SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

FLAG-IDA
ACUTE MYELOID LEUKAEMIA (AML)

PROTOCOL REF: MPHAFLAGHA
(Version No. 1.2)

Approved for use in:

Induction chemotherapy for patients with high risk acute myeloid leukaemia (AML) with proven or suspected CNS involvement or in relapse/ refractory disease (AML or ALL). For patients under 60 years of age but can be used in older patients at clinician's discretion with recommended dose modifications.

Blueteq not required

Dosage:

Drug	Dose	Route	Frequency
Filgrastim	**30 million units (<70kg)** **48 million units (>70kg)**	s/c injection	Day 1 to 7
Fludarabine	***30mg/m^2**	IV infusion	Days 2 to 6
Cytarabine	****2000mg/m^2**	IV infusion	Days 2 to 6
Idarubicin	***8mg/m^2**	IV infusion	Days 4 to 6

*Consider reducing fludarabine dose to 25mg/m^2 and idarubicin to 5mg/m^2 if aged over 70 years as per AML18 protocol for mini-Flagida
**For patients aged 60 years and over the cytarabine dose should be halved to 1g/m^2 daily

Maximum of 2 cycles

Administration (+/- Counselling Points):

Unless urgent clinical need precludes insertion, should be given via central line

Patients will need admitting for therapy

Patients will required irradiated blood products (lifelong) –the patients receive information booklets about irradiated blood when counselled by the specialist nurses. It contains an alert card that the patient carries around with them. The specialist nurses then contact the lab.

Emetogenic risk:

Severely emetogenic

Supportive treatments:

- **Ensure that the filgrastim prescribed as part of the SACT treatment plan (days 1 to 7) is available on the MAR once transitioned and verified by a pharmacist**
- Allopurinol for 28 days (first cycle only). Consider rasburicase and IV hydration in patients at high risk of tumour lysis syndrome
- Aciclovir 400mg twice daily
- Ciprofloxacin 500mg twice daily (until neutrophils >1.0x10^9/L for 2 consecutive days)
- Chlorhexidine 0.2% mouthwash 10mL four times daily
- Co-trimoxazole 480mg daily (continue for 6 months after completion of treatment)
- Metoclopramide 10mg three times daily prn
- Norethisterone 5-10mg TDS (women of childbearing potential)
- Nystatin 1mL four times daily
- Ondansetron 8mg twice daily IV for 5 days (day 2 to 6 of chemotherapy) and then oral when required.
- Posaconazole 300mg twice daily for 2 doses and then once daily thereafter (until neutrophils >1.0x10^9/L for 2 consecutive days)
- Prednisolone 0.5% eye drops 1 drop four times daily into each eye for 10 days

Extravasation risk:

Fludarabine – non- vesicant

Cytarabine – non-vesicant

Idarubicin – vesicant

Refer to the CCC policy for the ‘Prevention and Management of Extravasation Injuries’

Dosing in renal and hepatic impairment:

Renal Dose Modifications		
	Creatinine clearance (mL/min)	**Dose Modification**
Fludarabine	30 - 70	50% dose
	<30	Omit
	Haemodialysis	80% dose (start dialysis 12 hour after administration)
Cytarabine	31 - 59	50% dose
	<30	Omit
	Haemodialysis	50% dose (start dialysis 4-5 hours after administration)
Idarubicin	<30 or haemodialysis	Consider 67% dose

Hepatic Dose Modifications		
Fludarabine	No data available for use in hepatic impairment. Use with caution	
Cytarabine	Sever dysfunction: Consider 25-50% of original dose and increase as tolerated	
Idarubicin	**Bilirubin (micromol/L)**	**Dose Modification**
	45 - 86	50% dose
	>86	Omit

Interactions:

Please refer to the SPC for full list of interactions and further information

Fludarabine

- Pentostatin: Increased pulmonary toxicity if concomitant use.
- Dipyridamole and other inhibitors of adenosine uptake: may reduce the therapeutic efficacy of fludarabine

Cytarabine

- Digoxin: Possible reduction of digoxin levels – monitor levels closely.
- Intrathecal methotrexate: Possible increased risk of severe neurological adverse reactions such as headache, paralysis, coma and stroke like episodes when given concomitantly with IV cytarabine.

Idarubicin:

- The use of idarubicin in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), requires monitoring of cardiac function throughout treatment.
- Cyclosporin A: The co-administration of cyclosporin A as a single chemosensitizer significantly increased idarubicin AUC (1.78-fold) and idarubicinol AUC (2.46-fold) in patients with acute leukaemia. The clinical significance of this interaction is unknown. A dose adjustment may be necessary in some patients.

Treatment schedule:

Day	Time	Drug	Dose	Route	Diluent and rate
1	18:00	**Filgrastim**	**30 or 48 million units**	**s/c**	n/a
2	08:30	**Ondansetron**	**8mg**	**IV**	100mLs sodium chloride over 15 mins
	09:00	**Fludarabine**	***30mg/m^2**	**IV**	100mls sodium chloride 0.9% over 30 mins
	13:00	**Cytarabine**	****2000mg/m^2**	**IV**	1000mls sodium chloride 0.9% over 4 hours
	18:00	**Filgrastim**	**30 or 48 million units**	**s/c**	n/a
	20:00	**Ondansetron**	**8mg**	**IV**	100mLs sodium chloride over 15 mins
3	08:30	**Ondansetron**	**8mg**	**IV**	100mLs sodium chloride over 15 mins
	09:00	**Fludarabine**	***30mg/m^2**	**IV**	100mls sodium chloride 0.9% over 30 mins
	13:00	**Cytarabine**	****2000mg/m^2**	**IV**	1000mls sodium chloride 0.9% over 4 hours
	18:00	**Filgrastim**	**30 or 48 million units**	**s/c**	n/a
	20:00	**Ondansetron**	**8mg**	**IV**	100mLs sodium chloride over 15 mins
4	08:30	**Ondansetron**	**8mg**	**IV**	100mLs sodium chloride over 15 mins
	09:00	**Fludarabine**	***30mg/m^2**	**IV**	100mls sodium chloride 0.9% over 30 mins
	13:00	**Cytarabine**	****2000mg/m^2**	**IV**	1000mls sodium chloride 0.9% over 4 hours

	17:00	**Idarubicin**	***8mg/m^2**	**IV**	100mls sodium chloride 0.9% over 60 mins
	18:00	**Filgrastim**	**30 or 48 million units**	**s/c**	n/a
	20:00	**Ondansetron**	**8mg**	**IV**	100mLs sodium chloride over 15 mins
5	08:30	**Ondansetron**	**8mg**	**IV**	100mLs sodium chloride over 15 mins
	09:00	**Fludarabine**	***30mg/m^2**	**IV**	100mls sodium chloride 0.9% over 30 mins
	13:00	**Cytarabine**	****2000mg/m^2**	**IV**	1000mls sodium chloride 0.9% over 4 hours
	17:00	**Idarubicin**	***8mg/m^2**	**IV**	100mls sodium chloride 0.9% over 60 mins
	18:00	**Filgrastim**	**30 or 48 million units**	**s/c**	n/a
	20:00	**Ondansetron**	**8mg**	**IV**	100mLs sodium chloride over 15 mins
6	08:30	**Ondansetron**	**8mg**	**IV**	100mLs sodium chloride over 15 mins
	09:00	**Fludarabine**	***30mg/m^2**	**IV**	100mls sodium chloride 0.9% over 30 mins
	13:00	**Cytarabine**	****2000mg/m^2**	**IV**	1000mls sodium chloride 0.9% over 4 hours
	17:00	**Idarubicin**	***8mg/m^2**	**IV**	100mls sodium chloride 0.9% over 60 mins
	18:00	**Filgrastim**	**30 or 48 million units**	**s/c**	n/a
	20:00	**Ondansetron**	**8mg**	**IV**	100mLs sodium chloride over 15 mins
7	18:00	**Filgrastim**	**30 or 48 million units**	**s/c**	n/a

*Consider reducing fludarabine dose to 25mg/m^2 and idarubicin to 5mg/m^2 if aged over 70 years as per AML18 protocol for mini-Flagida

**For patients aged 60 years and over the cytarabine dose should be halved to 1g/m^2 daily

Main toxicities:

Fludarabine
Bone marrow suppression (thrombocytopenia, anaemia, neutropenia). Nausea, vomiting, alopecia, cough, fever, fatigue, weakness, diarrhoea. CNS side effects have been rarely described (agitation, confusion, visual disturbance).
Cytarabine
Bone marrow suppression, 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 recognized 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

Please refer to the SPC for full list of toxicities and further information

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Comments
Clinical Assessment	X	X	X	
SACT Assessment (including PS and toxicity assessment)	X	X	X	
Informed Consent	X			
FBC	X	X	X	
U&E, LFT, Calcium profile, Magnesium, LDH, urate	X	X	X	
CrCl (Cockcroft and Gault)	X	X	X	
Hepatitis B sAg and core Antibody and hepatitis C antibody, HIV 1+2, EBV, CMV, VZV	X			
ECG and ECHO	X			ECG/ECHO for all patients should be documented before starting anthracycline, unless stated by medical team that it is not required
Pregnancy test	X			If clinically indicated
Height	X			
Weight	X	X	X	
Blood glucose	X			
Bone Marrow Biopsy	X	X	X	Repeat after each cycle of chemotherapy on day 28

Dose Modifications and Toxicity Management:

Haematological toxicity:

First cycle to start regardless of neutrophil and platelet count.

Subsequent cycles to proceed when-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Note therapy can proceed if values are below these levels if cytopenias known to be secondary to disease.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

See section entitled 'Dosing in Renal and Hepatic Impairment'

References:

1. Summary of Product Characteristics for Fludarabine (Accord), viewed April 2023 (available at https://www.medicines.org.uk/emc)
2. Summary of Product Characteristics for Idarubicin (Accord), viewed April 2023 (available at https://www.medicines.org.uk/emc)
3. Summary of Product Characteristics for Cytarabine (Hospira), viewed April 2023 (available at https://www.medicines.org.uk/emc)
4. Summary of Product Characteristics for Zarzio 30MU syringe, viewed April 2023 (available at https://www.medicines.org.uk/emc)

5. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.
6. NHSE Cheshire and Merseyside Strategic Clinical Networks Protocol. Flag-Ida, Haematology CNG, 2015.
7. AML18 Clinical Trial Protocol v15.0. EudraCT: 2013-002730-21. NCRI. Accessed 24/4/23.

Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
Date document posted on the Intranet	For completion by DCM

Version History

Date	Version	Author name and designation	Summary of main changes
		Aileen McCaughey	New protocol
May 2023	1.1	**Jennifer Gibson**	Three yearly review. Transferred to new template. Added main toxicities information. Info added re cytarabine dosing if >60yrs. Treatment schedule updated.
October 2023	1.2	**Sophie Hughes**	Update re ECHO/ECG pre anthracycline