Gemtuzumab ozogamicin DAUNOrubicin and cytarabine Therapy (AML induction)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Gemtuzumab ozogamicin is indicated for combination therapy with DAUNOrubicin and cytarabine for the treatment of patients age 15 years and above with previously untreated, de novo CD33 positive Acute Myeloid Leukemia (AML), except acute promyelocytic leukaemia	C92	00612a	ODMS 01/11/2020

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Induction

Gemtuzumab ozogamicin is administered in combination with DAUNOrubicin and cytarabine as detailed in the treatment table below for 1 cycle.

Note: Please See Dose Modifications for Schedule modification for patients presenting with hyperleukocytosis (leukocyte count ≥ 30x 10^9/L)

Treatment Course	Day	Drug	Dose	Route	Diluent & Rate
Cycle 1 **Induction**	1[i]	Gemtuzumab ozogamicin[a]	3 mg/m^2 (up to a maximum of one 5 mg vial)	IV	50mls NaCl 0.9% over 2 hours[b,c,d]
	1, 3 and 5 (3 doses)	DAUNOrubicin	60 mg/m^2 [e]	IV	Slow IV push via side arm NaCl 0.9% infusion (A central line is preferred)
	1 to 10 Inclusive	Cytarabine	100 mg/m^2 AM	IV infusion	100mls NaCl 0.9% over 30 mins
	1 to 10 Inclusive	Cytarabine	100 mg/m^2 PM (**12 hours after start of AM infusion)**	IV infusion	100mls NaCl 0.9% over 30 mins
[a]Administration of a single dose of gemtuzumab 3mg/m^2 in combination with DA for first induction course is recommended as per NCRI AML Working Party COVID-19 Recommendations for patients with favourable or intermediate risk cytogenetics (1) **Note : the alternative dosing of gemtuzumab 3 mg/m^2(up to a maximum of one 5 mg vial) on day 1, 4, and 7 in line with SPC recommendations in combination with DAUNOrubicin and cyatarbine as detailed above may be considered at the discretion of the prescribing Consultant (Please refer to SPC(7))**					
[b]Gemtuzumab ozogamicin should be diluted to a concentration of 0.075 to 0.234 mg/ml and must not be given by IV BOLUS [c]Protect from light. [d]Gemtuzumab ozogamicin must be supplied in PVC containers with DEHP, or polyolefin and administered with in-line, low proteinbinding 0.2 micron polyethersulphone (PES) filter					
[e]Lifetime cumulative dose of DAUNOrubicin is 550mg/m^2 **In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors [ii] and to the age of the patient**					

ELIGIBILITY:

- Indications as above
- ECOG status 0-2
- Previously untreated AML without known high risk/ adverse risk features
    - **AML with adverse-risk cytogenetics:** The efficacy of gemtuzumab ozogamicin has been shown in AML patients with favourable- and intermediate-risk cytogenetics, with limited effect in patients with adverse cytogenetics.
    - In patients being considered for additional doses of gemtuzumab ozogamicin, if cytogenetics testing shows adverse cytogenetics, gemtuzumab ozogamicin should be discontinued
- Normal cardiac function, assessed by echography or MUGA

EXCLUSIONS:

- Secondary AML (previous myeloproliferative or myelodysplastic syndrome) or therapy associated AML (exposure to chemotherapy or radiation)
- Hypersensitivity to gemtuzumab ozogamicin, DAUNOrubicin, cytarabine, or any of the excipients
- CNS involvement in acute myeloid leukaemia,
- Severe uncontrolled infection
- Liver (serum aminotransferase concentrations ≥2·5 upper limit of normal [ULN], serum bilirubin ≥2 ULN)
- Renal (serum creatinine ≥2·5 ULN) dysfunction
- Patients with symptomatic congestive heart failure
- LVEF <45% (The treatment of patients with baseline LVEF <45% should only be initiated at the discretion of the treating consultant)

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS

Baseline tests:

- FBC, renal and liver profiles
- Glucose, Uric acid
- Coagulation profile: APTT, PT, fibrinogen
- ECG, ECHO
- Chest X-ray
- Pregnancy test

Regular tests:

- FBC, renal and liver profiles prior to each dose of gemtuzumab ozogamicin
- PT, APTT, Fibrinogen prior to each dose of gemtuzumab ozogamicin
- ECG (QTc interval)

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- **Schedule modification for hyperleukocytosis**
  - Due to the risk of tumour lysis patients with WCC >30x 10^9/L should not receive gemtuzumab ozogamicin until WCC is reduced.
  - Cytoreduction can be achieved by administering hydroxycarbimide or by initiating the chemotherapy (Daunorubicin and cytarabine) and delaying the gemtuzumab ozogamicin until day 4.

