# Efficacy and Safety of Gemtuzumab Ozogamicin in Patients With CD33-Positive Acute Myeloid Leukemia in First Relapse

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***Purpose:*** **Three open-label, multicenter trials were conducted to evaluate the efficacy and safety of single-agent Mylotarg (gemtuzumab ozogamicin; CMA-676; Wyeth Laboratories, Philadelphia, PA), an antibody-targeted chemotherapy agent, in patients with CD33-positive acute myeloid leukemia (AML) in untreated first relapse.**

***Patients and Methods:*** **The study population comprised 142 patients with AML in first relapse with no history of an antecedent hematologic disorder and a median age of 61 years. All patients received Mylotarg as a 2-hour intravenous infusion, at a dose of 9 mg/m$^2$, at 2-week intervals for two doses. Patients were evaluated for remission, survival, and treatment-emergent adverse events.**

***Results:*** **Thirty percent of patients treated with Mylotarg obtained remission as characterized by 5% or less blasts in the marrow, recovery of neutrophils to at least 1,500/$\mu$L, and RBC and platelet transfusion independence. Although patients treated with Mylotarg had relatively high incidences of myelosuppression, grade 3 or 4 hyperbilirubinemia (23%), and elevated hepatic transaminase levels (17%), the incidences of grade 3 or 4 mucositis (4%) and infections (28%) were relatively low. There was a low incidence of severe nausea and vomiting (11%) and no treatment-related cardiotoxicity, cerebellar toxicity, or alopecia. Many patients received Mylotarg on an outpatient basis (38% and 41% of patients for the first and second doses, respectively). Among the 142 patients, the median total duration of hospitalization was 24 days; 16% of patients required 7 days of hospitalization or less.**

***Conclusion:*** **Administration of the antibody-targeted chemotherapy agent Mylotarg to patients with CD33-positive AML in first relapse induces complete remissions with what appears to be a favorable safety profile.**

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ACUTE MYELOID leukemia (AML) is the most common type of acute leukemia in adults. It occurs with an annual incidence of 2.4 per 100,000 adults in the United States. The incidence increases with age and is 12.6 per 100,000 for adults age 65 years or older.[1] The median age of the total AML patient population at initial presentation is approximately 62 to 64 years.[2] When patients with newly diagnosed AML are treated with combination chemotherapy, remission rates of 50% to 80% are obtained.[1,3] The median duration of first complete remission (CR1) averages approximately 1 year. Approximately 60% to 80% of patients who achieve CR1 eventually relapse. Even with current treatment regimens, less than 30% of all AML patients survive for 3 years.[4,5]

Patients with relapsed or refractory AML have less chance of obtaining remission than patients with newly diagnosed AML. The goals of reinduction chemotherapy vary from achievement of a long-term complete remission (CR) to providing a bridge to hematopoietic stem-cell transplantation (HSCT), or to temporary prolongation of life and palliation of symptoms. Most regimens in current use cause substantial toxicity. Rates of second CR (CR2) range from less than 10% to greater than 80% depending on the age, duration of CR1, and cytogenetic characteristics of the patients treated.[6-19] Without HSCT, the median duration of CR2 is generally not more than 6 to 8 months, with a long-term disease-free survival rate of approximately 5% to 10%. Survival rates of CR2 patients increase with HSCT. Patients who receive allogeneic HSCT from HLA-matched siblings or unrelated donors have long-term survival rates of

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25% to 40%.[20] Because of donor limitations and substantial morbidity often caused by reinduction efforts, however, only a minority of patients are currently candidates for allogeneic HSCT.

More than 80% of AML patients have myeloid blast cells that express the CD33 surface antigen.[21,22] This antigen also is present on the leukemic stem cells from at least some patients.[23] It is present on normal maturing hematopoietic progenitor cells and absent from normal hematopoietic stem cells. The CD33 antigen is not expressed by nonhematopoietic cells or tissues. On the basis of these properties, antibodies to the CD33 antigen have been explored as possible specific agents for AML, either in their unmodified form or as carriers for antileukemic agents. When iodinated anti-CD33 monoclonal antibody was used, it rapidly accumulated in the marrow of AML patients and internalized into leukemia cells.[24-26] This observation suggested that CD33 might be an appropriate target for an antibody-chemotherapy conjugate.

Calicheamicin, a highly potent antitumor antibiotic that cleaves double-stranded DNA at specific sequences,[27] was conjugated to a humanized anti-CD33 monoclonal antibody to produce Mylotarg (gemtuzumab ozogamicin; CMA-676; Wyeth Laboratories, Philadelphia, PA).[28] Mylotarg was evaluated for its ability to specifically target and kill leukemia cells in three test systems: cultured HL-60 leukemia cells, HL-60 human xenograft tumors, and marrow specimens from AML patients in colony-forming assays. In all cases, killing of leukemia cells was highly specific compared with chemotherapy agents linked to antibodies directed against nonspecific antigens. Thus, Mylotarg was evaluated in a dose-escalation trial with relapsed or refractory CD33-positive AML patients. Leukemic cells were eliminated from the peripheral blood and bone marrow of eight of the 40 patients, and Mylotarg was reasonably well tolerated.[29]

Phase II studies then were initiated to evaluate Mylotarg. The data presented here demonstrate the efficacy and safety of Mylotarg in patients with CD33-positive AML in first relapse.

