Chemotherapy Protocol

ACUTE MYELOID LEUKAEMIA

Ambulatory Regimen

AmB – Gemtuzumab Ozogamicin (Mylotarg®) + Daunorubicin + Cytarabine (1st Consolidation)

Regimen

- AML – AmB – Gemtuzumab Ozogamicin + Daunorubicin + Cytarabine (1st consolidation)

Indication

Gemtuzumab Ozogamicin is funded as part of chemotherapy for previously untreated CD33 positive acute myeloid leukaemia in patients aged 15 years and over where the following is met:

- The prescriber is fully aware of the potential for gemtuzumab ozogamicin inducing hepatotoxicity including veno-occlusive liver disease/sinusoidal obstruction syndrome
- The patient has a confirmed diagnosis of CD33-positive acute myeloid leukaemia but does not have acute promyelocytic leukaemia.
- The patient has previously untreated acute myeloid leukaemia
- The patient is aged 15 years and over
- The patient has had cytogenetics performed
- The patient is fit for intensive induction chemotherapy
- Gemtuzumab ozogamicin is to be given with the combination of daunorubicin and cytarabine (DA) regimen unless either entered into the national AML19 clinical trial * in which case it can also be given in combination with midostaurin for patients with a FLT3 mutation according to the trial protocol or if entered in the myechild01 trial in which gemtuzumab ozogamicin can be given according to the trial protocol

***For patients entered into the AML19 or the VICTOR clinical trials the dose and schedule of the daunorubicin plus cytarabine (DA) regimen used in combination with gemtuzumab ozogamicin should be that specified in the current trial protocol.**

Note: For teenagers aged ≥15 years and young adults not entered into the Myechild01 trial, gemtuzumab ozogamicin can be combined with standard chemotherapy agents appropriate to the age of the patient.

- The dose and schedule of administration of gemtuzumab ozogamicin will be given as in the summary of product characteristics (i.e. in the first cycle of induction chemotherapy [but not in the second cycle of induction chemotherapy] and, if the patient has attained complete remission, in up to 2 cycles of consolidation chemotherapy) unless the patient has been entered into the national AML 18 and 19, Myechild01 or VICTOR trials when the trial dose and schedule of gemtuzumab ozogamicin combinations can be used.
- Gemtuzumab ozogamicin is to be otherwise used as set out in its summary of product characteristics.
- The result of the cytogenetics test has shown that the patient has one of the following:
  - Favourable risk stratification according to the 2017 ELN risk stratification
  - Intermediate risk stratification according to the 2017 ELN risk stratification
  - The result of the cytogenetics test was unsuccessful
  - The result of the cytogenetics is awaited and there is a clinical need for urgent systemic therapy to be commenced. If this is the case, it is mandatory that gemtuzumab ozogamicin will be discontinued as soon as cytogenetic results indicate adverse cytogenetics. Such discontinuation of gemtuzumab ozogamicin may be before all of the 1st cycle of induction treatment has been administered.

Toxicity

Drug	Adverse Effect
Gemtuzumab Ozogamicin	Haemorrhage, infection, pyrexia, nausea, chills, vomiting, thrombocytopenia, fatigue, headache, stomatitis, diarrhoea, abdominal pain, neutropenia, veno-occlusive disease, sinusoidal obstruction syndrome
Daunorubicin	Nausea, vomiting, diarrhoea, fever, rash, anorexia, oral and anal inflammation or ulceration, and hepatic dysfunction
Cytarabine	Nausea, alopecia, chronic and acute cardiac failure and dysrhythmias

The adverse effects listed are not exhaustive. Please refer to the relevant summary of product characteristics for further details.

Monitoring

- Respiratory viral throat swab with **negative result** to be performed 72 hours prior to commencing consolidation chemotherapy
- Women of childbearing age must have a negative pregnancy test prior to commencing chemotherapy

- FBC, and U&Es (including potassium, calcium, phosphate and uric acid) LFTs and coagulation screen on day 1 (the FBC may not be necessary for induction treatment)
- Blood pressure, fluid balance and weight throughout
- Recent bone marrow aspirate
- A baseline MUGA scan or echocardiogram should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, obese, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy. MUGA scan or ECHO should be repeated if there is suspicion of cardiac toxicity at any point during treatment, or if cumulative anthracycline dose approaches the maximum cumulative dose. A baseline ECG should be performed.

