Chemotherapy Protocol

ACUTE MYELOID LEUKAEMIA ALL

CLOFARABINE-CYTARABINE

In-Patient Regimen

Clofarabine not licensed in adult patients. This may require funding

Regimen

- Acute Myeloid Leukaemia – InP-Clofarabine-Cytarabine

Indication

- Relapsed/refractory acute myeloid leukaemia and acute lymphocytic leukemia

Toxicity

Drug	Adverse Effect
Clofarabine	Nausea, vomiting, febrile neutropenia, headache, rash, diarrhoea, pruritus, pyrexia and palma-plantar erythrodysaesthesia syndrome, cytokine release syndrome (tachypnoea, hypotension, pulmonary oedema).
Cytarabine	Nausea, vomiting, diarrhoea, fever, rash, anorexia, oral and anal inflammation or ulceration, hepatic dysfunction.

Patients treated with clofarabine carry a lifelong risk of transfusion associated graft versus host disease (TA-GVHD). Where blood products are required these patients must receive only irradiated blood products for life. Local blood transfusion departments must be notified as soon as the decision to treat is made and the patient must be issued with an alert card to carry with them at all times.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- FBC, LFTs and U&Es each day prior to the administration of clofarabine
- Blood pressure, fluid balance and weight throughout the administration period.
- Bone marrow aspirate and trephine between days 18-21

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Patients are being treated with curative intent therefore dose modifications and delays should be kept to a minimum. Please discuss all dose reductions / delays with the relevant consultant before prescribing. The approach may be different depending on the clinical circumstances.

Haematological

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/Dl (80g/L)

Hepatic Impairment

Drug	Bilirubin µmol/L		AST/ALT units/L	Dose (% of original dose)
Clofarabine				Use with caution in mild to moderate hepatic impairment Avoid in severe hepatic impairment
Cytarabine	greater than 34		N/A	50% Escalate doses in subsequent cycles in the absence of toxicity

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Clofarabine	30 - 60	50%
	less than 30	discuss with consultant
Cytarabine	less than 60	60%
	less than 45	50%
	less than 30	omit

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

For all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose of the causative agent(s) may then be reduced or discontinued at the discretion of the consultant.

Clofarabine

Neurotoxicity

Agitation, anxiety, somnolence and dystonia are all recognized side effects of clofarabine. In these situations, the infusion time of clofarabine should be increased to 120 minutes.

Tumour lysis and Systemic Inflammatory Response Syndrome (SIRS)

Administration of clofarabine results in a rapid reduction in peripheral leukaemia cells. Patients should be evaluated and monitored for signs and symptoms of tumour lysis syndrome and cytokine release (e.g. tachypnoea, tachycardia, hypotension, pulmonary oedema) that could develop into Systemic Inflammatory Response Syndrome (SIRS), capillary leak syndrome and/or organ dysfunction. Clofarabine should be discontinued immediately if patients show early signs or symptoms of SIRS, capillary leak syndrome or substantial organ dysfunction and appropriate supportive measures instituted. Prophylactic hydrocortisone 100mg/m^2 days 1-3 may prevent the development of this complication. Please refer to the British Society of Haematology guidelines on tumour lysis syndrome for further advice

Regimen

1-2 cycles (1 cycle will be set in ARIA)

Drug	Dose	Days	Administration
Clofarabine	40mg/m^2	1,2,3,4,5	Intravenous infusion in sodium chloride 0.9% over 60 minutes (variable volume, please refer to administration)
Cytarabine	1000mg/m^2	1,2,3,4,5	Intravenous infusion in 1000ml sodium chloride 0.9% over 120 minutes

Dose Information

- Cytarabine will be dose banded according to the national dose bands (100mg/ml)
- Clofarabine will be dose banded according to the national dose bands (1mg/ml)

Administration Information

Extravasation

- Clofarabine – neutral
- Cytarabine – neutral (irritant in large volumes)

Other

- Clofarabine administration may be increased to 120 minutes if neurotoxicity develops
- Clofarabine should be administered using a 0.2micron or 0.22 micron in line filter if the product has not been filtered during the manufacturing process
- Clofarabine doses of 74.9mg or less must be administered in 100ml of sodium chloride 0.9%. Doses of 75mg-124.9mg should be administered in 150ml sodium chloride 0.9% and doses of 125mg-130mg in 200ml sodium chloride 0.9%
- Cytarabine administration should be started four hours after completion of the clofarabine infusion

Additional Therapy

This is an inpatient regimen please ensure all supportive are prescribed on the inpatient chart or general electronic prescribing system.

