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Gemtuzumab ozogamicin

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Contents

Abstract

▲ Gemtuzumab ozogamicin is a humanised monoclonal IgG_4 antibody, linked to a cytotoxic calicheamicin derivative. It effects cell necrosis by specifically targeting the CD33 antigen which is expressed on the surface of leukaemic cell blasts in more than 90% of patients with acute myeloid leukaemia (AML), but is not present on normal stem cells.

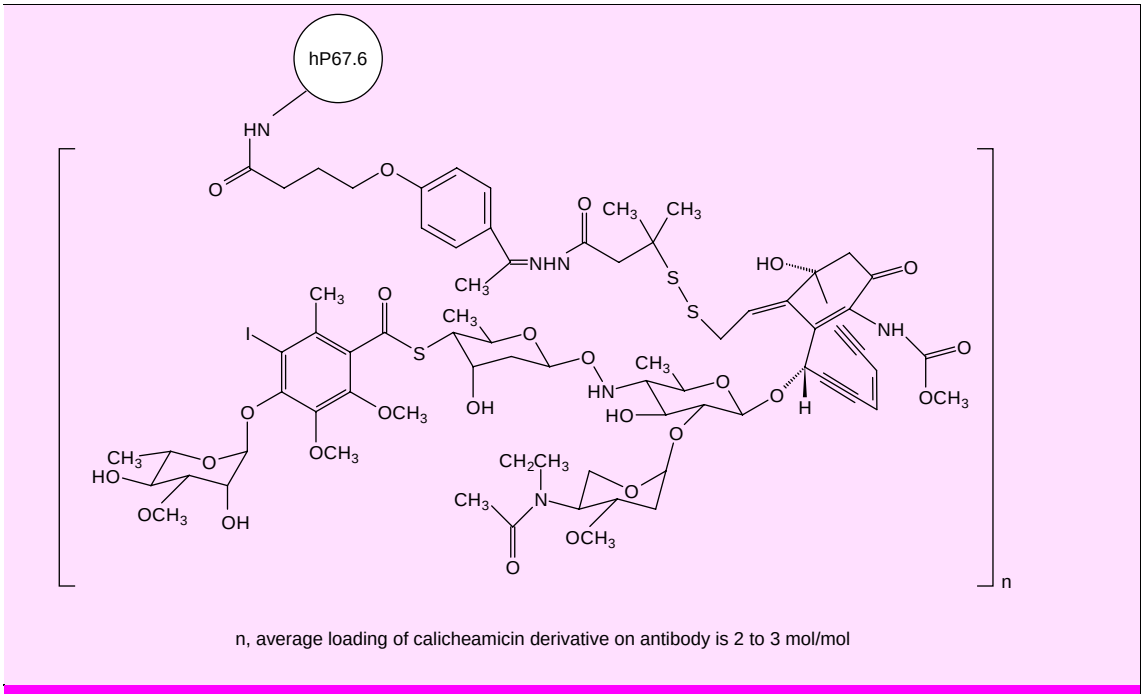
▲ Therapy with gemtuzumab ozogamicin (2 doses of 9 mg/m^2) in 3 noncomparative studies produced complete remission in 16% of adult patients with AML in first relapse, and complete remission with incomplete platelet recovery in an additional 13% of patients. Rates of remission did not differ between those aged less than 60 years and older than 60 years.

▲ Many patients were able to receive both doses of gemtuzumab ozogamicin therapy as outpatients. Survival duration was similar between those treated as outpatients and those requiring hospitalisation.

▲ About one-third of 11 children and adolescents treated with 2 doses of 9 mg/m^2 gemtuzumab ozogamicin in a phase I study showed <5% bone marrow blasts after completion of therapy.

▲ The most commonly encountered adverse events in clinical trials with gemtuzumab ozogamicin were myelosuppression, increased levels of hepatic enzymes, infection, fever, bleeding, chills, nausea and vomiting and dyspnoea. No treatment-related renal failure or alopecia was reported.

Features and properties of gemtuzumab ozogamicin	
Indications	
Acute myeloid leukaemia	
Mechanism of action	
Humanised monoclonal antibody (hP67.6) conjugated with a calicheamicin derivative	DNA antagonist
Dosage and administration	
Usual dosage in clinical trials	9 mg/m^2
Route of administration	Intravenous infusion administered over 2 hours
Frequency of administration	2 doses 14 days apart
Pharmacokinetic profile (hP67.6)	
Peak plasma concentration	2.86 mg/L
Area under the plasma concentration-time curve	123 mg/L•h
Clearance	0.265 L/h
Elimination half-life	72.4h
Adverse events	
Common events	Myelosuppression, raised hepatic enzyme levels, infection, fever, bleeding, chills, nausea & vomiting, dyspnoea



n, average loading of calicheamicin derivative on antibody is 2 to 3 mol/mol

Gemtuzumab ozogamicin is composed of a humanised monoclonal antibody (hP67.6) joined to calicheamicin via a bifunctional linker.