## PATIENTS AND METHODS

### *Patients*

A total of 142 patients with AML in untreated first relapse participated in three similar studies to evaluate the efficacy and safety of Mylotarg as monotherapy. Each study had an open-label, single-arm design and was conducted at multiple centers. Eligible patients were those with CD33-positive AML in untreated first relapse. Patients were determined to have CD33-positive AML by analysis of bone marrow aspirates and by immunophenotyping.[29] For these studies, patients were considered to have CD33-positive AML if they had greater than 80% of leukemic blast cells with CD33 immunofluorescence staining four times above background staining. In study 1, which was conducted in the United States and Canada, and study 2, which was conducted in Europe, patients were required to be at least 18 years old and to have had a CR1 of at least 6 months' duration. In study 2, previous HSCT was permitted, and five patients with prior HSCT were enrolled. In study 3, patients were required to be at least 60 years old and to have had a CR1 of at least 3 months' duration. Other enrollment criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, no antecedent hematologic disorder that preceded initial presentation with AML, normal renal and liver function, and a peripheral WBC count of less than 30,000/$\mu$L. Patients who developed AML secondary to chemotherapy or exposure to toxins were ineligible for enrollment. On the basis of these criteria, enrollment for studies 1, 2, and 3 comprised 65, 40, and 37 patients, respectively, from May 12, 1997, through April 30, 1999.

Of 199 patients screened for CD33-positive AML, 78% (156 of 199) were eligible. Thus, 43 patients were ineligible: 30 because their CD33-positive leukemic blasts were not at least 80% by flow cytometry, one because the CD33 immunofluorescence staining was not greater than four-fold above background, six because they were not in relapse, five because they were misdiagnosed, and one because the bone marrow aspirate was inadequate. Fourteen of the eligible patients were not enrolled for various reasons, so the total enrollment for these studies was 142 patients.

Cytogenetic analyses were performed on 97 patients (68%) at first relapse. Three risk groups were defined as follows[30,31]: the favorable-risk group included patients with t(8;21), t(15;17), t(16;16), inv(16), or +14 chromosomal abnormalities; the poor-risk group included patients with t(9;22), −5/5q−, −7/7q−, inv(3q), i(17q), del(20q), +13, 11q abn, or 17p abn chromosome abnormalities or complex karyotypes; the intermediate-risk group included patients with normal cytogenetics or all other chromosome abnormalities; and the unknown-risk group included patients for whom cytogenetic analysis was not performed or for whom cytogenetic analysis was inconclusive.

Data collected from these studies were pooled so that increased numbers of patients could be analyzed. Pooling of the data was supported by similarities in diagnosis and treatment among the three studies; all the patients had CD33-positive AML in first relapse and received the same dose and schedule of Mylotarg. All patients signed informed consent. The protocols were approved and monitored by institutional review boards, and they were performed in a manner consistent with the Declaration of Helsinki and Good Clinical Practice guidelines.

### *Mylotarg Dosage*

On the basis of results obtained in the phase I dose-escalation trial,[29] patients received Mylotarg monotherapy as a 2-hour intravenous (IV) infusion at a dose of 9 mg/m$^2$ for up to three doses with at least 14 days, but no more than 28 days, between doses. This dose level was selected for the phase II studies because more than 75% of CD33 sites consistently were saturated at this dose, and hematologic toxicity at this dose was clinically considered dose limiting in the phase I study. Before patients received Mylotarg, they were required to have peripheral WBC counts less than 30,000/$\mu$L; hydroxyurea treatment was allowed to reduce peripheral WBC counts to that level. Patients routinely were premedicated with acetaminophen and antihistamines. Patients were eligible to receive the second dose of Mylotarg if they had recovered from reversible nonhematologic toxicities caused by the previous dose and had no evidence of uncontrolled infection,

disease progression, or detectable formation of antibodies reactive with the drug.

Patients who received two doses of Mylotarg without obtaining remission could receive a third dose of the drug under certain circumstances. Specifically, to receive a third dose, patients had to (1) meet all the criteria required for the second dose, (2) have had a greater than 50% decrease in percentage of bone marrow blasts from the screening bone marrow aspirate, and (3) have demonstrated more than 15% cellularity in a bone marrow biopsy performed after the second dose.

The outcome of patients was evaluated for the treatment period, which was defined as the time administration of the drug began until 28 days after completion of the Mylotarg therapy, and for the follow-up period, which was defined as the time subsequent to the treatment period until the date of data cutoff on July 28, 1999. After Mylotarg therapy, patients were treated with the form of therapy thought most appropriate by their treating physician.

### *Efficacy Assessments*

The primary efficacy end point in these studies was the rate of CR. A patient was required to meet the following criteria to be classified as having CR: (1) leukemic blasts absent from peripheral blood; (2) percentage of blasts in the bone marrow 5% or less as measured by morphologic studies, either bone marrow aspirate or biopsy; (3) peripheral-blood counts with hemoglobin level of 9 g/dL or greater; absolute neutrophil count (ANC) of 1,500/$\mu$L or higher, and platelet count of 100,000/$\mu$L or higher; and (4) RBC transfusion independence for 2 weeks and platelet transfusion independence for at least 1 week. Bone marrow slides were evaluated centrally by an experienced reviewer (J.M.B.) who was blinded to treatment outcome.

In a phase I trial with Mylotarg,[29] some patients met all the criteria for CR with the exception of full recovery of platelet counts before additional therapy was received. These patients were identified as having remission with incomplete platelet recovery ($CR_p$); $CR_p$ was defined in the same way as CR, except that platelet count was not specified although platelet transfusion independence for at least 1 week was required. The rate of $CR_p$ was included as a secondary efficacy end point in these phase II studies. The overall remission (OR) rate was the sum of the CR and $CR_p$ rates.

Patients were considered to have no remission (NR) if they did not meet all the criteria for CR or $CR_p$. The NR category included patients who had leukemic blasts in the peripheral blood or whose percentage of blasts in the bone marrow was more than 5%. Patients with NR also included those who met the bone marrow criteria for remission but did not meet the criteria for peripheral count recovery or were not transfusion independent.

Although remission rate is an important measurement to evaluate short-term efficacy, survival assessments are necessary to provide an evaluation of the durability of the response. Thus, relapse-free survival, landmark survival, and overall survival also were evaluated. Relapse-free survival was measured from the date of first documentation of CR or $CR_p$ to the date of documentation of relapse, death, or data cutoff. Landmark survival was measured from the end of the treatment period until the date of death or data cutoff. Landmark survival analysis was performed so that patients who died during the study treatment period or who received only one dose of Mylotarg were not included in the analysis, as these patients never had the opportunity to be considered remission patients. Overall survival was measured from the date of administration of the first dose of Mylotarg until the date of death or data cutoff. Survival data were evaluated by use of Kaplan-Meier estimates.

