Gemtuzumab ozogamicin (Mylotarg®) + DA + HD Cytarabine

INDICATION

Untreated de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia, with favourable, intermediate or unknown cytogenetics.

If cytogenetics results are awaited, urgent systemic can be started, but if results indicate adverse cytogenetics, discontinue treatment with gemtuzumab ozogamicin. **(NICE TA545 - BLUETEQ required)**

TREATMENT INTENT

Curative

PRE-ASSESSMENT

1. Blood tests - FBC, U&Es, LDH, urate, calcium, magnesium, creatinine, LFTs, glucose, hepatitis B core antibody and hepatitis BsAg, hepatitis C antibody, HIV after consent, group and save.
2. Ensure bone marrow findings and dates of findings are confirming diagnosis and are documented in notes prior to administration of therapy.
3. Urine pregnancy test - before cycle 1 of each new therapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy
4. ECG
5. ECHO or MUGA is highly advised if there is history or risk factors of congestive heart failure.
6. Record performance status (WHO/ECOG)
7. Record height and weight
8. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment
9. Fertility - it is very important the patient understands the potential risk of infertility; all patients should be offered fertility advice (see fertility guidelines).
10. Treatment should be agreed in the relevant MDT
11. Hydration and tumour lysis prevention; refer to tumour lysis protocol.
12. Gemtuzumab ozogamicin must not be started if WCC ≥ 30 x 10^9/L because of the risks of tumour lysis and hypersensitivity reactions. Hydroxycarbamide (40-60 mg/kg/day) can be used to reduce WCC before commencing gemtuzumab ozogamicin.
13. Patients are only eligible to receive gemtuzumab ozogamicin if ALT/AST ≤ 2.5 x ULN and bilirubin ≤ 2 x ULN, due to the risk of veno-occlusive disease, and have not experienced side effects to any previous exposure to gemtuzumab ozogamicin.
14. **Document medication history. Patients should not be given any azole antifungals for 3 days before and 5 days after Gemtuzumab administration due to risk of veno-occlusive disease.**

DRUG REGIMEN / CYCLE FREQUENCY

INDUCTION - Cycle 1

Days 1, 4 & 7 **Premedication**- give one hour prior to gemtuzumab ozogamicin: Paracetamol 1g PO, Chlorphenamine 10mg IV, Hydrocortisone 100mg IV.

GEMTUZUMAB OZOGAMICIN 3mg/m^2 (maximum dose is the extractable amount from a 5mg vial) in 50mL sodium chloride 0.9% intravenous infusion (to achieve a concentration of 0.075 mg/mL to 0.234 mg/mL) over 2 hours, via a 0.2micron low protein-binding in-line filter.

Days 1 to 3 **DAUNORUBICIN** 60 mg/m^2 daily in 250mL sodium chloride 0.9% intravenous infusion over 30 minutes

Days 1 to 7 **CYTARABINE** 100 mg/m^2 **BD** slow intravenous bolus (14 doses).
Giving cytarabine as a bolus is not as per SPC but is routine practice for standard induction in the UK.

A bone marrow examination should be performed on count recovery. If there was definitive evidence of clinically significant residual leukemia, a second cycle of induction therapy without gemtuzumab ozogamicin may be given. Patients who achieved complete remission after induction therapy will receive two cycles of consolidation treatment:

INDUCTION - Cycle 2 (only if required - **omit** gemtuzumab ozogamicin)
Start when ANC > 1 x10^9/L and Platelet >100x10^9/L

Days 1 to 2 **DAUNORUBICIN** 35 mg/m^2 daily in 250mL sodium chloride 0.9% intravenous infusion over 30 minutes

Days 1 to 3 **CYTARABINE** 1000 mg/m^2 **BD** in 250mL sodium chloride 0.9% intravenous infusion over 3 hours

CONSOLIDATION - Cycle 1 - Suitable for ambulatory administration (see appendix)
Start when ANC > 1 x10^9/L and Platelet > 100x10^9/L

Days 1 **Premedication**- give one hour prior to gemtuzumab ozogamicin: Paracetamol 1g PO, Chlorphenamine 10mg IV, Hydrocortisone 100mg IV.