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.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Prior to prescribing on day one of each cycle the following criteria must be met;

Criteria	Eligible level
Neutrophil	$1.0x10^9/L$
Platelet	$100x10^9/L$

Consider blood transfusion if patient symptomatic of anaemia or haemoglobin is less than 8g/dL.

Hepatic Impairment

Drug	Bilirubin (µmol)		AST/ALT (units/L)	Dose (% of original dose)
Gemtuzumab ozogamicin	>2xULN	Or	>2.5xULN	Postpone Gemtuzumab ozogamicin until recovery of total bilirubin to ≤ 2 × ULN and AST and ALT to ≤ 2.5 × ULN prior to each dose. Consider omitting scheduled dose if delayed more than 2 days between sequential infusions. Discontinue gemtuzumab ozogamicin if patient develops any signs of veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS)
Cytarabine	>34		n/a	50% and escalate doses in subsequent cycles in the absence of toxicity
Daunorubicin	25-50			75%
	51-85			50%
	>85			omit

Renal Impairment

Drug	Creatinine clearance (ml/min)	Dose (% of original dose)
Gemtuzumab ozogamicin	≥30ml/min	No dose adjustment necessary
	<30ml/min	No information
Cytarabine		No dose reduction necessary normally as doses not considered high dose
Drug	**Creatinine (µmol/L)**	**Dose (% of original dose)**
Daunorubicin	less than 105	100%
	105-265	75%
	More than 265	50%

Regimen

1 cycle will be set in aria

Drug	Dose	Days	Administration
Gemtuzumab ozogamicin	3mg/m^2 (max 5mg)	1	Intravenous infusion in 50ml sodium chloride 0.9% over 2 hours*
Daunorubicin	60mg/m^2	1	Intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes
Cytarabine	8000mg/m^2 (8 doses of 1000mg/m^2 every 12 hours	1000mg/m^2 BD every 12 hours at 9am and 9pm. 1, 2, 3, 4 (8 doses total)	**Administer via CADD Solis VIP pump.** Each CADD cassette will contain **4 doses** (or infusion bag if patient's BSA >2.0), in a final volume of 250ml (or 500ml if an infusion bag). Connect and disconnect infusions on day(s) stated as per patient schedule Connect infusion bag on Day 1 (first dose = PM Day 1) and disconnect on day 5 (after AM dose). **Each dose:** IV infusion of 1000mg/m2 in sodium chloride 0.9% over 3 hours.
Sodium Chloride 0.9% **(delivered via folfusor pump)**	100ml (at 0.5ml/h)	1, 2, 3, 4	Sodium chloride 0.9% to be administered via folfusor pump at 0.5ml/hr on Days 1 (PM) to 5 (AM). To be connected via Y-site with CADD pump to maintain line patency. Disconnect folfusor at the same time as disconnecting CADD infusion bag

*** Gemtuzumab ozogamicin must not be started if WCC ≥ 30 x 10^9 /L because of the risks of tumour lysis and hypersensitivity reactions.**

Dose Information

- Cytarabine will be dose banded according to the national dose bands (100mg/ml)
- Daunorubicin will be dose banded according to the national dose bands (5mg/ml)
- There is a recommended maximum cumulative lifetime dose of daunorubicin of 500-600mg/m2 or 400mg/m2 in patients with cardiac dysfunction or exposed to mediastinal irradiation

- The final concentration of daunorubicin should not exceed 1mg/ml.

Administration Information

- Gemtuzumab ozogamicin should be administered via a 0.2micron low protein-binding in-line filter.

