PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

AZACITIDINE (Subcutaneous) MYELOID

PROTOCOL REF: MPHAAVAML
(Version No. 1.1)

Approved for use in:

Azacitidine is recommended as a treatment option for adults who are not eligible for haematopoietic stem cell transplantation and have:

- intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS) **or**
- chronic myelomonocytic leukaemia (CMML) with 10–29% marrow blasts without myeloproliferative disorder **or**
- acute myeloid leukaemia (AML) with 20–30% blasts and multilineage dysplasia, according to the World Health Organization classification.

Note azacitidine is not recommended by NICE for use in AML with >30% bone marrow blasts in people >65 who are not eligible for haematopoietic stem cell transplant.

Blueteq registration is not 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)

Cycle length every 28 days.

Minimum of six cycles before assessing response.Treatment should continue until disease progression or unacceptable toxicity.

Administration and Counselling Points:

- Azacitidine should not be used interchangeably with oral azacitidine.
- 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.

Emetogenic risk:

Mildly emetogenic.

Supportive treatments:

- Allopurinol oral 300mg once daily for the first cycle
- Aciclovir 400mg twice daily oral
- Ondansetron 8mg twice daily when required
- Consider antifungal (posaconazole 300mg twice daily and antibacterial prophylaxis if neutropenic

Dosing in renal and hepatic impairment:

Renal Dose Modifications	
No dose adjustment required for renal impairment or haemodialysis If unexplained reductions in serum bicarbonate levels to less than 20 mmol/l occur, the dose should be reduced by 50% on the next cycle.	
Hepatic Dose Modifications	
Mild or moderate liver impairment	No adjustment required
Albumin <30g/L or advanced malignant hepatic tumours	Not recommended

Interactions:

No significant drug interactions.

Treatment schedule:

Day	Drug	Dose	Route	Infusion
Each day of treatment	**Azacitidine**	**75mg/m^2**	**SC**	Upper arm, thigh or abdomen. Rotate sites of injection, Doses greater than 4 mL should be injected into two separate sites

Main toxicities:

Azacitidine
Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea, tumour lysis syndrome, venous thromboembolism and peripheral neuropathy, differentiation syndrome, necrotising fasciitis, anorexia, insomnia, headache, confusion, dehydration, pleural effusion, dyspnoea, petechiae, pruritis, fatigue, bruising, elevated creatinine.

Investigations and treatment plan:

	Pre	Cycle 1 day 1	Ongoing
Informed consent	X		
Clinical Assessment	X	X	Each cycle
SACT Assessment (including performance status and toxicities assessment)		X	Each day of treatment
FBC, U+E, LFT, calcium profile, bicarbonate	X	X	Each cycle
Creatinine Clearance (C-G)	x		Each cycle
LDH, Bone Profile	X		Repeat as clinically indicated
Bone marrow biopsy	X		Repeat as clinically indicated
Height	X		
Weight		X	Each cycle
Pregnancy test	X		If applicable

Dose Modifications and Toxicity Management:

Haematological toxicity:

Cycle can proceed if:

ANC >1.0x10^9/L	Platelets >50x10^9/L

Cycle can continue despite cytopenias if thought to be due to disease at clinician discretion.

Haematological toxicity is defined as the lowest count reached in a given cycle (the nadir) if platelets ≤ 50 x 10^9/L and/or absolute neutrophil count (ANC) is ≤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 prior to the first treatment (i.e. White Blood Cells (WBC) ≥ 3.0 × 10^9/l and ANC ≥ 1.5 × 10^9/l, and platelets ≥ 75.0 × 10^9/l)

If haematological toxicity is observed following azacitidine treatment, the next cycle of the 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. However, if recovery has not been achieved within 14 days, the dose should be reduced according to the following table. Following dose modifications, the cycle duration should return to 28 days.

Cycle nadir counts		Dose in the next cycle, if recovery* is not achieved within 14 days (%)
ANC (× 10^9/l)	Platelets (× 10^9/l)	
≤ 1.0	≤ 50.0	50 %
> 1.0	> 50.0	100 %

*Recovery = counts ≥ nadir count + (0.5 × [baseline count – nadir count])

Patients WITH reduced baseline blood counts prior to the first treatment (i.e. WBC < 3.0 × 10^9/l or ANC < 1.5 × 10^9/l or platelets < 75.0 × 10^9/l)

Following azacitidine treatment, if the decrease in WBC, ANC or platelets from that prior to treatment is ≤ 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.

If the decrease in WBC, 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. However, if recovery has not been achieved within 14 days, bone marrow cellularity should be determined. If the bone marrow cellularity is > 50%, no dose adjustments should be made. If bone marrow cellularity is ≤ 50%, treatment should be delayed and the dose reduced according to the following table:

Bone marrow cellularity	Dose in the next cycle if recovery is not achieved within 14 days	
	Recovery* ≤ 21 days	Recovery* > 21 days
15-50 %	100 %	50 %
< 15 %	100 %	33 %

References:

1. 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.
2. NICE (2011) TA218, https://www.nice.org.uk/guidance/ta218 [Accessed 13/8/2023]
3. NICE (2016) TA399, https://www.nice.org.uk/guidance/ta399 [Accessed 13/8/23]
4. Celgene (2019) Azacitidine. Summary of product characteristics. https://www.medicines.org.uk/emc [Accessed 10/03/2020]

Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
Date document posted on the Intranet	For completion by DCM

Version History

Date	Version	Author name and designation	Summary of main changes
1.0	July 2020	**Niamh Mclaughlin Advanced Pharmacist HO**	**New protocol**
2.0	Sept 2023	**Jennifer Gibson Principal Pharmacist HO**	**3 yearly review. New template.**