### *Analysis of Variables for Factors Predictive of Response to Mylotarg*

An exploratory analysis of potential prognostic factors was performed with data from the 142 patients. Twenty-seven variables were examined, including demographics (age, sex, location of study [United States/Canada *v* Europe], body-surface area, ECOG performance status, and duration of CR1), treatment history (two courses of induction therapy to obtain CR1, previous treatment with high-dose cytarabine, and hydroxyurea treatment within 14 days of the first Mylotarg dose), and baseline laboratory data (hemoglobin level, ANC, WBC counts, platelet counts, bone marrow aspirate blast counts, bone marrow biopsy blast counts, peripheral-blood blast counts, expression of CD7, CD11, CD13, CD19, CD34, and CD56, quantitative expression of CD33, percentage of cells below the CD33 expression cutoff, multidrug resistance efflux, French-American-British classification, and cytogenetics). Logistic regression analysis was used for evaluation of response (OR *v* NR), and proportional hazards regression analysis was used for evaluation of landmark survival to obtain Wald $\chi^2$ *P* values. A univariate analysis was performed first, then all the results significant at the .15 level were placed into a multivariate model. Some patients were not included in the analyses because of missing data for various variables.

### *Treatment-Emergent Adverse Events*

Treatment-emergent adverse events (TEAEs) were events not present at baseline or those present at baseline that worsened during treatment. The severity of the TEAEs was evaluated by use of the National Cancer Institute common toxicity criteria (NCI-CTC) version 1. Events with a severity of grade 1 or 2 were considered mild or moderate and easily manageable. Grade 3 or 4 events were considered severe or life threatening.

### *Analysis for Antibodies Directed Against Components of Mylotarg*

Mylotarg contains three components: humanized monoclonal antibody hP67.6 against the CD33 antigen, a derivative of calicheamicin, and a linker that connects the antibody and the calicheamicin derivative. Patients potentially could produce antibodies against hP67.6 and the calicheamicin-linker portions of Mylotarg and were screened for these. Blood samples were obtained from patients before Mylotarg administration and on days 8 and 22 after each dose. Serum was analyzed for anti-hP67.6 and anticalicheamicin-linker antibodies by use of enzyme-linked immunosorbent assays (ELISAs). A postdose sample was considered positive for antibodies to hP67.6 or the calicheamicin linker if the optical density value in the ELISA was greater than or equal to 10 times the value in the ELISA of the predose sample.

## RESULTS

### *Patient Characteristics*

A total of 142 patients with AML in untreated first relapse were enrolled onto these phase II studies. Patient characteristics are listed in Table 1. The median age of the patients was 61 years (range, 22 to 84 years). The median duration of CR1 before Mylotarg treatment was 11.1 months (range, 3 to 117 months).

**Table 1. Patient Characteristics**

| Characteristic | Patients (N = 142) No. | % |
|---|---|---|
| Age, years | | |
| Median | 61 | |
| Range | 22-84 | |
| Sex | | |
| Women | 58 | 41 |
| Men | 84 | 59 |
| Ethnic origin | | |
| White | 133 | 94 |
| Black | 4 | 3 |
| Asian | 2 | 1 |
| Other | 3 | 2 |
| Duration of CR1, months | | |
| Median | 11.1 | |
| Range | 3-117 | |
| Postremission therapy for CR1 | | |
| Yes | 133 | 94 |
| No | 9 | 6 |
| Cytogenetics at relapse | | |
| Known | 97 | |
| Favorable-risk group | 5 | 5 |
| Intermediate-risk group | 54 | 56 |
| Poor-risk group | 38 | 39 |
| Unknown | 45 | |

Most of the patients in these trials had been treated aggressively after initial induction to prevent AML recurrence. One hundred thirty-three of the patients (94%) had received postremission therapy during CR1 (Table 1); 70% of the patients previously had received regimens that contained high-dose cytarabine (cytarabine at 3 g/m$^2$/dose for patients younger than 60 years and cytarabine at 1 g/m$^2$/dose for patients 60 years of age or older). The number of cycles of postremission chemotherapy varied from zero to 11 (median, two cycles). At the time of relapse, 97 patients had undergone cytogenetic evaluation; 5% of these patients were in the favorable-risk category, and 39% were in the poor-risk group.

*Treatment Response*

A total of 142 patients received the first dose of Mylotarg, 109 patients received the recommended two doses, and five patients received three doses. The primary reasons 28 patients did not receive two doses of Mylotarg were disease progression and infection. The overall rate of remission for the 142 patients treated with Mylotarg was 30% (Table 2). Twenty-three patients (16%) treated with Mylotarg obtained CR, and 19 (13%) obtained $CR_p$ to produce the OR rate of 30%. The median time to remission, that is, the time to meet all criteria for CR or $CR_p$, was 60 days for patients with CR as well as for those with $CR_p$ (95% confidence interval [CI], 50 to 69 days for CR patients and 51 to 84 days for $CR_p$ patients). Among all 142 patients, 46% of patients (65 of 142) had no more than 5% blasts in the bone marrow after one dose of Mylotarg based on analysis of bone marrow aspirates.

**Table 2. Patients by Remission Categories After Treatment With Mylotarg**

| Type of Remission | No. of Patients (N = 142) | % | 95% CI |
|---|---|---|---|
| CR | 23 | 16 | 11-23 |
| $CR_p$ | 19 | 13 | 8-20 |
| OR* | 42 | 30 | 22-38 |

*OR = CR + $CR_p$.

*Characteristics of Patients With CR and CR With Incomplete Platelet Recovery*

Patients with CR or $CR_p$ had a similar median age (60 years for CR patients and 59 years for $CR_p$ patients) and a similar median duration of first remission (12.6 months for CR patients and 11.1 months for $CR_p$ patients).

