Gemtuzumab ozogamicin (Mylotarg) +DA +Cytarabine

INDICATION

Untreated de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia, with favourable, intermediate or unknown cytogenetics. (NICE TA545- BLUETEQ required)

Gemtuzumab ozogamicin may be given in alternative regimen if patient is enrolled to AML19 clinical trial. See CDF criteria and clinical trial protocol for details.

TREATMENT INTENT

Curative

PRE-ASSESSMENT

1. Blood tests - FBC, coagulation screen, DAT, U&Es, LDH, ESR, urate, calcium, magnesium, creatinine, serum bicarbonate, LFTs, glucose, Hepatitis B core antibody and Hepatitis B surface Ag, Hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 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.
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 must not be started if WCC ≥ 30 x 10⁹/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.
13. Patients are only eligible to receive Gemtuzumab 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.
14. Patients should not be given any azole antifungals until 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/m² (max 5mg) in 100mL sodium chloride 0.9% intravenous infusion over 2 hours, via a 0.2micron low protein-binding in-line filter.

**Days 1 to 3** DAUNORUBICIN 60 mg/m² daily in 250mL sodium chloride 0.9% intravenous infusion over 30 minutes

**Days 1 to 7** CYTARABINE 200 mg/m² in 250mL sodium chloride 0.9% via continuous infusion over 24 hours

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 x10⁹/L and Platelet >100x10⁹/L

**Days 1 to 2** DAUNORUBICIN 35 mg/m² daily in 250mL sodium chloride 0.9% intravenous infusion over 30 minutes

**Days 1 to 3** CYTARABINE 1000 mg/m² BD in 250mL sodium chloride 0.9% intravenous infusion over 3 hours

**CONSOLIDATION- Cycle 1**
Start when ANC > 1 x10⁹/L and Platelet >100x10⁹/L

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

**GEMTUZUMAB OZOGAMICIN** 3mg/m² (max 5mg) in 100mL sodium chloride 0.9% intravenous infusion over 2 hours, via a 0.2micron low protein-binding in-line filter.

**Days 1** DAUNORUBICIN 60 mg/m² daily in 250mL sodium chloride 0.9% intravenous infusion over 30 minutes

**Days 1 to 4** CYTARABINE 1000 mg/m² BD in 250mL sodium chloride 0.9% intravenous infusion over 3 hours

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CONSOLIDATION - Cycle 2
Start when ANC > 1 x 10^9/L and Platelet > 100 x 10^9/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 (max 5mg) in 100mL sodium chloride 0.9% intravenous infusion over 2 hours, via a 0.2micron low protein-binding inline 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 Toxicity**

| Consolidation | Omit Gemtuzumab ozogamicin if platelet count does not recover to > 100 x 10^9/L or neutrophil dose not recover to > 0.5 x 10^9/L, within 14 days following the planned start day of consolidation. |

**Cytarabine:**

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction Cycle 1:</strong> No dose reduction necessary normally as doses not considered high dose</td>
<td>Bilirubin &gt; 34 micromol/L: give 50% dose Escalate doses in subsequent cycles in the absence of toxicity</td>
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<tr>
<td><strong>Induction Cycle2 and Consolidation:</strong></td>
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<tr>
<td>GFR &lt; 60 mL/min: give 60% dose</td>
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<tr>
<td>GFR &lt; 45 mL/min: give 50% dose</td>
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<td>GFR &lt; 30 mL/min: omit</td>
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**Daunorubicin:**

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Cr &lt; 105 micromol/L: give 100% dose</td>
<td>Bilirubin 20-50 micromol/L: give 75% dose Bilirubin 51-85 micromol/L: give 50% dose Bilirubin &gt; 85 micromol/L: omit</td>
</tr>
<tr>
<td>Cr 105-265 micromol/L: give 75% dose</td>
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<tr>
<td>Cr &gt; 265 micromol/L: give 50% dose</td>
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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**

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<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
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<tr>
<td>GFR ≥ 30 mL/min: No dose adjustment for mild or moderate renal impairment. GFR &lt; 30 mL/min: No information for severe renal impairment.</td>
<td>Bilirubin &gt; 2 x ULN or AST/ALT &gt; 2.5 x ULN: postpone Gemtuzumab ozogamicin until recovery. If the delay is more than 2 days, omit dose.</td>
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INVESTIGATIONS

- FBC, U&E, LFT

CONCURRENT MEDICATION

<table>
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<tr>
<th>Drug</th>
<th>Dose and duration</th>
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<tr>
<td>Allopurinol</td>
<td>300 mg daily for first 14 days of initial induction chemotherapy. (If a remission is attained the subsequent use of allopurinol is not required)</td>
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<tr>
<td>Aciclovir</td>
<td>200 mg three times a day for duration of treatment and for 3 months after completion</td>
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<tr>
<td>Fungal prophylaxis</td>
<td>As per local protocol, omit azole antifungals until 5 days after Gemtuzumab ozogamicin administration</td>
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<tr>
<td>Proton pump inhibitor</td>
<td>As per local formulary</td>
</tr>
<tr>
<td>Prednisolone 0.5 – 1% eye drops or Dexamethasone 0.1% eye drops (depending on local formulary)</td>
<td><strong>Induction Cycle 2 and Consolidation Cycles only:</strong> 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</td>
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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:** alopecia, chronic and acute cardiac failure and dysrrhythmias. There is a recommended maximum cumulative lifetime dose of daunorubicin of 600 mg/m².

**Cytarabine:** oral ulceration, hepatic dysfunction. 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:** venoocclusive disease (VOD), infusion related reaction. 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.
EXTRAVASATION RISK

Cytarabine: neutral
Daunorubicin: vesicant
Gemtuzumab ozogamicin: irritant

TREATMENT-RELATED MORTALITY

5-10%

REFERENCES


REVIEW

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<th>Name</th>
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