Gemtuzumab Ozogamicin (Mylotarg®)

Indication

Gemtuzumab ozogamicin, with daunorubicin and cytarabine (DA), is recommended as an option for untreated de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia, in people 15 years and over, only if:

- they start induction therapy when either the cytogenetic test confirms that the disease has favourable, intermediate or unknown cytogenetics (that is, because the test was unsuccessful) or when their cytogenetic test results are not yet available **and**
- they start consolidation therapy when their cytogenetic test confirms that the disease has favourable, intermediate or unknown cytogenetics (because the test was unsuccessful).

(NICE TA545)

Note:
NOT currently funded in combination with agents other than DA or with differing schedules, outside of clinical trials.
NOT indicated for known adverse risk cytogenetics.

ICD-10 codes

Codes with a pre fix C92

Regimen details

Induction course 1:

Day	Drug	Dose	Route
1, 4 and 7	Gemtuzumab Ozogamicin	3mg/m^2 (max 5mg)	IV infusion

Consolidation course 1 and 2:

Day	Drug	Dose	Route
1	Gemtuzumab Ozogamicin	3mg/m^2 (max 5mg)	IV infusion

Note: may be used in different schedules within clinical trials.

Cycle frequency

28 days

Number of cycles

First induction only. **Gemtuzumab should not be administered during second induction therapy.**
2 consolidation courses.

Administration

Gemtuzumab should be administered in 100mL sodium chloride 0.9% over 2 hours via an in-line low protein binding 0.2 micron filter. The infusion should be protected from light during administration with a light blocking cover. The line does not need to be protected from light.

Patients should be closely monitored (including pulse, blood pressure and temperature) during the infusion and for 4 hours following infusion. Gemtuzumab can produce a post-infusion symptom complex of fever and chills, and less commonly hypotension and dyspnoea may occur within 24 hours of administration.

Pre-medication

60 minutes prior to infusion:
Chlorphenamine 10mg IV
Paracetamol 500mg-1g PO
Hydrocortisone 100mg IV

For patients with a high tumour burden premedication to reduce uric acid levels (with allopurinol or rasburicase) and pre hydration is recommended.

Emetogenicity

This regimen has mild emetic potential.

Additional supportive medication

Allopurinol or rasburicase
Prophylactic anti-infectives as per local policy
Antiemetics as required.

Note: Patients should **not** be given azole antifungals until 5 days after Gemtuzumab administration.

Extravasation

Gemtuzumab is a potential irritant.

Investigations – pre first cycle

Investigation	**Validity period**
FBC + coagulation screen	7 days
LFTs	7 days
U+E including creatinine	7 days
LDH	7 days
Calcium	7 days
Magnesium	7 days
Glucose	7 days
Pregnancy test (WCBP)	7 days

Hepatitis B core antibody and Hepatitis BsAg, Hepatitis C antibody
EBV, CMV, VZV, HIV 1+2

ECG +/- echocardiogram – if clinically indicated.

Investigations – pre subsequent cycles

Investigation	**Validity period**
FBC	24 hours
LFTs*	24 hours
U+E including creatinine	24 hours
Pregnancy test (WCBP)	7 days

* **LFTs should be checked prior to each dose**

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
WCC	< 30 x 10^9/L
Creatinine Clearance	≥ 30mL/min
ALT/AST	< 2.5 x ULN
Bilirubin	< 2 x ULN

Dose modifications

- **Haematological toxicity**

Induction:

Gemtuzumab must **not** be started if WCC ≥ 30 x 10^9/L due to risk of tumour lysis and hypersensitivity reactions. Hydroxycarbamide (40-60 mg/kg/day) can be used to reduce WCC before commencing gemtuzumab.

Consolidation:

Thrombocytopenia

If platelets < 100 x 10^9/L delay treatment:

- If recovers to ≥ 100 x 10^9/L within 14 days initiate consolidation therapy
- If platelets ≥ 50 x 10^9/L but < 100 x 10^9/L within 14 days Gemtuzumab should be discontinued, continue with chemotherapy alone.
- If platelets remain < 50 x 10^9/L for more than 14 days discuss with consultant. A bone marrow aspirate should be performed to re-assess patients status.

Neutropenia

If neutrophil count does not recover to > 0.5 x 10^9/L within 14 days discontinue gemtuzumab.

- **Renal impairment**

No dose modification required for mild-moderate renal impairment. Gemtuzumab has not been studied in patients with severe renal impairment and the pharmacokinetics is unknown. If CrCl < 30mL/min discuss with consultant.

- **Hepatic impairment**

No dose modification required if ALT/AST ≤ 2.5 x ULN and bilirubin ≤ 2 x ULN. Gemtuzumab must be withheld if ALT/AST > 2.5 x ULN or bilirubin > 2 x ULN due to the risk of veno-occlusive disease (VOD).

- **Other toxicities**

Hepatotoxicity

Hepatotoxicity, including life-threatening, and sometimes fatal hepatic failure and VOD/sinusoidal obstruction syndrome (SOS) have been reported in patients receiving gemtuzumab. Patients should be closely monitored for signs and symptoms of VOD/SOS, including elevations in ALT/AST, bilirubin, and alkaline phosphatase (**LFTs should be checked prior to each dose**), hepatomegaly (which may be painful), rapid weight gain, and ascites.

If AST/ALT > 2.5 x ULN and/or bilirubin > 2 x ULN treatment should be withheld until recovery of bilirubin to ≤ 2 × ULN and AST/ALT to ≤ 2.5 × ULN. Consider omitting dose if delayed by more than 2 days between infusions.

In patients who experience VOD/SOS, gemtuzumab should be discontinued and patients treated according to standard medical practice. Moderate to severe VOD should be managed with defibrotide as per local VOD policy.

For patients who proceed to haematopoetic stem cell transplant (HSCT), close monitoring of LFTs is recommended during the post-HSCT period, due to increased risk of VOD.

Infusion related reactions:
Patients should be monitored for signs and symptoms of infusion related reactions, including fever and chills, hypotension, tachycardia, and respiratory symptoms during the infusion and for the first 24 hours after. Premedication with a corticosteroid, antihistamine and paracetamol is as above. Infusion should be interrupted immediately for patients who develop severe reactions, especially dyspnoea, bronchospasm, or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Treatment should be discontinued if patients develop signs or symptoms of anaphylaxis.

Tumour lysis syndrome (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.

Adverse effects – for full details consult product literature/ reference texts

- **Serious side effects**

Severe and prolonged myelosuppression
Thrombocytopenia
Haemorrhage
Infusion related reactions
Pulmonary toxicity, including dyspnoea, oedema, ARDS
Hepatotoxicity, including VOD.

- **Frequently occurring side effects**

Nausea, vomiting
Constipation, diarrhoea
Headache
Hyperglycaemia
Mucositis
Rash

Significant drug interactions

No formal drug-interaction studies performed
Azole antifungals should also be avoided until 5 days after gemtuzumab administration

Additional comments

Gemtuzumab is contraindicated in pregnancy or if breast feeding or previous hypersensitivity.

References

- National Institute for Health and Clinical Excellence. NICE TA545. Accessed 31 January 2019 via www.nice.org.uk
- Summary of Product Characteristics Gemtuzumab Ozogamicin (Pfizer) accessed 31 January 2019 via www.medicines.org.uk
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- Castaigne, S. et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet. 2012 Apr 21;379(9825)
- Castaigne, S. et al. Final analysis of the ALFA 0701 study. Blood. 2014. 124:376

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