The difference between patients with CR and $CR_p$ is that the $CR_p$ patients did not recover peripheral platelet levels to 100,000/$\mu$L. The median time to recovery of all levels of platelet counts was longer for the $CR_p$ patients than for the CR patients. The median time to recovery of 25,000 platelets/$\mu$L was 34 days from the first dose of Mylotarg for CR patients and 51 days for $CR_p$ patients (Fig 1). Similarly, the median time to recovery of 50,000 platelets/$\mu$L was 38 days for CR patients and 66 days for $CR_p$ patients. The 23

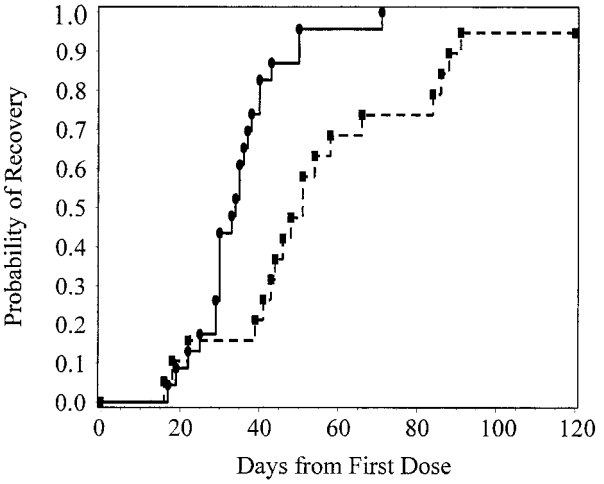


**Fig 1. Kaplan-Meier plot of time to recovery of platelet counts to 25,000/$\mu$L for patients with CR (●) and $CR_p$ (■) (log-rank test; $P = .0002$). There were 23 CR patients (median, 34 days) and 19 $CR_p$ patients (median, 51 days).**

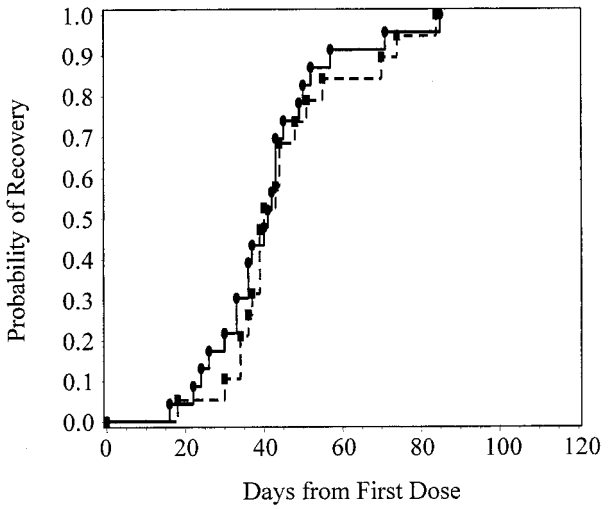


**Fig 2. Kaplan-Meier plot of time to recovery of ANCs to 500/$\mu$L for patients with CR (●) and $CR_p$ (■) (log-rank test; $P = .696$). There were 23 CR patients (median, 41 days) and 19 $CR_p$ patients (median, 40 days).**

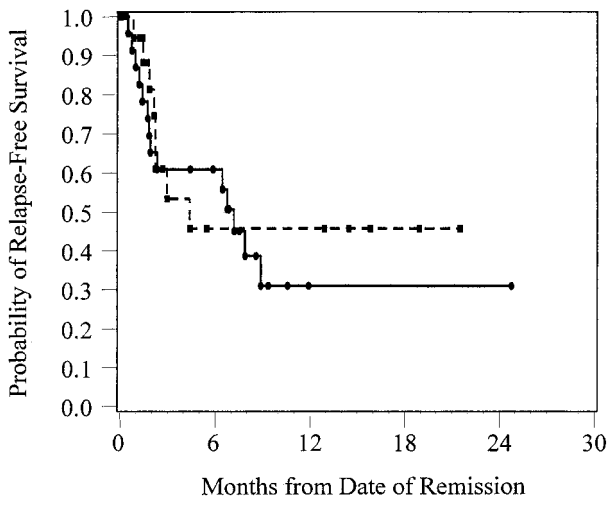


**Fig 3. Relapse-free survival for patients with CR (●) and $CR_p$ (■) (log-rank test; $P = .624$). There were 23 CR patients (median, 7.2 months) and 19 $CR_p$ patients (median, 4.4 months).**

CR patients had recovery of 100,000 platelets/$\mu$L in a median time of 50 days.

Although the median time to recovery of peripheral platelet concentrations was longer for $CR_p$ patients than for CR patients, the median times to recovery of ANC were similar. The median time to ANC recovery of 500/$\mu$L was 41 days from the first dose of Mylotarg for CR patients and 40 days for $CR_p$ patients (Fig 2). The definition of both CR and $CR_p$ requires an ANC of at least 1,500/$\mu$L. The median times to ANC recovery of 1,500/$\mu$L for CR and $CR_p$ patients were 45 days and 54 days, respectively. Patients who received the second dose of Mylotarg 14 to 17 days after the first dose had a shorter duration of neutropenia than those who received the second dose 18 days or longer after the first dose.

During the treatment period, platelet and RBC transfusions were given. For patients who received transfusions, the number of platelet and RBC transfusions—but not the specific number of units—were reported. The median number of platelet transfusions for the 23 patients with CR was four (95% CI, three to seven). The median number of platelet transfusions for the 19 patients with $CR_p$ was 12 (95% CI, nine to 19). This difference was statistically significant ($P = .0008$, Wilcoxon rank sum test). The median number of platelet transfusions during the treatment period for the 100 NR patients was 13 (95% CI, 11 to 15). The median number of RBC transfusions was two (95% CI, two to four) for the CR patients and five (95% CI, four to eight) for the $CR_p$ patients ($P = .0018$, Wilcoxon rank sum test). The median number of RBC transfusions for the 100 NR patients was five (95% CI, five to six).

