

Chemotherapy Protocol

Acute Myeloid Leukaemia

CYTARABINE (SC) - VENETOCLAX

Regimen

- AML – Cytarabine (SC) -Venetoclax

Indication

- Newly diagnosed acute myeloid leukaemia (AML).
- Patient has had/is having molecular analysis performed.
- Patient has de novo AML or secondary AML.
- Patients most recent bone marrow blast count shows more than 30% blasts
- Standard intensive chemotherapy is unsuitable due to age, fitness or the presence of significant co-morbidities
- Patient has been prospectively assessed for the risk of development of tumour lysis syndrome with venetoclax and that appropriate risk mitigation strategies have been put in place.
- Venetoclax will be continued until disease progression or unacceptable toxicity or withdrawal of patient consent or an elective decision to discontinue treatment consequent to a sustained complete remission to therapy. If venetoclax is stopped for any of the above reasons, no further venetoclax can be prescribed.
- a formal medical review as to whether treatment with venetoclax should continue will occur at least by the end of the second cycle of treatment.
- Antifungal prophylaxis with posaconazole or voriconazole will be given (unless there is intolerance of such antifungal prophylaxis).
- ECOG performance status 0,1, 2, 3

Warnings

- Hospitalisation is recommended for the first 5 days of cycle one, during the dose titration of venetoclax and for 24 hours after dose titration.
- the patient must be assessed specifically for potential drug interactions with venetoclax.

Toxicity

Drug	Adverse Effect
Cytarabine	Nausea, vomiting, diarrhoea, fever, rash, anorexia, oral and anal inflammation or ulceration, and hepatic dysfunction.
Venetoclax	Thrombocytopenia, neutropenia, febrile neutropenia, anaemia, Upper respiratory tract infection, neutropenia, anaemia, nausea, diarrhoea, vomiting, fatigue, pneumonia, electrolyte disturbances, TLS, and decreased appetite.

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

Monitoring

Drugs

- Viral screening is required before starting treatment including Hepatitis B surface antigen, core antibody and HIV status.
- FBC, U&Es (including potassium, serum bicarbonate, blood urea nitrogen, phosphate, LDH, creatinine, adjusted calcium and uric acid) and LFTs should be measured prior to starting therapy and pre-existing electrolyte abnormalities corrected. There is a risk of tumour lysis syndrome (TLS) hence it is necessary to monitor potassium, uric acid, phosphate, adjusted calcium, LDH and creatinine at 6 to 8 hours and at 24 hours after the first dose and during each dose increase 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 (see section on TLS below).

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).

Adverse Reaction	Occurrence	Dosage Modification
Haematologic Adverse Reactions		
Grade 4 neutropenia (ANC less than 500/microlitre) with or without fever or infection; or grade 4 thrombocytopenia (platelet count less than 25×10^3 /microlitre)	Occurrence prior to achieving remission	In most instances, do not interrupt venetoclax in combination with cytarabine.
	First occurrence after achieving remission and lasting at least 7 days	Delay subsequent cycle of venetoclax in combination with cytarabine and monitor blood counts. Administer granulocyte-colony stimulating factor (G-CSF) if clinically indicated for neutropenia. Upon resolution to grade 1 or 2, resume venetoclax at the same dose in combination with cytarabine.
	Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer	Delay subsequent cycle of venetoclax in combination with cytarabine and monitor blood counts. Administer G-CSF if clinically indicated for neutropenia. Upon resolution to grade 1 or 2, resume venetoclax at the same dose in combination with cytarabine and reduce venetoclax duration by 7 days during each of the subsequent cycles, such as 21 days instead of 28 days.

Hepatic Impairment

Cytarabine

Drug	Bilirubin	AST/ALT	Dose (% of original dose)
Cytarabine	Greater than 34	N/A	50% Escalate doses in subsequent cycles in the absence of toxicity

Venetoclax

No dose adjustments are required in patients with mild (normal total bilirubin and AST/ALT > ULN or total bilirubin 1-1.5xULN or Child-Pugh A) or moderate hepatic impairment (total bilirubin 1.5-3xULN or Child-Pugh B). 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.

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

If grade 3-4 abnormal liver function tests (ALT, AST or bilirubin) hepatotoxic drugs should be withheld (including azole antifungals) until resolved to grade 2 or below. Withhold venetoclax if no improvement to grade 2 or below. Venetoclax may be restarted at the original dose when resolved to grade 2 or below.

