PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

AZACITIDINE AND VENETOCLAX ACUTE MYELOID LEUKAEMIA

PROTOCOL REF: MPHAAVAML
(Version No. 1.0)

Approved for use in:

- Patient's with untreated acute myeloid leukaemia who are unsuitable for intensive chemotherapy.

Blueteq registration required

Dosage Cycle One:

Drug	Dose	Route	Frequency
Azacitidine	**75mg/m^2**	SC	Once daily for 7 consecutive weekdays (cannot be given over a weekend)
Venetoclax	**Day 1: 100mg** **Day 2: 200mg** **Day 3: 300mg** **Days 4 to 28: 100mg**	PO	Once daily

Dosage Subsequent Cycles:

Drug	Dose	Route	Frequency
Azacitidine	**75mg/m^2**	SC	For 7 consecutive weekdays, Starting from Day 1
Venetoclax	**100mg once daily**	PO	Days 1 to 28 (often reduced to 14 or 21 days due to tolerance or response)

28-day cycle.

Treatment should continue until disease progression or unacceptable toxicity. Patient may proceed to allograft when in remission and a donor is available (minimum two cycles).

Administration and Counselling Points:

Tumour Lysis Syndrome (TLS)

- Patients at high/medium risk of TLS must be admitted for their first dose of venetoclax for monitoring purposes.
- Risk factors include: circulating blasts, high leukaemic burden in bone marrow, elevated LDH and existing renal impairment (consider reduced initial dosing)
- All patients should have white blood cell count <25 × 10^9/L prior to initiation of venetoclax. Cytoreduction prior to treatment may be required.
- TLS can occur within 6-8 hours of initiation and/or dose titration.

TLS Blood Monitoring

- Pre-initiation: chemistry profile and bone profile (including potassium, phosphate, calcium, creatinine, urea and uric acid) should be performed prior to venetoclax initiation. All electrolyte abnormalities must be corrected before commencing/titrating venetoclax.
- Dose titration: TLS blood monitoring above should be checked 6 to 8 hours after each dose titration and 24 hours after the final dose titration (patients will need admitting for monitoring if this can't be done in the day case setting). All electrolyte abnormalities must be corrected before commencing/titrating venetoclax.

Azacitidine Administration:

- Allow the azacitidine to reach room temperature before administering.
- The contents of the syringe(s) should be re-suspended immediately prior to administration by vigorously rolling the syringe(s) between the palms until a uniform, cloudy suspension is achieved. The product should be discarded if it contains any large particles or agglomerates.
- Inject subcutaneously using a 25 gauge needle into the upper arm, thigh or abdomen.
- The needle should not be purged prior to injection, in order to reduce the incidence of local injection site reactions.
- Injection sites should be rotated between arms, thighs and abdomen, new injections should be given at least 2.5cm away from previous sites.

Venetoclax Administration

- Take daily at approximately the same time each day.
- Take with or just after food or a meal (preferably morning to facilitate lab monitoring).
- Swallow whole. Do not crush or chew medication.
- Avoid grapefruit products, Seville oranges and star fruit due to interaction.
- Maintain adequate hydration - aim to drink 1.5–2 litres of water daily, starting 2 days before and throughout the dose-titration phase (due to risk of tumor lysis syndrome (TLS), especially during days of dose titration.

Missed Doses

- If the 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 the 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.
- If dose missed for more than two weeks within the first cycle then restart titration.
- If vomiting occurs following dose administration, no additional doses should be taken on that day and the next dose should be taken at the normal time.

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

- Allopurinol 300mg once daily for cycle 1, starting 2 days before treatment. Consider rasburicase in high risk patients. IV fluids may be required prior to the first dose and each subsequent dose increase to reduce TLS risk.
- Aciclovir 400mg twice a day
- Posaconazole 300mg twice daily for 1 day, once daily thereafter**. To start on day 4 of cycle one. NB If a patient does not require posaconazole (e.g. in remission after the first two cycles and is not neutropenic; or cannot tolerate), the venetoclax dose should be increased to 400mg once daily, starting 2 to 3 days after stopping the posaconazole.**

- Ciprofloxacin 500mg twice daily
- Ondansetron 8mg twice daily when required

Extravasation risk:

- Azacitidine - Non-vesicant

Interactions:

Strong CYP3A Inhibitors (excluding posaconazole)

Exclude concomitant use of venetoclax with strong CYP3A inhibitors (e.g. itraconazole, ketoconazole, voriconazole, clarithromycin, ritonavir, saquinavir, telaprevir, telithromycin) at initiation and during the dose-titration phase. For patients on steady daily dose venetoclax, reduce the venetoclax dose by 75% when used concomitantly with strong CYP3A inhibitors (if not already reduced due to concurrent azole antifungal prophylaxis). Resume the venetoclax dose used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor. Grapefruit products, Seville oranges, and starfruit (carambola) should be avoided for 3 days prior to and during treatment with venetoclax as they contain inhibitors of CYP3A.

Moderate CYP3A Inhibitors and P-gp Inhibitors

Avoid concomitant use of moderate CYP3A inhibitors (e.g. ciprofloxacin, diltiazem, erythromycin, fluconazole, verapamil) or P-gp inhibitors (e.g amiodarone, azithromycin, captopril, carvedilol, cyclosporine, felodopine, quinidine, ranolazine, ticagrelor) with venetoclax during initiation and dose-titration phase. Consider alternatives but if an inhibitor must be used, reduce the initiation/titration doses of venetoclax by 50%. Monitor for signs of toxicity. Resume the venetoclax dose that was used prior to initiating the inhibitor 2 to 3 days after discontinuation of the inhibitor.

CYP3A Inducers

Avoid concomitant use of venetoclax with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St John's Wort) or moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided. Alternative treatments with less CYP3A induction should be considered.

For more detailed interactions please refer to the SPC:

- Azacitidine: https://www.medicines.org.uk/emc/product/6468/smpc#gref
- Venteoclax: https://www.medicines.org.uk/emc/product/10476/smpc#gref

Treatment schedule Cycle 1:

NB. Venetoclax is given continuously throughout the cycle. Azacitdine is given for 7 days but only on weekdays. The days of treatment may vary depending which day of the week day 1 falls. To assist with biochemistry monitoring, the regime should ideally be started between Monday and Thursday unless clinically urgent.

Day	Drug	Dose	Route
1	**Venetoclax**	**100mg**	**PO**
	Azacitidine	**75mg/m^2**	**SC**
2	**Venetoclax**	**200mg**	**PO**
	Azacitidine	**75mg/m^2**	**SC**
3	**Venetoclax**	**300mg**	**PO**
	Azacitidine	**75mg/m^2**	**SC**
4, 5, 8 and 9	**Azacitidine**	**75mg/m^2**	**SC**
4 to 28	**Venetoclax**	**100mg**	**PO**

Treatment schedule for subsequent cycles:

NB: Venetoclax is given on days 1 to 14. Azacitdine is given for 7 days but only on weekdays. The days of treatment may vary depending on which day of the week day 1 falls.

Day	Drug	Dose	Route
1 to 5, 8 and 9	**Azacitidine**	**75mg/m^2**	**SC**
1 to 28 (often reduced to 1 to 14)	**Venetoclax**	**100mg**	**PO**

Investigations and treatment plan:

	Pre	Cycle 1 D1	Cycle 1 D2	Cycle 1 D3	Cycle 1 D4	Cycle 1 D5	Cycle 1 D8	Cycle 1 D9	Cycle 2+ D1	Cycle 2+ D2	Cycle 2+ D3	Cycle 2+ D4	Cycle 2+ D5	Cycle 2+ D8	Cycle 2+ D9	Ongoing
Informed consent	x															
Clinical Assessment	x								x							Every cycle
SACT Assessment (including PS and toxicities assessment)		x	x	x	x	x	x	x	x	x	X	x	x	x	x	Prior to each azacitidine dose
FBC, LFT, Chemistry profile	x	x		x		x	x		x							Bloods must be taken within 7 days prior to day 1 of each cycle
TLS blood monitoring		x	x	x	x	x										6-8 hours after each titration and 24 hours after final titration
CrCl (Cockcroft and Gault)	x	x								x						Every cycle
Bone marrow	x								x							Prior to cycle 2 and as clinically indicated
Height	x															
Weight recorded		x							x							Every cycle
Pregnancy test	x															If applicable

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea, tumour lysis syndrome, venous thromboembolism and peripheral neuropathy.

Dose Modifications and Toxicity Management:

Haematological toxicity:

Cycle 1 should proceed regardless of cytopenias and should not be interrupted for haematological toxicity prior to documentation of marrow response (day 21-28).

Subsequent cycles should proceed if –

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 75 x 10^9/L

If ANC<1.0 x10^9/L or platelets <75 x10^9/L:

Haematological Toxicity		Modification
Following cycle 1 – if not in complete remission	**Prior to next cycle:** Neutrophils <1.0 x10^9/L or Platelets <75 x10^9/L	If blast clearance confirmed then GCSF may be commenced until neutrophil recovery. If not then continue treatment without reduction in dose / cycle length.
After complete remission	**Prior to next cycle:** Neutrophil <1.0 x10^9/L or Platelets <75 x10^9/L	Delay for 1 week, consider commencing GCSF until resolution. Recommence venetoclax at previous dose once recovered.
	Neutrophil <0.5 x10^9/L or Platelets <25 x10^9/L **Persisting beyond day 42 of previous cycle**	1st occurrence: - Reduce venetoclax from 28 days to 21 days
		Subsequent occurrence: - Reduce venetoclax from 21 to 14 days - Consider reduction of azacitidine to 5 days per cycle

Patients who do not achieve complete remission after cycle 2 should be discussed at MDT.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non-Haematological toxicity

In the event of any grade 3 or 4 toxicities venetoclax should be withheld until resolved to ≤grade 2 and restarted at the original dose.

Dosing in renal and hepatic impairment:

Azacitidine

Renal	
No dose adjustment required for renal impairment or haemodialysis	
Liver	
Mild or moderate liver impairment	No adjustment required
Albumin <30g/L or advanced malignant hepatic tumours	Not recommended

Venetoclax

Renal	
CrCl (ml/min)	**Recommendation**
30 to 80	No dose adjustment required but these patients may require more intensive prophylaxis and monitoring to reduce the risk of TLS at initiation and during the dose-titration phase
<30 or dialysis	Limited information available. Clinical decision
Liver	
ALT >175 units/L and/or bilirubin > 63 µmol/L	Withhold venetoclax and any hepatotoxic drugs (e.g. azoles) until ALT reduces to <175 and bilirubin <63. Then restart all applicable drugs at the original dose.
Severe hepatic impairment	Reduce venetoclax by 50%

References:

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3. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.
4. Di Nardo et al. (2018), Safety and efficacy of venetoclax with decitabine and azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. Di Nardo et al. Lancet Oncol 19: 216-228
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7. National Cancer Drug Fund List (04/2022),.NHS England, Version 1.210, pg57: https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-v1.210.pdf
8. Venetoclax with azacitidine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable. NICE Guidance [TA765]. Published 02/2022. https://www.nice.org.uk/guidance/ta765

Circulation/Dissemination

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Version History

Date	Version	Author name and designation	Summary of main changes
July 2022	1.0	**Thomas Sanders** **Advanced Pharmacist- Clinical Trials**	New Regimen Protocol