

## **CHEMOTHERAPY PROTOCOL FOR ADMINISTRATION OF VENETOCLAX**

### **Therapeutic Indications:**

Venetoclax monotherapy is indicated for the treatment of chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed B cell receptor pathway inhibitor.

Venetoclax monotherapy is indicated for the treatment of CLL in the absence of 17P deletion or TP53 mutation in adult patients who have failed both chemo-immunotherapy and a B cell receptor pathway inhibitor.

### **Prior to a course of Venetoclax**

- Check bone marrow function by FBC: platelets must be  $\geq 25$ , Hb  $\geq 8.0$  without transfusion support within 14 days or evidence of bleeding
- Check PT and APTT: must not exceed  $> 1.5$  time ULN
- Check U&Es, creatinine and eGFR (Cockcroft-Gault): must be  $\geq 50$ ml/min
- Check LFTs: AST/ALT and bilirubin must be  $\leq 1.5$  times ULN (unless Gilbert's syndrome)
- Check inorganic phosphate, uric acid, calcium, LDH
- Check HIV, Hep B and Hep C status
- Review results of CT scan neck, thorax, abdomen. Assess tumour burden / tumour lysis risk
- Assess risk of tumour lysis and need for hospitalization for treatment initiation - see 'Prevention of tumour lysis syndrome'
- Female patients of child-bearing potential must use one specified method of birth control from day 1 to at least 30 days after last dose
- Female patients of child-bearing potential must have a negative pregnancy tests on day 1 of treatment and must not be breast-feeding
- Male patients must agree to refrain from sperm donation from day 1 until 90 days after the last dose
- Review current medications – see 'Interactions'
- Patients must agree not to consume grapefruit or Seville oranges or star fruit
- Note risk of neutropenia and severe infection especially in patients with multiple prior lines of therapy and consider antimicrobial and GCSF prophylaxis on an individual patient basis. See 'Interactions'
- Written consent for course

### **Prior to a dose increase**

- Check FBC, renal, liver, phosphate, calcium, uric acid
- Assess tumour lysis risk

**Administration:**

The starting dose is 20 mg of Venetoclax once daily for seven days.

Venetoclax should be swallowed whole with water and a meal in the morning

The dose must be gradually increased over a period of five weeks up to the recommended daily dose of 400 mg as shown in table 1.

**Table One: Dose increase schedule**

WEEK	DAILY DOSE OF VENETOCLAX
1	20 mg
2	50 mg
3	100 mg
4	200 mg
5 and beyond	400 mg

Treatment should be continued until disease progression or no longer tolerated by the patient.

**Premedication**

Antihyperuricaemic agent / allopurinol

Metoclopramide 10mg tds po prn for delayed emesis

Antimicrobial prophylaxis as required

**Prevention of tumour lysis syndrome:**

Venetoclax can cause rapid reduction in tumour and thus poses a risk for TLS in the initial five week dose titration phase.

Patients with a high tumour burden (example: any lymph node with a diameter greater than 5 cm) or high absolute lymphocyte count (lymphocyte count greater than or equal to  $25 \times 10^9/L$ ) are at greater risk of tumour lysis syndrome when initiating Venetoclax.

Reduced renal function (creatinine clearance less than 80 mls/min) further increases the risk. The risk may decrease as the tumour burden decreases with Venetoclax treatment.

**Risk Assessment**

Risk assessment of risk of tumour lysis must be performed on all patients prior to commencing Venetoclax.

CT scan whole body must be performed and full biochemistry screen (potassium, uric acid, phosphorous, calcium and creatinine) should be assessed and pre-existing abnormalities corrected.

**Hydration and Tumour Lysis Prophylaxis**

Patients should be adequately hydrated during the dose titration phase. Patients should be instructed to drink plenty of water starting two days before and throughout the dose titration phase. Patients should be particularly instructed to drink 1.5 to 2 litres of water daily, two days prior to the days of dosing at initiation and each subsequent dose increase.

Patients at high risk should be given intravenous fluids or for those who cannot maintain an adequate level of hydration.

Antihyperuricemic agents should be administered two to three days prior to starting treatment and may be continued through the titration phase. Consideration should be given to the use of Rasburicase in high risk patients ( see BCSH guidelines).

Laboratory assessments, full blood count and full biochemical profile, including uric acid, should be assessed pre-commencement of Venetoclax and prior to each subsequent dose increase during the titration phase.

Blood biochemistry should be monitored at six to eight hours and 24 hours after the first dose of Venetoclax. Electrolyte abnormalities should be corrected promptly. The next Venetoclax dose should not be administered until the 24 hour blood biochemistry results have been evaluated.

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 have subsequent dose increases.

Some patients may require hospitalisation on the day of the first dose of Venetoclax for more intensive prophylaxis monitoring during the first 24 hours. This measure can be considered for further dose increases at clinician discretion.

**Dose modifications for tumour lysis syndrome:**

If the patient experiences blood biochemistry changes suggestive of TLS, the following days Venetoclax should be withheld. If resolved within 24 to 48 hours of the last dose, treatment with Venetoclax can be resumed at the same dose.

For events of clinical tumour lysis syndrome or blood biochemistry changes requiring more than 48 hours to resolve, treatment should be resumed at a reduced dose (see table 2).

