Wrightington, Wigan and Leigh NHS
NHS Foundation Trust

Regimen: Azacitidine Subcutaneous and Venetoclax

Document History					
Version Number		Issue Date		Review date	
0.1					
Changes from previous version:					
Authors					
Haematologist	Dr C Gregory	Pharmacist	K Moss	Nurse Specialist	J Banks

Name	DOB	Hospital No.	Consultant	Allergies

Indication	Treatment of adult patients who have Acute Myeloid Leukaemia and are not eligible for haematopoietic stem cell transplantation.
Pre-treatment evaluation checklist	**Mandatory Fields: (Incomplete fields can result in delayed treatment)**

Height (cm)	
Weight (kg)	
Surface Area DuBois (m^2); if adjusted state SA used to dose	
WHO Performance	
Testing for Hepatitis B, Hepatitis C and HIV	Date_____
Baseline bloods requested (see below)	□
Sperm banking or oocyte/embryo preservation must be offered to males <55yrs and pre-menopausal women concerned about fertility	□
Consented by:	Date_____
Provide contact details for Clinical Nurse Specialist for further information	□
Allopurinol prescribed to start 3 days prior to venetoclax	□
Complete Current Medication List and discontinue any inappropriate medication (e.g. immunosuppressive drugs)	□
Dose modifications considered. Details:	□
Cancer care suite informed for date	Date_____
Arrangements made to discuss at MDT	Date_____
Patient given blood form for at least 1 week prior to chemotherapy	□
CDF completed	□
All patients should have white blood cell count <25 × 109/l prior to initiation of venetoclax and cytoreduction prior to treatment may be required.	□

Consultant / Speciality Doctor Signature _____ Date _____

Baseline Blood Tests	FBC, U&E, Bone, LFT, eGFR, Urate, LDH and Sodium Bicarbonate levels
Bloods Prior to each cycle	FBC, U&E, Bone, LFT

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Current Medication List

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Dose Banding

As part of cost saving initiatives NHS England have required dose banding for many chemotherapy agent.

After calculating Body Surface Area use this chart to work out the correct dose to prescribe:

BSA (m^2)												
Chemotherapy	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	**1.9**	**2.0**	**2.1**	**2.2**	**2.3**	**2.4**
Azacitidine (75mg/m^2)												
100%	100	110	110	120	130	140	140	150	160	160	180	180
50%	55	55	55	60	65	70	70	75	80	80	90	90

Drug Regimen

Day	Drug	Dose	Route	Comments
1	Venetoclax	100mg	PO	Monitor U&Es, LFTs and Bone Profile for Tumour Lysis Syndrome at pre-dose, 6 to 8 hours after each new dose during titration and 24 hours after reaching final dose.
2	Venetoclax	200mg	PO	
3+	Venetoclax	400mg	PO	
Days 1 to 5 then 8 and 9	Azacitidine	75mg/m^2	SC	Total 7 doses See below

1. Inject Azacitidine subcutaneously into upper arm, thigh or abdomen.
2. Injection sites should be rotated.
3. New injections should be given at least 2.5cm from the previous site and never into areas where the site is tender, bruised, red or hardened.
4. Doses > 4ml should be equally divided into 2 syringes and injected into two separate sites.
5. After removal from the refrigerated conditions, it should be allowed up to 30min prior to administration to reach a temperature of about 20-25◦C. If the elapsed time is > 30minutes, the suspension should be discarded and a new dose prepared.
6. The contents of the syringe must be re-suspended by rolling the syringe between palms of hands to ensure uniform cloudy suspension before administration

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Cycle frequency	Repeat every 28 days for a minimum of 6 cycles and should be continued as long as the patient continues to benefit or until disease progression. Grade 4 non-haematological toxicity - discontinue treatment.
Medication Concurrent	**Ondansetron** 8mg 8 hourly 10 days PRN **Allopurinol** 300mg OD (reduce to 100mg od if creatinine clearance < 20ml/min) for first two cycles **Aciclovir** (oral) 400mg BD consider if previous history of VZV or HSV reactivation If allergic/ intolerant to any of the above named drug for discuss with consultant for an alternative