The initial aim of chemotherapy for acute myeloid leukaemia (AML) is to induce a remission. In addition to causing severe myelosuppression, conventional chemotherapy has pronounced adverse effects, including nausea and vomiting, mucositis, alopecia, neuropathy, and renal and hepatic dysfunction.[1] Treatment is especially difficult in those aged over 60 years, as their ability to withstand the intensity of chemotherapy is reduced, and factors such as cytogenetics, intrinsic multidrug resistance and morphology are more unfavourable.[2] Monoclonal antibody-based chemotherapy is therefore attractive as a treatment because it selectively targets leukaemic cells while sparing normal stem cells, which may result in improved tolerability compared with conventional chemotherapy.[3]

1. Pharmacodynamic Profile

• Gemtuzumab ozogamicin is an antineoplastic agent which targets the CD33 antigen. It is composed of a recombinant humanised IgG_4 monoclonal antibody (hP67.6) conjugated with a calicheamicin derivative via a bifunctional linker. The average overall ratio of calicheamicin to antibody is approximately 2 to 3, with about 50% of the antibody unconjugated.[4] Gemtuzumab ozogamicin is 2000-fold more cytotoxic for the HL-60 human leukaemia cell line than the unconjugated calicheamicin derivative alone.[5]

• The CD33 antigen is expressed on the surface of leukaemic blasts in approximately 90% of patients with AML.[6,7] In addition, it is expressed on normal and leukaemic myeloid colony-forming cells, including leukaemic clonogenic precursors, but is not expressed on pluripotent haematopoietic stem cells or on nonhaematopoietic cells.[8]

• Binding of gemtuzumab ozogamicin with the CD33 antigen results in the formation of a complex that is internalised, after which the calicheamicin derivative is released into the lysosomes of the my-

eloid cell, binding to DNA, and resulting in DNA strand breaks and cell apoptosis.[9,10]

- Rapid saturation of available CD33 binding sites is seen in leukaemic blasts isolated from patients with AML who have been treated with gemtuzumab ozogamicin (9 mg/m^2). This is followed by rapid internalisation of the complex into the cell.[10,11]

- *In vitro*, gemtuzumab ozogamicin is cytotoxic to the CD33-positive (CD33+) HL-60 cell line and produces significant inhibition of colony formation in cultures of adult leukaemic bone marrow cells.[5,12] Gemtuzumab ozogamicin also suppresses the cell growth of HL-60, NOMO-1, NB-4 and NKM-1 cell lines at concentrations of 5, 10 and 100 μg/L in a dose-dependent manner. However, no effect is seen on the multidrug-resistant cell lines NOMO-1/ADR and NB-4/MDR, even at concentrations of 10 000 μg/L.[13]

- Long term complete tumour regression has been induced by gemtuzumab ozogamicin over an almost 6-fold dose range in nude mice implanted with HL-60 xenografts (further details are not available).[5]

2. Pharmacokinetic Profile

- A mean maximum humanised antibody (hP67.6) plasma concentration (C_{max}) of 2.86 ± 1.35 mg/L was achieved after single dose intravenous infusion of gemtuzumab ozogamicin (9 mg/m^2) to adult CD33+ patients with AML in relapse (n = 58). The C_{max} value for unconjugated calicheamicin was 0.079 ± 0.093 mg/L.[14]

- Mean area under the plasma concentration-time curve (AUC) for hP67.6 was 123 ± 105 mg/L · h. Concentration profiles of total calicheamicin in plasma followed the same time course as those of the humanised CD33 antibody and the mean AUC value was reported as 2.47 ± 1.82 mg/L · h.[14]

- Plasma elimination half-lives ($t_{½}$) after administration of gemtuzumab ozogamicin (9 mg/m^2) to adult patients with AML were 72.4 ± 42.0h and 45.1 ± 25.2h for antibody and total calicheamicin, respectively. Total body plasma clearance of hP67.6 was 0.265 ± 0.229 L/h. These pharmacokinetic parameters were not affected by gender, nor were differences observed between those aged <60 years and ≥60 years.[14,15]