**Table 2 : dose modification for tumour lysis syndrome and other toxicity ( inc neutropenia and thrombocytopenia )**

<b>Dose at interruption (mg)</b>	<b>Restart dose (mg)</b>
400	300
300	200
200	100
100	50
50	20
20	10
<b>The modified dose should be continued for 1 week before increasing the dose</b>	

For patients who have had a dosing interruption lasting more than one week during the first five weeks of dose titration or more than two weeks when at the daily of 400 mg TLS risk should be reassessed to determine if restarting at a reduced dose is necessary (eg. all or some levels of the dose titration )

When resuming treatment after interruption due to tumour lysis syndrome, the instruction for prevention of tumour lysis syndrome should be followed (see above).

**Dose modification for thrombocytopenia:**

Venetoclax should be withheld for grade 4 thrombocytopenia (platelet count < 25)

Once the toxicity has resolved to grade one (platelet count >75) 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 in **table 2** should be followed when resuming treatment with Venetoclax following resolution. Larger dose reductions at the discretion of physician.

For patients who require dose reductions to less than 100 mg for more than two weeks, discontinuation of Venetoclax should be considered.

### **Dose reductions for neutropenia:**

Consideration should be given to the use of granulocyte colony-stimulating factor (G-CSF).

Treatment with Venetoclax should be withheld for any grade 3 or 4 neutropenia with infection or fever (neutrophil count < 1) or grade 4 neutropenia (neutrophil count < 0.5).

Once the toxicity has resolved to grade 1 (neutrophil count > 1.5) 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 in **table 2** should be followed when resuming treatment with Venetoclax following resolution.

Larger dose reduction at clinician discretion.

Patients requiring dose reduction to less than 100 mg for more than two weeks should be considered for discontinuation of Venetoclax.

### **Side Effects:**

Upper respiratory tract infection

Pneumonia

Urinary tract infection

Infections

Anaemia, Neutropenia, Thrombocytopenia, Lymphopenia

Tumour lysis syndrome (hyperphosphatemia, hyperkalaemia, hyperuricemia, hypocalcaemia, renal impairment)

Diarrhoea

Vomiting

Nausea

Constipation

Fatigue

### **Special Considerations ( see SPC )**

**Elderly** – No specific dose adjustment is required

**Renal impairment** - No dose adjustment is needed for patients with mild to moderate renal impairment (creatinine clearance  $\geq$  30 mls/min and < 90 mls/min). More intensive tumour lysis prophylaxis recommended.

**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.

### **Method of Administration:**

Oral use. Swallow the tablets whole with water approximately the same time each day. The tablets should be taken with a meal. The tablets should not be chewed, crushed or broken before swallowing.

During the dose titration phase, Venetoclax should be taken in the morning to facilitate laboratory monitoring.

Women of childbearing potential must use a highly effective method of contraception while taking Venetoclax.

### **Missed Dose:**

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

If the 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.

## **Interactions ( see SPC )**

### **Seek Pharmacy advice for polypharmacy – numerous interactions**

CYP3A inhibitors may increase Venetoclax plasma concentration.

Concomitant use of Venetoclax with strong CYP3A inhibitors (e.g. ketoconazole, Ritonavir, clarithromycin, Itraconazole, Voriconazole, Posaconazole) on initiation and during the dose titration phase is contraindicated due to increased risk of tumour lysis syndrome. Concentration of Venetoclax may increase by five to eight-fold.

At initiation and during the dose titration phase, concomitant use of Venetoclax with moderate CYP3A inhibitors (e.g. erythromycin, ciprofloxacin, diltiazem, fluconazole, verapamil) should be avoided. Alternative treatments should be considered if a moderate CYP3A inhibitor must be used. The initiation dose of Venetoclax and the doses for the titration phase should be reduced by at least 50% and the patient should be monitored more closely.

For patients who have completed the dose titration phase and are on a steady daily dose of Venetoclax, the Venetoclax dose should be reduced by 50% when used concomitantly with moderate CYP3A inhibitors, by 70% when used concomitantly with strong CYP3A inhibitors. Monitoring should occur more frequently.

Grapefruit products, Seville oranges and star fruit (carambola) should be avoided during treatment with Venetoclax as they contain inhibitors of CYP3A

### **P-GP and BCRP inhibitors:**

Rifampicin may significantly increase the dose of Venetoclax. Concomitant use of Venetoclax with P-GP and BCRP inhibitors at initiation and during the dose titration phase should be avoided. If a P-GP and BCRP inhibitor must be used, the patient should be monitored closely for signs of toxicity.

### **Agents that may decrease Venetoclax plasma concentration:**

CYP3A inducers – concomitant use of Venetoclax with strong CYP3A inducers (e.g. carbamazepine, phenytoin and rifampicin) or moderate CYP3A inducers (e.g. efavirenz, etravirine, modafinil and nafcillin) should be avoided. Preparations containing St John's wort are contraindicated – efficacy may be reduced.

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

**Warfarin:** increase in plasma concentration with venetoclax use

### **Substrates of P-GP, BCRP and OATP1B1:**

Venetoclax is a D-GP, BCRP and OATP1B1 inhibitor in vitro. Co-administration of narrow therapeutic index substrates (e.g. digoxin, novel oral anticoagulants such as Dabigatran, everolimus, sirolimus) with Venetoclax should be avoided.

If such narrow therapeutic index substrates must be used, they should be used with caution and administration should be separated from Venetoclax as much as possible to minimise potential interaction.

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

### **Pregnancy and Breastfeeding:**

Not recommended during pregnancy or breastfeeding.

**Dr D.E. Howarth**

**Consultant Haematologist**

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