Chemotherapy Protocol

Chronic Lymphocytic Leukaemia

VENETOCLAX (high risk)

Regimen

- CLL – Venetoclax (high risk)

Indication

- Venetoclax is indicated for the treatment of adult

results have been evaluated (see section on TLS below). Consider admitting the patient for monitoring for TLS monitoring and treatment.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Consider blood transfusion or the use of erythropoietin according to NICE TA323 if patient symptomatic of anaemia or has haemoglobin of less than 8g/dL (80g/L).

Treatment with venetoclax should be withheld for grade 3 or 4 febrile neutropenia and/or infection, or other 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, the dose reduction guidelines in Table 2 should be followed when resuming treatment with venetoclax following recovery. A larger dose reduction may occur at the discretion of the physician. Discontinuation of venetoclax should be considered in patients who require dose reductions to less than 100 mg for more than 2 weeks

Hepatic Impairment

No dose adjustments are required in patients with mild 4.77753(s)-0.29938431968( )-4.77779(p)1.71

tumour lysis syndrome that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase. It is strongly recommended to admit the patient for monitoring initially.

The risk of tumour lysis syndrome is a continuum based on multiple factors, including co-morbidities. Patients with high tumour burden (e.g., any lymph node with a diameter greater than or equal to 5cm or high absolute lymphocyte count greater than or equal to $25x10^9$/L) are at greater risk of tumour lysis syndrome when initiating venetoclax and should be treated as high risk. Reduced renal function (creatinine clearance less than 80ml/min) further increases the risk. The risk may decrease as tumour burden decreases with venetoclax treatment. Drug interactions may also contribute. Always check for drug interactions.

Concomitant use of venetoclax with strong or moderate CYP3A inhibitors increases

Abnormality	Dose Modification and Management
	potassium less than ULN continue to monitor for TLS 2 and 4 hours later
Potassium more than or equal to 6.0mmol/l and/or symptomatic (e.g. muscle cramps, weakness, paraesthesia, nausea, vomiting or diarrhoea)	Hold venetoclax until resolution Refer to local hyperkalaemia guideline and seek advice from renal team. Recheck calcium, creatinine, phosphate, potassium and uric acid every hour
Hyperuricaemia	
Uric acid more than or equal to 476micromol/l	Hold venetoclax until resolution. Consider giving rasburicase if not given in last 24 hours.
Hypocalcaemia	
Adjusted calcium less than 1.75mmol/l or patient symptomatic (e.g. muscle cramps, hypotension, tetany, cardiac arrhythmias) in the presence of hypocalcaemia.	Hold venetoclax until resolution. Administer calcium gluconate 10% 10 to 20ml in 100ml sodium chloride 0.9% over 15minutes with ECG monitoring. Recheck calcium, creatinine, phosphate, potassium and uric acid every one to two hours.
Hyperphosphataemia	
Phosphate more than 1.45mmol/l and less than 1.67mmol/l	Withold venetoclax until resolution Does not require treatment. Recheck calcium, creatinine, phosphate, potassium and uric acid in 1 hour.
Phosphate 1.67 to 2.1mmol/L	Withold venetoclax until resolution to less than 1.45mmol/l Discuss with renal team as a phosphate binder may be necessary (e.g. calcium carbonate, sevelamer, lanthanum) Recheck calcium, creatinine, phosphate, potassium and uric acid in 1 hour.
Phosphate more than 2.1mmol/l	Withold venetoclax until resolution to less than 1.45mmol/l Discuss with renal team as a phosphate binder or haemodialysis may be required. Recheck calcium, creatinine, phosphate, potassium and uric acid in 1 hour.
Creatinine	
Increase of more than or equal to 25% from baseline.	Hold venetoclax until resolution Administer intravenous fluids. Recheck potassium, phosphate, uric acid, calcium and creatinine in 1 to 2 hours
LDH	
Increase of more than 50% from baseline	Hold venetoclax until level is back to baseline (check level weekly). Restart at previous dose level. If occurred on first dose restart at 10mg daily.

