

CYTARABINE (Ara-C) LOW DOSE

INDICATIONS

Low-dose cytarabine (Ara-C) is used as non-curative/ palliative therapy for the following disorders:

- Myelodysplastic syndrome (MDS) with intermediate, high-risk disease and some patients with very high-risk disease by the International Prognostic Score System (IPSS-R).
- Chronic Myelomonocytic Leukemia-2 (CMML-2)
 - Blasts/ promonocyte: 5-19% in PB and/or 10-19% in BM or Auer rods, irrespective of blast/ promonocyte percentage.
- Acute myeloid leukaemia (AML)
- Myelofibrosis with increased blasts (10-19%) in elderly patients.

TREATMENT INTENT

Disease modification

PRE-ASSESSMENT

1. Ensure diagnosis is confirmed prior to administration and document in notes.
 2. Record clinical impact of disease, blood film, bone marrow aspirate and trephine, immunophenotype, cytogenetic results and calculate relevant prognostic score.
 3. Blood tests - FBC, DCT, U&Es, LDH, ESR, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, hepatitis B core antibody and hepatitis B surface Ag, hepatitis C antibody, EBV, CMV, VZV, HIV, group and save.
 4. Pregnancy Test - for all women with childbearing potential before each new chemotherapy course. Exclude pregnant or lactating women.
 5. ECG +/- Echo - if clinically indicated.
 6. Record performance status (WHO/ECOG)
 7. Record height and weight.
 8. Treatment should be agreed in the relevant MDT.
 9. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent and ensure this is in the hospital record prior to treatment.
 10. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts.
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DRUG REGIMEN

The first cycle may begin irrespective of baseline haematological parameters. Thereafter, cycles should commence cycles with neutrophils $\geq 1 \times 10^9/L$ and platelets $\geq 100 \times 10^9/L$

Days 1 - 10 **CYTARABINE** 20mg TWICE a day subcutaneously. Each dose to be 12 hours apart (20 doses in total).

Subcutaneous cytarabine is administered in the out-patient setting providing patients/carers have been trained, assessed and confirmed competent for self-administration.

Refer to Myeloid NSSG -> Patient information > Patient/Carer instructions for the administration of Subcutaneous Cytarabine

CYCLE FREQUENCY

Cycle repeats every 28 - 42 days, counts may be supported by G-CSF where necessary. If tolerated, patients should receive a minimum of 4 courses. There is no maximum cycle number.

EVALUATION OF FIRST RESPONSE

1. Unless there is obvious clinical progression, perform a marrow after completion of cycle 4, if clinically appropriate.
2. Grade the response with IWG criteria 2003 for AML or IWG 2006 criteria for MDS (depending on initial diagnosis) by evaluating the peripheral blood and marrow response. There are five possible outcomes:
 - **Complete response (CR) or CRi (CR with incomplete haematologic recovery)**
 - **Partial Response (PR)** – complete peripheral count recovery but 5-15% blasts.
 - **Haematological improvement (HI)** - this is where Low-dose cytarabine (Ara-C) has not reduced the blast count and there is an improvement in the peripheral counts.
 - **Stable disease (SD)** - where Low-dose cytarabine (Ara-C) has not reduced the blast count and may not have improved the counts but it is preventing disease progression and the patient is well and mainly out of hospital.
 - **Resistant disease.** Non-responders with increasing blast count in the marrow and no improvement of peripheral counts or evidence of disease progression in the blood.

MONITORING

1. Until response, weekly FBC to decide on blood component therapy, weekly U&Es and LFTs
2. After response, monthly FBC, U&Es and LFTs

GUIDANCE FOR STOPPING

1. Evaluate response after 4 cycles. If resistant disease and/or no patient benefit, stop therapy.
2. If after initial response there is evidence of disease progression, stop therapy.
3. Progressive disease at any stage - stop therapy

FURTHER EVALUATION

Beyond cycle 4 consider a bone marrow assessment at 12 months and 12-monthly thereafter.

DOSE MODIFICATIONS

Haematological toxicity

The first cycle should commence at full dose regardless of baseline haematological values.

Subsequent cycles should start with neutrophils $\geq 1 \times 10^9/L$ and platelets $\geq 100 \times 10^9/L$, therapy may continue below this level of recovery at the clinician's discretion if myelosuppression is a symptom of disease burden. Dose delay or dose modification is up to the discretion of the Consultant Haematologist.

- In general, cytopenia is usually due to disease before cycle 4 and it is usually prudent to continue treatment.
- Cytopenia after a response may be due to disease recurrence or drug toxicity and a bone marrow evaluation is usually helpful unless there is evidence of circulating disease.

Non-haematological toxicity

Renal impairment	Hepatic impairment
No dose modifications for renal impairment.	Mild / moderate impairment: No dose adjustment necessary Severe impairment: 25 - 50% dose and increase as tolerated

INVESTIGATIONS

FBC, U&E and LFT prior to administration of chemotherapy.

CONCURRENT MEDICATION

Drug	Dose and duration
Tumour lysis prophylaxis (cycle 1)	IV/PO hydration +/- allopurinol 300mg once daily for 7 days OR Rasburicase for very high-risk patients (refer to tumour lysis protocol). Prophylaxis may be repeated at clinician discretion.
Viral prophylaxis	Aciclovir 200 mg three times a day for duration of treatment and for 3 months after completion
Fungal prophylaxis	High risk of fungal infection in persistent neutropenia (consider posaconazole or voriconazole use), lower risk otherwise. Refer to Antifungal guidelines Stop high-risk prophylaxis when neutrophils $> 1.0 \times 10^9/L$.

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EMETIC RISK

Low

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

- Haematologic toxicity – see above.
- Nausea.
- Diarrhoea
- Oral ulceration.
- Hepatic dysfunction.
- Fatigue.
- Rarely at this dose – maculopapular rash, conjunctivitis and malaise.
- Injection site reactions

TREATMENT RELATED MORTALITY

Mortality risk is mainly due to underlying AML (20% post-cycle 1, rising to approx. 30% after cycle 2)

REFERENCES

1. Burnett, A. K., Milligan, D., Prentice, A. G., Goldstone, A. H., McMullin, M. F., Hills, R. K., and Wheatley, K. (2007). A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer* 109, 1114-1124.
2. Krens S D et al (2019). Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol*; 20: e201–08

REVIEW

Name	Revision	Date	Version	Review date
Prof Paresh Vyas, Consultant Haematologist	New document	February 2016	1.0	
Cheuk-kie Jackie Cheung, Haematology Pharmacist. NSSG Myeloid Group	Annual protocol meeting	Oct 2019	1.1	Oct 2021
Yen Lim, Haematology Pharmacist. NSSG Myeloid Group	Annual protocol meeting. Renal/hepatic dosing updated.	Nov 2021	1.2	Nov 2023
Connor Sweeney, Consultant Haematologist	Annual protocol meeting	Sep 2023	1.3	Sep 2025
Donna Constantine Advanced Cancer Pharmacist	Minor formatting adjustments. Minor adjustments to supportive care.	Jan 2026	2.0	Nov 2028

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