- Dose modification for adverse reactions: Dose modification of gemtuzumab ozogamicin is recommended based on individual safety and tolerability

Renal and Hepatic Impairment:

Table 1: Dose modification in renal and hepatic impairment

<table>
<tr><th>Drug</th><th>Renal Impairment</th><th colspan="3">Hepatic Impairment</th></tr>
<tr><td rowspan="3">Gemtuzumab ozogamicin</td><td rowspan="3">• No dose adjustment is required in patients with mild to moderate renal impairment.
• Gemtuzumab ozogamicin has not been studied in patients with severe renal impairment.
• Gemtuzumab ozogamicin does not undergo renal clearance; the pharmacokinetics in patients with severe renal impairment is unknown.</td><td>Bilirubin</td><td>AST / ALT</td><td>Dose</td></tr>
<tr><td>>2 × ULN</td><td>>2.5 × ULN</td><td>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.</td></tr>
<tr><td colspan="3">No adjustment of the starting dose is required in patients with hepatic impairment defined by total bilirubin ≤ 2 × upper limit of normal (ULN) and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 2.5 × ULN</td></tr>
</table>

DAUNOrubicin	Creatinine (micromol/L)	Dose	Bilirubin (micromol/L)	Dose
	<105	100%	<20	100%
	105-265	75%	20-50	75%
	>265	50%	>50	50%
Cytarabine	No dose reduction necessary for induction cycle 1 as dose not considered high (<1g).		If bilirubin >34micromol/L, give 50% dose. Escalate doses in subsequent cycles in the absence of toxicity.	

Table 2: Dose Modification for Adverse Events

Adverse reactions	Recommended dose modification
Venoocclusive disease (VOD)/ sinusoidal obstruction syndrome (SOS).	Discontinue gemtuzumab ozogamicin
Infusion related reactions	Interrupt the infusion and institute appropriate medical management based on the severity of symptoms. Patients should be monitored until signs and symptoms completely resolve and infusion may resume. Consider permanent discontinuation of treatment for severe or life-threatening infusion reactions

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Gemtuzumab ozogamicin Low **(Refer to local policy).**
DAUNOrubicin Moderate **(Refer to local policy).**
Cytarabine < 1g Low **(Refer to local policy).**

PREMEDICATIONS:

Premedication with a corticosteroid, antihistamine, and paracetamol is recommended 1 hour prior to dosing to help ameliorate gemtuzumab ozogamicin infusion-related symptoms. Please refer to table 5.

Table 5: Suggested pre-medications prior to gemtuzumab ozogamicin infusion:

Drugs	Dose	Route
Paracetamol	1g	PO 60minutes prior to gemtuzumab ozogamicin infusion
Chlorphenamine	10mg	IV bolus 60minutes prior to gemtuzumab ozogamicin infusion
Hydrocortisone	100mg	IV bolus 60 minutes prior to gemtuzumab ozogamicin infusion

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis (**Refer to local policy).**
- Proton pump Inhibitor (**Refer to local policy).**
- Anti-viral prophylaxis (**Refer to local policy).**
- Anti-fungal prophylaxis (**Refer to local policy).** Avoid azoles while on gemtuzumab and for five days after gemtuzumab treatment has finished owing to potential risks of hepatotoxicity.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

- **Myelosuppression:** This is a very myelosuppresive regimen. DAUNOrubicin and cytarabine are potent bone marrow suppressants. Patients receiving this drug must be under close medical supervision and, during induction therapy, should have leucocyte and platelet counts performed daily.

