

Brand Name: Mylotarg

Generic Name: gemtuzumab ozogamicin

Manufacturer: Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.

Drug Class: CD33-directed antibody-drug conjugate

Uses:

Labeled Uses:

- Newly-diagnosed CD33-positive acute myeloid leukemia (AML) in adults
- Relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older

Unlabeled Uses:

- Acute promyelocytic leukemia, FAB M3

Mechanism of Action:

Gemtuzumab ozogamicin is a CD33-directed antibody-drug conjugate. Gemtuzumab, the antibody portion of the antibody-drug conjugate, recognizes human CD33 antigen. Ozogamicin or N-acetyl gamma calicheamicin, the small molecule portion of the antibody-drug conjugate, is a cytotoxic agent that links covalently to gemtuzumab via a linker. The antibody-drug conjugate binds to CD33-expressing tumor cells, is internalized into the tumor cell and then undergoes hydrolytic cleavage to separate the antibody from the cytotoxic agent. The cytotoxic agent, N-acetyl gamma calicheamicin, then induced double-strand DNA breaks in the tumor cells, which, induces cell cycle arrest and apoptosis.

Pharmacokinetics:

Absorption:

T _{max}	30 minutes
V _d	21.4 L
t _{1/2}	62 hours after 1 st dose, 90 hours after 2 nd dose
Clearance	0.35 L/h after 1 st dose, 0.15 L/h after 2 nd dose
Protein binding	97% bound
Bioavailability	80-100%

Metabolism: N-acetyl gamma calicheamicin dimethyl hydrazide is extensively metabolized, primarily through a non-enzymatic reduction of the disulfide moiety.

Elimination: The antibody is cleared from the plasma at 0.35 L/hr after a single dose 9 mg/m² IV dose and decreases to 0.15 L/hr after a second dose administered 14 days later.

Efficacy:

Sievers EL, Larson RA, Stadmauer EA, Estey E, Lowenberg B, Dombret H, et al. Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. *J Clin Oncol.* 2001;19(13): 3244-3254.

Study Design: three study, open-label, multicenter safety and efficacy study

Description of Study: The three study, open-label, multicenter safety and efficacy study was conducted study was comprised of 142 patients with AML in the first relapse located in both the United States and Europe. The patients were of a median age of 61 years old and no history of an antecedent hematologic disorder. The patients received a 9 mg/m² dose of gemtuzumab ozogamicin as a two hour intravenous infusion at two week intervals for two doses. The primary endpoints were complete remission, while the secondary endpoints were survival time and treatment-emergent adverse events. The results of the study found that 30% of the patients treated with Mylotarg reached remission. Adverse events that had the highest incidence included: myelosuppression at 97-99%, grade 3 or 4 hyperbilirubinemia at 23%, elevated transaminase levels at 17%, grade 3 or 4 mucositis at 4%, infections at 28% and severe nausea and vomiting at 11%.

Limitations: One limitation to the study would be the high drop out rate; 109 of 142 received two doses, due to disease progression, death and infection. Another limitation to the study included a lack of diversity among the study population, as 94% of the study population was white. In this study, patients were excluded from the study if they had short first remission durations or developed AML that arose from myelodysplastic syndrome or secondary to previous treatment with chemotherapy, which is a limitation due to the removing of poor prognostic patients from the patient population.

Conclusion: The author's conclusion of the study is that Mylotarg (gemtuzumab ozogamicin) has a favorable efficacy profile in treating CD33+ AML patients in their first relapse. My conclusion is that Mylotarg may be efficacious in treating CD33+ AML patients in their first relapse but I also think that there may be better treatment regimens out there for this population. I would like to see a study comparing Mylotarg to another commonly used regimen in CD33+ AML patients in their first relapse.

Roboz GJ, Knovich MA, Bayer RL, Schuster MW, Seiter K, Powell BL, et al. Efficacy and safety of gemtuzumab ozogamicin in patients with poor-prognosis acute myeloid leukemia. *Leukemia & Lymphoma.* 2002: 43(10); 1951-1955.