Renal Impairment

Venetoclax

No dose adjustment for venetoclax is needed for patients with mild, moderate or severe impairment (CrCl \geq 15ml/min and <90ml/min). Venetoclax should be administered to patients with severe renal impairment (CrCl \geq 15ml/min and 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. 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.

Cytarabine

No dose adjustment necessary.

Tumour Lysis Syndrome

All patients should have white blood cell count less than $25 \times 10^9/l$ prior to initiation of venetoclax and cyto-reduction prior to treatment may be required.

All patients should be adequately hydrated and receive anti-hyperuricaemic agents prior to initiation of first dose of venetoclax and during dose-titration phase.

Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with venetoclax.

Monitor blood chemistries for TLS at pre-dose, 6 to 8 hours after each new dose during titration and 24 hours after reaching final dose.

For patients with risk factors for TLS (e.g. circulating blasts, high burden of leukaemia involvement in bone marrow, elevated pre-treatment LDH or reduced renal function) additional measures should be considered, including increased laboratory monitoring and reducing venetoclax starting dose.

Table 1 - Tumour lysis syndrome (TLS) management whilst on venetoclax

Abnormality	Dose modification and management
Hyperkalaemia	
Potassium more than or equal to 0.5mmol/l increase from prior value (and within upper limit of normal (ULN))	Hold venetoclax until resolution Recheck calcium, creatinine, phosphate, 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.
Potassium 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
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.	Consider holding venetoclax until resolution. If required 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.
Hyperphosphatemia	
Phosphate more than 1.45mmol/l and less than 1.67mmol/l	Withhold 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	Withhold 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	Withhold 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

If biochemical changes suggestive of tumour lysis syndrome occur, the next venetoclax dose should be withheld and remainder of treatment dose 0.2mg/kg/day (less any prophylactic dose already given) should be given. Blood electrolytes (potassium, phosphate, uric acid, calcium and creatinine) should be carefully monitored and responded to every 2 hours to assess TLS response or progression until patient stable. 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.

Table 2: Venetoclax dose modifications

Dose modification for TLS and other toxicities during venetoclax treatment	
Dose at interruption (mg)	Restart dose (mg)
400	300
300	200
200	100
100	50
50	20
20	10

[Other grade 3 or 4 toxicity related to venetoclax](#)

Venetoclax should be withheld until the toxicity has resolved to grade 2 or below and restarted at the original dose.

[Regimen](#)

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

Cycle 1

Drug	Dose	Days	Administration
Cytarabine	20mg/m ²	1, 2, 3, 4, 5, 6, 7, 8, 9, 10	Subcutaneous injection
Venetoclax	100mg	1	Oral
	200mg	2	
	400mg	3	
	100mg*	4-28	

Cycle 2 onwards

Drug	Dose	Days	Administration
Cytarabine	20mg/m ²	1, 2, 3, 4, 5, 6, 7, 8, 9, 10	Subcutaneous injection
Venetoclax	100mg*, **	1-28 inclusive	Oral

*Venetoclax dose from day 4 of cycle 1 adjusted due to interaction with azole antifungal prophylaxis. If azole antifungal prophylaxis is contraindicated venetoclax 600mg once a day is funded.

** Consideration should be given to the dosing scheduled in cycle 2 onwards being for 14 days of each 28 days as per the NICE clinical expert submission.

[Dose Information](#)

- Cytarabine will be dose banded according to the national dose bands (20mg/ml).
- Venetoclax is available as 10mg, 50mg and 100mg film-coated tablets.

[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.

- Subcutaneous cytarabine may be administered in the out-patient setting. For patients to receive this care in the community there must be clear arrangements for medical authorisation, support, problem-solving and emergency action between community services and the referring hospital.
- Cycles should ideally begin on a Monday, Tuesday or Wednesday so that only one weekend is included in each 10 days of cytarabine treatment.