Gemtuzumab ozogamicin

- **Hepatotoxicity:** Hepatotoxicity, including life-threatening and sometimes fatal hepatic failure and VOD/SOS have been reported in patients treated with gemtuzumab ozogamicin. Due to the risk of VOD/SOS, signs and symptoms of VOD/SOS should be closely monitored; these may include hepatomegaly (which may be painful), rapid weight gain, and ascites, elevations in ALT, AST, total bilirubin, and alkaline phosphatase, which should be monitored daily post administration of gemtuzumab ozogamicin. If VOD develops, consideration should be given to treating VOD with defibrotide.
- For patients who proceed to HSCT, monitoring of liver tests is recommended during the post-HSCT period, as appropriate. No definitive relationship was found between VOD and time of HSCT relative to higher gemtuzumab ozogamicin monotherapy doses; however, the ALFA-0701 study recommended an interval of 2 months between the last dose of gemtuzumab ozogamicin and HSCT.
- **Infusion related reactions (including anaphylaxis):** In clinical studies infusion related reactions, including anaphylaxis were reported. Infusion of gemtuzumab ozogamicin should be performed under close clinical monitoring and pre-medications are recommended 1 hour prior to gemtuzumab ozogamicin dosing please refer to table 4 above. Discontinuation of treatment should be strongly considered for patients who develop signs or symptoms of anaphylaxis, including severe respiratory symptoms or clinically significant hypotension.
- **Tumour lysis syndrome (TLS):** In patients with hyperleukocytic AML, leukoreduction should be considered with hydroxyurea to reduce the peripheral WBC count to below $30x10^9$/L prior to administration of gemtuzumab ozogamicin to reduce the risk of inducing TLS. Patients should be monitored for signs and symptoms of TLS and treated according to standard medical practice. Appropriate measures to help prevent the development of tumour lysis-related hyperuricaemia, such as hydration, administration of antihyperuricemics (e.g., allopurinol) or other agents for treatment of hyperuricaemia (e.g., rasburicase) must be taken.
- **Contraception:** Women of childbearing potential or partners of females of childbearing potential should be advised to use 2 methods of effective contraception during treatment with gemtuzumab ozogamicin for at least 7 months (females) or 4 months (males) after the last dose.

DAUNOrubicin

- **Cardiotoxicity:** Extreme caution should be exercised when using DAUNOrubicin in patients with cardiac disorders or in the elderly. Cardiotoxicity if it occurs is likely to be heralded by either a persistent tachycardia, shortness of breath, swelling of feet and lower limbs or by minor changes in the electrocardiogram and for this reason an electrocardiographic examination should be made at regular intervals during the treatment. Cardiotoxicity usually appears within 1 to 6 months after initiation of the therapy. It may develop suddenly and not be detected by routine ECG. It may be irreversible and fatal but responds to treatment if detected early.
- **Extravasation:** DAUNOrubicin is a potent vesicant. Give through the side arm of a fast flowing infusion ideally through a central access line to avoid/minimise the risk of extravasation.

Cytarabine

- **Cytarabine syndrome:** Treatment with cytarabine may cause a 'Cytarabine Syndrome' characterised by flu-like symptoms, skin rash and occasionally chest pain.

DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information.

ATC CODE:

Gemtuzumab ozogamicin	L01XC05
DAUNOrubicin	L01DB02
Cytarabine	L01BC01

REFERENCES:

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2. Burnett et al. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: Results from the MRC AML 15 Trial J Clin Oncol 2011; 29 (4): 369-377
3. Castaigne et al. Effect of gemtuzumab ozogamicin ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. The Lancet 2012 Vol 379:9825 – 1508-1516
4. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network. Available at http://londoncancer.org/media/65600/renal-impairment-dosage-adjustment-for-cytotoxics.pdf
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Version	Date	Amendment	Approved By
1	14/12/2020		

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] The administration of a single dose of gemtuzumab ozogamicin is an unlicensed administration schedule for this indication in Ireland. Patient's should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" means of administration has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy

[ii] Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.

Risk factors for developing anthracycline-induced cardiotoxicity include:
- high cumulative dose, previous therapy with other anthracyclines or anthracenediones
- prior or concomitant radiotherapy to the mediastinal/pericardial area
- pre-existing heart disease
- concomitant use of other potentially cardiotoxic drugs

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient.