FLA-IDA

INDICATION

Induction chemotherapy for patients with acute myeloid leukaemia (AML) or in relapse/ refractory disease (AML or ALL). Its use is particularly for patients under 60 years of age but it can be applied to older patients according to clinician's assessment.

Note: The chemotherapy in this protocol is as for FLAG-IDA. It is anticipated that this protocol is most likely to used in patients with AML with a high white count, or in ALL patients.

TREATMENT INTENT

Curative

PRE-ASSESSMENT

1. Ensure diagnosis is confirmed with appropriate tests and is documented in notes.
2. Blood tests - FBC, DCT, U&Es, LDH, ESR, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, β2 microglobulin, hepatitis B core antibody and hepatitis B surface antigen, hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent, group and save.
3. Pregnancy Test - for all women with childbearing potential before each new chemotherapy course.
4. ECG +/- Echo - *if clinically indicated*.
5. Record performance status (WHO/ECOG).
6. Record height and weight.
7. 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 prior to treatment.
8. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice (see fertility guidelines).
9. Send a "group and save" sample to transfusion and inform patient and transfusion laboratory that they will require **irradiated blood products** for all future transfusions. Ensure irradiation card is attached to the patient's notes. See ‘Guidelines for the use of blood components in adult haematology’.
10. Hydration and tumour lysis prevention in patients with bulk disease (refer to tumour lysis protocol)
11. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts in practical.
12. Treatment should be agreed in the relevant MDT.
13. **Central venous access should be used, e.g. Hickman line or PICC. In urgent cases it may be necessary to start chemotherapy via a peripheral cannula.**

DRUG REGIMEN/CYCLE FREQUENCY

Days 1 to 5	**FLUDARABINE** 30 mg/m^2 daily in 100 mL sodium chloride 0.9% intravenous infusion over 30 minutes (5 doses). Fludarabine infusion must precede the administration of cytarabine by 4 hours.
Days 1 to 5	**CYTARABINE*** 2 g/m^2 daily in 250 mL sodium chloride 0.9% intravenous infusion over 4 hours (5 doses).
Days 3, 4 and 5	**IDARUBICIN** 8 mg/m^2 intravenous bolus daily (3 doses).

NB: *For patients aged 60 years and over the cytarabine dose should be halved to 1g/m^2 daily (total 5g/m^2 over 5 days).

Course 2 can be considered upon count recovery (general guidance: neutrophils >1 x10^9/L; platelets >100 x10^9/L). Idarubicin use and dosage must be carefully considered in Course 2 (total lifetime anthracycline dose and high risk of delayed regeneration). Maximum two courses.

DOSE MODIFICATIONS

Fludarabine

Renal impairment	Hepatic impairment
GFR > 70 mL/min: 100% dose GFR 30-70 mL/min: 80% dose GFR < 30 mL/min: Contra-indicated	No dose changes recommended

Cytarabine - discuss with consultant

Renal impairment	Hepatic impairment
High dose 1-3 g/m^2 GFR < 31-59 mL/min: 50% dose GFR < 30 mL/min: omit Haemodialysis: give 50% dose, start HD 4-5 hours after administration	Mild/moderate impairment: no dose adjustment necessary Severe impairment: 25-50% dose and increase as tolerated

Idarubicin - discuss with consultant

Renal impairment	Hepatic impairment
GFR ≥ 30mL/min: 100% dose GFR < 30ml/min: 67% dose	Bilirubin 45-86 micromol/L: 50% dose Bilirubin >86 micromol/L: Not recommended

Maximum cumulative dose: Idarubicin-related cardiomyopathy was reported in 5% of patients who received cumulative intravenous doses of 150 to 290 mg/m^2.

INVESTIGATIONS

- FBC, U&E, LFT, Coagulation screen.
- Recent bone marrow aspirate - this should be evaluated cytologically before proceeding with Course 2.

CONCURRENT MEDICATION

Drug	Dose and duration
Allopurinol	300 mg daily for first 14 days of initial induction chemotherapy. (If a remission is attained, the subsequent use of allopurinol is not required)
Fungal prophylaxis	As per local protocol
Aciclovir	200 mg three times a day for duration of treatment and for 3 months after completion
Proton pump inhibitor	As per local formulary
Prednisolone 0.5-1% eye drops or Dexamethasone 0.1% eye drops (depending on local formulary)	One drop into each eye QDS. Continue for 5 days after cytarabine (due to risk of cytarabine-induced conjunctivitis). In the event of conjunctivitis consider increasing the frequency to 2-hourly until resolution of symptoms. Liaison with local ophthalmologists may be necessary in this situation

PCP prophylaxis can be considered according to clinical assessment: co-trimoxazole or pentamidine according to local guidelines.

EMETIC RISK

Day 1-5: High

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Fludarabine	Nausea, vomiting, alopecia, cough, fever, fatigue, weakness, diarrhoea. CNS side-effects have been rarely described (agitation, confusion, visual disturbance).,
Cytarabine	Nausea, diarrhoea, abdominal pain, oral ulceration, hepatic dysfunction, CNS, GI and pulmonary toxicity, reversible corneal toxicity, somnolence, convulsion, pulmonary oedema. A cytarabine syndrome is also recognised in which patients suffer from fever, myalgia, bone pain, occasional chest pains, maculopapular rash, conjunctivitis and malaise. It usually occurs 6 - 12 hours following administration. Neurotoxicity also reported, e.g. cerebellar damage.
Idarubicin	Cardiotoxicity may occur - cumulative dose associated with cardiotoxicity is not known but it is thought that a total dose of 60-80 mg/m^2 is not problematic. Red discoloration of urine for 2 to 3 days after administration. Alopecia. Nausea and vomiting. Elevation of liver enzymes may occur.

Others: myelosuppression, infections, mucositis.

EXTRAVASATION RISK

Cytarabine: neutral
Fludarabine: neutral
Idarubicin: vesicant

TREATMENT RELATED MORTALITY

AML induction therapy is associated with a relatively high mortality risk of generally between 5-10%. This should be discussed with the patient at the time of consent. This risk is not only due to the chemotherapy but also consequent on the fact that patients treated with AML induction are already unwell as a consequence of having uncontrolled / untreated AML

REFERENCES

1. Estey E, Thall P, Andreeff M, Beran M, Kantarjian H, O'Brien S, Escudier S, Robertson LE, Koller C, Kornblau S, et al. Use of granulocyte colony-stimulating factor before, during, and after fludarabine plus cytarabine induction therapy of newly diagnosed acute myelogenous leukemia or myelodysplastic syndromes: comparison with fludarabine plus cytarabine without granulocyte colony-stimulating factor. J Clin Oncol. 1994 Apr;12(4):671-8.
2. Gandhi V, Estey E, Keating MJ, Plunkett W. Fludarabine potentiates metabolism of cytarabine in patients with acute myelogenous leukemia during therapy. J Clin Oncol. 1993 Jan;11(1):116-24.
3. AML-HR Trial MRC Working Party Protocol (1998).
4. 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 Vyas, Dr Lynn Quek	Mortality risk added, pre-assessment review, concurrent medications, PCP	Feb 2016, Apr 2017	4.0	
Cheuk-kie Jackie Cheung, Haematology Pharmacist. NSSG Myeloid Group	Annual protocol meeting. Cytarabine diluent changed.	Oct 2019	4.1	Oct 2021
Yen Lim, Haematology Pharmacist Andy Peniket, Consultant Haematologist NSSG Myeloid Group	Annual protocol meeting. Updated renal/hepatic dosing.	Nov 2021	4.2	Nov 2023