*Survival Characteristics of Patients Treated With Mylotarg*

Relapse-free survival for patients who obtained CR or $CR_p$ is shown in Fig 3. The curves for the CR and $CR_p$ patient groups are similar, and the differences between the CR and $CR_p$ groups were not statistically significant (log-rank test; $P = .624$). The median relapse-free survival times were 7.2 months for the CR patients, 4.4 months for the $CR_p$ patients, and 6.8 months for the combined populations.

Landmark survival beginning after the treatment period also was evaluated. Landmark survival analysis produced similar curves for the CR and $CR_p$ patients, although the curve for the NR patients was quite different (Fig 4). The median landmark survival times were 12.6 months for the CR patients, at least 11.1 months for the $CR_p$ patients, and 2.9 months for the NR patients. Clearly, patients who were treated with Mylotarg and obtained remission survived longer than those who were treated with Mylotarg and did not obtain remission. For the 142 patients, the median overall survival was 5.9 months (Kaplan-Meier analysis not shown). The probability of survival at 1 year was 31%.

*Therapy After Mylotarg Treatment*

As postremission therapy, patients in the OR group received HSCT, chemotherapy, or no additional therapy as deemed appropriate by their physicians. Fifteen OR patients received HSCT (two first received chemotherapy), four OR patients received chemotherapy alone, and 23 OR patients received no further therapy. In addition, 12 NR patients received HSCT (three first received chemotherapy), 42 NR

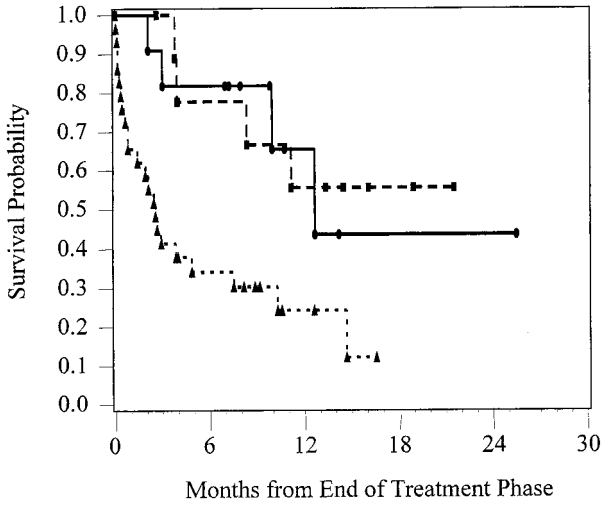


Fig 4. Landmark survival for patients with CR (●), $CR_p$ (■), and NR (▲). There were 23 CR patients (median, 12.6 months), 19 $CR_p$ patients (median, > 11.1 months), and 63 NR patients (median, 2.9 months).

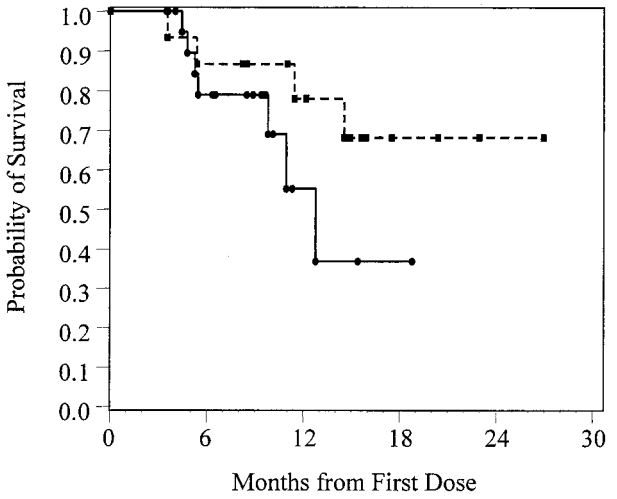


Fig 6. Overall survival for OR patients who received HSCT(■) and for OR patients who received no further therapy (●) as postremission therapy. Fifteen OR patients received HSCT (median, > 14.5 months), and 23 OR patients received no further therapy (median, 12.8 months).

patients received chemotherapy alone, and 46 NR patients received no further therapy after Mylotarg therapy.

Relapse-free survival for the OR patients who received HSCT and the OR patients who received no further therapy is shown in Fig 5. The median relapse-free survival times were at least 8.9 months for the OR patients who received HSCT and 2.1 months for the OR patients who received no further therapy. Overall survival times for these patients are shown in Fig 6. The median overall survival times for the OR patients who received HSCT and those who received no further therapy were at least 14.5 months and 12.8 months, respectively. Overall survival times for the NR patients who received HSCT and the NR patients who received no further therapy are shown in Fig 7. The median overall survival times for the NR patients who received HSCT and the NR patients who received no further therapy were 4.2 months and 2.5 months, respectively. Thus, patients who received

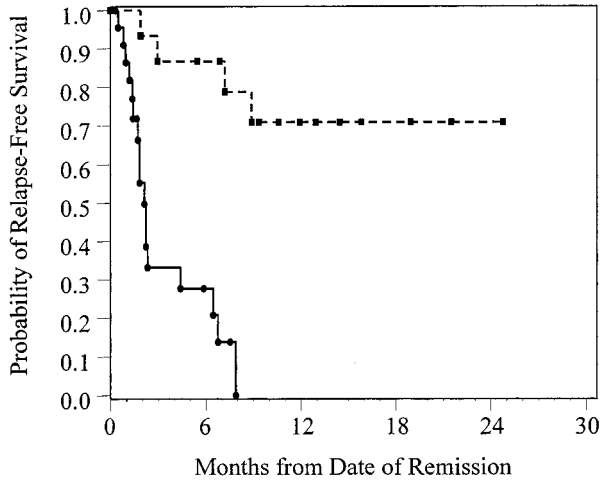


Fig 5. Relapse-free survival for OR patients who received HSCT (■) and for OR patients who received no further therapy (●) as postremission therapy. Fifteen OR patients received HSCT (median, > 8.9 months), and 23 OR patients received no further therapy (median, 2.1 months).

