**Chemotherapy Protocol**

# Myelodysplastic Syndrome (MDS)
# Acute Myeloid Leukaemia (AML)
# Chronic Myelomonocytic Leukaemia (CMML)

**Azacitidine SC (5+2 days)**

**This is not a licensed dosage schedule**

## Regimen

- Haematology – Azacitidine SC (5+2 days)

## Indication

- 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 syndrome according to the International Prognostic Scoring System (IPSS) or
  - chronic myelomonocytic leukaemia with 10-29% marrow blasts without proliferative features
  - acute myeloid leukaemia with 20% and above blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification and
  - if the manufacturer provides azacitidine with the discount agreed as part of the patient access scheme.
- Post transplant

## Toxicity

| Drug | Adverse Effect |
|---|---|
| Azacitidine | Gastrointestinal disturbance, injection site reactions, haemorrhagic events, febrile neutropenia, sepsis, pneumonia, necrotising fasciitis, hypokalaemia, tumour lysis syndrome, bone marrow suppression, leg ulcers |

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

## Monitoring

### *Drugs*

- FBC weekly for the first cycle
- LFTs, U&Es and serum bicarbonate at baseline and then prior to each subsequent cycle or more frequently as clinically indicated.

- Patients should be assessed for the risk of tumour lysis syndrome (TLS) before starting azacitidine treatment. Appropriate TLS prophylaxis should be started depending on individual risk severity, according to national/local guidelines.

- Patients with a known history of cardiovascular or pulmonary disease should undergo a full cardiopulmonary assessment before and during treatment with azacitidine.

## Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

### *Haematological*

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent.

Consider blood transfusion in the management of patients who are symptomatically anaemic, in order to maintain haemoglobin levels greater than 8g/dL (80g/L).

The first cycle of azacitidine should be commenced irrespective of the haematological parameters.

For subsequent cycles dose adjustments are based on the following equation for the definition of haematological recovery;

The counts are greater than or equal to;

nadir count + (0.5[baseline count-nadir count])

When the baseline counts are normal (neutrophil counts greater than $1.5x10^9$/L and the platelet count is greater than $75x10^9$/L) follow the table immediately below;

| Nadir Counts | | | |
|---|---|---|---|
| Neutrophil ($10^9$/L) | | Platelet ($10^9$/L) | Dose for the next cycle if recovery is not achieved within 14 days of the last dose |
| less than or equal to 1 | or | less than or equal to 50 | Delay until recovery then use 50% of the dose |
| more than 1 | or | more than 50 | Delay until recovery then use 100% |

If recovery is achieved within 14 days no dose adjustment is necessary.

When the baseline counts are low (neutrophil counts less than $1.5x10^9$/L and the platelet count less than $75x10^9$/L) then follow the table immediately below;

| At nadir, the % reduction from baseline in neutrophils or platelets | | Improvement in any cell line differentiation? | Recovery* within 14 days of last dose? | Action |
|---|---|---|---|---|
| less than 50% | | | Not applicable | Treat on time with no dose reduction |
| more than 50% | and | yes | Not applicable | Treat on time with no dose reduction |
| more than 50% | and | no | yes | Delay treatment until recover. On recovery, re-treat without reduction |
| more than 50% | and | no | no | Delay treatment until recovery. On recovery, check marrow cellularity. If more than 50% re-treat without dose reduction. If less than 50%, dose as in the table below |

Dose in the next cycle if recovery is not achieved within 14 days of last dose following the table immediately below;

| **Bone marrow cellularity** | **Recovery less than or equal to 21 days** | **Recovery greater than 21 days** |
|---|---|---|
| 15-50% | 100% | 50% |
| less than 15% | 100% | 33% |

*Hepatic Impairment*

No formal studies have been conducted in patients with hepatic impairment. Patients with severe hepatic organ impairment should be carefully monitored for adverse events.

No specific modification to the starting dose is recommended for patients with hepatic impairment prior to starting treatment. However, subsequent dose modifications should be based on haematological parameters.

Azacitidine is contraindicated in patients with advanced malignant hepatic tumours.

### *Renal Impairment*

Azacitidine has not been studied in patients with impaired renal function. No specific modification to the starting dose is recommended in patients with renal impairment. Patients with severe renal impairment should be closely monitored for adverse effects.

| Creatinine/Blood urea nitrogen (BUN) | Serum bicarbonate (micromol/L) | Dose (% of original dose) |
|---|---|---|
| Greater than 2xULN | | Delay until normal or baseline, then resume at 50% dose. |

Severe renal tubular dysfunction manifesting as hypophosphatemia, hypokalemia or hyponatremia with or without increases in serum creatinine occurs infrequently. Monitor serum bicarbonate, urea and creatinine. If serum bicarbonate is less than 19mmol/L due to azacitidine then replace with oral sodium bicarbonate. Reduce the dose of azacitidine by 50% at the next cycle.

### Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

*Hypersensitivity*

Serious hypersensitivity reactions have been reported in patients receiving azacitidine. In case of an anaphylactic-like reaction, treatment with azacitidine should be immediately discontinued and appropriate symptomatic treatment initiated.

Azacitidine is contra-indicated in those allergic to mannitol.

*Skin*

The majority of skin and subcutaneous adverse reactions were associated with the injection site. None of these adverse reactions led to discontinuation of azacitidine, or reduction of azacitidine dose in the pivotal studies. The majority of adverse reactions occurred during the first two cycles and tended to decrease with subsequent cycles. Subcutaneous adverse reactions such as injection site rash/inflammation/pruritus, rash, erythema and skin lesion may require management with concomitant medicinal products, such as antihistamines, corticosteroids and non-steroidal anti-inflammatory medicinal products (NSAIDs). These cutaneous reactions have to be distinguished from soft tissue infections, sometimes occurring at injection site. Soft tissue infections, including cellulitis and necrotising fasciitis in rare cases leading to death, have been reported with azacitidine.

## Regimen

**28 day cycle for a minimum of 6 cycles, then continue until disease progression or intolerance (6 cycles will be set in Aria).**

| Drug | Dose | Days | Administration |
|---|---|---|---|
| Azacitidine | 75mg/m$^2$ | 1, 2, 3, 4, 5, 8, 9 | Subcutaneous injection in water for injections over one minute |

## Dose Information

- Azacitidine will be dose banded according to the national dose bands (25mg/ml).

## Administration Information

- 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 2.5 cm 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 be a Monday

## Additional Treatments

Anti-emetics

Take 15-30 minutes prior to chemotherapy

- ondansetron 8mg oral or intravenous

As take home medication

- metoclopramide 10mg three times when required oral
- ondansetron 8mg once a day on days 2, 3, 4, 5, 8, 9 oral or intravenous

Allopurinol 300mg once a day for 7 days for cycle one only oral

Hydrocortisone 1% applied sparingly to the injection site when required for the relief of inflammation cycle one only

Senna 15mg at night when required for the relief of constipation

## Coding

- Procurement – X71.5
- Delivery – X72.3, X72.4

References


1. Fenaux, P., Mufti, GJ., Hellstrom-Lindberg, E., Santini, V., Fineli, C., and Giagounidis, A., *et al.* (2009). Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncology*.**10** (3), 223-232.
2. Silverman, LR., Demakos, EP., Peterson, BL., Kornblith., AB, Holland, JC., and Odchimar-Reissig, R., *et al.* (2002). Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. *Journal of clinical oncology*. **20** (10), 2429-2440.
3. Celgene Limited (2016). Vidaza 25mg/mL powder for suspension for injection Summary of Product Characteristics. Online at http://www.medicines.org.uk/emc/medicine/21508, accessed 18 October 2016.
4. National Institute for Health and Care Excellence (2011). Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia. [TA218]. London: National Institute for Health and Care Excellence.
5. University College London Hospitals NHS Foundation Trust (2009). Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3). Online at http://www.londoncancer.org/media/65600/renal-impairment-dosage-adjustment-for-cytotoxics.pdf, accessed 18 October 2016

## REGIMEN SUMMARY

Azacitidine SC (5+2 days)

### Cycle 1

### Day 1, 2, 3, 4, 5, 8, 9

1. Ondansetron 8mg oral or intravenous

2. Azacitidine 75mg/$m^2$ in water for injection over one minute subcutaneous injection
   Administration Instructions
   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 2.5 cm 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 be a Monday

### Take Home Medicines (day 1 only)

1. Metoclopramide 10mg three times a day when required for nausea oral
   Administration Instructions
   Please supply 28 tablets or nearest equivalent original pack

2. Allopurinol 300mg once a day for 7 days oral

3. Hydrocortisone 1% cream, apply to the injection site for relief of inflammation up to four times a day when required topical
   Administration Instructions
   Please supply 30g or nearest equivalent original pack

4. Senna 15mg at night when required for the relief of constipation oral
   Administration Instructions
   Please supply 28 tablets or nearest equivalent original pack

### Cycles 2, 3, 4, 5, 6

### Day 1, 2, 3. 4, 5, 8, 9

5. Ondansetron 8mg oral or intravenous

6. Azacitidine 75mg/$m^2$ in water for injection over one minute subcutaneous injection
   Administration Instructions
   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 2.5 cm 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 be a Monday

## DOCUMENT CONTROL

| Version | Date | Amendment | Written By | Approved By |
|---|---|---|---|---|
| 1 | April 2017 | None | Eleanor Taylor<br>Pharmacist | Dr Deborah Richardson<br>Consultant<br>Haematologist |

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines.