

Protocol CLO212. A Phase II, Open-Label Study of Clofarabine in Pediatric Patients with Refractory or Relapsed Acute Lymphoblastic Leukemia

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NAME OF SPONSOR/COMPANY:

Genzyme Corporation, 500 Kendall Street, Cambridge, Massachusetts 02142

INVESTIGATORS AND STUDY CENTER(S)

This was a multicenter study conducted at 16 sites in the United States.

STUDIED PERIOD

Date first patient dosed: 13 June 2002
Date last dose administered: 24 September 2004

PHASE OF DEVELOPMENT

Phase II

OBJECTIVES

The primary objective of this study was to determine the overall remission (OR) rate in pediatric patients with refractory or relapsed acute lymphoblastic leukemia (ALL) treated with clofarabine. Secondary objectives included documenting the rate of complete remission (CR), complete remission in the absence of total platelet recovery (CRp), and partial remission (PR); duration of remission and overall survival (OS); safety profile and tolerability of clofarabine for this population and dosing regimen; and the pharmacokinetic profile and intracellular pharmacology and metabolism of clofarabine in selected patients.

METHODOLOGY

This was a Phase II study of clofarabine administered as a single agent to pediatric patients with refractory or relapsed ALL. Patients could receive up to 12 cycles of treatment with clofarabine. Patients were assessed for disease response by analysis of their bone marrow aspirate/biopsy. An Independent Response Review Panel (IRRP) confirmed the response for each patient. Safety was evaluated from reported adverse events (AEs) and laboratory toxicities among all patients who received at least 1 dose of clofarabine.

NUMBER OF PATIENTS (PLANNED AND ANALYZED)

The study was designed to enroll 60 patients. In total, 62 patients were enrolled, but 1 of those patients never received study drug. Therefore, 61 patients were analyzed for safety and efficacy.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Patients who met all of the following inclusion criteria were eligible to participate in the study: diagnosis of ALL with $\geq 25\%$ blasts in the bone marrow; 21 years old or younger at the time of initial diagnosis; not eligible for therapy of higher curative potential, in second or subsequent relapse and/or refractory; a Karnofsky Performance Status (KPS) ≥ 70 ; signed or had their parent or guardian sign an informed consent; able to comply with study procedures and follow-up examinations; adequate organ function within 2 weeks before registration into the study including kidney and liver function.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION

Patients received clofarabine 52 mg/m²/day by intravenous (IV) infusion over 2 hours for 5 consecutive days.

DURATION OF TREATMENT

Treatment cycles with clofarabine could be repeated every 2 – 6 weeks for up to 12 cycles dependent on recurrence of leukemia or recovery of normal hematopoiesis (absolute neutrophil count [ANC] $\geq 0.75 \times 10^9/L$).

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION

No reference therapy was used in this open-label study.

CRITERIA FOR EVALUATION

Criteria for Evaluation – Efficacy

Primary Endpoint:

Overall response rate, which was determined by the sum of the number of patients determined to be either CR or CRp divided by the total number of eligible patients.

Secondary Endpoints:

- Determining the rate of CR, CRp, and PR in the study population
- Duration of remission and overall survival
- Safety profile of clofarabine for this population
- Pharmacokinetic profile of clofarabine in selected patients

Complete Remission (CR). To qualify for CR, patients had to meet each of the following criteria: No evidence of circulating blasts or extramedullary disease; an M1 bone marrow ($\leq 5\%$ blasts); and recovery of peripheral counts (platelets $\geq 100 \times 10^9/L$ and ANC $\geq 1.0 \times 10^9/L$).

Complete Remission in the Absence of Total Platelet Recovery (CRp). To qualify for a CRp, patients had to meet all of the criteria for a CR with the exception of platelet recovery to $\geq 100 \times 10^9/L$.

Partial Remission (PR). To qualify for a PR, patients had to meet all of the following criteria: Complete disappearance of circulating blasts; an M2 bone marrow ($\geq 5\%$ and $\leq 25\%$ blasts) and appearance of normal progenitor cells; and an M1 marrow that did not qualify for CR or CRp.

Criteria for Evaluation – Safety

Safety was evaluated from reported AEs and laboratory toxicities among all patients who received at least 1 dose of clofarabine.

STATISTICAL METHODS

Statistical Methods - Efficacy:

All patients who received at least one dose of study drug (partial or complete dose) were included in the intent-to-treat (ITT) analyses. Statistical summaries of the data included N, mean, standard deviation, median, minimum and maximum (range) values for continuous variables and frequencies and percentages for categorical variables. Kaplan-Meier methodology was used to summarize time-to-event variables. Any confidence intervals (CI) for estimated parameters were constructed with a significance level of $\alpha = 0.05$. Objective response to treatment with clofarabine was summarized using four ordinal disease response categories (CR, CRp, PR, and treatment failure). The OR rate and rate of any remission (CR, CRp, or PR) were summarized using a 95% CI. Survival and duration of remission were analyzed two ways: where transplant patients were censored at time of transplant and alternately, where transplant patients were not censored at the time of transplant but at the last available visit. Clinical benefit was further analyzed by summarizing the number and percent of patients in remission who were able to go successfully on to transplant following clofarabine therapy.

Statistical Methods - Safety:

Safety analyses included summaries of AEs (including serious adverse events [SAEs]), deaths and changes in laboratory results.