GEMTUZUMAB OZOGAMICIN 3mg/m^2 (maximum dose is the extractable amount from a 5mg vial) in 50mL sodium chloride 0.9% intravenous infusion (to achieve a concentration of 0.075 mg/mL to 0.234 mg/mL) over 2 hours, via a 0.2micron low protein-binding in-line filter.

Days 1 **DAUNORUBICIN** 60 mg/m^2 daily in 250mL sodium chloride 0.9% intravenous infusion over 30 minutes

Days 1 to 4 **CYTARABINE** 1000 mg/m^2 **BD** in 250mL sodium chloride 0.9% intravenous infusion over 3 hours

CONSOLIDATION - Cycle 2 - Suitable for ambulatory administration (see appendix)
Start when ANC > 1 x10^9/L and Platelet > 100x10^9/L

Days 1 **Premedication**- give one hour prior to gemtuzumab ozogamicin
Paracetamol 1g PO, Chlorphenamine 10mg IV, Hydrocortisone 100mg IV.

GEMTUZUMAB OZOGAMICIN 3mg/m^2 (maximum dose is the extractable amount from a 5mg vial) in 50mL sodium chloride 0.9% intravenous infusion (to achieve a concentration of 0.075 mg/mL to 0.234 mg/mL) over 2 hours, via a 0.2micron low protein-binding in-line filter.

Days 1 to 2 **DAUNORUBICIN** 60 mg/m^2 daily in 250mL sodium chloride 0.9% intravenous infusion over 30 minutes

Days 1 to 4 **CYTARABINE** 1000 mg/m^2 **BD** in 250mL sodium chloride 0.9% intravenous infusion over 3 hours

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DOSE MODIFICATIONS

Haematological Toxicities

Platelets < 100 x 10^9/L at the start of consolidation	Postpone start of consolidation course by up to 14 days. If platelet count recovers to ≥ 100 x 10^9/L within 14 days, proceed with consolidation. If platelet count recovers to 50-100 x 10^9/L within 14 days, omit gemtuzumab ozogamicin from the consolidation course. If platelet count remains < 50 x 10^9/L for greater than 14 days, review consolidation therapy and consider BM biopsy to reassess the patient's status
Neutrophils < 0.5 x 10^9/L at the start of consolidation	Postpone start of consolidation course by up to 14 days. If neutrophil count does not recover to to ≥ 0.5 x 10^9/L within 14 days, do not administer gemtuzumab ozogamicin in the consolidation cycle.

Cytarabine

Renal impairment	Hepatic impairment
Induction Cycle 1: No dose reduction necessary normally as doses not considered high dose **Induction Cycle 2 and Consolidation:** GFR < 31-59 mL/min: give 50% dose GFR < 30 mL/min: omit Haemodialysis: give 50% dose, start HD 4-5 hours after administration	Mild/moderate impairment (Child-Pugh Stage A or B): no dose adjustment necessary Severe impairment (Child-Pugh Stage C): 25-50% dose and increase as tolerated

Daunorubicin

Renal impairment	Hepatic impairment
GFR 30-50 mL/min or Cr 105-265 micromol/L: give 75% dose GFR <30 mL/min or Cr > 266 micromol/L: give 50% dose Haemodialysis: give 50% dose	Bilirubin 20-50 micromol/L: give 75% dose Bilirubin > 50 micromol/L: give 50% dose

Maximum cumulative dose = 600 mg/m^2 (in normal cardiac function)
= 400 mg/m^2 (in patients with cardiac dysfunction or exposed to mediastinal irradiation).

Gemtuzumab ozogamicin

Renal impairment	Hepatic impairment
GFR ≥ 30mL/min: No dose adjustment for mild or moderate renal impairment. GFR < 30mL/min: No information for severe renal impairment.	Bilirubin > 2 × ULN or AST/ALT > 2.5 × ULN: postpone gemtuzumab ozogamicin until recovery. If the delay is more than 2 days, consider omitting dose. **Discontinue gemtuzumab ozogamicin if patient develops any signs of veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS)**

INVESTIGATIONS

- FBC, U&E, LFT at the start of every cycle, and as clinically indicated

The patient should be closely monitored for signs and symptoms of veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS). These include elevations in LFTs, hepatomegaly (which may be painful), rapid weight gain and ascites.

Discontinue gemtuzumab ozogamicin if patient develops any signs or symptoms of VOD/SOS.

CONCURRENT MEDICATION

Drug	Dose and duration
Allopurinol	300 mg daily for first 14 days of initial induction chemotherapy. (If a remission is attained the subsequent use of allopurinol is not required)
Aciclovir	200 mg three times a day for duration of treatment and for 3 months after completion
Fungal prophylaxis	As per local protocol. **Omit azole antifungals for 3 days before and 5 days after Gemtuzumab ozogamicin administration**
Proton pump inhibitor	As per local formulary
Prednisolone 0.5 – 1% eye drops or Dexamethasone 0.1% eye drops (depending on local formulary)	**Induction Cycle 2 and Consolidation Cycles only:** One drop into each eye QDS. Continue for 5 days after cytarabine (due to risk of cytarabine-induced conjunctivitis). In the event of conjunctivitis consider increasing the frequency to 2-hourly until resolution of symptoms. Liaison with local ophthalmologists may be necessary in this situation

EMETIC RISK

Induction Cycle 1: Days 1-3: Moderate, Days 4-7: Low
Induction Cycle 2: Days 1-2: High, Day 3: Moderate

Consolidation Cycle 1: Day 1: High, Days 2-4: Moderate
Consolidation Cycle 2: Days 1-2: High, Days 3-4: Moderate

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Commonly reported (>10%): Febrile neutropenia, thrombocytopenia, anaemia, leucopenia, infections, hyperglycaemia, diarrhoea, nausea, vomiting, headache, stomatitis, electrolyte imbalance, deranged liver function tests.

Other drug specific adverse effects:

Daunorubicin: Posterior Reversible Encephalopathy Syndrome (PRES), alopecia, mucositis, chronic and acute cardiac failure and dysrhythmias. There is a recommended maximum cumulative lifetime dose of daunorubicin of 600 mg/m^2.

Low Dose Cytarabine (<1g/m^2): diarrhoea, abdominal pain, oral ulceration, hepatic dysfunction.

High Dose Cytarabine (≥1g/m^2): CNS, GI and pulmonary toxicity, reversible corneal toxicity, somnolence, convulsion, pulmonary oedema.

A cytarabine syndrome is also recognised in which patients suffer from fever, myalgia, bone pain, occasional chest pains, maculopapular rash, conjunctivitis and malaise. It usually occurs 6 to 12 hours following administration.

Gemtuzumab ozogamicin: veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS), tumour lysis syndrome, infusion related reaction, chills, haemorrhage, pyrexia, fatigue, abdominal pain.
Due to the risk of VOD, liver function tests, hepatomegaly (which may be painful), rapid weight gain, and ascites should be closely monitored before each dose. All haematopoietic stem cell transplant patients with previous gemtuzumab ozogamicin exposure should receive ursodeoxycholic acid prophylaxis from the start of conditioning chemotherapy

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EXTRAVASATION RISK

Cytarabine: neutral
Daunorubicin: vesicant
Gemtuzumab ozogamicin: irritant

TREATMENT-RELATED MORTALITY

5-10%

REFERENCES

1. 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
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3. Pfizer. Mylotarg 5mg summary of product characteristics. Last updated 24/11/2020. Accessed on 26/10/2021 via http://www.medicines.org.uk/emc
4. Pfizer. Cytarabine 100mg/ml Summary of Product Characteristics. Last updated 6/4/2022. Accessed on 13/11/2022 via http://www.medicines.org.uk/emc

REVIEW

Name	Revision	Date	Version	Review date
Cheuk-kie Jackie Cheung, Haematology Pharmacist. NSSG Myeloid Group	New document. Annual protocol meeting	Oct 2019	1.0	Oct 2021
Yen Lim, Haematology Pharmacist. NSSG Myeloid Group	Maximum dose and volume/concentration clarified. Cytarabine duration amended. SPC updates incorporated. Renal/hepatic dosing updated. Annual protocol meeting.	Nov 2021	2.0	Nov 2023
Yen Lim, Haematology Pharmacist. NSSG Myeloid Group	Cytarabine in induction changed to BD bolus	Nov 2022	3.0	Nov 2024
Connor Sweeney, Haematology Consultant Donna Constantine, Advanced Cancer Pharmacist	Addition of ambulatory schedule via CADD infusion pump for consolidation phase only.	Feb 2024	3.1	Nov 2024

CONSOLIDATION PHASE - AMBULATORY ADMINISTRATION

Ensure that this is prescribed using the specific ambulatory ARIA regimen.

