% 1 L over 8 hours (125mL/hour). DO NOT ADD POTASSIUM TO FLUIDS.

Day 1: (day of commencement or dose escalation)

- Give rasburicase if required prior to administration of venetoclax (omit allopurinol if rasburicase given
- Give venetoclax first dose at 0600hrs (prescribe as stat dose)
- Continue IV hydration
- 6-8 hours following dose (i.e 12-1400hrs), check bloods as above in realtime and act on any evidence of TLS

Day 2:

- 24 hours following first dose (i.e. 0600hrs) check bloods as above.
- **DO NOT GIVE SECOND DOSE OF VENETOCLAX UNTIL RESULTS CHECKED**, go ahead confirmed and dose prescribed by nominated person.
- If bloods are satisfactory, give second dose and discharge patient with the remainder of the first weeks supply.
- If suspected TLS manage as per local policy and follow recommendations below.

Outpatient management:
Day 0: (day prior to commencement or dose escalation)

- Day unit staff to check bloods as above.
- Ensure anti hyperuricaemics have been started.
- Dispense first dose of venetoclax for the patient to take home ready to take on day 1

Day 1: (day of commencement or dose escalation)

Advise patient to take venetoclax first dose at 0500-0600hrs

- 6-8 hours following dose patient to attend day unit for blood test. Bloods to be checked in realtime by nominated person
- If suspected TLS manage as per local policy and follow recommendations below.
- If no evidence of TLS patient to be discharged home (remaining venetoclax to be stored by day unit)

Day 2:

- Patient to attend for blood test early morning (0900 or earlier if possible) **DO NOT GIVE NEXT DOSE UNTIL RESULTS CHECKED** in realtime by nominated person and go ahead confirmed.
- If bloods are satisfactory, ask the patient to take the second dose and discharge patient with the remainder of the first weeks supply.
- If suspected TLS manage as per local policy and follow recommendations below.

Treatment of TLS:
The following changes on biochemistry require action and indicate TLS:

Potassium > 0.5mmol/L increase from prior value or >ULN
Urate > 476 umol/l (8.0mg/dL)
Corrected Calcium <1.75 mmol/L
Phosphate > 0.16 mmol/l rise from baseline or >ULN
Creatinine >25% increase from baseline (even if in normal range)

- If one electrolyte abnormality with stable creatinine repeat TLS bloods within 1-2 hours. If changes resolve no need for further bloods or additional management
- If two or more electrolyte abnormalities or rise in creatinine initiate TLS treatment and withhold venetoclax
- If TLS resolved within 24-48 hours of last dose continue with same dose on resolution.
- If takes more than 48 hours continue with reduced dose on resolution. Discuss with consultant. If rapid dose escalation required due to progressive disease consider admission for IV hydration.

Other toxicities:
For any other grade 3-4 toxicity:
- Withhold venetoclax.
- Once resolved to grade 1 or baseline resume with same dose.
- If recurs once resolved continue with dose reduction.

If dose reductions to <100mg for more than 2 weeks are required consider discontinuing treatment.

Adverse effects

Myelosuppression
Tumour lysis syndrome
Diarrhoea, constipation
Nausea and vomiting
Upper respiratory tract infection
Fatigue
Electrolyte abnormalities
Hypotension and bronchospasm (infusion related and usually transient)
Cardiac disorders
Angioedema
Pruritus, rash
Headache

Significant drug interactions

Note this list is not exhaustive. Always refer to the product SPC and consult with a pharmacist.

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). 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.

Warfain:
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.

Rituximab:

Nil significant, although data is limited.

Additional comments

References

- National Institute for Health and Clinical Excellence. NICE TA561. Accessed 25 July 2019 via www.nice.org.uk
- Summary of Product Characteristics Venetoclax (AbbVie) accessed 25 July 2019 via www.medicines.org.uk
- Summary of Product Characteristics Rituximab (Roche) Intravenous accessed 25 July 2019 via www.medicines.org.uk
- Seymour, J.F. et al. Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. N Engl J Med 2018; 378:1107-1120

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Date: September 2019