Azacitidine

Indication

Azacitidine is indicated in adults who are not eligible for haematopoietic stem cell transplantation and have one of the following:

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

(NICE TA 218)

ICD-10 codes

Codes with the following prefixes D46, C92, C93

Regimen details

Day	Drug	Dose	Route
Day 1-7	Azacitidine	75mg/m^2	SC
OR *Day 1-5 (Monday-Friday) and 8-9 (Monday and Tuesday)	Azacitidine	75mg/m^2	SC

* Note: this dosing schedule is unlicensed, however may be used as a more practical method of administration.

Cycle frequency

28 days (7 days of treatment, followed by 21 days' rest, or 19 days rest if the 5+2 dosing schedule is used)

Number of cycles

Minimum of 6 cycles. To continue until disease progression or unacceptable toxicity.

Administration

Azacitidine is administered by SC injection over 1 minute.
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. A uniform cloudy suspension should be achieved.

The needle should not be purged prior to injection in order to reduce the incidence of local injection site reactions. Azacitidine should be injected subcutaneously using a 25-gauge needle into the upper arm, thigh or abdomen. Sites of injection 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. It is recommended that the injected region is gently massaged after the injection has been delivered. Doses greater than 4mL (i.e. >100mg) should be divided and injected into two separate sites.

The drug should be administered over approximately one minute and then the injection site covered with sterile gauze.

Azacitidine has a very short expiry: up to 8 hours if stored between 2-8°C immediately after reconstitution. If stored at room temperature, it only has 45 minutes expiry. If refrigerated, allow up to 30 minutes prior to administration to reach room temperature. The shelf life of azacitidine can be extended by reconstituting with refrigerated (2°C to 8°C) water for injections. When azacitidine is reconstituted using refrigerated water for injections, the chemical and physical in-use stability of the reconstituted medicinal product is 22 hours if stored between 2°C to 8°C.

Pre-medication

8mg PO ondansetron (or equivalent) is recommended 30 minutes prior to each dose.

Emetogenicity

This regimen has high emetic potential.

Additional supportive medication

Allopurinol 300mg OD (100mg OD if creatinine clearance <20mL/min) for first 2 cycles.
Antiemetics as per local policy, and as above.
H_2 antagonist or proton-pump inhibitor as per local policy.
Laxatives for constipation as per local policy.
Antifungal prophylaxis may be required if baseline cytopenia or persistent neutropenia.
Topical steroids and/or antihistamines for local site reactions.

Extravasation

N/A

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	7 days
U + E (including creatinine)	7 days
LFTs	7 days
Serum bicarbonate	7 days

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	72 hours, weekly during nadir
U + E (including creatinine)	72 hours
LFTs	72 hours
Serum bicarbonate	72 hours

Standard limits for administration to go ahead

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

Investigation	**Limit**
Neutrophils	See haematological toxicity
Platelets	See haematological toxicity
Serum creatinine	≤ 2 x ULN

Dose modifications

- **Haematological toxicity**

Cycle one: no dose modifications, the first cycle of azacitidine should be commenced regardless of baseline FBC.

Dose modifications for subsequent cycles are required if the nadir neutrophils < 1.0 x 10^9/L and/or platelets < 50 x 10^9/L.

Normal baseline FBC (WCC ≥ 3.0 x 10^9/L, neutrophils ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L) :

Nadir counts			Dose for next cycle (if recovery not within 14 days of last cycle*)
Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	
≤ 1.0	or	≤ 50	Delay until recovery, then 50% dose
> 1.0	or	>50	Delay until recovery, then 100% dose

* if recovery within 14 days, no dose adjustment is necessary

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]).

Reduced baseline FBC (WCC < 3.0 x 10^9/L, neutrophils < 1.5 x 10^9/L or platelets < 75 x 10^9/L) :
Following treatment if the decrease in WCC, neutrophils or platelets from the value prior to treatment is ≤ 50% or >50% but with an improvement in any cell line differentiation, the next cycle may continue as planned.

If the decrease in WCC, neutrophils or platelets is > 50% with no improvement in cell line differentiation, the next cycle should be delayed until recovery. If recovery within 14 days no dose adjustment is required. If recovery has not been achieved within 14 days, bone marrow cellularity should be determined. If the bone marrow cellularity us > 50%, no dose adjustments are required. If ≤ 50%, treatment should be delayed and dose reduced as follows:

Bone marrow cellularity	Dose for next cycle (if recovery not within 14 days of last cycle*)	
	Recovery ≤ 21 days	**Recovery > 21 days**
15-50%	100%	50%
<15%	100%	33%

Dose reductions and treatment delays are not recommended in the first 3 cycles of azacitidine and repeat BM biopsies can be avoided if there is no evidence of disease progression on the peripheral blood film.

- **Renal impairment**

Azacitidine may be administered in renal impairment without initial dose adjustment. As azacitidine and its metabolites are excreted via the kidneys close monitoring is required.
If serum bicarbonate levels < 20mmol/L (without explanation) reduce subsequent cycle doses to 50%.
If serum creatinine or blood urea nitrogen ≥ 2 x ULN (without explanation) reduce subsequent cycle doses to 50%.

- **Hepatic impairment**

No formal studies have been carried out in patients with hepatic impairment. Patients with severe hepatic impairment should be closely monitored for adverse events. No starting dose modification is required. Doses should be adjusted according to haematological values.
Azacitidine is contraindicated in patients with malignant hepatic tumours.

- **Other toxicities**

Azacitidine should be used with caution in patients with cardiac and pulmonary disease.

Any grade 3-4 non-haematological toxicity (except alopecia) should be managed as follows:
1st occurrence: delay next cycle until ≤ grade 2 (for a maximum period of 56 days), then continue with dose of 75mg/m^2 for 5 days only.
2nd occurrence: delay next cycle until ≤ grade 2, then continue with dose of 50mg/m^2 for 5 days only.

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

- **Serious side effects**

Myelosuppression
GI haemorrhage
Infertility
Conjunctival haemorrhage
Hepatic failure
Renal failure
Interstitial lung disease

- **Frequently occurring side effects**

Myelosuppression
Hypertension
Dizziness
Headache
Nausea, vomiting
Diarrhoea, constipation
Dyspnoea
Rash
Arthralgia
Fatigue

- **Other side effects**

Hypokalaemia
Confusion, anxiety

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

Nil known

Additional comments

References

- Summary of Product Characteristics Azacitidine (Celgene) accessed 24 Feb 2015 via www.medicines.org.uk
- National Institute for Health and Clinical Excellence. TA218. Accessed 24 Feb 2015 via www.nice.org.uk
- Silverman, LR et al; Further Analysis of Trials With Azacitidine in Patients With Myelodysplastic Syndrome:JCO 2006; 24 (24): 3895-3903.

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Date: February 2015