- Antiemetics

  Starting 15 - 30 minutes prior to chemotherapy

  - metoclopramide 10mg three times a day when required oral or intravenous
  - ondansetron 8mg twice a day on days 1, 2, 3, 4, 5 oral or intravenous

- Hydrocortisone 50-100mg intravenous bolus immediately prior to the clofarabine infusion to prevent infusion related reactions
- Aciclovir 400mg twice a day until neutrophils are greater than $1x10^9$/L oral
- Discuss the need and choice of antifungal with a consultant
- Prednisolone eye drops 0.5% into each eye four times a day. Continue for 5 days after cytarabine administration
- Allopurinol 300mg once a day for first 7 days of initial induction chemotherapy (if a remission is attained, the subsequent use of oral allopurinol is not required) or consider intravenous rasburicase in high risk individuals
- Mouthwashes according to local or national policy on the treatment of mucositis
- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- Azole antifungal agents are contra-indicated during clofarabine administration
- Take care with aminoglycosides during clofarabine administration
- Co-trimoxazole is not recommended as it delays the recovery of the blood count

Coding

- Procurement – X71.5
- Delivery – NA

References
1.Clofarabine (Evoltra) Summary of product characteristics. Last updated 28th September 2016.
2.Faderl S, Gandhi V, O'Brien S et al. Results of a phase 1-2 study of clofarabine in combination with cytarabine (ara-C) in relapsed and refractory acute leukaemias. Blood (2005); 105(3): 940-7.

REGIMEN SUMMARY

InP-Clofarabine-Cytarabine

Other than those listed below, supportive medication for this regimen will not appear in Aria as prescribed agents. The administration instructions for each warning describes the agents which must be prescribed on the in-patient chart or general electronic prescribing system

Day 1, 2, 3, 4, 5

1. Warning – Check blood transfusion status
   Administration Instructions
   Patients treated with clofarabine carry a lifelong risk of transfusion associated graft versus host disease.
   Where blood products are required these patients must receive ONLY IRRADIATED BLOOD PRODUCTS for life.
   Ensure transfusion departments are notified and the patient has been issued with an alert card to carry with them at all times.

2. Warning – Check supportive medicines prescribed
   Administration Instructions
   - metoclopramide 10mg three times a day when required for the relief of nausea oral or intravenous
   - ondansetron 8mg twice a day for 5 days oral or intravenous
   - hydrocortisone 50-100mg intravenous bolus immediately prior to clofarabine for infusion related reactions
   - aciclovir 400mg twice a day oral
   - discuss the need and choice of antifungal with a consultant. Azole antifungal agents are contra-indicated during clofarabine administration
   - co-trimoxazole is not recommended as it delays the recovery of the blood count
   - allopurinol 300mg once a day (review cycle 2) or rasburicase
   - prednisolone 0.5% eye drops, 1 drop each eye four times a day. Continue for 5 days after cytarabine

3. Clofarabine 40mg/m^2 in sodium chloride 0.9% intravenous infusion over 60 minutes.
   Administration Instructions
   Clofarabine administration may be increased to 120 minutes if neurotoxicity develops

   Clofarabine should be administered using a 0.2micron or 0.22 micron in line filter if the product has not been filtered during the manufacturing process.

   Clofarabine doses of 74.9mg or less must be administered in 100ml of sodium chloride 0.9%. Doses of 75mg to 124.9mg should be administered in 150ml sodium chloride 0.9% and doses between 125mg-130mg in 200ml sodium chloride 0.9%

4. Warning – Administration times
   Administration Instructions
   The cytarabine should be given four hours after the clofarabine infusion

5. Cytarabine 1000mg/m^2 in 1000ml sodium chloride 0.9% intravenous infusion over 120 minutes.
   Administration Instructions
   Cytarabine administration should be started four hours after completion of the clofarabine infusion

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	February 2017	New protocol	Lucy Shade Pharmacist	

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospitals NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines.