Protocol CLO222: A Phase II, Open-Label Study of Clofarabine in Pediatric Patients with Refractory or Relapsed Acute Myelogenous 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 14 sites in the United States.

STUDIED PERIOD

Date first patient dosed: 28 May 2002

Date last dose administered: 26 July 2004

PHASE OF DEVELOPMENT

Phase II

OBJECTIVES

The primary objective of this study was to determine the overall remission (OR) rate of clofarabine in pediatric patients with refractory or relapsed acute myelogenous leukemia (AML) who were administered clofarabine at 52 mg/m^2/day over 2 hours daily by intravenous infusion (IVI) for 5 consecutive days.

Secondary objectives included documenting complete responses (CRs), complete responses in the absence of platelet recovery (CRp[s]), partial remissions (PRs), durations 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 AML. Patients could receive up to 12 cycles of treatment with clofarabine. Patients were assessed for disease response by analyzing 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 40 patients. In total, 43 patients were enrolled, but 1 of those patients never received study drug. Therefore, 42 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 AML with ≥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 first or subsequent relapse and/or refractory; patients with acute promyelocytic leukemia (M3) were to have

been treated with at least 2 regimens-a retinoic acid-containing regimen and an arsenic trioxide-containing regimen; 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/m^2/day by IVI 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 depending on toxicity and response.

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 OS
- Safety profile of clofarabine for this population
- Pharmacokinetic profile and intracellular pharmacology and metabolism 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 (<5% blasts); and recovery of peripheral counts (platelets ≥100 × 10^9/L and ANC ≥1.0 × 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 ≥100 × 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 (≥5% and <25% blasts) and appearance of normal progenitor cells; or 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 1 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 alternatively, 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 42 patients was 13 years (Range: 2-22 years). The median number of prior regimens was 2 (Range: 1-5). Of the 42 patients, 43% had received at least one prior transplant and 67% were refractory to their most recent treatment regimen.

Clofarabine showed activity in this highly refractory, multiply relapsed, aggressively treated population with leukemia. According to the IRRP, the overall remission rate (CR + CRp) was 2% (95% CI: 0% to 13%) and 26% of the patients achieved at least a PR (1 CRp and 10 PR), with a median duration of remission of 20.0 weeks (95% CI: lower limit = 6.1 weeks). Responses (CRp or PR) were observed in 6/28 (21%) patients who had been refractory to their most recent regimen. Of the 11 patients who responded, 7 proceeded to transplant at the end of the study. Median times to progression were 25.1 weeks (95% CI: lower limit 9.4 weeks) for patients who responded and 6.0 weeks (95% CI: 3.9 to 9.1 weeks) for all patients. Median survival times without censoring for HSCT were 32.1 weeks for responders and 23.4 weeks (95% CI: 11 to 30.3 weeks) for all patients. Overall, 13/42 (31%) patients (1 CRp, 6 PR, 3 NE, and 3 TF) went on to receive a bone marrow transplant or PBSCT after treatment with clofarabine. Survival times for patients who went on to transplant ranged from 24.4 to 160.1+ weeks without censoring for HSCT.

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. Overall, seven patients were alive at the two year follow-up time, including the 1 patient who had achieved a CRp and 2 of the 10 patients who achieved a PR. All of the surviving patients had received a transplant after clofarabine therapy or alternative therapy.

Summary / Conclusions – Pharmacokinetics
Evaluable pharmacokinetic data were available for 19/42 (45%) patients. Clofarabine was rapidly eliminated from plasma with a terminal half-life of between 5 to 6 hours.

Summary / Conclusions – Safety Results
The median number of cycles was 2 (range 1-5). A total of 7/42 (17%) patients had study drug dosing delayed, reduced or interrupted. The most frequently reported drug-related AEs as reported in ≥20% of patients were nausea, vomiting, febrile neutropenia, headache, and pyrexia.

One patient developed drug-related systemic inflammatory response syndrome (SIRS) which resolved completely.

Febrile neutropenia, pyrexia, nausea, vomiting, hypotension, neutropenia, catheter-related infection, and septic shock were the most frequently reported SAEs without regard to causality. The most common drug-related SAEs were febrile neutropenia, neutropenia, pyrexia, and hypotension.

Two (5%) of the 42 patients discontinued due to an AE, ventricular arrhythmia and malignant neoplasm progression, neither of which was considered to be drug related.

Ten patients (10/42 [24%] patients) died during the study or within 30 days of last dose of clofarabine was administered. Five (12%) patients died from an AE; 3 deaths were due to non drug-related AEs, 1 death was drug-related (septic shock and multi-organ failure), and 1 death was considered multifactorial with cardiorespiratory arrest secondary to drug-related sepsis. Five (12%) patients died from disease progression.

Most patients had grade 3 or 4 hematologic abnormalities reported during the study as would be expected for acute leukemia patients, however most of these abnormalities were present at baseline. Hepatobiliary abnormalities were common after clofarabine treatment.

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 left ventricular systolic dysfunction (LVSD). Thus, while direct

cardiotoxicity of clofarabine cannot be completely ruled out, most of the patients in this study who had mild-to-moderate LVSD also had other factors that were possibly responsible for the LVSD.

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