FLAG-Ida

For treatment of relapsed, refractory AML and ALL, and for high risk AML
Also may be used for CML myeloid blast crisis
Its use is particularly for patients under 60 years of age but can be applied to older patients according to clinician assessment.

Drugs/Dosage/Administration:

Day	Drug	Dose	Route	Frequency
1 – 7, then according to clinical situation and Consultant decision	G-CSF (see Comments)	Lenograstim 263mcg **or** Filgrastim 300mcg	s/c bolus	Once daily
2 – 6 (5 doses)	Fludarabine	30mg/m^2 in 0.9% sodium chloride	IV in 100 – 250ml 0.9% sodium chloride over 30 minutes	Once daily
2 – 6 (5 doses)	Cytarabine	2000mg/m^2 in 500ml 0.9% sodium chloride (If age > 60, give 1000mg/m^2)	IV over 4 hours, starting exactly 4 hours after start of Fludarabine infusion	Once daily
4 – 6 (3 doses)	Idarubicin	8mg/m^2	IV over 5 to 10 minutes via a fast-running saline drip	Once daily, ideally before fludarabine & cytarabine due to its short expiry
2 – 8	Corticosteroid eye drops e.g. Maxidex	One drop	To each eye	Every 4 hours, increasing to 2 hourly if eyes become sore

Other drugs: For patients with potential for tumour lysis syndrome, ensure initiation of prophylactic measures according to Alliance guidelines for management of TLS.
PCP prophylaxis - prescribe according to unit practice/protocol (generally until 6 months after completion of treatment, or according to CD_4 counts)
Posaconazole to be taken during each cycle of chemotherapy, only when neutrophils drop* to < 0.5x10^9/L and until they are > 0.5x10^9/L.

*In the first cycle of treatment, give prophylaxis from the start of the cycle regardless of the initial neutrophil count.

Frequency: 1 - 2 cycles as specified above, with the second cycle given only if the following criteria are met: ≤ 15% blasts in bone marrow after Cycle 1
not considered to have adverse genetic abnormalities
neutrophils > 1.0 x 10^9/L and platelets > 100 x 10^9/L

Note of caution with regard to giving 2 cycles: AML 15 reported that FLAG-Ida led to more prolonged myelosuppression and hence greater supportive care requirements than DA.

Reason for Update: posaconazole tablets available; suspension dose removed	Approved by Chair of Alliance TSSG: Dr A Laurie
Version: 7	Date: 16.3.15
Supersedes: Version 6	Review Date: April 2017
Prepared by: S Taylor	Checked by: C Tucker

Main Toxicities: myelosuppression; alopecia; mucositis; conjunctivitis (cytarabine); encephalopathy (fludarabine); cardiomyopathy (idarubicin); prolonged T cell immunosuppression (fludarabine); ovarian failure; infertility

Anti-emetics: highly emetogenic on Days 2 – 6

Extravasation: Idarubicin is a vesicant

Regular Investigations:		
	FBC	alternate days until neutropenia or thrombocytopenia occur, then daily to recovery
	U&Es	Day 1, then three times weekly
	LFTs	Day 1, then once weekly
	Mg^{2+} & Ca^{2+}	Day 1
	Uric acid	baseline
	Echo / MUGA	see Comments
	Cr^{51}-EDTA/24 hour urine	if serum creatinine > 150µmol/L

Comments: Maximum cumulative dose of Idarubicin not known, but 60 - 80mg/m^2 not considered to be problematic. **Consider previous anthracycline exposure.**
A baseline MUGA / echo should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, obese, smoker, ≥ 70 years old, previous exposure to anthracyclines, previous thoracic radiotherapy. MUGA scan/echo should be repeated if there is suspicion of cardiac toxicity at any point during treatment.

It is important that patient receives G-CSF one day before starting chemotherapy

All patients must receive irradiated blood products for all future transfusions - inform patient and blood bank.

Sperm banking if appropriate and time allows.

Dose Modifications

Haematological Toxicity:		
	Cycle 1:	There are no modifications for myelosuppression
	Cycle 2:	Proceed once neutrophils > 1.0 x 10^9/L and platelets > 100 x 10^9/L If low counts are thought to be due to marrow infiltration, discuss with Consultant.

Renal Impairment:

CrCl (ml/min)	Fludarabine Dose
> 70	Give 100% dose
30 – 70	Give 50% dose
< 30	Contra-indicated

The SPC states that renal impairment can affect the clearance of idarubicin. However, there is no dosing advice according to creatinine clearance. The advice is as follows:

Serum Creatinine (µmol/l)	Idarubicin Dose
100 – 175	Give 50% dose
> 175	Clinical decision

NB. A serum creatinine > 99 µmol/L may not correspond to renal impairment, particularly in younger patients. However, if there *is* evidence of impaired renal function eg reduced creatinine clearance, Cr^{51}-EDTA, or according to Cockcroft and Gault, then it is reasonable to use the serum creatinine to guide the dose reduction.

Hepatic Impairment:

Bilirubin (µmol/L)	Idarubicin Dose	Cytarabine Dose
21 – 34	Give 50% dose	Give 100% dose
> 34	Not recommended	Give 50% dose

Patient Information: Macmillan leaflets for Fludarabine, Idarubicin and Cytarabine

References:
Parker, JE et al; Br J Haem (1997); 99 (4): 939 - 944
AML 15 trial, MRC 2004
AML 17 trial, V5 May 2010