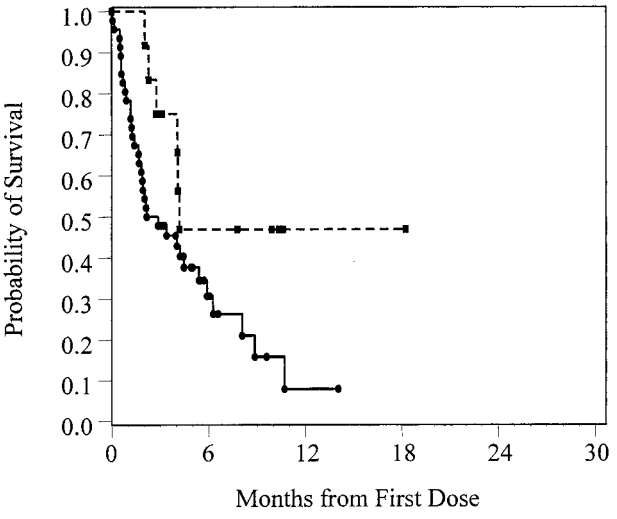


Fig 7. Overall survival for NR patients who received HSCT (■) and NR patients who received no further therapy (●) after Mylotarg treatment. Twelve NR patients received HSCT (median, 4.2 months), and 46 NR patients received no further therapy (median, 2.5 months).

HSCT after Mylotarg treatment survived longer than those who received no further treatment.

The median overall survival time for the four OR patients who received chemotherapy alone was at least 4.7 months. The median overall survival time for the 42 NR patients who received chemotherapy alone was 4.0 months.

Overall survival of the eight CR and seven $CR_p$ patients who received HSCT in postremission also was analyzed. Kaplan-Meier analysis indicated that the differences between the CR and $CR_p$ patient groups were not statistically significant (log-rank test; $P = .271$; data not shown). The median overall survival times were 14.5 months for the CR patients, at least 5.4 months for the $CR_p$ patients, and at least 14.5 months for the combined populations.

Equal numbers of CR patients (four) received allogeneic and autologous HSCT, six $CR_p$ patients received allogeneic HSCT, and one received autologous HSCT. For NR patients, 10 and two received allogeneic and autologous HSCT, respectively. These patients were evaluated for survival at 100 days. Three of the four CR patients who had allogeneic HSCT survived for 100 days. All six of the $CR_p$ patients who had allogeneic HSCT survived for 100 days. At the time of data cutoff, 100-day survival data were available for nine NR patients; three survived for 100 days. All patients who had autologous HSCT survived for 100 days.

### *Effect of Pretreatment Factors on Mylotarg Treatment Outcome*

Mylotarg was equally active in patients with both a short duration ($< 1$ year) and a long duration ($\geq 1$ year) of CR1. For those patients with a CR1 of less than 1 year (n = 80), the OR rate after Mylotarg treatment was 28%. For those patients with a CR1 of at least 1 year (n = 62), the OR rate after Mylotarg treatment was 32%. The median overall survival for patients with a CR1 of less than 1 year was 4.7 months; the median overall survival for patients with a CR1 of at least 1 year was 11.7 months as determined from Kaplan-Meier estimates (data not shown).

Response rates to Mylotarg were similar in younger and older patients. The OR rate for patients younger than 60 years (n = 62) was 34%. The OR rate for patients 60 years of age or older (n = 80) was 26%. The median overall survival for patients younger than 60 years and those 60 years of age or older was 5.9 months (Kaplan-Meier analysis not shown). Patients with AML with favorable-, intermediate-, and poor-risk cytogenetics at first relapse had similar response rates (Table 3).

In an exploratory multivariate analysis, 27 variables (derived from demographics, treatment history, or baseline laboratory data) were examined to determine their potential as prognostic factors for the treatment outcome of patients. Although preliminary, this analysis suggested that a greater likelihood of achieving OR consistently was associated with higher values of baseline hemoglobin, lower levels of peripheral-blood blast cell counts, no expression of the CD13 marker, and lower values of baseline multidrug resistance efflux[29] (Table 4). Multivariate analysis also suggested that there might be a relationship among patient survival and favorable ECOG performance status, longer duration of CR1, lower values of peripheral-blood blast cell counts, and no CD34 expression. The other variables examined, including increased CD33 expression, were not related to response category or patient survival ($P > .05$). Sufficient data were not available to include all patients in the multivariate analysis; therefore, these results are considered preliminary.

**Table 3. Remission Response of Patients After Treatment With Mylotarg Based on Cytogenetic Risk at First Relapse**

| | | OR Patients | | NR Patients | |
|---|---|---|---|---|---|
| Risk Group | No. | No. | % | No. | % |
| Favorable | 5 | 2 | 40 | 3 | 60 |
| Intermediate | 54 | 19 | 35 | 35 | 65 |
| Poor | 38 | 12 | 32 | 26 | 68 |
| Unknown | 45 | 9 | 20 | 36 | 80 |

### *TEAEs After Mylotarg Treatment*

TEAEs were classified as infusion-related events, that is, those that occurred on the day of Mylotarg administration, and as events that occurred during the remainder of the treatment period. Hematologic adverse events are described separately because they were observed in virtually all

**Table 4. Results of Multivariate Exploratory Analysis for Prognostic Factors**

| Analysis | Prognostic Variable | Relationship to Outcome | Wald $\chi^2$ $P$* |
|---|---|---|---|
| OR *v* NR, n = 111 | | | |
| | Hemoglobin level at baseline | + | .018 |
| | Peripheral-blood blast cell counts | − | .022 |
| | CD13 expression | − | .001 |
| | MDR efflux level at baseline | − | .001 |
| Landmark survival, n = 93 | | | |
| | ECOG performance status | + | .010 |
| | Duration of CR1 | + | .010 |
| | Peripheral-blood blast cell counts | − | .001 |
| | CD34 expression | − | .003 |

Abbreviation: MDR, multidrug resistance.