CADD pump

- The total 8 doses of cytarabine will be provided in one infusion bag, to be administered as intermittent infusion via a CADD pump from day 1 at 9PM until day 5 at 9AM
- Sodium chloride 0.9% 100ml to be run as continuous infusion to keep CADD infusion line patent. Administer concurrently with cytarabine via Y-site with at 0.5 mL/hour on days 1 (PM) to day 5 (AM). This infusion device should be disconnected at the same time as the CADD infusion bag on day 5.

Extravasation

- Daunorubicin – vesicant
- Cytarabine – neutral
- Gemtuzumab ozogamicin - irritant

Additional Therapy

This regimen is to be administered in the ambulatory setting. Please refer to the schedule for each individual patient.

- **Antiemetics**
  - Ondansetron 8mg twice a day for 5 days oral or intravenous
  - Metoclopramide 10mg three times a day when required for the relief of nausea oral or intravenous
- **Antimicrobial prophylaxis**
  - Discuss the need and choice of Antifungal prophylaxis with a consultant. Azoles should be omitted for 3 days before gemtuzumab ozogamicin and 5 days after gemtuzumab ozogamicin administration.
  - Aciclovir 400mg twice a day oral
- **Prednisolone eye drops 0.5%** into each eye four times a day. Continue for 5 days after cytarabine administration
- **Gastric protection** with a proton pump inhibitor or H_2 antagonist

- **Mouthcare** for the prophylaxis or treatment of mucositis in accordance with local or national guidelines.

References

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3. Pfizer Limited. Cytarabine 100mg/ml summary of product characteristics. Available from: https://www.medicines.org.uk/emc/product/3803/smpc. Last updated 03/2022. Accessed 01/12/2022
4. Lambert J et al. Gemtuzumab ozogamicin for de novo acute myeloid leukemia: final efficacy and safety updates from the open-label, phase III ALFA-0701 trial, Haematologica 2019. 104(1):113-9
5. NSSG chemotherapy protocol. Available from: https:/nssg.oxford-haematology.org.uk/myeloid/protocols/ML-80-gemtuzumab-ozogamicin-da-cytarabine.pdf
6. Kent and Medway SACT Protocol No HAEM-AML-029. Available from: https://www.kmcc.nhs.uk/s3/assets/files/haem-aml-029-gemtuzumab-ozogamicin-(in-combination-with-da)-v2.pdf

REGIMEN SUMMARY

AmB – Gemtuzumab Ozogamicin – Daunorubicin- Cytarabine (1st consolidation)

Other than those listed below, supportive medication for this regimen will not appear in Aria as prescribed agents. Supportive care should be prescribed on ARIA and given to the patient on day 1.

Cycle 1

Day 1

1. Paracetamol 1000mg orally
   Administration instruction:
   To be given 1 hour prior to Gemtuzumab ozogamicin infusion

2. Chlorphenamine 10mg intravenous injection
   Administration instruction:
   To be given 1 hour prior to Gemtuzumab ozogamicin infusion

3. Hydrocortisone 100mg intravenous injection
   Administration instruction:
   To be given 1 hour prior to Gemtuzumab ozogamicin infusion

4. Ondansetron 8mg oral or intravenous

5. Gemtuzumab ozogamicin 3mg/m^2 (max 5mg) in 50ml sodium chloride 0.9% intravenous infusion over 2 hours
   Administration instructions:
   To be administered via a 0.2micron low protein-binding in-line filter.
   The WCC must be below 30 prior to starting gemtuzumab ozogamicin

6. Daunorubicin 60mg/m^2 in 100ml sodium chloride 0.9% intravenous infusion over 30 minutes
   Administration instructions:
   Alternatively, daunorubicin can be administered as a slow intravenous bolus over 20 minutes, according to local practice.
   Whatever the mode of administration, the final concentration of daunorubicin must not exceed 1mg/mL

7. Warning – Cytarabine delivered via one CADD
   Administration Instructions:
   Cytarabine is administered TWICE a day at 12 hour intervals (0900 and 2100) via CADD pump. Sodium chloride infusion must be administered concurrently. Always refer to the patient schedule for supportive treatments and fluids