This regimen assumes availability of a CADD® pump or other alternative ambulatory infusion device with intermittent and delayed scheduling capability.

ELIGBILITY

Patients must meet the general criteria for ambulatory treatment as specified in any local ambulatory policy. Discuss with local nursing teams.

- E.g. Presence of a carer; lives within specified distance of treatment center, available transport for emergencies, adherence to planned visits and treatment.

Ambulatory treatment involves a number of repeat visits to the hospital for administration and post-treatment monitoring or supportive care, this may not be suitable for all patients.

N.B. The ambulatory pathway is **not suitable** for patients during induction treatment.

CONSOLIDATION - Cycle 1 – Ambulatory schedule
Start when ANC > 1 x10^9/L and Platelet > 100x10^9/L.

Day 1 **Premedication**- give one hour prior to gemtuzumab ozogamicin: Paracetamol 1g PO, Chlorphenamine 10mg IV, Hydrocortisone 100mg IV.

GEMTUZUMAB OZOGAMICIN 3mg/m^2 (maximum dose is the extractable amount from a 5mg vial) in 50mL sodium chloride 0.9% intravenous infusion (to achieve a concentration of 0.075 mg/mL to 0.234 mg/mL) over 2 hours, via a 0.2micron low protein-binding in-line filter.

Day 1 **DAUNORUBICIN** 60 mg/m^2 daily in 250mL sodium chloride 0.9% intravenous infusion over 30 minutes

Days 1 to 5 **CYTARABINE*** 8000 mg/m^2 in 245mL sodium chloride 0.9% intravenous as intermittent infusions via CADD® pump. Starting the evening of day 1 to deliver 8 total doses.

SODIUM CHLORIDE 0.9% continuous infusion via elastomeric pump at 0.5ml/hr. Connect via Y-site with CADD® pump to maintain line patency.

CONSOLIDATION – Cycle 2 – Ambulatory schedule
Start when ANC > 1 x10^9/L and Platelet > 100x10^9/L

Days 1 **Premedication**- give one hour prior to gemtuzumab ozogamicin Paracetamol 1g PO, Chlorphenamine 10mg IV, Hydrocortisone 100mg IV.

GEMTUZUMAB OZOGAMICIN 3mg/m^2 (maximum dose is the extractable amount from a 5mg vial) in 50mL sodium chloride 0.9% intravenous infusion (to achieve a concentration of 0.075 mg/mL to 0.234 mg/mL) over 2 hours, via a 0.2micron low protein-binding in-line filter.

Days 1 to 2 **DAUNORUBICIN** 60 mg/m^2 daily in 250mL sodium chloride 0.9% intravenous infusion over 30 minutes

Days 1 to 5 **CYTARABINE*** 8000 mg/m^2 in 245mL sodium chloride 0.9% intravenous as intermittent infusions via CADD® pump. Starting the evening of day 1 to deliver 8 total doses.

SODIUM CHLORIDE 0.9% continuous infusion via elastomeric pump at 0.5ml/hr. Connect via Y-site with CADD® pump to maintain line patency.

*__Cytarabine CADD administration Instructions__

Single dose= Cytarabine 1000mg/m2 in 30ml sodium chloride 0.9% over 180 minutes at 10ml/hour.

Total CADD volume= 245mL (an additional 5mL saline overage is included)

Cytarabine is administered TWICE a day at 12-hour intervals (1000 and 2200) on days 1 to 5 (8 doses in total) **starting on the evening of day 1**. Connect cassette alongside Y-sited saline infusor on day 1 and disconnect on day 5 following completion of final cytarabine dose.