Che other py Protoco_

Chronic Ly phocytic Le e i

R R X MAB ENE OCLAX high ris Cyc_e enetoc dose titr tion

Regimen

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.

Hae atological

Consider blood transfusion or the use of erythropoietin according to NICE TA323 if patient

Other

enetocla Tu our Lysis Syndro e TLS

Venetoclax can cause a rapid reduction in tumour, and thus poses a risk for tumour lysis syndrome in the initial 5-week dose-titration phase. Changes in electrolytes consistent with 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 if at risk of TLS.

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 CYP3A inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, ritonavir) at initiation and during the dose-titration phase is contraindicated due to increased risk for TLS.

At initiation and during the dose-titration phase, concomitant use of venetoclax with moderate CYP3A inhibitors (e.g., ciprofloxacin, diltiazem, erythromycin, 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%. Patients should be monitored more closely for signs and symptoms of TLS.

Prior to initiating venetoclax, tumour burden assessment, including radiographic evaluation (e.g. CT scan), must be performed for all patients. Blood chemistry (potassium, uric acid, phosphate, adjusted calcium, LDH and creatinine) should be assessed and pre-existing abnormalities corrected. cc sde781326d77753(i)4.4( )-4.7768048(y)10.576(t)-4.78( )-

A nor ity	Dose Modific tion nd M n ge ent
limit of normal (ULN))	potassium and uric acid in 1hour. If further 0.2mmol/l or more rise in potassium do an ECG and consider calcium gluconate and calcium resonium in line with local hyperkalaemia policy. Continue to monitor for TLS every 2 hours Resume protocol testing if change in potassium is less than 0.2mmol/l and no other evidence of TLS resume venetoclax.
Potasssium more than ULN but less than 6.0mmol/l	Hold venetoclax until resolution Do an ECG and consider calcium gluconate and calcium resonium in line with local hyperkalaemia policy. Recheck calcium, creatinine, phosphate, potassium and uric acid in 1 hour. If 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
yper ric e	
Uric acid more than or equal to 476micromol/l	Hold venetoclax until resolution. Consider giving rasburicase if not given in last 24 hours.
ypoc c e	
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.
yperphosph e	
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.

Abnormality	Dose Modification and Management
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
LD	
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.

Regimen

Cyc_e _ d^y cyc_e enetoc^ dose titr^tion

1 cycle will be set in ARIA. For cycle 2 see VR-Rituximab-Venetoclax cycle 2 onwards protocol.

his cyc_e wi_ e set p on AR A in d^y _oc s th^t c^n e prescri ed independent_y

Dr g	Dose	D^ys	Ad inistr^tion
Venetoclax	20mg*	1, 2, 3, 4, 5, 6, 7	Oral
	50mg*	8, 9, 10, 11, 12, 13, 14	
	100mg*	15, 16, 17, 18, 19, 20, 21	
	200mg*	22, 23, 24, 25, 26, 27, 28	
	400mg*	29, 30, 31, 32, 33, 34, 35	

*Day 1, 8, 15, 22 and 29 will be dispensed as a separate supply to allow evaluation for TLS on day 2, 9, 16, 23 and 30

Dose Information

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

VR-Rituximab-Venetoclax (high risk)

Cyc e

D y

1. 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.

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

3. 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 of water daily, 2 days prior to and the days of dosing at initiation and each subsequent dose increase. 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

4. 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. Administer the venetoclax at least 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.

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

   Oral chemotherapy.

Day 1

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

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

Day 1

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

18. 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 1 only

19. Venetoclax 50mg once a day for 6 days oral
    Administration Information
    Start on day 9 of the cycle. Dispense 6 days only.

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

    Oral chemotherapy

20. Allopurinol 300mg once a day for 28 days oral
    Administration information
    Start on day 12 of the cycle.

Day 2

21. 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.

    Oral chemotherapy

Take Home Medicines Day 2 only

22. Venetoclax 100mg once a day for 1 day oral
    Administration information
    Administer 100mg once a day on day 15 only. If appropriate please record the time of administration in the journal 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.

    Dispense only one dose

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

    Oral chemotherapy

Take Home Medicines Day 3 only

23. Venetoclax 100mg once a day for 6 days oral

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.

e o e Medicines D y on y

DOC MEN CON ROL

ersion	D te	A end ent	ritten By	Appro ed By
1	December 2019	None	Harriet Launders Pharmacist	Dr Andrew Duncombe Consultant Haematologist

Toaa smac t-2.234.846715 3555(4) g32101(m)-h.1971(t

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated fro s896077687(o)p7.996 6