8. Cytarabine 4000mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% as intermittent infusions via CADD pump.
   Administration Instructions
   Administer via CADD Solis VIP pump. Cytarabine is administered TWICE a day at 12 hour intervals (0900 and 2100) on days 1, 2, 3, 4 (8 doses in total).
   Each CADD cassette contains **4 doses**. One dose**: Cytarabine 1000mg/m2 over 3 hours.**
   For patients with **BSA >2.00**, treatment will be delivered in **500ml** infusion bags, each containing **4 doses of 1000mg/m2.**
   Please set up the appropriate infusion rate and dose volumes on the CADD to ensure the full volume is administered.
   Connect infusion bag on **Day 1** (first dose =PM dose) and disconnect on **Day 3** (after AM dose).

9. Sodium Chloride 0.9% 100ml continuous infusion at 0.5ml/hr.
   Administration Instructions

Sodium chloride 0.9% to be administered via folfusor pump at 0.5ml/hr over 4 days.
To be connected via Y-site with CADD pump to maintain line patency.
Disconnect folfusor at the same time as disconnecting CADD infusion.

Take Home Medicines (day 1 only)

10. Metoclopramide oral 10mg up to three times a day when required.
    Administration Instructions – For the relief of nausea and vomiting. Pharmacy please supply two original packs.

11. Ondansetron 8mg twice a day starting on the evening of day one of the cycle for 5 days oral

12. Aciclovir 400mg twice a day for 28 days
    Administration Instructions – Pharmacy please supply 28 days or an original pack if appropriate.

13. Benzydamine oral rinse 10mL four times a day
    Administration Instructions Please supply one original pack.

14. Nystatin 1ml four times a day
    Administration instructions – please supply 1 x OP

15. Sodium Chloride 0.9% oral rinse 10mL four times a day
    Administration instructions – pharmacy please supply 50 x 10mL pods

16. Gastric Protection
    Administration Instructions The choice of gastric protection is dependent on local formulary choice and may include;
    - esomeprazole 20mg once a day oral
    - omeprazole 20mg once a day oral
    - lansoprazole 15mg once a day oral
    - pantoprazole 20mg once a day oral
    - rabeprazole 20mg once a day oral
    - cimetidine 400mg twice a day oral
    - famotidine 20mg once a day oral
    - nizatidine 150mg twice a day oral
    - ranitidine 150mg twice a day oral

    Please supply 28 days or the nearest original pack size.

17. Prednisolone 0.5% minims eye drops. Instil 1 drop into both eyes four times a day for 9 days.

Day 3

18. Warning – Cytarabine delivered via one CADD
    Administration Instructions:
    Cytarabine is administered TWICE a day at 12 hour intervals (0900 and 2100) via CADD pump. Sodium chloride infusion must be administered concurrently. Always refer to the patient schedule for supportive treatments and fluids

19. Cytarabine 4000mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% as intermittent infusions via CADD pump.
    Administration Instructions
    Administer via CADD Solis VIP pump. Cytarabine is administered TWICE a day at 12 hour intervals (0900 and 2100) on days 1, 2, 3, 4 (8 doses in total).
    Each CADD cassette contains **4 doses**. One dose**: Cytarabine 1000mg/m2 over 3 hours.**
    For patients with **BSA >2.00**, treatment will be delivered in **500ml** infusion bags, each containing **4 doses of 1000mg/m2.**
    Please set up the appropriate infusion rate and dose volumes on the CADD to ensure the full volume is administered.
    Connect infusion bag on **Day 3** (first dose =PM dose) and disconnect on **Day 5** (after AM dose).

20. Sodium Chloride 0.9% 100ml continuous infusion at 0.5ml/hr.

Administration Instructions
Sodium chloride 0.9% to be administered via folfusor pump at 0.5ml/hr over 4 days.
To be connected via Y-site with CADD pump to maintain line patency.
Disconnect folfusor at the same time as disconnecting CADD infusion.

Always refer to the patient schedule for supportive treatments and fluids

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	July 2026	None	Alexandre Guedes Pharmacist	Dr Hwai Jing Hiew

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.