*Only $P$ values $< .05$ are given.

patients and were related to the pharmacologic goal of Mylotarg therapy.

Grade 3 or 4 infusion-related TEAEs reported with an incidence of at least 4% were chills (11%), fever (7%), and hypotension (4%). The postinfusion symptom complex (fever, chills, and, less commonly, hypotension and dyspnea) was similar to that observed with other antibody-based therapies[32] and occurred despite prophylactic treatment with acetaminophen and antihistamines. Grade 3 or 4 hypotension occurred several hours after the end of the infusion period but was transient and reversible with IV fluid support.

The incidence of postinfusion symptoms was significantly lower after the second dose of Mylotarg than after the first dose. Although 34% of patients had grade 3 or 4 events after the first dose, only 12% of patients experienced such events after the second dose ($P < .001$; two-sided Fisher's exact test). No episodes of grade 3 or 4 hypotension were observed after the second dose of Mylotarg.

Severe (grade 3 or 4) TEAEs that occurred with an incidence of at least 5% during the treatment period included sepsis (16%), fever (15%), chills (13%), nausea and vomiting (11%), dyspnea (9%), hypertension (9%), hypotension (8%), pneumonia (7%), and asthenia (7%). Treatment-related cardiotoxicity, cerebellar toxicity, or alopecia were not observed.

Myelosuppression is an expected complication of both conventional chemotherapy and antibody-targeted chemotherapy with Mylotarg. Although pluripotent hematopoietic stem cells are CD33-negative, more differentiated progenitor cells express CD33 and are therefore targeted by Mylotarg, which results in myelosuppression. Nearly all patients had grade 3 or 4 neutropenia (97%) and thrombocytopenia (99%). Fifteen percent of patients experienced grade 3 or 4 bleeding, which included epistaxis (3%) and intracranial hemorrhage (4%).

Mucositis-related adverse events included stomatitis, oral ulcers, or mouth pain. During the treatment period, 50 patients had mucositis-related adverse events. However, only five (4%) of 142 patients experienced severe mucositis (grade 3 or 4 stomatitis) during this period.

During the treatment period, 40 (28%) of 142 patients had grade 3 or 4 infections of any type. The most frequent grade 3 or 4 infection-related TEAEs were sepsis (16%) and pneumonia (7%).

Twenty-three percent of patients (33 of 142) had grade 3 or 4 hyperbilirubinemia (grade 3 is 1.5 to three times above the upper limit of the normal range for version 1 of the NCI-CTC). Only one patient had a bilirubin elevation more than 10 times the upper limit of the normal range (grade 4 hyperbilirubinemia, NCI-CTC version 2). The median time to onset of grade 3 or 4 hyperbilirubinemia was 8 days, and the median duration was 20 days. A total of 17% of patients (24 of 142) had grade 3 or 4 increases in AST or ALT levels (grade 3 is five to 20 times the upper limit of the normal range for both versions 1 and 2 of the NCI-CTC). The median time to onset of these AST or ALT increases was 8 days, and the median duration was 20 days. Abnormalities of liver function generally were transient and reversible.

Several patients exhibited more serious hepatic abnormalities. One patient died with liver failure in the setting of tumor lysis syndrome and multisystem organ failure 22 days after treatment. Another patient died after an episode of persistent ascites and hepatosplenomegaly 156 days after treatment.

Some patients received HSCT either before or after Mylotarg treatment. The five patients who received HSCT before Mylotarg treatment had no notable events. Among 27 patients who received HSCT after Mylotarg treatment, three (two with NR and one with CR) died of hepatic veno-occlusive disease 22 to 37 days after transplantation.

*Deaths After Mylotarg Treatment*

A total of 19 (13%) of the 142 patients died during the treatment period. The causes of death included progression of disease (n = 8), multiorgan failure (n = 4), CNS hemorrhage (n = 5), and sepsis (n = 2). The median time to death was 21 days for these 19 patients.

*Hospitalizations of Patients Treated With Mylotarg*

These studies allowed patients to receive Mylotarg on an outpatient basis. However, many patients already were hospitalized for complications of recurrent leukemia. For the first and second doses of Mylotarg, 38% (54 of 142 patients) and 41% (47 of 114 patients), respectively, received Mylotarg therapy as outpatients; 24% (34 of 142 patients) received both doses as outpatients. Treatment of patients with AML in first relapse typically requires intensive supportive care. This includes lengthy hospitalizations for chemotherapy administration and treatment of therapy-related complications, which include infections, bleeding, and nonhematologic toxicities. Among the 142 patients, the median duration of hospitalization during the treatment period was 24 days (range, 0 to 133 days). The median total duration of hospitalization for CR patients was 18 days (range, 0 to 50 days), and for $CR_p$ patients it was 13 days (range, 0 to 71 days). For patients with NR, the median total duration of hospitalization was 27 days (range, 0 to 133 days).

Several patients had only a short total duration of hospitalization. There were 16% (23 of 142 patients) with 7 or fewer days of hospitalization during the treatment

period of these studies, including 4% (five of 142 patients) with no hospitalization.

*Immunogenicity of Mylotarg in Treated Patients*

According to the criteria of our assay, none of the 142 patients had antibody responses detected to the hP67.6 monoclonal antibody or the calicheamicin linker on day 8 or day 22 after each dose. In addition, four patients in these phase II clinical trials later received a second course of Mylotarg therapy and did not develop positive antibody responses to the components of the drug.

## DISCUSSION

The results of the previous phase I clinical trial data demonstrated that the elimination of CD33-expressing cells with antibody-targeted chemotherapy can lead to remissions in patients with AML.[29] Those results have now been extended with phase II data that demonstrate the clinical utility of an antibody-targeted cytotoxic chemotherapy agent in the treatment of patients with relapsed AML. Mylotarg monotherapy of 142 patients with CD33-positive AML in first relapse was associated with a 30% OR rate and with apparent safety advantages compared with other therapies used to treat patients with AML. Two prognostic factors for patients with AML in first relapse, age and duration of CR1,[7-10,12,13] had relatively little effect on response rates to Mylotarg.

The 30% OR rate reflects a combination of patients with CR and those with $CR_p$. The $CR_p$ category of remission was designed prospectively to evaluate patients in second remission who had platelet recovery to less than 100,000/$\mu$L before the administration of other therapy after remission. In every other way, $CR_p$ patients met the criteria for CR and had a similar overall outcome. Severe neutropenia and particularly thrombocytopenia were expected, because CD33 is expressed by hematopoietic precursor cells such as colony-forming unit–granulocytic-erythrocytic-monocytic-megakaryocytic cells,[21] and persistent thrombocytopenia was observed in several patients in the phase I study.[29] Within these studies, it seems that $CR_p$ patients were clinically comparable to CR patients, as relapse-free survival, landmark survival, rate of HSCT, and overall survival after HSCT were similar between these two groups. However, failure to recover platelets in time could delay or prevent administration of subsequent chemotherapy to $CR_p$ patients who are not transplantation candidates. Longer follow-up of these groups of patients and studies of Mylotarg in other clinical situations are needed to draw definitive conclusions regarding the comparability of CR and $CR_p$ patients.

The results of the exploratory multivariate analysis must be considered preliminary, because not all patients could be included. Nevertheless, they indicated that a potential relationship of several variables to a positive response, which includes lower values of baseline multidrug resistance efflux,[29] should be explored further in future studies. These results do not support a relationship between increased CD33 expression and response or survival, which indicates that patients entered onto these studies apparently had levels of CD33 that were above the threshold required for response.

Patients with short first remission durations and those with AML that arose from myelodysplastic syndrome or secondary to previous treatment with chemotherapy were excluded from these trials. These patient populations have a dismal outcome with conventional agents, and it is not yet known whether Mylotarg monotherapy will be efficacious. To address this issue, patients currently are being enrolled onto a prospective trial to evaluate the use of Mylotarg in patients with untreated high-risk myelodysplastic syndrome.

The data presented here demonstrate that Mylotarg has a different toxicity profile than other effective treatments for patients with AML in first relapse. The infusion-related complex was similar to that observed with other antibody treatments.[32] The occurrence of hypotension several hours after administration of Mylotarg in 4% of patients means that an observation period is required to prevent the occurrence of symptomatic hypotension away from clinical supervision. Elevations of hepatic enzymes and bilirubin occurred with moderate frequency, and evidence of more serious hepatic damage was observed in several patients. Mylotarg was associated with grade 4 neutropenia and thrombocytopenia in virtually all patients, as would be expected with a drug targeted to CD33-expressing cells. The incidence of severe mucositis was relatively low (4%) compared with most other studies, in which severe mucositis was reported in 5% to 34% of relapsed and refractory AML patients treated by conventional chemotherapy.[13,15-18] Although severe infections occurred in 28% of patients, this also is relatively low compared with other studies that reported incidences of 45% to 65% for relapsed and refractory patients.[13,16-18] Alopecia was not observed, which is consistent with the targeted nature of the treatment. Although there is the suggestion that Mylotarg might be associated with less serious toxicity than reported with the use of conventional chemotherapy, no prospective randomized trials have been performed to confirm these findings.

It is important that Mylotarg was not associated with treatment-related cardiac or cerebellar toxicity, which suggests that this therapy may be useful in patients for whom these side effects of anthracyclines or cytarabine have

been limiting. Thus, Mylotarg also may be useful in combination therapy with other antileukemic agents as, to a large extent, nonhematologic toxicities are different. Studies of Mylotarg in combination with anthracycline and cytarabine are underway.

Although patients with relapsed AML often are hospitalized for the treatment of complications of AML before the start of therapy, the first and second doses of Mylotarg were given as outpatient therapy to approximately one third of the patients enrolled onto these studies. Thus, patients do not need to be hospitalized for a week of continuous IV therapy, as is the case with standard anthracycline and cytarabine regimens. The outpatient nature of the treatment, combined with a relatively low rate of severe infections, led to a median total duration of hospitalization of 24 days. Sixteen percent of patients were hospitalized for 7 or fewer days during the treatment period. These data suggest that treatment with Mylotarg may be associated with fewer days of hospitalization than other treatment regimens for patients with relapsed AML, but confirmation from a randomized trial would be more definitive.

Because older patients with recurrent AML experience the deleterious effects of conventional chemotherapy at a high rate, Mylotarg monotherapy was approved by the Food and Drug Administration on May 17, 2000, to provide a new treatment option for patients with CD33-positive AML in first relapse who are 60 years of age or older and who are not candidates for other cytotoxic chemotherapy. Given that younger patients are more likely to tolerate conventional therapy and achieve remission, studies that use Mylotarg in combination with cytarabine with and without anthracycline are currently underway in this patient population.

Since monoclonal antibodies were developed in 1975,[33] many attempts have been made to produce an antibody-targeted chemotherapy. Humanization of mouse monoclonal antibodies was a critical step in the development, and Mylotarg uses a humanized anti-CD33 antibody. Although humanization reduces the likelihood of antibody production to the antibody portion of the molecule, some of the agents conjugated to antibodies, such as the toxins,[34] were found to be immunogenic themselves. Antibody responses to the calicheamicin-linker component of Mylotarg were detected in two patients during the phase I study,[29] but none of the phase II study patients had antibody responses detectable by our assay criteria. For antibody-targeted chemotherapy to be successful, a highly potent agent must be conjugated to the antibody, and calicheamicin seems to meet this requirement. The target antigen needs to internalize on antibody binding, as occurs with CD33. Finally, the linker technology must keep the antibody and cytotoxic agent together in the serum yet allow cleavage and release once internalized inside the target cells. The same antibody-targeting technology used to produce Mylotarg has the potential to produce treatments for other malignancies by use of different antibodies, and exploration of other antibody-targeted chemotherapy agents continues in the laboratory.

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## APPENDIX

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