Oral Azacitidine (Onureg) (AML)

Indication

Maintenance treatment for acute myeloid leukaemia (AML) in adults who:

- Are in complete remission (CR) or complete remission with incomplete blood count recovery (CRi), after induction therapy with or without consolidation treatment, and
- Cannot have or do not want a haematopoietic stem cell transplant (HSCT)

(NICE TA 827)

Note: The licensing trial (Wei, A et al, N Engl J Med 2020; 383:2526-2537) excluded patients with AML associated with inv(16), t(8;21), t(16;16), t(15;17), or t(9;22) karyotypes or molecular evidence of such translocations. The benefit of maintenance therapy has only been shown in patients with intermediate and adverse risk cytogenetics AML.

ICD-10 codes C92.0, C92.3 C92.5, C92.6, C92.8, C93.0, C94.0

Regimen details

Day	Drug	Dose	Route
1-14 (followed by a 14 day rest period)	Azacitidine	300mg OD	Oral

In the case of disease relapse, (while on treatment with oral azacitidine), with 5-15% blasts in peripheral blood or bone marrow an extension of the dosing schedule from 14 to 21 days should be considered:

Day	Drug	Dose	Route
1-21 (followed by a 7 day rest period)	Azacitidine	300mg OD	Oral

Cycle frequency

28 days

Number of cycles

Until >15% blasts, unacceptable toxicity or HSCT

Administration

NB. Oral azacitidine (Onureg) should not be used interchangeably with injectable azacitidine. Check dosing and route of administration carefully.

Azacitidine is available as 200mg and 300mg film coated tablets and can be taken with or without food. They should be swallowed whole with a glass of water at about the same time each day. The tablets should not be split, crushed, dissolved, or chewed. If a dose of azacitidine is missed, or not taken at the usual time, the dose should be taken as soon as possible on the same day. The next scheduled dose should then be taken at the normal time the following day. Two doses should not be taken on the same day. If vomiting occurs following dosing, another dose must not be taken on the same day. Instead return to the normal time of dose administration the following day.

Pre-medication

8mg PO ondansetron (or equivalent) is recommended 30 minutes prior to each dose for at least the first two cycles. If after 2 cycles the patient has not experienced any nausea or vomiting then the antiemetic can be stopped.

Emetogenicity

This regimen has high emetic potential.

Additional supportive medication

Loperamide as required

If patients are in CRi and neutrophils <1.0 x 10^9/L then antifungal and antibiotic prophylaxis should be considered, as per local policy.

Extravasation

N/A

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	7 days
U&Es (including creatinine)	7 days
LFTs	7 days

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC*	7 days (see below)
U&Es (including creatinine)	7 days
LFTs (including ALT and AST)	7 days

*With cycles 1 and 2, check FBC every other week. Following 2 cycles (assuming no dose adjustments made) then an FBC can be checked prior to each cycle. If a dose adjustment is made, then an FBC should be checked every other week for 2 cycles following the dose adjustment (and then can return to monitoring pre-cycle only)

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	≥ 0.5 x 10^9 /L
Platelet count	≥ 25 x 10^9 /L
Bilirubin	≤ 1.5 x ULN
AST/ALT	≤ ULN

Dose modifications

In the case of toxicity (as outlined below) dose modification can be made initially reducing the dose of azacitidine to 200mg OD and then if toxicity persists the length of treatment can be reduced by 7 days.

Patients can return to their original dose and/or schedule in a step-wise fashion provided that the increased dose or length of treatment course is tolerable and at least two cycles of treatment have been given at the reduced dose/modified schedule.

- **Haematological toxicity**

Neutropenia:

Neutrophil count	Action
0.5 x 10^9 /L or <1.0 x 10^9 /L with fever (1st occurrence)	Interrupt azacitidine. Consider use of GCSF as clinically indicated Resume the treatment cycle at the same dose once neutrophils ≥ 1 x 10^9 /L
0.5 x 10^9 /L or <1.0 x 10^9 /L with fever (Occurrence in 2 consecutive cycles)	Interrupt azacitidine Consider use of GCSF as clinically indicated Resume the treatment cycle at a reduced dose of 200mg OD once neutrophils ≥ 1.0 x 10^9 /L. If patient continues to experience toxicity after dose reduction, reduce the treatment duration to 7 days If toxicity re-occurs despite dose and schedule reduction, discontinue azacitidine.