Study Design: open-label, single arm, safety and efficacy study

Description of Study: The open-label, single arm, safety and efficacy study was testing gemtuzumab ozogamicin in patients with poor prognosis acute myeloid leukemia, meaning the patient has had a relapse of AML less than or equal to six months from the first complete remission, has AML refractory to chemotherapy at initial induction or at first relapse, has AML in second or greater relapse, has myeloid blast crisis of chronic myeloid leukemia, has refractory anemia with excess blasts in transformation or is untreated and greater than or equal to 70 years old or greater than or equal to 55 years old

with abnormal cytogenetics. Patients were administered a single 9 mg/m² dose of gemtuzumab ozogamicin over a 2 hour IV infusion on days 1 and 15. Patients also received acetaminophen and diphenhydramine as pre-medications to the gemtuzumab ozogamicin therapy. The endpoints of the study included: complete remission, partial remission and total response rate. Four patients or 9% achieved complete remission and the mean duration of complete remission was four months. Two patients achieved a partial remission and the mean duration was four months. There was a 14% total response rate. There were six early deaths reported. There was a 95% incidence of hematological toxicity, 84% incidence of infection, 12% incidence of bleeding and 21% incidence of hepatic adverse events.

Limitations: One limitation to this study was the lack of exclusion criteria, as the only exclusion criteria listed was: end organ dysfunction or uncontrolled infection. Another limitation to the study would be the low number of participants with a study population of only 43 individuals. Along with the small study population, only 26 of the 43 individuals received two doses of the drug. This study also failed to report statistical values for the study, therefore making it very difficult to interpret the findings as statistically significant. One last limitation found in this study is that only 42% of the study population was CD33 antigen positive.

Conclusion: The authors' conclusion is that patients with relapse/refractory AML will experience equivalent or slightly better response rates and toxicity profiles with gemtuzumab ozogamicin versus a single-agent standard chemotherapy regimen. My conclusion is that this study is not useful in determining the efficacy in poor prognosis AML patients due to the lack of statistical data being reported.

Larson RA, Boogaerts M, Estey E, Karanes C, Stadmauer EA, Sievers EL, et al. Antibody-targeted chemotherapy of older patients with acute myeloid leukemia in first relapse using Mylotarg (gemtuzumab ozogamicin). *Leukemia*. 2002; 16(9):1627-36.

Study Design: three study, open-label, multicenter, safety and efficacy study

Description of Study: The purpose of this study was to determine the safety and efficacy of Mylotarg as monotherapy in CD33-positive AML patients, greater than or equal to 60 years of age who are experiencing a first relapse. This study included a study population of 101 patients greater than or equal to 60 years old with a CD33-positive AML diagnosis in the first relapse. The patients also had a ECOG performance status of 0-2, no antecedent hematological disorder preceding initial presentation with AML, no therapy-related AML, normal renal and liver function, and peripheral WBC counts of less than 30,000 per microliter. The studies took place in three locations: United States, Canada and Europe. A dose of Mylotarg 9 mg/m² was administered intravenously over a two-hour infusion for two doses with 14-28 days between doses. Efficacy was assessed through rate of remission, including both complete remission and complete remission with incomplete platelet recovery. Relapse-free survival and survival were also included in the efficacy assessments. All assessments were evaluated in the treatment phase and the follow-up phase. Adverse events were also recorded. At the end of the study, 77 of

the 101 patients received two doses of Mylotarg and 20 patients received one dose of Mylotarg. Twelve of the 20 patients only received one dose due to disease progression and eight due to adverse events. The overall remission rate for those treated with Mylotarg was 28% (95% CI, 19-38%) with a complete remission rate of 13% and a complete remission with incomplete platelet recovery rate of 15%. The overall median survival was 5.4 months (95% CI, 3.8-7.2 months) with the patients enrolled in the trial. Breaking that down further, those who had a complete remission had an average survival of 14.5 months, those with complete remission with incomplete platelet recovery had an average survival of 11.8 months and those with no remission had an average survival of 4.1 months. There was no statistically significant difference when comparing the complete remission survival to the complete remission with incomplete platelet recovery group survival but there was statistical significance found when comparing each of those two groups to the no response group ($p = 0.0001$ and $p = 0.025$).

Limitations: One limitation to this study is the high drop out rate due to disease progression or adverse events. Another limitation to this study would be the high incidence of intermediate and poor cytogenetics in the study population. Power is not discussed in this study; therefore it is unknown and is viewed as a limitation. There was an uneven distribution of men versus women in this study with a 62 to 38% split. The lack of statistically significant findings resulted in a limitation for the study.

Conclusion: The authors conclude that Mylotarg is an effective monotherapy treatment for AML patients greater than or equal to age 60 in their first relapse. My conclusion is that the study did not have enough statistically significant findings for me to determine if Mylotarg has efficacy in treating AML patients greater than or equal to age 60 in their first relapse.