- The C_{max} and AUC of hP67.6 observed in 5 CD33+ paediatric patients (age 2 to 14 years) with relapsed AML following 2 doses of gemtuzumab ozogamicin (6 mg/m^2) were 1.4 mg/L and 48.5 mg/L · h, respectively. Drug clearance and $t_{½}$ (0.296 L/h and 51.6h) were similar to those seen in adult patients (n = 14) receiving 2 doses of 9 mg/m^2 gemtuzumab ozogamicin (0.353 L/h and 66.5h, respectively).[16]

3. Therapeutic Use

Treatment in Adult Patients with Relapsed AML

Data for phase II trials have not been reported individually. Therefore this review focuses on pooled results of the 3 noncomparative phase II studies conducted in patients with untreated CD33+ AML in first relapse.[17]

Studies 1 (n = 65) and 2 (n = 40) were conducted in patients aged ≥18 years who had relapsed after a first complete remission (CR1) lasting at least 6 months. In study 2, prior haematopoietic stem cell transplantation (HSCT) was permitted and 5 patients with prior HSCT were enrolled. Eligibility criteria for study 3 (n = 37) included age ≥60 years and relapse after CR1 of at least 3 months. Additionally, patients in all studies were required to have normal renal and hepatic function and a peripheral white blood cell count of <30 000/μl.

The primary end-point was complete remission (CR), defined as no leukaemic blasts in peripheral blood, ≤5% blasts in the marrow, absolute neutrophil count (ANC) ≥1500/μl, haemoglobin ≥90 g/L, platelet count ≥100 000/μl and platelet and RBC transfusion independence for 1 and 2 weeks, respectively. Patients who met all remission criteria but who had platelet counts <100 000/μl were also considered to be in remission. These 2 groups combined are referred to as those achieving overall remission.

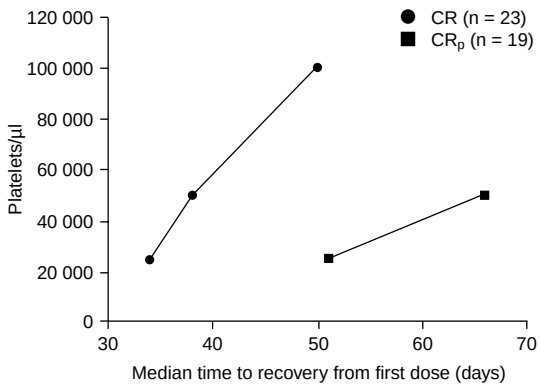


Fig. 1. Median time to platelet recovery from first treatment with gemtuzumab ozogamicin (two 9 mg/m^2 doses) for patients with acute myeloid leukaemia in first relapse. Medians for platelet recovery to 25 000, 50 000 and 100 000/μl are presented for patients who achieved complete remission (CR) and complete remission without platelet recovery (CR_p) after 2 doses of gemtuzumab ozogamicin. Pooled results from 3 noncomparative phase II studies (n = 142). NB: Patients in CR_p did not achieve 100 000 platelets/μl.[17]

• 142 CD33+ patients with untreated AML in first relapse with a median age of 61 years (range 22 to 84 years), most commonly received 2 intravenous infusions of gemtuzumab ozogamicin 9 mg/m^2 [after pretreatment with paracetamol (acetaminophen) and antihistamines] 14 to 28 days apart. Patients were evaluated for remission, survival (both relapse-free and overall) and treatment-emergent adverse effects (TEAEs).

• CR was achieved in 23 patients (16%); additionally, 19 patients (13%) achieved remission with incomplete platelet recovery (CR_p) for an overall remission rate of 30%. The median time to platelet recovery for the 2 groups is shown in figure 1. 34% of patients aged <60 years achieved remission, as did 26% of those aged ≥60 years.[17,18] Cytogenetic profile did not influence response to treatment, and overall remission rates did not differ greatly between those with CR1 greater or less than 1 year.

• Median relapse-free survival for all patients in remission was 6.8 months with no significant difference between those in CR (7.2 months) and CR_p (4.4 months) [p = 0.624].

• Median overall survival was 5.9 months for all patients, and 6 of the 23 patients in CR (26%) remained leukaemia-free for at least 6 months or until date of death. The survival probability for all patients at 1 year was 31%.[17,18]

• Of the patients who subsequently received HSCT, patients in CR survived for an average of 14.5 months, and patients in CR_p for ≥5.4 months, compared with 4.2 months for patients who did not achieve remission.[17]

Effect of Treatment on Rates of Hospitalisation

• 38% of patients received their first dose of gemtuzumab ozogamicin as outpatients, of whom 9% were never hospitalised during the initial 8-week period. The median time to hospitalisation thereafter was 8 days, with 88% of patients admitted 72 hours or more after the first dose. 30% of patients received both first and second treatments of gemtuzumab ozogamicin as outpatients.[19] Platelet counts of greater than 50 000/μl at both screening and baseline were independently predictive of being treated as an outpatient at first dose. Survival duration was similar between those receiving both doses as outpatients and those who were hospitalised.[20]

Treatment in Children and Adolescents with Relapsed AML

• Preliminary results of a noncomparative phase I study involving 18 paediatric patients (median age 12 years, range 1 to 16 years) with either refractory or relapsed CD33+ AML have been reported. 36% of 11 patients treated with gemtuzumab ozogamicin at 9 mg/m^2 for 2 doses showed <5% bone marrow blasts after the second dose.[21]

4. Tolerability

• The tolerability of gemtuzumab ozogamicin (dosages between 0.25 and 9 mg/m^2 for ≤3 doses) was evaluated in a phase I study in 40 patients with

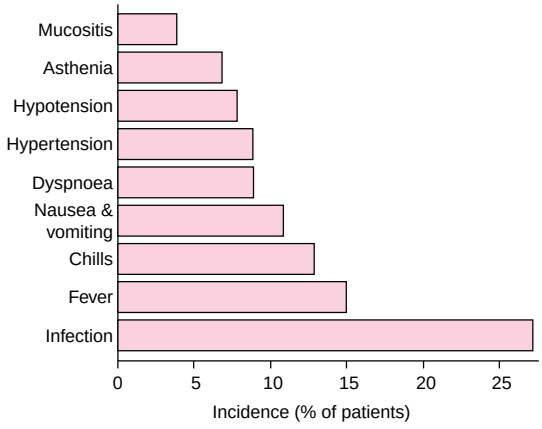


Fig. 2. Incidence of grade 3 and 4 nonhaematological gemtuzumab ozogamicin-associated adverse events in patients enrolled in 3 noncomparative phase II studies (n = 142). Grade 3 and 4 adverse effects evaluated using US National Cancer Institute Common Toxicity Criteria (version 1).[17,22]

relapsed or refractory AML. Fever and chills (predominantly grade 1 or 2) occurred in 80% of patients, with onset generally 2 to 4 hours after beginning treatment. Reversible hepatic enzyme elevation was reported in 20% of patients. Humoral responses to the calicheamicin-linker complex were noted in 2 patients. However, no therapy-related toxic effects were observed on central nervous system, cardiac or renal functions.[11]

- In clinical trials of patients with CD33+ AML in first relapse (n = 142) who received 2 doses of gemtuzumab ozogamicin 9 mg/m^2 14 to 28 days apart, the most commonly reported postinfusion (day 1) grade 3 and 4 TEAEs were chills (11%), fever (7%) and hypotension (4%). Severe hypotension was reported several hours after infusion, but this appeared transient and was reversible with intravenous fluid support. Whereas 34% of patients experienced severe effects after the first dose, only 12% experienced these after the second dose ($p < 0.001$).[17]

- The most frequently reported grade 3 and 4 TEAEs during the treatment period from the first dose until 28 days after the second dose were neutropenia (97%), thrombocytopenia (99%) and anaemia (47%). 15% of patients experienced severe bleeding, including epistaxis (3%) and intracranial haemorrhage (4%). Other reported adverse effects were infection 28% [including sepsis (16%) and pneumonia (7%)], fever (15%), chills (13%), nausea and vomiting (11%), dyspnoea (9%), hypertension (9%), hypotension (8%) and asthenia (7%) [fig. 2].[17,22]

- 23% of patients experienced severe hyperbilirubinaemia, with a median time to onset of 8 days and duration of 20 days. 17% of patients showed grade 3 or 4 increases in AST or ALT levels. Evidence of more serious hepatic damage was observed in 2 patients (1 with liver failure and 1 with persistent ascites and hepatosplenomegaly). No treatment-related cardiotoxicity, renal failure or alopecia was reported.[17]

- Additionally, adverse events observed in children and adolescents (n = 18) with either refractory or relapsed CD33+ AML who received gemtuzumab ozogamicin (6 or 9 mg/m^2) were similar to those seen in adult patients. These included infusion-related fever, chills, hypotension, shortness of breath, and grade 4 neutropenia and thrombocytopenia. One patient developed grade 3 gastrointestinal bleeding and congestive heart failure after treatment with 6 mg/m^2.[21]

5. Gemtuzumab ozogamicin: Current Status

Gemtuzumab ozogamicin has been approved for use in the US for the treatment of CD33+ AML in patients aged ≥60 years who are in first relapse and who are not considered candidates for other cytotoxic chemotherapy. Gemtuzumab ozogamicin has shown clinical efficacy in this indication and is relatively well tolerated; mucositis occurs infrequently; however, the drug is not indicated for those with hepatic dysfunction.

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