SUMMARY / CONCLUSIONS

Summary / Conclusions – Efficacy

The median age of the 61 patients was 12 years (range 1-20 years). The median number of prior regimens was 3 (range 2-6). Thirty percent of patients had received at least one transplant before study entry. Thirty-five of 61 (57%) patients were refractory to their most recent treatment regimen.

The overall remission rate (CR + CRp) was 20% (95% CI: 11 to 32%) as determined by the IRRP. Thirty percent of the patients had at least a PR as determined by the IRRP (7 CR, 5 CRp and 6 PR). The response rates determined by the investigators were similar to the IRRP determined response rates. Responses (CR, CRp or PR) were seen in 9/35 (26%) patients who had been refractory to their most recent regimen. Of the 12 patients who achieved a CR or CRp, 6 achieved the best response after 1 cycle and 6 achieved the best response after at least 2 cycles (5 after 2 cycles and 1 after 3 cycles). Responses were observed in patients with both T-cell and B-cell lineage. Among the patients who achieved a response, 4 patients continued in remission at the time of last follow up. Furthermore, 10/61 (16%) patients went on to receive a transplant after treatment with clofarabine, 6 of whom were alive as of last follow up. Post transplant survival times (measured from time of transplant to death) for patients who went on to transplant ranged from 10.6 to 139.9+ weeks.

Among the 12 patients who achieved a CR or CRp, 5 patients proceeded to a transplant. Four of these patients who achieved CR or CRp received a transplant while in remission, one patient proceeded to transplant following relapse. One additional patient proceeded to transplant following alternative therapy. Among the remaining 6 patients who did not receive a transplant, remission duration ranged from 4.3 weeks to 58.6 weeks with 2 patients maintaining a CR for 47.9 and 58.6 weeks after clofarabine therapy alone.

At the time of this report, 7/61 (11.5%) patients were alive at last follow-up time, including 2 of the 7 patients who had achieved a CR, 2 of the 5 patients who achieved a CRp, and 2 of the 6 patients who had achieved a PR. All surviving patients were followed for a maximum of 2 years following the final study visit, or until disease relapse, or death, whichever occurred first.

The following table shows the remission and survival duration for patients who achieved at least a PR:

Duration of Remission and Overall Survival

	Censored at the time of transplant	Not censored at the time of transplant
	Median weeks (95% CI)	Median weeks (95% CI)
REMISSION DURATION		
CR +CRp	11.7 (95% CI: 6.1-47.9)	32.0 (95% CI: 9.7-47.9)
CR+CRp+PR	11.7 (95% CI: 6.1-35.4)	21.5 (95% CI: 7.6-47.9)
SURVIVAL		
CR+CRp	66.6 (95% CI: 53.7-72.4)	69.5 (95% CI: 58.6-NE)
CR+CRp+PR	58.6 (95% CI: 36.3-66.6)	66.6 (95% CI: 42.0-NE)

Performance status improved for 11/54 (20%) patients.

Summary / Conclusion – Pharmacokinetics

Evaluable pharmacokinetic data were available for 22/61 (36%) patients. Clofarabine had good tissue distribution with a volume of distribution of 161 L and was rapidly eliminated from plasma with a terminal half-life of approximately 5.9 hours.

Summary / Conclusions - Safety Results

The median number of cycles was 2 (range 1-12). Fourteen of 61 (23%) patients had study drug dosing delayed, reduced or interrupted. Each of the 61 patients experienced at least one AE. The most frequently reported drug-related AEs as reported in ≥10% of patients were nausea, vomiting, febrile neutropenia, rash, headache, pyrexia, anxiety, diarrhea, pruritus, fatigue, and palmar-plantar erythrodysesthesia syndrome.

Febrile neutropenia, pyrexia, hypotension, neutropenia, sepsis and pneumonia were the most frequently reported SAEs as reported in ≥10% of patients. Only 1 of the 61 (2%) patients discontinued due to an AE, drug-related grade 4 hyperbilirubinemia.

Sixteen patients (16/61, 26%) died during the study or within 30 days of last dose or study discontinuation, or as a result of an adverse event that started during the study. Of these 16 deaths, 2 deaths were reported as possibly drug related by the

investigator, 8 deaths were attributed to disease progression or to a disease related adverse event and 6 deaths were reported as multifactorial, including events that were assessed as both disease and study drug related.

A small number of patients experienced symptoms captured as capillary leak syndrome, which were assessed as related to the administration of study drug. Whether this was the result of underlying disease progression, infection, pre-existing conditions, or study drug cannot be clearly determined. It is possible that a capillary leak-like syndrome could result from cytokine release due to the rapid destruction of leukemia cells. This could be particularly relevant to patients with a high tumor burden.

Most patients had Grade 3 or 4 hematologic abnormalities reported during the study as would be expected of acute leukemia patients, however most of these abnormalities were present at baseline.

The most frequently reported grade 3 or 4 chemistry parameters post-treatment ($\geq 10\%$ patients overall) regardless of causality included elevated AST, elevated ALT, elevated total bilirubin, elevated creatinine, and hyperglycemia. Some abnormal serum chemistries may also reflect poor nutritional status, toxicities from previous therapies, concomitant medications, or associated with tumor lysis, diarrhea or vomiting.

Pericardial effusion was a frequent finding in these patients. In a majority of cases it was minimal to small and without hemodynamic significance. A few patients were noted to have LV systolic dysfunction which was often transient. Thus, while direct cardiotoxicity of clofarabine cannot be completely ruled out, most of the patients in this study who had mild-to-moderate left ventricular systolic dysfunction (LVSD) also had other factors that were possibly responsible for the LVSD.

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