Azacitidine – 5 day schedule

This is an unlicensed schedule

Indication

Treatment of adults not eligible for haematopoietic stem cell transplantation who have:

- Intermediate-2 and high-risk MDS according to the International Prognostic Scoring System (IPSS) or
- CMML with 10–29% blasts in marrow or
- AML with 20–30% blasts and multilineage dysplasia
- Azacitidine is provided via a company led PAS scheme

Unlicensed schedule - it is acceptable where day case care is unavailable or local policy

Regimen details

Table 1 – Treatment regimen details

DRUG	DOSE	DILUENT	ROUTE	FREQUENCY/DURATION
Azacitidine	100mg/m^2	Water For Injection	Subcutaneous Injection	Daily for 5 days

Cycle frequency

Repeat cycle every 28 days

Number of cycles

There is no maximum number of cycles, responding patients continue azacitidine until disease progression
If there is no clinical response, consider a bone marrow after completion of Cycle 6

Administration

- Before administration the contents of the syringe must be re-suspended by inverting the syringe 2-3 times and vigorously rolling the syringe between the palms for 30 seconds
- Azacitidine should be administered by subcutaneous injection into the upper arm, thigh or abdomen. Injection sites should be rotated. 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
- Doses of greater than 100mg (4mL) should be injected into two separate sites
- Day one of the cycle should always be a Monday

Pre-medication

No specific pre-medication required

Emetogenicity – consult anti-emetic policy for full details

Low-Moderate Risk – Use oral metoclopramide or oral ondansetron approximately 30minutes pre-chemotherapy

Additional supportive medication

None specific

Extravasation

Table 2 – Extravasation Risk Category for each intravenous drug in the regimen

Azacitidine	Inflammitant

Apply hydrocortisone 1% sparingly to the injection site when required for the relief of inflammation

Investigations – pre first cycle

Table 3 - Standard Investigations prior to first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
Calcium profile	14 days

Prior to a course of treatment

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. Calculate IPSS score
3. Treatment should be agreed in the relevant MDT
4. Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function
5. Written consent for course
6. Perform FBC weekly in the first 3 cycles or more frequently if clinically indicated –subsequent cycles check FBC every 2 weeks

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST), Calcium profile

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Table 4 – Standard test result limits for each administration to go ahead

Investigation	Limit
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 50 x 10^9/L
Creatinine clearance	≥ 60 mL/min
Bilirubin	≤ 1.5 x ULN
AST	< 1.5 x ULN

Dose modifications

The below are recommended by the SPC. Clinician judgement should be exercised in their use:

Haematological toxicity = nadir when Platelets ≤ 50 x 10^9/L and/or ANC ≤ 1 x 10^9/L
Recovery = blood count ≥ nadir count + (0.5 x [baseline count – nadir count])

<u>If baseline WBC ≥ 3 x 109 /L, ANC ≥ 1.5 x 109 /L, Platelets ≥ 75 x 109 /L prior to Cycle 1 follow Table 5</u>

<u>If baseline WBC < 3 x 109 /L, ANC < 1.5 x 109 /L, Platelets < 75 x 109 /L prior to Cycle 1 follow Table 6</u>

Table 5

Haematological toxicity	Modification
ANC ≤ 1x 10^9/L and / or	Next cycle should be delayed until Platelet and ANC recovery. If recovery occurs within 14 days, no dose adjustment is needed.
Platelets ≤ 50 x 10^9 /L	Next cycle should be delayed until Platelet and ANC recovery. 50% dose in the next cycle if recovery is not achieved within 14 days

Table 6

Haematological toxicity	Modification
WBC or ANC or Platelet decrease ≤ 50% from baseline, or > 50% but with improvement in any cell line differentiation	Next cycle should not be delayed and no dose adjustment made
WBC or ANC or Platelet decrease > 50% from baseline, with no improvement in cell line differentiation	Next cycle should be delayed until Platelet and ANC recovery. If recovery occurs within 14 days, no dose adjustment is necessary
	Next cycle should be delayed until Platelet and ANC recovery. If recovery has not been achieved within 14 days, determine bone marrow cellularity. Recovery > 21 days and bone cellularity 15-50% dose at 50% Recovery > 21 days and bone cellularity < 15% dose at 33%

Table 7 - Dose modification for renal & hepatic impairment

Renal impairment	Hepatic impairment
After Cycle 1, if serum bicarbonate levels < 20 mmol/L, dose at 50% in the next cycle. If Cr or blood urea nitrogen ≥ 2 x baseline and > ULN, next cycle should be delayed until values return to normal or baseline and dose at 50% in the next cycle.	Carefully monitor in severe impairment. Subsequent dose modifications should be based on haematology laboratory values. Contraindicated in advanced malignant hepatic tumours

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Haematological toxicity: particularly during the first 2 cycles

Hepatic impairment: Patients with extensive tumour burden due to metastatic disease have been reported to experience progressive hepatic coma and death during Azacitidine treatment, especially in such patients with baseline serum albumin <30g/L.

Cardiac and pulmonary disease: Patients with a known history of cardiovascular or pulmonary disease have shown significantly increased incidence of cardiac events with Azacitidine

Necrotising fasciitis: Azacitidine should be discontinued in patients who develop necrotising fasciitis and appropriate treatment should be promptly initiated.

- **Frequently occurring side effects**

pneumonia, nasopharyngitis, febrile neutropenia, neutropenia, leukopenia, thrombocytopenia, anaemia, anorexia, decreased appetite, hypokalemia, insomnia, dizziness, headache, dyspnoea, epistaxis, diarrhoea, vomiting, constipation, nausea, abdominal pain, petechiae, pruritus, rash, ecchymosis, arthralgia, musculoskeletal pain, pyrexia, fatigue, asthenia, chest pain, injection site erythema, injection site pain, injection site reaction (unspecified), weight decreased.

Significant drug interactions – for full details consult product literature/ reference texts

Based on *in vitro* data, azacitidine metabolism does not appear to be mediated by cytochrome P450 isoenzymes (CYPs), UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and glutathione transferases (GSTs); interactions related to these metabolizing enzymes *in vivo* are therefore considered unlikely.
Clinically significant inhibitory or inductive effects of azacitidine on cytochrome P450 enzymes are unlikely.
No formal clinical drug interaction studies with azacitidine have been conducted.

Additional comments

References

1. NICE (2011) TA 218, https://www.nice.org.uk/guidance/ta218. Accessed 01/02/2021
2. Celgene (2020) Azacitidine Summary of product characteristics. http://www.medicines.org.uk/emc. Accessed 01/02/2021
3. Thames Valley SCN (2019) Aacitidine Treatment Protocol, http://nssg.oxford-haematology.org.uk/myeloid/protocols/ML-38-azacitidine.pdf. Accessed 01/02/2021