Chemotherapy Protocol

ACUTE MYELOID LEUKAEMIA -AZACITADINE (ORAL)

Regimen

- AML – AZACITADINE (ORAL)

Indication

Oral azacitidine as maintenance therapy in newly diagnosed AML patients in remission following at least induction chemotherapy and who are not candidates for, or who choose not to proceed to, haemopoietic stem cell transplantation where the following criteria is met:

- The patient has newly diagnosed acute myeloid leukaemia (AML)
- The patient has been treated with standard intensive cytarabine-based induction chemotherapy.
- The patient is currently in complete remission (CR) or is in complete remission with incomplete blood count recovery (CRi)
- The patient is not a candidate for, or has chosen not to proceed to, haemopoietic stem cell transplantation (HSCT).
- Maintenance therapy with oral azacitadine will be as monotherapy
- Oral azacitadine maintenance therapy will be continued until disease progression up to a maximum of 15% blasts is observed in peripheral blood/bone marrow or until unacceptable toxicity occurs or there is a withdrawal of patient consent, whichever is sooner.
- The prescribing clinician understands that the usual 300mg once daily 14 day treatment scheduled every 28 days for oral azacitadine can be extended to a 21 day treatment schedule every 28 days if disease relapse with a blast count of 5-15% is observed in the peripheral blood or bone marrow.
- The patient is fit for treatment with oral azacitadine maintenance therapy and has an ECOG performance status of 0-3.
- Oral azacitadine can only be prescribed in this maintenance indication in this group of AML patients and cant be used interchangeably with injectable azacitadine.

Toxicity

Drug	Adverse Effect
Azacitadine	nausea, vomiting, diarrhoea, neutropenia, fatigue/asthenia, constipation, thrombocytopenia, abdominal pain, respiratory tract infection, arthralgia, decreased appetite, febrile neutropenia, back pain, leucopenia, pain in extremity, pneumonia

The adverse effects listed are not exhaustive. Please refer to the relevant summary of product characteristics for further details.

Monitoring

- Full blood counts should be performed prior to initiation of therapy. Full blood count monitoring is also recommended every other week for the first 2 cycles (56 days), every other week for the next 2 cycles after dose adjustment, and monthly thereafter, prior to the start of subsequent cycles of treatment.

- U&Es and LFTs prior to each cycle.

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

Consider blood transfusion or the use of erythropoietin according to NICE TA323 if patient symptomatic of anaemia or has haemoglobin of less than 8g/dL (80g/L).

Criteria	Recommended action
Grade 4 neutropenia or grade 3 neutropenia with fever	First occurrence • Interrupt azacitadine • Resume the treatment cycle at the same dose once neutrophils return to Grade 2 or lower. • Use supportive care such as granulocyte colony stimulating factor (GCSF), as clinically indicated Occurrence in 2 consecutive cycles • Interrupt Azacitadine • Resume the treatment cycle at a reduced dose of 200 mg after neutrophils return to Grade 2 or lower. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or re-occurs after dose and schedule reduction, discontinue azacitadine. • Use supportive care such as GCSF, as clinically indicated
Grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding	First occurrence • Interrupt azacitadine. • Resume the treatment cycle at the same dose once platelets return to Grade 2 or lower. Occurrence in 2 consecutive cycles • Interrupt azacitadine. • Resume the treatment cycle at a reduced dose of 200 mg

	after platelets return to Grade 2 or lower. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • • If the toxicity continues or re-occurs after dose and schedule reduction, discontinue azacitadine.

Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin (BIL) ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN, or BIL 1 to 1.5 × ULN and any AST).

Patients with moderate (BIL > 1.5 to 3 × ULN) and severe hepatic impairment (BIL > 3 × ULN) should be monitored more frequently for adverse reactions and appropriate dose adjustment should be made.

Renal Impairment

Azacitadine can be administered to patients with mild, moderate or severe renal impairment without initial dose adjustment.

Other

Criteria	Recommended action
Grade 3 or higher nausea, vomiting or diarrhoea	• Interrupt Azacitadine • Resume the treatment cycle at the same dose once toxicity has resolved to Grade 1 or lower. • Use supportive care such as anti-emetic therapy and treat diarrhoea at the onset of symptoms • If event re-occurs, interrupt dose until resolved to Grade 1 or lower and reduce the dose to 200 mg. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or re-occurs after dose and schedule reduction, discontinue azacitadine.
Other Grade 3 or higher non haematological events	• Interrupt azacitadine and provide medical support according to local recommendations. • Resume the treatment cycle at the same dose once toxicity has resolved to Grade 1 or lower. • If the toxicity re-occurs, interrupt Azacitadine until resolved to Grade 1 or lower and reduce dose to 200 mg. • If a patient continues to experience

	the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or re-occurs after dose and schedule reduction, discontinue Azacitadine.

Regimen

28 day cycle until disease progression or intolerance (12 cycles will be set in ARIA)

Drug	Dose	Days	Administration
Azacitadine	300mg once a day	1-14*	oral

*In the case of disease relapse, with 5% to 15% blasts in peripheral blood or bone marrow, in conjunction with a clinical assessment, an extension of the dosing schedule from 14 to 21 days of repeated 28-day cycles should be considered. Dosing should not exceed 21 days during any 28-day period. Azacitadine should be discontinued if more than 15% blasts are observed in either the peripheral blood or bone marrow or at the physician's discretion.

Dose Information

- Azacitadine is available as 200mg and 300mg film-coated tablets

Administration Information

- If a dose of azacitadine is missed, or not taken at the usual time, the dose should be taken as soon as possible on the same day. Then, the next scheduled dose should be taken at the normal time the following day. Two doses should not be taken on the same day

- If a dose is vomited, another dose must not be taken on the same day. Instead return to the normal time of dose administration the following day.

- Azacitadine can be taken with or without food. The tablets should be swallowed whole with a glass of water at about the same time each day. They should not be split, crushed, dissolved or chewed.

Additional Therapy

- Anti-emetics
  As take home medication
  - metoclopramide 10mg three times when required oral –
  - ondansetron 8mg twice a day on days 1-14 oral

- Anti-infective prophylaxis with
  - aciclovir 400mg twice a day

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

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to azacitadine.

- It must be made clear to all staff, including those in the community, that azacitadine is should only be prescribed under the supervision of a consultant haematologist or oncologist.

- There are many drug interactions associated with azacitadine. Please check for interactions when initiating treatment.

- Azacitadine has minor influence on the ability to drive and use machines. Fatigue has been reported with the use of Azacitadine. Therefore, caution is recommended when driving or operating machines.

References

1. Bristol-Myers Squibb Pharma. Onureg 200 mg film-coated tablets summary of product characteristics. Available from: https://mhraproducts4853.blob.core.windows.net/docs//858bc5ecf70c5ee203df4b39987e83f32e7e8a9c. Last updated 01/07/2021.
2. Wei AH et al. Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission. N Engl J Med 2020; 383:2526-2537.

REGIMEN SUMMARY

Azacitadine (oral)

Take Home Medicines

1. Azacitadine 300mg once a day oral for 14 days
   Administration instructions:
   Oral SACT
   Swallow whole
   To be taken at the same time each day starting on day 1 of the cycle.

2. Ondansetron 8mg twice a day oral for 14 days
   Administration instructions:
   To be taken 15-30 minutes prior to azacitadine. A further dose can be taken 12 hours later.

3. Aciclovir 400mg twice a day oral for 28 days

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

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	November 2022	None	Alexandra Pritchard Pharmacist	Dr Deborah Richardson Consultant Haematologis

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.