Thames Valley Cancer Alliance

Myeloid group

AZACITIDINE and VENETOCLAX

INDICATION

Untreated adult AML when intensive chemotherapy is unsuitable **(NICE TA 765 – Blueteq required**)

TREATMENT INTENT

Disease modification

PRE-ASSESSMENT

1. Blood tests - FBC, coagulation screen, DAT, U&Es, urate, creatinine, eGFR, LFTs, glucose, Hepatitis B core antibody and Hepatitis B surface Ag, Hepatitis C antibody after consent, group and save.
2. Ensure histology is confirmed prior to administration of chemotherapy and document in notes
3. Record clinical impact of disease, blood film, bone marrow aspirate and trephine, immunophenotype, cytogenetic results.
4. Urine pregnancy test - before cycle 1 of each new therapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy.
5. ECG.
6. Record performance status (WHO/ECOG).
7. Record height and weight.
8. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment, and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
9. Consider dental assessment / advise dental check is carried out by patient's own dental practitioner before treatment starts.
10. Treatment should be agreed in the relevant MDT.
11. Ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures.
12. Hydration and tumor lysis syndrome (TLS) prophylaxis: provide prophylactic hydration and anti-hyperuricaemics. **To mitigate the risk of TLS, white cell count should be 25 × 10^9/L or lower**; consider the use of leukapheresis or hydroxycarbamide to achieve this if required. Correct any pre-existing abnormalities in serum electrolytes prior to initiation of treatment with venetoclax.
13. **Patients at higher risk of TLS require admission to hospital for at least 3 days of cycle 1.**
14. Document pre-admission medicines and check for drug interactions. If patient is already on voriconazole or posaconazole, see alternative venetoclax loading regimen.

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DRUG REGIMEN

Day 1 hydration: Patients should receive hydration for prevention of TLS. On cycle 1, day 1 hydrate with 1 – 1.5 L fluids (PO/IV) prior to venetoclax dosing. Encourage at least 2L oral fluids daily during ramp up phase.

Cycle 1

AZACITIDINE 75 mg/m^2 SC once daily Days 1 to 5 (Monday to Friday), weekend rest, then **AZACITIDINE** 75 mg/m^2 SC once daily Days 8 to 9 (Monday to Tuesday)
Start posaconazole / voriconazole (strong CYP3A inhibitor) on day 1: **VENETOCLAX*** 10 mg PO on **Day 1**, 20 mg PO on **Day 2**, 50mg PO on **Day 3**, then **100 mg** PO once daily on from **Day 4 onwards**. Take with or after a meal.

* Venetoclax dose is adjusted due to interaction with azole antifungal prophylaxis. Venetoclax dosing will need to be adjusted if patient is also taking other drugs with potential for interactions. See dose modifications, drug interactions and concurrent medication sections below.

Duration of venetoclax: The licensed and commissioned duration for venetoclax treatment is 28 days for cycle 1. Emerging clinical experience highlights some patients will have prolonged cytopenias after this dosing regimen. Discuss with consultant regarding duration of venetoclax according to patient comorbidities. Using an attenuated course of venetoclax in cycle 1 is unlicensed.

Patients should have a BM biopsy between day 21 - 28 (ideally between day 21 - 24) which will guide the dosing for cycle 2.

Cycle 2 and beyond

Scenario 1
If BM biopsy shows residual leukaemia with greater than 10% blasts after cycle 1:

AZACITIDINE 75 mg/m^2 SC once daily Days 1 to 5 (Monday to Friday), weekend rest, then **AZACITIDINE** 75 mg/m^2 SC once daily Days 8 to 9 (Monday to Tuesday)
VENETOCLAX 100 mg PO once daily on Days 1-21 or 28. Take with or after a meal. Duration of venetoclax will vary between patients. Discuss with consultant.

Scenario 2
If BM biopsy shows MLFS (morphological leukaemia-free state) with incomplete count recovery after cycle 1, the next cycle must be delayed until platelets >50 x 10^9/L **AND** neutrophils >0.5 x10^9/L (or neutrophils >1.0x10^9/L – consultant decision). The next cycle consider reduction of venetoclax duration by 7 days if there is prolonged cytopenia. (consultant decision)

AZACITIDINE 75 mg/m^2 SC once daily Days 1 to 5 (Monday to Friday), weekend rest, then **AZACITIDINE** 75 mg/m^2 SC once daily Days 8 to 9 (Monday to Tuesday)
VENETOCLAX 100 mg PO once daily on Days 1-14. Take with or after a meal. Duration of venetoclax will vary between patients. Discuss with consultant.

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Cycle 2 and beyond (continued)

Scenario 3
If BM biopsy shows CR/CRi after cycle 1:

AZACITIDINE 75 mg/m^2 SC once daily Days 1 to 5 (Monday to Friday), weekend rest, then **AZACITIDINE** 75 mg/m^2 SC once daily Days 8 to 9 (Monday to Tuesday)
VENETOCLAX 100 mg PO once daily on Days 1-14. Take with or after a meal.

All patients
After cycle 2, patients should have a BM biopsy either at count recovery (to document disease response) OR on day 42 if incomplete count recovery (to assess if resistance disease or empty marrow). If in CR after cycle 1, repeat BM biopsy only at relapse.

AMBULATORY CARE FOR CYCLE 1

Patients at **low risk** of TLS may receive cycle 1 as an outpatient with close monitoring of blood tests assessing tumour lysis. The white cell count should be ≤ 25 x 10^9/L prior to initiation, which reduces the chance of TLS. The patient should meet ambulatory criteria for treatment – consult local policy.

Low risk disease is defined as:
- LDH < 2 times upper limit of normal
- No pre-existing renal impairment
- No known renal involvement with leukaemia

Ambulatory monitoring for TLS: Check creatinine and U&Es (uric acid, potassium, phosphate, and calcium) within 48 hours prior to starting treatment. For each venetoclax dose escalation, repeat TLS blood tests 6-8 hours post-dose (consider venous blood gas for rapid potassium result), and 24 hours post-dose. Administration of the next venetoclax dose does not require delay whilst awaiting results from the 24-hour post-dose blood test.

If there is evidence of TLS, the patient should be admitted to hospital and managed as per local TLS protocol.

CYCLE FREQUENCY

Cycle frequency will be determined by degree of myelosuppression. Treatment breaks of up to 10 weeks are allowed for this regimen.

If patient is not in CR/CRi after 1-2 cycles, discuss patient in the myeloid MDT and consider changing treatment.

There is no maximum number of cycles; continue as long as the patient continues to benefit, or until disease progression/unacceptable toxicity. Responding patients continue treatment until response is lost. When patients become cytopenic after response, this is usually due to either a hypocellular marrow (drug toxicity) or recurrent disease.

After 6 cycles of treatment, discuss ongoing therapy in the myeloid MDT.

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DOSE MODIFICATIONS

If the patient is not currently on an azole (strong CYP3A inhibitor) on cycle 1 day 1:

VENETOCLAX 100 mg PO on **Day 1**, 200 mg PO on **Day 2**, then **400 mg** PO once daily from **Day 3 onwards**. Take with or after a meal.

Dose adjustment for haematological toxicity:

- Venetoclax-based regimens are associated with significant haematological toxicity. Discuss all dose adjustments with consultant.
- Venetoclax or azacitidine should not be interrupted for haematological toxicity during Cycle 1 prior to documentation of marrow response on D21-28.

<table>
<tr><th colspan="2">Haematological toxicity</th><th colspan="2">Modification</th></tr>
<tr><td>Before Complete Remission</td><td>Neutrophil <0.5 or 1 x 10^9/L (consultant decision) or
Platelet <50 x10^9/L
prior to start of next cycle</td><td colspan="2">Delay next cycle until count recovery and review results of Day 21 bone marrow aspirate.
If blast clearance confirmed G-CSF may be commenced until neutrophil recovery.</td></tr>
<tr><td rowspan="4">After Complete Remission</td><td rowspan="4">Neutrophil <1x 10^9/L or
Platelet <75 x10^9/L
prior to start of next cycle</td><td colspan="2">Delay subsequent cycle of venetoclax in combination with azacitidine and monitor blood counts. Administer G-CSF if clinically indicated for neutropenia.</td></tr>
<tr><td colspan="2">If Grade 4 haematological toxicity (Neutrophil <0.5 x10^9/L or Platelet <25 x10^9/L) persists beyond Day 42 of the previous cycle:</td></tr>
<tr><td>First Occurrence</td><td>Keep venetoclax at the same dose</td></tr>
<tr><td>Second Occurrence</td><td>Reduce venetoclax duration from previous cycle by 7 days.
Consider reduction of duration of azacitidine 75mg/m^2 to 5 days per cycle</td></tr>
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Dose adjustments for non-haematological toxicity:

- Venetoclax should ideally not be interrupted for any other non-haematological toxicity for patients who are not in complete remission. Confirm with consultant.

Non-haematological toxicity	Modification
Renal impairment	No azacitidine dose reduction required. No venetoclax dose reduction required for mild or moderate renal impairment (CrCl 15-90 mL/min). No information available for severe renal impairment (CrCl <15mL/min) or dialysis. If CrCl < 30mL/min, monitor patient closely for signs of TLS, particularly during ramp-up phase.
Grade 3 - 4 abnormal liver function tests (ALT, AST and bilirubin)	Withhold hepatotoxic drugs (including azole antifungals) until resolved to grade 2 or below. Do not withhold venetoclax unless discussed with consultant. If withholding venetoclax, once grade 2 or below, re-start venetoclax at the original dose.

Severe hepatic impairment (Child-Pugh C)	Reduce venetoclax dose by 50%. Azaciditine is contraindicated if albumin is <30 g/L or patient has advanced malignant hepatic tumours.
Other Grade 3 - 4 toxicities related to venetoclax	Discuss with consultant. Venetoclax should be withheld until the toxicity has resolved to grade 2 or below and restarted at the original dose.

Discontinuation of Strong CYP3A inhibitor
Resume the venetoclax dose that was used prior to initiating the interacting medication 2 to 3 days after discontinuation. Ramp-up is not required upon discontinuation.

INVESTIGATIONS

FBC, coagulation screen, LFTs, U&Es at the start of every cycle and as clinically indicated.
Weekly FBCs while awaiting count recovery.

Only at cycle 1
Monitoring of tumour lysis syndrome: check creatinine and U&Es (uric acid, potassium, phosphate, and calcium) pre-dose (<4 hours) and 6-8hrs post-dose for each dose escalation, and at 24hrs after administration of the maximum venetoclax dose. If ambulating as low risk, please see details in ambulatory section above.

BM biopsy on day 21 and as clinically indicated.

CONCURRENT MEDICATION

Drug	Dose / Duration
ALLOPURINOL	300mg PO once daily for 7 days, starting prior to first dose of venetoclax
ACICLOVIR	200mg PO three times a day and for 3 months after completion
FUNGAL PROPHYLAXIS	• Voriconazole PO 400mg twice daily for 1 day, then 200mg twice daily, ***OR*** • Posaconazole PO 300mg twice daily for 1 day, then 300mg once daily **Start on Cycle 1 day 1 of regimen but ensure venetoclax dose is adjusted; see DRUG REGIMEN section above** **Note**: if the patient develops toxicities to posaconazole and voriconazole such that these anti-fungal agents have to be discontinued, venetoclax dosing at a maximum daily dose of 400mg is funded. Increase dose of venetoclax 2 - 3 days after discontinuation of azole.
G-CSF	Do not start until blast clearance confirmed on BM biopsy. G-CSF may be commenced until neutrophil recovery.

Antibiotic prophylaxis is sometimes given as local practice (e.g. ciprofloxacin or levofloxacin), however the **MHRA advises against unnecessary use of fluoroquinolones** due to frequent and significant adverse events and risk vs. benefit should be carefully considered.

EMETIC RISK

Moderate

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Haematological and gastrointestinal adverse events (AEs) were the most common toxicities observed. Gastrointestinal AEs were primarily grade 1-2 (nausea, diarrhoea, vomiting, decreased appetite). Common grade 3-4 AEs included febrile neutropenia, decreased WBC count, anaemia, thrombocytopenia, neutropenia and pneumonia.

Tumour lysis syndrome was observed in 1.1% of patients on VIALE-A trial with venetoclax in combination with azacitidine.

DRUG INTERACTIONS

Note this list is not conclusive. Always refer to the product SPC and consult with a pharmacist.

Voriconazole and Posaconazole

Antifungals that are strong CYP3A inhibitors may be used alongside venetoclax provided the maintenance venetoclax dose is reduced to 100mg OD (25% dose).

Strong and moderate CYP3A Inhibitors

For patients requiring concomitant use of venetoclax with strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, clarithromycin, ritonavir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, diltiazem, erythromycin, fluconazole, verapamil), venetoclax dosing should be adjusted according to the dose modification table below.

Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. If the interacting medication is stopped, the venetoclax dose that was used prior to initiating the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor.

Dose modifications for use with CYP3A Inhibitors

Inhibitors	Initiation and titration phase	Steady daily dose (After titration phase)
Strong CYP3A inhibitor	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg	Reduce the venetoclax dose to 100 mg or less (or by at least 75% if already modified for other reasons)
Moderate CYP3A inhibitor	Reduce the Venetoclax dose by at least 50%	

CYP3A Inducers

Avoid concomitant use of venetoclax with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampicin, St. John's Wort) or moderate CYP3A inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin). Consider alternative treatments with less CYP3A induction.

Be aware of the following agents that may have their concentrations affected by venetoclax: warfarin, dabigatran, statins, digoxin, everolimus, sirolimus. Consult SPC for further information.

Patients must not consume grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within the 3-day period prior to the first venetoclax

administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction.

TREATMENT RELATED MORTALITY

Estimated at 3%

REFERENCES

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REVIEW

Name	Revision	Date	Version	Review date
Maria Monro, Haematology Pharmacist Prof Paresh Vyas, Haematology consultant	New document	May 2020	1.0	May 2021
Yen Lim, Haematology Pharmacist Prof Paresh Vyas & Dr Andy Peniket, Haematology consultants	Updated funding following NICE TA publication, updated dosing schedule.	Jul 2022	2.0	Jul 2024

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Yen Lim, Haematology Pharmacist NSSG Myeloid Group	Annual protocol day. Preferred venetoclax loading regimen clarified. Reduced recommended duration of hospital admission. Supports updated.	Nov 2022	3.0	Nov 2024
Connor Sweeny, Haematology Consultant Donna Constantine, Advanced Cancer Pharmacist	Removal of interim COVID indication. Addition of ambulatory treatment details. Referencing updates for TLS risk. MHRA fluoroquinolone warning.	Feb 2024	3.1	Nov 2024