Chemotherapy Protocol

ACUTE MYELOID LEUKAEMIA

CYTARABINE (2000)-FLUDARABINE-IDARUBICIN (FLA-IDA)

In-Patient Regimen

Regimen

- Acute Myeloid Leukaemia – InP-Cytarabine (2000)-Fludarabine-Idarubicin (FLA-Ida)

Indication

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

- The standard dose of cytarabine is 2000mg/m^2. The dose may be decreased to 1000mg/m^2 in those who are over the age of sixty or are less fit.

Toxicity

Drug	Adverse Effect
Cytarabine	Nausea, vomiting, diarrhoea, fever, rash, itching, anorexia, oral and anal inflammation or ulceration, hepatic dysfunction, ocular pain, foreign body sensation, photophobia and blurred vision, dizziness, headache, confusion, cerebellar toxicity, myalgia and bone pain
Fludarabine	Transfusion related GVHD, neurotoxicity, opportunistic infections, GI disturbances
Idarubicin	Myelosuppression, cardiac toxicity (cardiac failure, arrhythmias or carcardiomyopathies), red discoloration of the urine, alopecia, nausea or vomiting, oral mucositis, elevation of liver enzymes and bilirubin

Patients treated with fludarabine 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

- U&Es, LFTs and FBC prior to starting a cycle of treatment

- Prior to starting treatment consider an ECG, ECHO or MUGA scan if there is a cardiac history, the patient is elderly or has a previous history suggestive of potential cardiac disease.

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.

Haematological

In general the treatment can proceed if the neutrophils are greater than $1x10^9$/L and the platelets are greater than $100x10^9$/L. Always' check with the relevant consultant.

Consider blood transfusion if the 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)
Cytarabine	greater than 34		N/A	50% Escalate doses in subsequent cycles in the absence of toxicity
Fludarabine	N/A		N/A	No dose adjustment required
Idarubicin	40-85		N/A	50%
	Greater than 85		N/A	Clinical decision

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cytarabine	less than 60	60%
	less than 45	50%
	less than 30	Discuss with consultant
Fludarabine	greater than 70	100%
	30-70	50%
	less than 30	Discuss with consultant
Idarubicin	20-50	75%
	10-20	75% with caution
	less than 10	50% with caution

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.

Regimen

3 cycles (1 cycle will be set in ARIA)

Cycles two and three should proceed when there is neutrophil and platelet recovery.

Drug	Dose	Days	Administration
Cytarabine	2000mg/m^2	1, 2, 3, 4, 5	Intravenous infusion in 1000ml sodium chloride 0.9% over 240minutes
Fludarabine	30mg/m^2	1, 2, 3, 4, 5	Intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes
Idarubicin	8mg/m^2	3, 4, 5	Intravenous bolus over 5-10 minutes

Dose Information

- Cytarabine will be dose banded according to the national dose bands (100mg/ml)
- The standard dose of cytarabine is 2000mg/m^2. The dose may be decreased to 1000mg/m^2 in those who are elderly or less fit.
- Fludarabine will be dose banded according to the national dose band (25mg/ml)
- Idarubicin will be dose banded according to the national dose band (1mg/ml)
- The maximum safe cumulative dose of idarubicin is not known, although 150mg/m^2 would be considered problematic. Always consider previous anthracycline exposure.

Administration Information

Extravasation

- Cytarabine – neutral (irritant in large volumes)
- Fludarabine – neutral
- Idarubicin - vesicant

Other

- The administration of fludarabine must precede that of cytarabine by four hours

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
  - ondansetron 8mg twice a day on days 1, 2, 3, 4, 5, 6, 7 oral

- Aciclovir 400mg twice a day until neutrophils are greater than $1x10^9$/L

- Consier pentamidine 300mg nebule every 28 days until the neutrophils are greater than $1x10^9$/L

- 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 daily for first 7 days of initial induction chemotherapy.

- 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.

Coding

- Procurement – X71.5

- Delivery – NA

References

1. Estey E, Thall P, Andreeff M 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; 12 (4): 671-8.

REGIMEN SUMMARY

InP-Cytarabine (2000)-Fluarabine-Idarubicin (FLA-Ida)

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

1 Warning – Check blood transfusion status
Administration Instructions
Patients treated with fludarabine 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

2. Warning – Check supportive medicines prescribed
Administration Instructions
- ondansetron 8mg twice a day oral or intravenous for 7 days
- metoclopramide 10mg three times a day when required for nausea oral or intravenous
- aciclovir 400mg twice a day oral
- consider pentamidine 300mg once every 28 days nebule
- Discuss the need and choice of antifungal with a consultant
- consider allopurinol 300mg once a day for 7 days oral (review cycle 2 or if consolidation treatment)
- prednisolone 0.5% eye drops, 1 drop each eye four times a day. Continue for 5 days after cytarabine administration is complete

Always refer to the patient schedule for supportive treatments and fluids

3. Fludarabine 30mg/m^2 intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes
Administration Instruction
The fludarabine must precede the administration of the cytarabine by four hours

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

5. Cytarabine 2000mg/m^2 in 1000ml sodium chloride 0.9% intravenous infusion over 240minutes
Administration Instructions
The cytarabine should be given four hours after the fludarabine

Days 3, 4, 5

6. Warning – Check supportive medicines prescribed
Administration Instructions
- ondansetron 8mg twice a day oral or intravenous for 7 days
- metoclopramide 10mg three times a day when required for nausea oral or intravenous
- aciclovir 400mg twice a day oral
- consider pentamidine 300mg once every 28 days nebule
- antifungal according to consultant preference
- consider allopurinol 300mg once a day for 7 days oral (review cycle 2 or if consolidation treatment)
- prednisolone 0.5% eye drops, 1 drop each eye four times a day. Continue for 5 days after cytarabine administration is complete

Always refer to the patient schedule for supportive treatments and fluids

7. Idarubicin 8mg/m^2 intravenous bolus over 5-10 minutes

8. Fludarabine 30mg/m^2 intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes
   Administration Instruction
   The fludarabine must precede the administration of the cytarabine by four hours

9. Warning – Administration times
   Administration Instructions
   The cytarabine should be given four hours after the fludarabine

10. Cytarabine 2000mg/m^2 in 1000ml sodium chloride 0.9% intravenous infusion over 240minutes
    Administration Instructions
    The cytarabine should be given four hours after the fludarabine

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	April 2018	Idarubicin renal impairment updated. Idarubicin cumulative dose updated.	Dr Deborah Wright Pharmacist	Harriet Launders Haematology Pharmacist
1	March 2017	New protocol	Dr Deborah Wright Pharmacist	Dr Deborah Richardson Consultant Haematologist

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 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.