មន្ទីរពេទ្យ កាល់ម៉ែត HOPITAL Calmette	**SOP for Venetoclax and Decitabine for treatment of Acute Myeloid Leukaemia**	Date/Place November 2025/PP	Number of page

OBJECTIVES

- To provide guidelines for Physicians and Nurses for the administration of venetoclax and decitabine in the treatment of patients with acute myeloid leukaemia (AML)

SCOPE

This document outlines the indication for treatment, dose adjustments, special considerations and antimicrobial advice during therapy

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STANDARD OPERATING PROCEDURE FOR Venetoclax/ Decitabine for Palliative Chemotherapy in Acute Myeloid Leukaemia

Indication
Adult AML in patients when intensive chemotherapy is unsuitable

Treatment Intent
Induction and maintenance until disease progression or intolerance

Pre-assessment
1. Confirmation of diagnosis (aspirate +/- biopsy, flow cytometry, genetic test) 2. Blood test: CBC, electrolyte, liver and kidney function, CRP, LDH, uric acid, albumin, calcium, phosphate, Hep B, Hep C, HIV 3. Chest X-ray, ECG and heart ultrasound 4. Record performance status (ECOG) 5. Record height and weight 6. Consent signed 7. Hydration and tumour lysis prevention: provide hydration and anti-hyperuricaemics. To prevent TLS (see TLS protocol) white cell count should be < 25 x10^9/L by - Consider using hydroxyurea and evaluation 48 hours, - If no improvement, start Cytarabine 100mg to 500mg IV 1 to 2 doses. 8. Correct pre-existing electrolyte abnormalities prior to starting treatment 9. IV access 10. Recommend hospital admission for the first cycle then consider day care treatment 11. Document pre admission medications and check for drug interactions 12. Consider pregnancy test (for women of child bearing age) before cycle 1

Toxicity
Haematological toxicity common (see below).
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 (observed in 1.1% of patients on VIALE-A trial)

Drug Regimen- Cycle 1

Day 1 Hydration: Patients should receive 1.5-2 litres or IV and/ or oral fluids before venetoclax dosing. Encourage 2 litres of oral fluid daily during the venetoclax dose increase phase.

DECITABINE: 20mg/m^2 Days 1-5 Intravenous once daily (5 days in total)
VENETOCLAX: 100mg PO Day 1 (Take with/ after a meal)
VENETOCLAX: 200mg PO Day 2
VENETOCLAX: 400mg PO Day 3

If starting fluconazole:
VENETOCLAX: 200mg PO Day 4 onwards. Start Fluconazole with Venetoclax dose adjustment.

If starting voriconazole:
VENETOCLAX: 100mg PO Day 4 onwards. Start voriconazole with Venetoclax dose adjustment.

Note: Venetoclax dose is adjusted due to interaction with azoles, 100mg and 200mg QD for voriconazole and fluconazole respectively. Dose may need further adjustment if on other drugs with potential interactions. See sections below.

Duration of venetoclax: 28 days for cycle 1. Duration can be adjusted depending on the clinical situation.

Patients should have a bone marrow assessment between day 21-28 which will guide dosing for cycle 2

After bone marrow aplasia (or blast < 5%), confirmed on bone marrow assessment, hold Venetoclax for 7 days and consider starting G-CSF when neutrophil count less than 0.5 until it reaches > 1.0

Drug Regimen - Cycle 2 and beyond

If bone marrow shows residual leukaemia with > 5% blasts after cycle 1:
DECITABINE: 20mg/m^2 Days 1-5 Intravenous once daily (5 days in total)
VENETOCLAX: 200mg PO Day 1-21 (or 28) depending on patient co-morbidities (if fluconazole used). (100mg if Voriconazole is used).

If bone marrow shows morphological remission (blasts < 5%) with incomplete count recovery after cycle 1
Delay next cycle until:

- Platelets > 50
- Neutrophils > 1.0

Consider reducing the duration of venetoclax by 7 days if there is prolonged cytopenias

DECITABINE: 20mg/m^2 Days 1-5 Intravenous once daily (5 days in total)
VENETOCLAX: 100-200mg PO Day 1-14 . Duration will vary between patients. (200mg if on fluconazole, 100mg if on voriconazole)

If bone marrow shows morphological remission (blasts < 5%) with complete count recovery after cycle 1
DECITABINE: 20mg/m^2 Days 1-5 Intravenous once daily (5 days in total)
VENETOCLAX 100mg-200mg PO once daily Days 1-14 or 21 days ((200mg if on fluconazole, 100mg if on voriconazole)

Note:
- The duration of Venetoclax in subsequent cycles should be reduced by 50% in case of the delay of blood count recovery (Ex: 14days /7days / 5days / 3days).
- If the neutropenia < 0.5 lasts more than 7 days, interrupt Venetoclax.

All Patients post remission
- If Neutrophil count < 0.5, start G-CSF until it reaches 1.5
- After cycle 2, patients should have a bone marrow aspirate either at count recovery (to document disease response) OR on day 42 if incomplete count recovery (to assess disease or empty marrow).
- If complete remission after cycle 2, repeat bone marrow only if there is a suspicion of relapse AML.

Cycle Frequency

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

If the patient is not in remission after cycle 2, consider stopping/ changing treatment.

There is no maximum number of cycles; continue if the patient continues to benefit, or until disease progression or unacceptable toxicity.

Dose modification- Venetoclax

If patient is not on an azole (Strong CYP3A inhibitor) on cycle 1, day 1:
VENETOCLAX 100mg PO on Day 1
VENETOCLAX 200mg PO Day 2
VENETOCLAX 400mg PO Day 3 onwards.

Dose adjustments for haematological toxicity:
Venetoclax or decitabine should not be interrupted for haematological toxicity in cycle 1, prior to documentation on bone marrow response (Day 21-28)

Haematological toxicity (before morphological remission)

Toxicity	Modification
Neutrophil <0.5 or platelet < 50	Delay next cycle until count recovery and review results of Day 21 aspirate. If blast clearance is confirmed G-CSF may be commenced until neutrophil recovery.
Haematological toxicity (before morphological remission)	
Neutrophils < 1 or platelets < 75	Delay next cycle until count recovery and consider G-CSF
Neutrophils < 0.5 or platelets < 25 persisting beyond day 42 of previous cycle	First occurrence: continue current venetoclax dose and consider to reduce its duration Second occurrence: reduce venetoclax duration from previous cycle by 7 days and consider reducing decitabine doses per cycle
Non Haematological Toxicity	
Avoid interruptions for non haematological toxicity if possible for patients who are not in complete remission	
Renal Impairment	
No dose adjustment required if creatinine clearance 15-90ml/min. If creatinine clearance < 30ml/min monitor closely for TLS	
Hepatic Impairment	
If bilirubin 3x the upper limit of normal or ALT > 5x upper limit of normal withhold azole antifungals before withholding venetoclax. In severe hepatic impairment (Child Pugh-C) reduce venetoclax dose by 50%	

Dose Modification- Decitabine	
Renal impairment	**Hepatic Impairment**
No dose reduction necessary	No dose reduction necessary

Drug Interactions
Voriconazole and azole antifungals are strong CYP3A inhibitors may be used alongside venetoclax provided the maintenance venetoclax dose is reduced to 100mg OD (25% dose). Fluconazole is a less strong CYP3A inhibitor- the dose of venetoclax should be reduced by 50%
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

Inhibitors	**Initiation and titration phase**	**Steady daily dose (after titration)**
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 Inductors
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. 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.

Investigations
FBC, coagulation screen (twice weekly) U+E, LFT, eGFR Group and save Viral screen: HIV, Hepatitis B core antibody and Hepatitis B surface Ag, Hepatitis C antibody Recent bone marrow aspirate Monitor for tumour lysis cycle 1 only: check TLS bloods pre-dose and 6-8hrs after each dose escalation and 24 hours after administration of maximum venetoclax dose

Supportive medication	
Drug	**Dose and duration**
Allopurinol	300mg once daily for first 7 days of cycle 1
Aciclovir	400mg twice daily for duration of treatment
Esomeprazole	40 mg once daily for duration of treatment
Voriconazole	400mg (for 2 doses 12 hours apart), then 200mg twice daily for duration of treatment (If azole is stopped- increase dose of venetoclax 3 days after stopping azole) **GIVE voriconazole or fluconazole NOT BOTH**
Fluconazole	100mg (alternative to voriconazole)
Ondansetron	8mg orally twice daily on decitabine days only
G-CSF (filgrastim)	Consider if blast clearance confirmed on bone marrow biopsy