FLAG-Ida

Indication:
Induction treatment in AML.
Relapsed or resistant AML or ALL.

ICD-10 codes
Codes with a pre-fix C91 or C92.

Regimen details

Day	Drug	Dose	Route
1 to 7	GCSF	As per local policy (up to 28 days)	SC
2 – 6 (5 doses)	Fludarabine	30 mg/m^2 daily	IV infusion
2 – 6 (5 doses)	Cytarabine	2 g/m^2 daily* (4 hours after fludarabine)	IV infusion
4, 5 and 6 (3 doses)	Idarubicin	8 mg/m^2 daily	IV bolus

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

Cycle 2:
Fludarabine, cytarabine and G-CSF as per cycle 1. Idarubicin use and dosage must be carefully considered and discussed with the consultant.

Cycle frequency
Every 4-6 weeks

Number of cycles
2

Administration
Central venous access should be used, e.g. Hickman line, wherever possible. In urgent cases it may be necessary to start chemotherapy via a peripheral cannula until a central line can be arranged.

Fludarabine is administered in 100 mL sodium chloride 0.9% over 30 minutes. Fludarabine infusion must precede the administration of cytarabine by 4 hours.

Cytarabine is administered in 500 mL sodium chloride 0.9% intravenous infusion over 4 hours.

Idarubicin is administered as a slow bolus over 5-10 minutes via a fast running drip**.**

Pre-medication:
Fluid intake should be at least 3 litres per day (including oral and/or intravenous)

Emetogenicity:
This regimen has moderate emetic potential.

Additional supportive medication

Allopurinol 300mg OD (100mg OD if CrCl < 20mL/min) for the first 14 days of initial induction chemotherapy. (If a remission is attained, subsequent use of allopurinol is not required).
Antifungal prophylaxis (as per local policy) daily from start of chemotherapy until end of neutropenia.
Antiviral prophylaxis as per local policy.
PCP prophylaxis as per local policy.
H_2 antagonist or PPI as per local policy.
Mouthwashes as per local policy.
Prednisolone 0.5% eye drops QDS (to avoid chemical conjunctivitis from high-dose cytarabine). 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.

Extravasation

Cytarabine and Fludarabine are neutral (Group 1)
Idarubicin is vesicant (Group 5)

Investigations – pre first cycle

Investigation	**Validity period**
FBC (with film)	7 days
U+Es (including creatinine)	7 days
LFTs	7 days
LDH	7 days
Glucose	7 days

ECG and echocardiogram if cardiac history, previous anthracycline exposure or other potential cardiac risk factors.

Investigations – pre subsequent cycles

Investigation	**Validity period**
FBC (with film)	7 days
U+Es (including creatinine)	7 days
LFTs	7 days
LDH	7 days
Glucose	As clinically indicated

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	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
CrCl	≥ 70mL/min
Bilirubin	< 1.5 x ULN

Dose modifications

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L delay treatment until count recovery.

- **Renal impairment**

CrCl (mL/min)	**Fludarabine dose**
> 70	100%
30-70	50%
< 30	Contra-indicated

Discuss with consultant as some circumstances may warrant 100% dose despite renal impairment.

CrCl (mL/min)	**Cytarabine dose**
> 60	100%
45-60	60%
30-44	50%
< 30	Discontinue

Creatinine (µmol/L)	**Idarubicin dose**
< 100	100%
100-175	50%
> 175	Omit

- **Hepatic impairment**

Cytarabine dose should be reduced to 50% if bilirubin > 1.5 x ULN. Doses may be escalated in subsequent cycles in the absence of toxicity (consultant decision).

Bilirubin (x ULN)	**Idarubicin dose**
< 1.5	100%
1.5 – 2	50%
> 2	omit

No dose modification required for fludarabine.

- **Other toxicities**

For any toxicity grade ≥ 2, discuss with consultant.

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

- **Serious side effects**

Myelosuppression
Infertility
Cardiotoxicity
Hepatotoxicity
CNS toxicity (cytarabine)
Prolonged T-cell depletion (leading to risk of transfusional GVHD)
Acute pulmonary toxicity

- **Frequently occurring side effects**

Myelosuppression
Constipation, diarrhoea
Stomatitis, mucositis
Alopecia
Nausea and vomiting
Anorexia
Conjunctivitis

- **Other side effects**

Electrolyte disturbances
Fatigue
CNS side-effects (including agitation, confusion, visual disturbance)
Hepatic dysfunction
Cytarabine syndrome (fever, myalgia, rash)
Red discolouration of urine

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

Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.

Fludarabine:
Pentostatin: use in combination not recommended due to risk of pulmonary toxicity.
Dipyridamole and other inhibitors of adenosine: may reduce the therapeutic efficacy of fludarabine.

Cytarabine:
Digoxin: cytarabine may affect plasma digoxin levels – consider monitoring.

Idarubicin:
Cardiotoxic drugs: avoid concomitant use
Cyclosporin A: may increase idarubicin levels

Additional comments

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

Contact local Blood Transfusion lab and inform of the need for irradiated blood products. The need for irradiated blood products is indefinite following the administration of fludarabine.

References

- Summary of Product Characteristics Fludarabine (Sanofi) accessed 17 November 2016 via www.medicines.org.uk
- Summary of Product Characteristics Cytarabine (Pfizer) accessed 17 November 2016 via www.medicines.org.uk
- Summary of Product Characteristics Idarubicin (Pfizer) accessed 17 November 2016 via www.medicines.org.uk
- AML19 Trial protocol, Version 5.0, March 2016

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