If biochemical changes suggestive of tumour lysis syndrome occur, the next venetoclax dose should be withheld .15818( )277.998]TJ 4569(o)1.32104(h)1.32034(oh)1.3211.32101(m)-4.4569.dio971( )-4

Dose Information

- Venetoclax is available as 10mg, 50mg and 100mg film-coated tablets.

- For patients who have had a dosing interruption lasting more than 1 week during the first 5 weeks of dose titration or more than 2 weeks when at the daily dose of 400mg, tumour lysis syndrome risk should be reassessed to determine if restarting at a reduced dose is necessary.

Administration Information

- Venetoclax film-coated tablets are for oral use. Patients should be instructed to swallow the tablets whole with a meal and water at approximately the same time each day. 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.

- It is imperative that the time of administration of the venetoclax is recorded on ARIA and the correct blood tests are taken at the correct time as part of any increase in the dose.

- If a patient misses a dose of venetoclax 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.

Additional Therapy

- Antiemetics

  As take home medication

  - metoclopramide 10mg three times a day when required oral

- Allopurinol 300mg once a day oral for 28 days oral starting on day 12 of cycle 1 to continue for 28 days.

- Calcium carbonate 1.5g or 1.25g (in line with local protocol) three times a day for 28 days oral starting on day 1 of cycle 1 only. Used as a phosphate binder to reduce the risk of dose delay due to hyperphosphataemia during the initial titration phase. Dose should be taken with food.

- Rasburicase 7.5mg intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes on cycle 1 days 1, 2, 8 and 9.

- 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 beftr4.47947( )-4.77687(t)-4.77687(i)15847(n)1.31968(i)4.47947(t) 6sTd (·)n1(u(y)10.576( )-4.77687

REGIMEN SUMMARY

Venetoclax (high risk)

Cycle 1

Day 1

Day 2

8. Rasburicase 7.5mg intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes

9. Sodium chloride 0.9% 500ml intravenous infusion over 120 minutes
   Administration Instruction
   Advise patient to drink an additional 1.5 litres of water during the day.

Take Home Medicines (day 2 only)

10. Venetoclax 20mg once a day for 6 days oral
    Administration Information
    Start on day 2 of the cycle. Dispense six days only.

    Take with or just after food. Take with a full glass of water.

    Oral chemotherapy

Day 8

11. Warning – Check in-patient administration
    Administration Instructions
    If the patient has been admitted for monitoring please check what was prescribed and administered either on the in-patient electronic or / and paper system and adjust this prescription accordingly. This prescription is designed for out-patient use and may not be used for an in-patient.

12. Rasburicase 7.5mg intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes
    Administration Instruction
    Administer after baseline blood sample has been taken

13. Sodium chloride 0.9% 1000ml intravenous infusion over 240 minutes
    Administration Instruction
    Advise patient to drink an additional litre of water during the day. 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 2L on daTd [ )10.43819( )-5.74

Take Home Medicines (day 8)

15. Venetoclax 50mg once a day for 1 day oral
    Administration Information
    Administer 50mg once a day on day 8 only, please record the time of administration by administering the "warning – administer venetoclax" in ARIA. This is to facilitate the diagnosis of TLS from the blood results. Administer the venetoclax one hour after the start of the sodium chloride 0.9% infusion. Ensure all the correct blood tests have been taken at the correct time.

    Dispense only one dose

    Take with or after food. Take with a full glass of water

    Oral chemotherapy

Day 9

16. Rasburicase 7.5mg intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes

17. Sodium chloride 0.9% 500ml intravenous infusion over 120 minutes
    Administration Instruction

Take Home Medicines (Day 16 only)

22. Venetoclax 100mg once a day for 6 days oral
    Administration Information
    Start on day 16 of the cycle. Dispense 6 days only.

    Take with or just after food. Take with a full glass of water.

    Oral chemotherapy

Day 22

23. Warning - Administer venetoclax
    Administration Instructions
    Administer venetoclax as per the dosage in the take home medicines, please record the time of administration by administering this warning in ARIA. This is to facilitate the diagnosis of TLS from the blood results.
    Ensure all the correct blood tests have been taken at the correct time and that the patient is drinking a minimum of 2 liters of fluid a day.

    Take with or after food. Take with a full glass of water.