Chemotherapy Protocol

Chronic Lymphocytic Leukaemia

VENETOCLAX (low risk)

Funding may be required for this regimen.

Regimen

- CLL – Venetoclax (low risk)

Indication

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

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

Toxicity

Drug	Adverse Effect
Venetoclax	Upper respiratory tract infection, neutropenia, anaemia, hyperphosphataemia and other electrolyte disturbances, tumour lysis syndrome (TLS), gastrointestinal disturbance, raised blood creatinine, fatigue.

The adverse effects listed are not exhaustive. Please refer to the relevant summary of product characteristics for further details.

Monitoring

Drugs

- Tumour burden assessment, including radiographic evaluation (e.g., CT scan) must be performed for all patients prior to starting venetoclax therapy.

- FBC, U&Es and LFTs should be measured prior to starting therapy and any pre-existing abnormalities corrected. For patients at risk of tumour lysis syndrome (TLS), blood chemistries should be monitored at 6 to 8 hours and at 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 chemistry results have been evaluated. The same monitoring schedule should be followed at each subsequent dose increase. 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 1 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 or moderate hepatic impairment. These patients should be monitored more closely for signs of toxicity at initiation and during the dose-titration phase as a trend for increased adverse events was observed in patients with moderate hepatic impairment in a population pharmacokinetic analysis.

It is not recommended to administer venetoclax to patients with severe hepatic impairment as safety in this patient group has not been established.

Renal Impairment

No dose adjustment is required for patients with mild or moderate renal impairment. However, patients with reduced renal function (CrCl less than 80 ml/min) may require more intensive prophylaxis and monitoring to reduce the risk of tumour lysis syndrome at initiation and during the dose-titration phase.

Safety in patients with severe renal impairment or on dialysis has not been established, and a recommended dose for these patients has not been determined.

Venetoclax should be administered to patients with severe renal impairment only if the benefit outweighs the risk and patients should be monitored closely for signs of toxicity due to increased risk of TLS.

Tumour Lysis Syndrome

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 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. Reduced renal function (creatinine clearance less than 80ml/min) further increases the risk. The risk may decrease as tumour burden decreases with venetoclax treatment. The table below defines the risk. Drug interactions may also contribute. Always check for drug interactions.

TLS Risk Category	Criteria
Low	All measurable lymph nodes with the largest diameter less than 5cm and a lymphocyte count less than $25x10^9$/L
Medium	All measurable lymph nodes with the largest diameter between 5cm to 10cm and a lymphocyte count less than $25x10^9$/L
High	Any measurable lymph node with the largest diameter more than 10cm or lymphocyte count greater than $25x10^9$/L and any measurable lymph nodes with the largest diameter between 5cm to 10cm or a lymphocyte count greater than $100x10^9$/L

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, phosphorus, calcium, and creatinine) should be assessed and pre-existing abnormalities corrected. The prophylaxis measures listed below should be followed.

Patients should be adequately hydrated during the dose-titration phase. 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 tumour lysis syndrome or for those who cannot maintain an adequate level of oral hydration.

Anti-hyperuricemic agents should be administered 2 to 3 days prior to starting treatment with venetoclax in patients with high uric acid levels or at risk of tumour lysis syndrome and may be continued through the titration phase.

Concomitant use of venetoclax with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during the dose-titration phase. These agents must not be prescribed together during this part of treatment

If biochemical changes suggestive of tumour lysis syndrome occur, the next venetoclax dose should be withheld. If the changes resolve within 24 to 48 hours of the last dose, treatment with venetoclax can be resumed at the same dose.

If clinical tumour lysis syndrome or biochemistry changes occur, that require more than 48 hours to resolve, treatment should be resumed at a reduced dose (see table below). When resuming treatment with venetoclax after interruption due to tumour lysis syndrome, the instructions for prevention of tumour lysis syndrome should be followed.

Dose modification for TLS and other toxicities during venetoclax treatment	
Dose at interruption (mg)	**Restart dose (mg[a])**
400	300
300	200
200	100
100	50
50	20
20	10
[a]The modified dose should be continued for 1 week before increasing the dose.	