Thrombocytopaenia:

Platelet count	Action
Platelets < 25 x 10^9/L or <50 x 10^9/L with bleeding (1st occurrence)	Interrupt azacitidine. Resume the treatment cycle at the same dose once platelets ≥ 50 x 10^9 /L
Platelets < 25 x 10^9/L or <50 x 10^9/L with bleeding (Occurrence in 2 consecutive cycles)	Interrupt azacitidine Resume the treatment cycle at a reduced dose of 200mg OD once platelets ≥ 50 x 10^9 /L. If patient continues to experience toxicity after dose reduction, reduce the treatment duration to 7 days If toxicity re-occurs despite dose and schedule reduction, discontinue azacitidine.

- **Renal impairment**

Oral azacitidine can be given to patients with mild, moderate or severe renal impairment without initial dose adjustment.

- **Hepatic impairment**

For patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin 1 - 1.5 × ULN and any AST) no dose adjustment is recommended.

In patients with moderate (bilirubin > 1.5 to 3 × ULN) and severe hepatic impairment (bilirubin > 3 × ULN) more frequent monitoring for adverse reactions should be conducted and appropriate dose adjustment should be made in the case of specific toxicity.

- **Other toxicities**

Toxicity	Definition	Dose adjustment
Nausea, vomiting or diarrhoea	≥ Grade 3	Hold azacitidine until toxicity ≤ grade 1, and then resume the cycle at the same dose of azacitidine. Supportive treatment should be administered i.e. antiemetics or loperamide as indicated. If the toxicity re-occurs, then azacitidine should be held until it is ≤ grade 1 and then azacitidine recommenced at the lower dose of 200mg OD. If the toxicity continues despite dose reduction, treatment duration should be reduced by 7 days. If toxicity continues despite dose and treatment duration reduction then oral azacitadine should be discontinued.
Other non-haematological toxicity	≥ Grade 3	Hold azacitidine until toxicity ≤ grade 1, and then resume the cycle at the same dose of azacitidine. Supportive treatment should be given as required (and according to local policy). If the toxicity re-occurs, then azacitidine should be held until it is ≤ grade 1 or and then azacitidine recommenced at the lower dose of 200mg OD. If the toxicity continues despite dose reduction, treatment duration should be reduced by 7 days. If toxicity continues despite dose and treatment duration reduction oral azacitadine should be discontinued.

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

- **Serious side effects**

Febrile neutropenia
Pneumonia
Pyrexia
Cellulitis
Sepsis
Influenza
Diarrhoea
Back pain
Atrial fibrillation
Cholecystitis
Anaemia
Thrombocytopaenia

- **Frequently occurring side effects**

Myelosuppression, including febrile neutropenia
Nausea
Vomiting
Diarrhoea
Constipation
Abdominal pain and pain in the extremities
Fatigue/asthenia
Decreased appetite and weight loss
Infections (respiratory tract infections, influenza, urinary tract infections, bronchitis, rhinitis)
Anxiety

- **Other side effects**

Side effects experienced with 21-day dosing schedule (not otherwise mentioned):
Hypokalaemia
Peripheral oedema

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

No formal clinical studies looking at drug-drug interactions with oral azacitidine have been conducted.

Azacitidine is not metabolised by CYP450 isoforms and clinically relevant inhibitory or inductive effects on CYP450 substrates are unlikely. No clinically relevant drug-drug interactions are expected when azacitidine is co-administered with P-gp, BCRP, OAT1, OAT3, OATP1B1, OATP1B3 or OCT2 substrates.

Please note the trial excluded anyone taking the following medications: Cytotoxic chemotherapeutic agents or experimental agents, Romiplostim and other TSAs (eg. Interleukin-11), Hydroxycarbamide, Lenalidomide, pomalidomide, thalidomide, Arsenic trioxide, Interferon and Retinoids.

Additional comments

Studies in mice and rats have shown reproductive and developmental toxicity. The potential risk to humans is not known but based on animal studies azacitidine is not recommenced during pregnancy.

Women of childbearing potential must use effective contraception during treatment and for 6 months following the last dose of azacitidine. Men must also agree to use effective contraception while taking the medication and for 3 months following the last dose of azacitidine.

There is no data for humans on how azacitidine effects fertility, however adverse effects of azacitidine on male fertility in animals have been documented.

It is not known whether azacitidine or its metabolites are excreted in milk, therefore it is advised that breastfeeding is contraindicated during azacitidine treatment.

Oral azacitidine contains lactose.

References

- Summary of Product Characteristics Azacitidine (Onureg) accessed 24 November 2022 via www.medicines.org.uk .
- National Institute for Health and Clinical Excellence. TA827 accessed 30 Oct 2022 via www.nice.org.uk
- Wei, A et al, Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission. N Engl J Med 2020; 383:2526-2537

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