Chemotherapy Protocol

Chronic Lymphocytic Leukaemia

VR-RITUXIMAB-VENETOCLAX (high risk) (Cycle 2 onwards)

Regimen

- CLL – VR Rituximab Venetoclax (high risk) Cycle 2 onwards

Indication

- Venetoclax with rituximab is indicated for the treatment of adult patients with previously treated chronic lymphocytic leukaemia (CLL) who have had at least one previous therapy.
- Note that venetoclax up titration to 400mg daily (or equivalent if dose reduced for concomitant use of interacting medicine), with careful monitoring for tumour lysis syndrome, should be completed **before** initiating rituximab.

Toxicity

Drug	Adverse Effect
Rituximab	Severe cytokine release syndrome, increased incidence of infective complications, progressive multifocal leukoencephalopathy
Venetoclax	Upper respiratory tract infection, neutropenia, anaemia, hyperphosphataemia, 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 – see ramp up protocol.

- Viral screening is required before starting treatment including Hepatitis B surface antigen, core antibody and HIV status.

- FBC, U&Es (including potassium, phosphate, LDH, adjusted calcium, magnesium and uric acid) and LFTs should be measured prior to each cycle

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 (neutrophils less than $1x10^9$/l) and/or infection, or other grade 4 haematological toxicities (neutrophils less than $0.5x10^9$/l or platelets less than $25x10^9$/l), 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

Table 1 Venetoclax dose modifications for TLS and other toxicities

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.	

Hepatic Impairment

No dose adjustments are required for either rituximab or venetoclax 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.

For venetoclax no dose adjustment is recommended in patients with mild or moderate hepatic impairment. Patients with moderate hepatic impairment should be monitored more closely for signs of toxicity at initiation and during the dose-titration phase.

A dose reduction of at least 50% throughout treatment is recommended for patients with severe hepatic impairment (Child Pugh C or bilirubin more than 3xULN). These patients should be monitored more closely for signs of toxicity.

Renal Impairment

No dose adjustments are required for either rituximab or venetoclax 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 (creatinine clearance less than 30ml/min) only if the benefit outweighs the risk and patients should be monitored closely for signs of toxicity due to increased risk of TLS.

Other

Venetoclax Tumour Lysis Syndrome (TLS)

See cycle 1 ramp up protocol for further detail

Rituximab

Infusion related adverse reactions have been observed in 10% of patients treated with rituximab.

Rituximab administration is associated with the onset of cytokine release syndrome. This condition is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. It may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, acute renal failure, elevated lactate dehydrogenase (LDH) and can lead to acute respiratory failure and death. This effect on the lungs may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray.

Cytokine release syndrome frequently occurs within one or two hours of initiating the first infusion.

Hypersensitivity reactions, including anaphylaxis, have been reported following the intravenous administration of proteins. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes of starting the infusion. Medicinal products for the treatment of allergic reactions should be available for immediate use in the event of hypersensitivity developing during the administration of rituximab.

Use of rituximab maybe associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological, cognitive or psychiatric symptoms that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed the rituximab must be permanently discontinued.

The presence of a viral upper respiratory tract infection at the time of treatment may increase the risk of rituximab associated hepatotoxicity. Patients should be assessed for any cold or flu-like symptoms prior to treatment

Regimen

28 day cycle to continue for 2 years from first dose of rituximab

Cycle 2

Drug	Dose	Days	Administration
Venetoclax	400mg	1-28 inclusive	Oral
Rituximab	375mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9%

Cycles 3 to 7

Drug	Dose	Days	Administration
Venetoclax	400mg	1-28 inclusive	Oral
Rituximab	500mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9%

Cycles 8 to 27

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

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: refer to cycle 1 ramp up protocol.
- Rituximab dose will be rounded to the nearest 100mg (up if halfway)

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.
- 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.

Extravasation

- Rituximab - neutral

Other

The rate of administration of rituximab varies. Please refer to the rituximab administration guidelines

Additional Therapy

- Antiemetics

  As take home medication

  - metoclopramide 10mg three times a day when required oral
- Anti-infective prophylaxis including:

  - aciclovir 400mg twice a day oral
  - consider co-trimoxazole 960mg once a day oral on Monday, Wednesday and Friday only
- 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.

- Rituximab pre-medication

  30 minutes prior to rituximab

  - chlorphenamine 10mg intravenous
  - hydrocortisone 100mg intravenous (may be omitted if the patient is already taking steroids)
  - paracetamol 1000mg oral

- Rituximab infusion reactions

  - hydrocortisone 100mg intravenous when required for rituximab infusion related reactions
  - salbutamol 2.5mg nebule when required for rituximab related bronchospasm
  - consider pethidine 25-50mg intravenous for rituximab related rigors that fail to respond to steroids.

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.

- Venetoclax interacts with many other medications. Always check for drug interactions.

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

Coding

- Procurement – X71.5 (cycles 1 and 8 to 27); X70.8 (cycles 2 to 7)

- Delivery – X71.3 (cycles 1 and 8 to 27); X72.9 (cycles 2 to 7)

References

1.Abbvie Limited (2016) Venetoclax film-coated tablets Summary of Product Characteristics. Online at http://www.medicines.org.uk/emc/medicine/32650, accessed 29 October 2019.
2. NICE guidance TA561 Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia.
4. Wessex Blood and Marrow Transplant Tumour Lysis Prevention and Management Policy (Adults) version 1.0

REGIMEN SUMMARY

VR-Rituximab-Venetoclax (high risk) Cycle 2 onwards

Cycle 1

1. **Warning:** this protocol starts at cycle 2 and should always be preceded by VR-Rituximab-Venetoclax dose titration. Check dates when prescribing cycle 2.

Cycle 2

Day 1

1. **Warning:** this protocol starts at cycle 2 and should always be preceded by VR-Rituximab-Venetoclax dose titration. Check dates when prescribing cycle 2.
2. Chlorphenamine 10mg intravenous injection
3. Hydrocortisone 100mg intravenous injection
4. Paracetamol 1000mg oral
5. Rituximab 375mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines
6. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions
7. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

Take Home Medicines

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

   Oral chemotherapy
9. 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
10. Aciclovir 400mg twice a day for 28 days oral
    Administration Instructions
    Please supply 28 days or an original pack if appropriate.

Cycles 3 to 7

Day 1

11. Chlorphenamine 10mg intravenous injection

12. Hydrocortisone 100mg intravenous injection

13. Paracetamol 1000mg oral

14. Rituximab 500mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines

15. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions

16. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

Take Home Medicines

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

    Oral chemotherapy

18. 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

19. Aciclovir 400mg twice a day for 28 days oral
    Administration Instructions
    Please supply 28 days or an original pack if appropriate.

Cycles 8 to 27

Take Home Medicines

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

    Oral chemotherapy

21. 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

22. Aciclovir 400mg twice a day for 28 days oral
    Administration Instructions
    Please supply 28 days or an original pack if appropriate.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	December 2019	None	Harriet Launders 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. These protocols should be used in conjunction with other references such as the Summary of Product Characteristics and relevant published papers.