Contraindications: Hypersensitivity to Mylotarg or any of its components

Precautions:

- Hepatotoxicity: Hepatotoxicity has been reported in patients receiving Mylotarg as a single agent or in combination with other chemotherapy agents. Venooclusive Liver Disease (VOD), a life-threatening and sometimes fetal hepatic event has also been reported with use of Mylotarg.
- Infusion-related reactions: Monitor patients for fever, chills, hypotension, tachycardia, hypoxia and respiratory failure as these can all be a sign of life-threatening or fatal infusion related-reactions. Infusion-related reactions, including anaphylaxis have occurred up to 24 hours after infusion of Mylotarg.
- Hemorrhage: Due to myelosuppression as a result of taking Mylotarg, the therapy can cause fatal or life-threatening hemorrhage from prolonged thrombocytopenia.
- QT interval prolongation: The use of other calicheamicin containing agents has resulted in QT interval prolongation.
- Use in AML with adverse-risk cytogenetics: Mylotarg in combination with daunorubicin and cytarabine for newly diagnosed de novo AML patients with adverse-risk cytogenetics did not improve event-free survival.

- Pregnancy: Embryo-fetal toxicity can occur in pregnant women; advise females of reproductive potential to use effective contraception during treatment with Mylotarg.

Adverse Effects:

Occurring in >10% of patients

Cardiovascular:

Hypotension (incidence not reported)

Dermatologic

Rash (16%)

Gastrointestinal

Constipation (21%)

Inflammatory disease of mucous membrane (21%)

Nausea (38%)

Neutropenic colitis

Vomiting (21%)

Hematologic

Febrile neutropenia all grades (18%)

Febrile neutropenia grade 3 or 4 (18%)

Hemorrhage all grades monotherapy (25%)

Hemorrhage all grades combination therapy (90%)

Hemorrhage grade 3 or 4 monotherapy (7-13%)

Hemorrhage grade 3 or 4 combination therapy (21%)

Thrombocytopenia grade 3 or 4 (19-35%)

Hepatic

ALT/SGPT level raised (16%)

AST/SGOT level raised (40%)

Hepatotoxicity (incidence not reported)

Immunologic

Bacterial infectious disease (incidence not reported)

Infectious disease (42-44%)

Sepsis (32%)

Neurologic

Headache (19%)

Renal

Hemorrhagic cystitis (incidence not reported)

Respiratory

Dyspnea (incidence not reported)

Fungal infection of the lung (incidence not reported)

Interstitial pneumonia (incidence not reported)

Other

Fatigue (46%)

Fever (79%)

Infusion reaction (incidence not reported)

Tumor lysis syndrome (incidence not reported)

Occurring in >1% to <10% of patients

Cardiovascular

Tachycardia (2%)

Gastrointestinal

Diarrhea (2%)

Hematologic

Neutropenia grade 3 or 4 (2-3%)

Hepatic

Hyperbilirubinemia (7%)

Veno-occlusive disease of liver (5%)

Respiratory

Pneumonia grade 3 (7%)

Pulmonary edema grade 3, acute (2%)

Other

Pain grade 3 (4%)

Drug Interactions:

- Co-administration of live vaccine and chemotherapeutic agents may result in an increased risk of infection by the live vaccine.
- Concurrent use of rotavirus vaccine and chemotherapeutic agents may result in an increased risk of infection by the live vaccine.
- Concurrent use of known QT interval prolonging agents with Mylotarg may result in increased risk for QT interval prolongation.

Dosing/Administration:

Adult Dosing

- Acute myeloid leukemia, newly diagnosed, CD33-positive
 - Combination regimen
 - Premedication: Acetaminophen 650 mg orally and diphenhydramine 50 mg orally/IV administered 1 hour prior to Mylotarg and methylprednisone 1 mg/kg or equivalent dose of other corticosteroid within 30 minutes prior to infusion
 - 1st Induction cycle: 3 mg/m² IV infusion over 2 hours on days 1, 4, and 7 in combination with daunorubicin 60 mg/m² on days 1 to 3 and cytarabine 200 mg/m² on days 1 to 7. MAX one 4.5 mg vial; may administer a second chemotherapy induction cycle without Mylotarg
 - 1st Consolidation cycle: 3 mg/m² IV infusion over 2 hours on day 1 in combination with daunorubicin 60 mg/m² on day 1 and cytarabine 1 g/m² IV every 12 hours on days 1 to 4. MAX one 4.5 mg vial
 - 2nd Consolidation cycle: 3 mg/m² IV infusion over 2 hours on day 1 in combination with daunorubicin 60 mg/m² on days 1 and 2 and cytarabine 1 g/m² IV every 12 hours on days 1 to 4. MAX one 4.5 mg vial
 - Single-agent regimen

- Premedication: Acetaminophen 650 mg orally and diphenhydramine 50 mg orally/IV administered 1 hour prior to Mylotarg and methylprednisone 1 mg/kg or equivalent dose of other corticosteroid within 30 minutes prior to infusion
 - Induction cycle: 6 mg/m² IV infusion over 2 hours on day 1 and 3 mg/m² on day 8
 - Continuation cycle: 2 mg/m² IV infusion over 2 hours on day 1 every 4 weeks; may administer up to 8 cycles of continuation therapy
- Acute myeloid leukemia, Relapsed or refractory, CD33-positive
 - Premedication: Acetaminophen 650 mg orally and diphenhydramine 50 mg orally/IV administered 1 hour prior to Mylotarg and methylprednisone 1 mg/kg or equivalent dose of other corticosteroid within 30 minutes prior to infusion
 - Usual dosage: 3 mg/m² IV infusion over 2 hours on days 1, 4, and 7. MAX one 4.5 mg vial

Pediatric Dosing (2 years or older)

- Acute myeloid leukemia, Relapsed or refractory, CD33-positive
 - Premedication: Acetaminophen 15 mg/kg orally and diphenhydramine 1 mg/kg (MAX 50 mg) orally/IV and methylprednisone 1 mg/kg orally/IV
 - May give additional doses of acetaminophen and diphenhydramine every 4 hours after initial pretreatment dose
 - Usual dosage: 3 mg/m² IV infusion over 2 hours on days 1, 4, and 7. MAX one 4.5 mg vial

Hepatic impairment

- Total bilirubin greater than 2 times UNL or AST and/or ALT greater than 2.5 times ULN: Delay treatment until recovery of total bilirubin to 2 times ULN or less and AST and ALT to 2.5 x ULN or less prior to each dose. If dose is delayed more than 2 days between sequential infusions, omit scheduled dose.

Other

- Patients with leukocyte count $30 \times 10^9/L$ prior to initiation: cytoreduction recommended
- Infusion related reactions
 - Reaction during or within 4 hours after infusion: interrupt infusion and provide supportive care
 - For mild, moderate and severe infusion reaction: consider resuming infusion at one-half or less of the rate at which the reaction occurred once symptoms resolve
 - Severe or life-threatening infusion reaction: permanently discontinue
- Severe or life-threatening nonhematologic toxicity: delay treatment until recovery to no more than mild. If dose is delayed for more than 2 days between sequential infusions, omit scheduled dose.
- Persistent neutropenia in patients receiving combination therapy

- Neutrophil count not recovered to 0.5×10^9 within 14 days following planned start date of consolidation cycle: discontinue Mylotarg treatment; do not administer Mylotarg in consolidation cycles
- Persistent thrombocytopenia in patients receiving combination therapy
 - Platelet count not recovered to 100×10^9 within 14 days following planned start date of consolidation cycle: discontinue Mylotarg treatment; do not administer Mylotarg in consolidation cycles

Conclusion:

Mylotarg is an effective last line therapy for adults and pediatric patients 2 years and older with relapsed or refractory CD33-positive AML and for adult patients with newly diagnosed CD33-positive acute myeloid leukemia (AML) who cannot tolerate other first line chemotherapeutic agents. Lack of sound efficacy studies leads me to not recommend this treatment as first line, but still recommend it as an option for those who have contraindications or tolerability issues to treatments with greater efficacy. Mylotarg has a long list of side effects that make it undesirable as a treatment, but useful if no other treatments seem suitable for the patient. Physicians should help patients weigh the risks and potential benefits with taking this drug before initiating therapy.

Recommended References:

1. Mylotarg [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc. subsidiary of Pfizer Inc; 2017.
2. Mylotarg. In: DRUGDEX® System [Internet Database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed: March 5, 2018.
3. Sievers EL, Larson RA, Stadmauer EA, Estey E, Lowenberg B, Dombret H, et al. Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. *J Clin Oncol.* 2001;19(13): 3244-3254.
4. Roboz GJ, Knovich MA, Bayer RL, Schuster MW, Seiter K, Powell BL, et al. Efficacy and safety of gemtuzumab ozogamicin in patients with poor-prognosis acute myeloid leukemia. *Leukemia & Lymphoma.* 2002; 43(10); 1951-1955.
5. Larson RA, Boogaerts M, Estey E, Karanes C, Stadmauer EA, Sievers EL, et al. Antibody-targeted chemotherapy of older patients with acute myeloid leukemia in first relapse using Mylotarg (gemtuzumab ozogamicin). *Leukemia.* 2002; 16(9):1627-36.

Prepared by: Ashley Pitzer, Doctor of Pharmacy Candidate