Venetoclax - Rituximab

INDICATION: Venetoclax (Venclyxto, AbbVie) plus Rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia who have received at least 1 prior therapy.

Prior to a course of treatment:

- Check FBC. Patient must have adequate marrow reserve – neutrophils >1.0, platelets >75 unless cytopenia is due to disease, e.g marrow infiltration, splenomegaly.
- Check renal and liver function. – *see dose modification and discuss with consultant if abnormal*
- Review concurrent medications – *see interaction below.*
- Check HIV, Hep B and Hep C status
- Check inorganic phosphate, uric acid, calcium, LDH
- Review results of CT scan neck, thorax, abdomen. Assess tumor burden / tumor lysis risk (below).
- Assess risk of tumor lysis and need for hospitalization for treatment initiation - see 'tumor lysis syndrome guideline'. Consider admission in patients with bulky mass, Lymph > 25 or creatinine clearance <60 ml/min
- Female patients of child-bearing potential must use barrier contraception from day 1 to at least 30 days after last dose
- Male patients must use barrier contraception from day 1 to at least 30 days after last dose agree to refrain from sperm donation from day 1 until 90 days after the last dose
- Written consent for course.
- Venetoclax will be available via the Cancer Drugs Fund (CDF). Application form on the Blueteq site. Registration required prior to start of treatment.

Administration:

- Venetoclax should be swallowed whole with water at the same time each day. Preferably 30mins after Breakfast.
- If a patient vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time the following day.
- In cases where a dose is missed or forgotten, the patient should take the dose as soon as possible, ensuring the dose is taken within 8 hours of the missed dose with food. Otherwise, the dose should not be taken.

Rituximab (see infusion protocol)	375mg/m^2 IV (cycle 1) 500mg/m^2 IV (cycles 2-6)	Day 1
Venetoclax	20 mg daily	Week 1
	50 mg daily	Week 2
	100 mg daily	Week 3
	200 mg daily	Week 4
	400 mg daily	Week 5 and beyond

Rituximab should be administered after the patient has completed the dose-titration schedule and has had the recommended daily dose of 400 mg venetoclax for 7 days. Rituximab 375 mg/m^2 is given intravenously on day 1 of cycle 1 (a cycle is 28 days), followed by 500 mg/m^2 on day 1 of cycles 2 to 6. Rituximab is stopped after cycle 6.

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

Venetoclax toxicities

Neutropenic sepsis	Tumor lysis syndrome.
Thrombocytopenia	Nausea & vomiting
Diarrhea	Infertility (offer semen cryopreservation)
Fatigue	Anaemia
Embryo-Fetal Toxicity	

Special Considerations

Elderly – No specific dose adjustment is required

Renal impairment - No dose adjustment is needed for patients with mild to moderate renal impairment (creatinine clearance >= 30 mls/min and < 90 mls/min). More intensive tumour lysis prophylaxis may be required. Admission will be considered for patients with CrC < 60 mL/min. Safety in patients with severe renal impairment (CrCl <30 mL/min) or on dialysis has not been established

Hepatic impairment – no dose adjustment is recommended in patients with mild to moderate hepatic impairment. A trend for increased events was observed in patients with moderate hepatic impairment and more intensive monitoring is advised. Not recommended to administer Venetoclax to patients with severe hepatic impairment.

Supportive treatment:

- Co-trimoxazole 480mg/day (or equivalent as per standard care). or an alternative, such as dapsone (100mg OD) PCP prophylaxis must continue throughout treatment and for at least 2 months afterwards.
- Aciclovir 400mg bd (or equivalent as per standard care). Continue throughout Venetoclax treatment and for at least 2 months after the last course of treatment.
- Allopurinol 300mg/day must be given at least 72 hours prior to the first dose of Venetoclax as prophylaxis for TLS, this must continue until at least the end of the Venetoclax dose escalation phase. This should be prescribed prior to initiation of chemotherapy, when patient is being consented. Patients with a high tumour burden must be given more intensive prophylaxis against TLS (e.g. rasburicase (200 ug/kg) and this must be initiated prior to starting Venetoclax and can be used up to 7 days.
- Patients should be adequately hydrated during the dose-titration phase to reduce the risk of TLS. Patients should be instructed to drink plenty of water daily starting 2 days before and throughout the dose-titration phase. Patients should be particularly instructed to drink 1.5 to 2.0 L of water daily, 2 days prior to and the days of dosing at initiation and each subsequent dose increase
- GCSF support may be required.

Managing Tumor lysis syndrome risk

Tumour Burden/ renal function		Prophylaxis		Blood Biochemistry Monitoring
		Hydration	**Anti-hyperuricemics**	**Setting and Frequency of Assessments**
Low	All lymph nodes <5 cm AND ALC <25 x109/L	Oral (1.5-2 L)	Allopurinol	Outpatient 1. Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg 2. Pre-dose and 6-8 hours at subsequent dose escalations
Medium	Any lymph node 5 cm to <10 cm OR ALC ≥25 x109/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	Outpatient 3. Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg 4. Pre-dose and 6 to 8 hours at subsequent dose escalations. 5. Consider hospitalisation for patients with creatinine clearance 60-80mL/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital
High (or creatinine clearance <60 ml/min)	Any lymph node ≥10 cm OR ALC ≥25 x109/L AND any lymph node ≥5 cm OR ALC >100 x 109/L OR **Creatinine clearance <60 ml/min**	Oral (1.5-2 L) and intravenous (150-200 mL/hr as tolerated)	Allopurinol; consider rasburicase if baseline urate is elevated	In hospital at first dose of 20 mg and 50 mg 6. Pre-dose, 4, 6-8,12 and 24 hours Outpatient at subsequent dose escalations 7. Pre-dose, 6 to 8 hours and 24 hours.

If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be per standard care

Ongoing dosing of Venetoclax

- Monitor electrolyte changes from last value at intervals >24 hours after either the first dose (20mg) or dose escalation (50mg) (eg, 48 or 72 hours)
- If the patient is hospitalised, no additional Venetoclax doses should be administered until resolution.
- Consider admission for close monitoring if potassium increases ≥1.0 mmol/L, or any level > upper limit of normal.
- Refer to local policies for management of electrolyte changes observed within the first 24 hours after either the first dose or dose escalation
- If a smaller potassium increase is observed that does not meet the criteria for admission above, recheck potassium, phosphate, urate, calcium and creatinine in 24 hours and confirm no evidence of tumour lysis prior to further Venetoclax dosing.

Dose modifications:

- In case of blood chemistry changes or symptoms suggestive of TLS, withhold the next Venetoclax day's dose. If resolved within 24 to 48 hours of last dose, resume at the same dose. For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose (see table below).
- Venetoclax should be withheld for any grade 3 or 4 non-haematological toxicities, grade 3 or 4 neutropenia with infection or fever, or grade 4 haematological toxicities, except lymphopenia.
- Once the toxicity has resolved to grade 1 or baseline level (recovery), therapy with Venetoclax may be restarted at the same dose.

- If the toxicity recurs, and for any subsequent occurrences, the dose reduction guidelines table below should be followed when resuming treatment with Venetoclax following resolution.
- If a larger dose reduction required, discuss with Consultant. For patients who require dose reductions to less than 100 mg for more than 2 weeks, discontinuation of Venetoclax should be considered.
- Administer G-CSF or growth factors for neutropenia as indicated (recommended to keep the neutrophil count above 1 x 10^9/L).

Dose modification for TLS and other toxicities

Dose at interruption	Restart dose
(mg)	**(mg)**
400	300
300	200
200	100
100	50
50	20
20	10

The modified dose should be continued for 1 week before increasing the dose.
For patients who have had a dosing interruption lasting more than 1 week during the first 5 weeks of dose escalation or more than 2 weeks when at the daily dose of 400 mg, TLS risk should be reassessed to determine if restarting at a reduced dose is necessary.

Interactions

Seek Pharmacy advice for polypharmacy – numerous interactions

Venetoclax is predominantly metabolized by CYP3A. CYP3A inhibitors may increase Venetoclax plasma concentration.

Inhibitors	Initiation and Ramp-Up Phase	Steady Daily Dose (After Ramp-Up Phase)
Strong CYP3A inhibitor	Contraindicated	Avoid inhibitor use or reduce the VENCLEXTA dose by at least 75%
Moderate CYP3A inhibitor	Avoid inhibitor use or reduce the VENCLEXTA dose by at least 50%	
P-gp inhibitor		

	Examples	Advice
Strong CYP3A inhibitors	clarithromycin, posaconazole, voriconazole, itraconazole, lopinavir, ritonavir, telaprevir, telithromycin, Ketoconazole, conivaptan, indinavir,	Avoid whilst on Venetoclax treatment. Strongly recommend alternative with less potent enzyme inhibition. Prohibited during dose escalation phase as may increase risk of TLS. If dose escalation has been completed and patient is on steady daily dose, reduce Venetoclax dose by at least 75%. Resume treatment dose that was used before administration of the inhibitor 2-3 days after discontinuing the inhibitor.
Moderate CYP3A inhibitors	Erythromycin, ciprofloxacin, fluconazole, Verapamil, diltiazem and dronedarone.	Avoid and consider alternatives but can be used with caution on Venetoclax treatment Reduce dose by at least 50%

		(<=200mg) daily. Resume treatment dose that was used before administration of the inhibitor 2-3 days after discontinuing the inhibitor
Weak CYP3A inhibitors	Azithromycin, fluvoxamine	Monitor patient closely for toxicity and follow dose modification guidance as needed.
Strong CYP3A inducers	Carbamazepine, phenytoin, St. John's wort, and rifampin	Should be avoided as may decrease plasma concentration of Venetoclax consider alternative treatments with less enzyme induction
Moderate CYP3A inducers	Bosentan, efavirenz, etravirine, modafinil, nafcillin	
Weak CYP3A inducers	Prednisolone, pioglitazone	
P-gp, BCRP and OATP1B1 substrates	Digoxin, methotrexate, rosuvastatin, dabigatran, everolimus, sirolimus	Venetoclax is a P-gp, BCRP and OATP1B1 inhibitor *in vitro* and so other substrates should be avoided.
Food	Grapefruit, Seville oranges (including marmalade), and starfruit	Avoid whilst on Venetoclax treatment as they contain inhibitors of CYP3A

Warfarin: increase in plasma concentration with Venetoclax use

Co-administration of bowel acid sequestrates with Venetoclax is not recommended as absorption may be reduced.

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

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