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 during cycle 1.
- Patients should be adequately hydrated during the venetoclax 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.
- Antifungal prophylaxis
 - Posaconazole tablets 300mg twice a day on D4, then 300mg once a day thereafter
 - Voriconazole tablets 400mg twice a day on D4, then 200mg twice a day thereafter

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

References

1. Agarwal SK et al (2017) Management of Venetoclax-Posaconazole Interaction in Acute Myeloid Leukemia Patients: Evaluation of Dose Adjustments. Clin Ther. 2017 Feb;39(2):359-367
2. Abbvie. Venclyxto® Summary of Product Characteristics. Updated 25.02.22. Accessed on 13.06.22 via <http://www.medicines.org.uk/emc>.
3. Bristol Myers Squibb Pharmaceuticals Limited. Vidaza® Summary of Product Characteristics. Updated 30/05.2022. Accessed on 14.06.2022 via <http://www.medicines.org.uk/emc>

4. Weu A G et al (2020). Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood*. 2020 June; 135 (24): 2137-2145.

REGIMEN SUMMARY

Cytarabine (SC) - Venetoclax

Cycle 1

Day 1

1. Cytarabine 20mg/m² subcutaneous bolus.

Administration Instruction

Administer into the thigh or abdomen. Rotate injection sites.

Ensure adequate provision is in place to allow administration in the community. Pharmacy if this is to be given in the community please label accordingly.

If this is being given in an out-patient setting please record the administration in the patients journal on ARIA.

Take home Day 1

2. 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.

3. Venetoclax 100mg 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.

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

Administration Instructions

Start 72 hours prior to the first dose of venetoclax

5. 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

6. Cytarabine 20mg/m² subcutaneous bolus.

Administration Instruction

Administer into the thigh or abdomen. Rotate injection sites.

Ensure adequate provision is in place to allow administration in the community. Pharmacy if this is to be given in the community please label accordingly.

If this is being given in an out-patient setting please record the administration in the patients journal on ARIA.

To take home day 2

7. 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.

8. Venetoclax 200mg 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.

Day 3

9. Cytarabine 20mg/m² subcutaneous bolus.

Administration Instruction
Administer into the thigh or abdomen. Rotate injection sites.

Ensure adequate provision is in place to allow administration in the community. Pharmacy if this is to be given in the community please label accordingly.

If this is being given in an out-patient setting please record the administration in the patients journal on ARIA.

To take home day 3

10. 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.

11. Venetoclax 300mg 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.

Day 4

12. Cytarabine 20mg/m² subcutaneous bolus.

Administration Instruction
Administer into the thigh or abdomen. Rotate injection sites.

Ensure adequate provision is in place to allow administration in the community. Pharmacy if this is to be given in the community please label accordingly.

If this is being given in an out-patient setting please record the administration in the patients journal on ARIA.

To take home day 4

13. 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.

14. Warning – Check Venetoclax Dose

Administration Instructions
If antifungal prophylaxis contraindicated consider increasing the dose of venetoclax to 600mg once a day

15. Venetoclax 100mg once a day for 25 days oral

Administration Information
Take with or just after food, or a meal. Take with a full glass of water.

If antifungal prophylaxis contraindicated consider increasing the dose of venetoclax to 600mg once a day.

16. Antifungal prophylaxis

Administration instructions
The choice of antifungal prophylaxis is dependent on local formulary and may include:

- a. Posaconazole tablets 300mg twice a day on D4, then 300mg once a day on day 5-28.
- b. Voriconazole tablets 400mg twice a day on D4, then 200mg twice a day on day 5-28.

Day 5, 6, 7, 8, 9, 10

17. Cytarabine 20mg/m² subcutaneous bolus.

Administration Instruction
Administer into the thigh or abdomen. Rotate injection sites.

Ensure adequate provision is in place to allow administration in the community. Pharmacy if this is to be given in the community please label accordingly.

If this is being given in an out-patient setting please record the administration in the patients journal on ARIA.

Cycle 2 onwards

To take home day 1

18. Cytarabine 20mg/m² subcutaneous bolus once a day for 10 days

Administration Instruction
Administer into the thigh or abdomen. Rotate injection sites.

Ensure adequate provision is in place to allow administration in the community. Pharmacy if this is to be given in the community please label accordingly.

If this is being given in an out-patient setting please record the administration in the patients journal on ARIA. There will be no means of electronically administering the agent on ARIA as it has been set up as a take home medicine.

19. Venetoclax 100mg 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.

If antifungal prophylaxis contraindicated consider increasing the dose of venetoclax to 600mg once a day.

20. 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

21. Antifungal prophylaxis

Administration instructions
The choice of antifungal prophylaxis is dependent on local formulary and may include:

- Posaconazole tablets 300mg once a day for 28 days.
- Voriconazole tablets 200mg twice a day for 28 days.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	June 2022	None	Alexandra Pritchard Pharmacist	Edward Belsham 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.