Toxicity
See SPC for full listings

Frequencies are defined as: very common (1/10), common (1/100 to < 1/10); uncommon (1/1,000 to < 1/100)

System Organ Class	Very common	Common
Infections	pneumonia	Neutropaenic sepsis, upper respiratory tract infection, urinary tract infection sinusitis, pharyngitis , rhinitis, herpes simplex
Blood and lymphatic system disorders	febrile neutropaenia	
Nervous system disorders	dizziness, headache	
Respiratory	dyspnoea	dyspnoea exertional, pharyngolaryngeal pain
Gastrointestinal disorders	diarrhoea, vomiting, constipation, nausea, abdominal pain	gastrointestinal haemorrhage, haemorrhoidal haemorrhage, stomatitis, gingival bleeding, dyspepsia
Skin and subcutaneous tissue disorders	petechiae, pruritus, rash, ecchymosis	purpura, alopecia, erythema, rash macular
General disorders	fatigue, pyrexia, chest pain, injection site erythema, injection site pain, injection site reaction	Injection site : bruising, haematoma, induration, rash, pruritus, inflammation, discoloration, nodule and haemorrhage

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Dose modifications			
Hepatic	No formal studies have been conducted in patients with hepatic impairment. Azacitidine is contraindicated in patients with advanced malignant hepatic tumours. Dose modifications are at clinician's discretion and should be based on haematological lab values.		
Renal	No formal studies have been conducted in patients with impaired renal function. No specific modification of the starting dose is recommended in patients with renal impairment prior to starting treatment. **If unexplained elevations in serum creatinine or urea to ≥2 fold above baseline values or above ULN occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50% on the next treatment cycle.**		
Haematological	**Venetoclax**		
	Adverse Reaction	**Occurrence**	**Dosage Modification**
	Haematological Adverse Reactions		
	Grade 4 neutropenia (ANC < 500/microlitre) with or without fever or infection; or grade 4 thrombocytopenia (platelet count <25 × 103/microlitre)	Occurrence prior to achieving remission[a]	In most instances, do not interrupt venetoclax in combination with azacitidine or decitabine or low dose cytarabine due to cytopenias prior to achieving remission.

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		First occurrence after achieving remission and lasting at least 7 days	Delay subsequent cycle of venetoclax in combination with azacitidine or decitabine or low dose 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 azacitidine or decitabine or low dose cytarabine.
		Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer	Delay subsequent cycle of venetoclax in combination with azacitidine or decitabine or low dose 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 azacitidine or decitabine or low dose cytarabine, and reduce venetoclax duration by 7 days during each of the subsequent cycles, such as 21 days instead of 28 days. Refer to the azacitidine prescribing information for additional information.
	Non-Haematological Adverse Reactions		

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	Grade 3 or 4 non-hematologic toxicities	Any occurrence	Interrupt venetoclax if not resolved with supportive care. Upon resolution to grade 1 or baseline level, resume venetoclax at the same dose.
	[a]Consider bone marrow evaluation.		
	CYP3A Inhibitor Dose Modifications In all patients, if a CYP3A inhibitor must be used, follow the recommendations for managing drug-drug interactions summarized in Table below. Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. The venetoclax dose that was used prior to initiating the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor. Management of potential Venetoclax interactions with CYP3A inhibitors:		
	Inhibitor	**Phase**	**AML Dosing**
	Strong CYP3A Inhibitor	Initiation and dose-titration phase	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg or less
		Steady daily dose (After dose-titration phase)	Reduce the venetoclax dose to 100 mg or less (or by at least 75% if already modified for other reasons)
	Moderate CYP3A Inhibitor[a]	All	Reduce the venetoclax dose by at least 50%
	[a]In patients with CLL, avoid concomitant use of venetoclax with moderate CYP3A inhibitors at initiation and during the dose-titration phase. Consider alternative medications or reduce the venetoclax dose as described in this table.		

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Azacitidine

Haematological toxicity is defined as the lowest count reached in a given cycle (nadir) if platelets ≤ 50 x 10^9/l and/or absolute neutrophil count (ANC) ≤ 1 x 10^9/l.

Recovery is defined as an increase of cell line(s) where haematological toxicity was observed of at least half of the difference of nadir and the baseline count plus the nadir count (i.e. blood count at recovery ≥ Nadir Count + (0.5 x [Baseline count – Nadir count]).

Patients without reduced baseline blood counts (i.e. White Blood Cells (WBC) ≥ 3.0 x 10^9/l and ANC ≥ 1.5 x 10^9/l, and platelets ≥ 75 x 10^9/l) prior to the first treatment

If haematological toxicity observed due to Azacitidine	delay next cycle until the platelet count and the ANC have recovered		
If **recovery** is achieved within 14 days	no dose adjustment is necessary		
If **recovery** has **not** been achieved within 14 days	dose should be reduced accordingly:		
	Nadir Counts		% Dose in the next cycle, if recovery* is not achieved within 14 days ANC (x10^9/l)
	ANC (x10^9/l)	Platelets(x10^9/l)	
	≤ 1.0	≤50	≤ 1.0
	>1.0	>50	>1.0
Following dose modifications	the cycle duration should return to 28 days		

***Recovery = counts ≥ Nadir count + (0.5 x [Baseline count – Nadir count])**

Patients with reduced baseline blood counts

(i.e. WBC < 3.0 x 10^9/l or ANC < 1.5 x 10^9/l or platelets < 75 x 10^9/l) prior to the first treatment)

If the decrease in WBC or ANC or platelets from that prior to treatment is less than 50 % or greater than 50 % but with an improvement in any cell line differentiation	The next cycle should not be delayed and no dose adjustment made.

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	If the decrease in WBC or ANC or platelets is greater than 50 % from that prior to treatment, with no improvement in cell line differentiation,	The next cycle of Azacitidine therapy should be delayed until the platelet count and the ANC have recovered
	If **recovery** is achieved within 14 days	no dose adjustment is necessary
	if **recovery** has **not** been achieved within 14 days	bone marrow cellularity should be determined **Consultant Decision. Refer to SPC for further information**
	Following dose modifications	the cycle duration should return to 28 days
References	Azacitidine SPC: https://www.medicines.org.uk/emc/medicine/21508 Updated 20/07/2020 Venetoclax SPC: https://www.medicines.org.uk/emc/product/10476/smpc Updated 03/11/2022 NICE Technology Appraisal Guidance [TA765] https://www.nice.org.uk/guidance/ta765/chapter/3-Committee-discussion	

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Case Note Copy

Consent Form 3
Patient agreement to investigation or treatment
(procedure where consciousness not impaired)

Name of Procedure
(Include brief explanation if medical term not clear)

Azacitidine and venetoclax chemotherapy

Statement of health professional (to be filled in by health professional with appropriate knowledge of proposed procedure, as specified in consent policy)

I have explained the procedure to the patient. In particular, I have explained:

The intended benefits: Treatment Acute Myeloid Leukaemia – life extension and improved quality
Serious of frequently occurring risks: Life threatening infections, bleeding and blood clots. Potentially permanent damage to heart/lungs/liver/kidneys/gut/nerves/skin/bladder. Nausea, vomiting, loss of appetite, sore mouth, taste changes, weight change, altered bowel habit, abdominal pain or discomfort. Allergic reactions and skin rashes. Tumour lysis syndrome

I have also discussed what the procedure is likely to involve, the benefits and risks of any available alternative treatments (including no treatment) and any particular concerns of those involved.

☐ **The following leaflet has been provided:** Azacitidine and Venetoclax information leaflets

Signed:_____ Date:_____

Name (PRINT):_____ Job Title:_____

Statement of interpreter (where appropriate)

I have interpreted the information above to the patient to the best of my ability and in a way in which I believe s/he can understand

Signed:_____ Date:_____ Name (PRINT)_____

Statement of patient

I agree to the procedure described above.
I understand that you cannot give me a guarantee that a particular person will perform the procedure. The person will, however, have appropriate experience.
I understand that the procedure will not involve local anaesthesia.

Signed:_____ Date:_____ Name (PRINT)_____

Confirmation of consent (to be completed by a health professional when the patient is admitted for the procedure, if the patient has signed the form in advance)

I have confirmed that the patient has no further questions and wishes the procedure to go ahead.

Signed:_____ Date:_____

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