Regimen

28 day cycle until disease progression or intolerance (6 cycles will be set in ARIA)

Cycle 1

This cycle will be set up on ARIA in 7 day blocks that can be prescribed independently

Drug	Dose	Days	Administration
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	

*Day one will be dispensed as a separate supply to allow evaluation for TLS on day 2

Cycle 2 onwards

Drug	Dose	Days	Administration
Venetoclax	400mg*	1-28 inclusive	Oral

*Day one of cycle two only will be dispensed as a separate supply to allow evaluation for TLS on day 2

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.
- 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.

- Grapefruit products, Seville oranges, and starfruit (carambola) should be avoided during treatment with venetoclax.

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 72 hours prior to venetoclax

- 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.

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to venetoclax.

- It must be made clear to all staff, including those in the community, that venetoclax must only be prescribed under the supervision of a consultant haematologist.

- There are many drug interactions associated with venetoclax. Always check for drug interactions. Some may affect timing of administration eg with TKIs

Coding

- Procurement – X71.5

- Delivery – X73.1

References
1.Abbvie Limited (2016) Venetoclax film-coated tablets Summary of Product Characteristics. Online at http://www.medicines.org.uk/emc/medicine/32650, accessed 16 January 2017.
2.Roberts AW, Davids MS, Pagel JM et al. (2016) Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia. New Engl J Med (2016): **374** (4); 311-22
3.Preston CL (ed), Stockley's Drug Interactions. London: Pharmaceutical Press. Online at https://www.medicinescomplete.com, accessed 16 January 2016.

REGIMEN SUMMARY

Venetoclax (low risk)

Take Home Medicines

Cycle 1

Day 1

1. Warning – Check hydration status
   Administration Instruction
   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.

2. Venetoclax 20mg once a day for 1 day oral
   Administration Information
   Take with or just after food, or a meal. Take with a full glass of water.

3. Allopurinol 300mg once a day for 28 days oral
   Administration Instructions
   Start 72 hours prior to the first dose of venetoclax

4. Metoclopramide 10mg three times a day when required for the relief of nausea oral
   Administration Instructions
   Please supply 28 tablets or nearest equivalent pack size

Day 2, 3, 4, 5, 6, 7

5. Venetoclax 20mg once a day for 6 days oral
   Administration Information
   Take with or just after food, or a meal. Take with a full glass of water.

Day 8

6. Warning – Dose escalation and hydration
   Administration instructions
   Please note this dose has been automatically escalated by ARIA, please check the dose is appropriate for the patient.

   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.

7. Venetoclax 50mg once a day for 7 days oral
   Administration Information
   Take with or just after food, or a meal. Take with a full glass of water.

Day 15

8. Warning – Dose escalation and hydration
   Administration instructions
   Please note this dose has been automatically escalated by ARIA, please check the dose is appropriate for the patient.

   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.

9. Venetoclax 100mg once a day for 7 days oral
   Administration Information
   Take with or just after food, or a meal. Take with a full glass of water.

Day 22

10. Warning – Dose escalation and hydration
    Administration instructions
    Please note this dose has been automatically escalated by ARIA, please check the dose is appropriate for the patient.

    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.

11. Venetoclax 200mg once a day for 7 days oral
    Administration Information
    Take with or just after food, or a meal. Take with a full glass of water.

Cycle 2

Day 1

12. Warning – Dose escalation and hydration
    Administration instructions
    Please note this dose has been automatically escalated by ARIA, please check the dose is appropriate for the patient.

    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.

13. Venetoclax 400mg once a day for 1 days oral
    Administration Information
    Take with or just after food, or a meal. Take with a full glass of water.

14. Allopurinol 300mg once a day for 28 days oral

15. Metoclopramide 10mg three times a day when required for the relief of nausea oral
    Administration Instructions
    Please supply 28 tablets or nearest equivalent pack size

Day 2

Take Home Medicines

1. Venetoclax 400mg once a day for 27 days oral
   Administration Information
   Take with or just after food, or a meal. Take with a full glass of water.

Cycle 3

Day 1

1. Venetoclax 400mg once a day for 28 days oral
   Administration Information
   Take with or just after food, or a meal. Take with a full glass of water.

16. Allopurinol 300mg once a day for 28 days oral

17. Metoclopramide 10mg three times a day when required for the relief of nausea oral
    Administration Instructions
    Please supply 28 tablets or nearest equivalent pack size

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	February 2017	None	Eleanor Taylor Pharmacist	Dr Andrew Duncombe Consultant Haematologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines.