

# A Phase I Dose-Escalation Study of Clofarabine in Patients with Relapsed or Refractory Low-Grade or Intermediate-Grade B-Cell or T-Cell Lymphoma

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## TRIAL INFORMATION

- **ClinicalTrials.gov Identifier:** NCT00338494
- **Sponsor(s):** Genzyme
- **Principal Investigator:** Francine Marie Foss
- **IRB Approved:** Yes

## LESSONS LEARNED

- Clofarabine can be active in relapsed and refractory lymphoid malignancies on a weekly dosing schedule.
- Responses were seen in patients with T-cell lymphomas, including cutaneous T-cell lymphoma, but not in patients with aggressive B-cell lymphomas.

## ABSTRACT

**Background.** Clofarabine is a second-generation purine nucleoside analog currently approved for the treatment of pediatric relapsed or refractory acute lymphoblastic leukemia. In adults, clofarabine has been investigated in several phase I and II trials as a single agent and in combination for relapsed or refractory acute leukemia. These studies have shown that clofarabine has activity and an acceptable safety profile in patients with hematological malignancies. In this phase I dose escalation trial, clofarabine was evaluated in patients with relapsed or refractory, low-grade or intermediate-grade, B-cell or T-cell lymphoma.

**Methods.** The starting dose of 10 mg/m<sup>2</sup> per week was administered intravenously (IV) for 3 consecutive weeks every 28 days, and doses were escalated in cohorts of three. The study objectives were to determine the maximum tolerated dose (MTD), characterize and quantify the toxicity profile, and determine the overall response rate of clofarabine administered once a week for 3 weeks and repeated every 4 weeks. Eligible patients were over the age of 18, had a histologically confirmed low-grade or intermediate-grade B-cell or T-cell lymphoma, and must have previously been treated with one standard chemotherapy regimen, excluding single-agent rituximab. The primary objectives included in statistical analyses were MTD, toxicity, and overall response rate (ORR). Four patients were enrolled in cohort 1 (clofarabine 10 mg/m<sup>2</sup>), four in cohort 2 (clofarabine 15 mg/m<sup>2</sup>), three in cohort 3 (clofarabine 20 mg/m<sup>2</sup>), two in

cohort 4 (clofarabine 30 mg/m<sup>2</sup>), and one in cohort 5 (clofarabine 40 mg/m<sup>2</sup>) (Table 2).

**Results.** MTD was not reached in the study. The most common toxicity observed was myelosuppression. A total of four (29%) patients experienced grade 3 leukopenia, with three (21%) patients experiencing grade 4 neutropenia. The myelosuppression was not considered to be a dose-limiting toxicity, as it resolved within 7 days.

Fourteen patients were enrolled: 10 patients with T-cell non-Hodgkin lymphoma (NHL) and 4 patients with B-cell NHL (see Table 1). All 14 patients received at least one dose of clofarabine and were evaluable for response. One patient with cutaneous T-cell lymphoma (CTCL) had a partial response; five (36%) had stable disease, and eight patients (57%) had no response. The one patient with a response had stage III erythroderma and was treated in the 10 mg/m<sup>2</sup> cohort; a nodal complete response by positron emission tomography scan was observed with a partial response of the skin.

**Conclusion.** In this study, weekly administration of clofarabine was demonstrated to be safe and associated with minimal hematologic toxicity at doses ranging from 10–40 mg/m<sup>2</sup>. In prior studies when dosed daily for 5 consecutive days, the MTD was shown to be 4 mg/m<sup>2</sup>. Weekly dosing within this dose range did not result in dose modifications, and the MTD was not reached. Clinical efficacy was observed in one patient with CTCL who was treated in the lowest-dose cohort. *The Oncologist* 2018;23:397–e30

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## DISCUSSION

Nabhan et al. reported a 42% response rate in a population of 31 patients with relapsed and refractory B-cell lymphoma treated with 4 or 6 mg/m<sup>2</sup> × 5 days, with hematologic toxicity being the major dose-limiting toxicity (DLT). Mulford et al. reported results from 29 patients with aggressive T-cell lymphomas, including 4 with transformed mycosis fungoides, treated with clofarabine for 3 consecutive days at doses ranging from 4–20 mg/m<sup>2</sup>. Pleural effusion and prolonged cytopenias were seen at the MTD of 28 mg/m<sup>2</sup>. Five of 29 (17%) patients had responses, including 1 with transformed mycosis fungoides, and 7 patients had disease stabilization. Tumor reductions were reported at all dose levels.

These studies included heavily pretreated patients and demonstrated clinical activity for clofarabine at different doses and schedules. Interestingly, and as we observed, there was no dose response relationship observed in these studies, although conclusions regarding efficacy are limited by small numbers in each cohort. The mechanism of action of clofarabine to block DNA synthesis via inhibition of ribonucleotide reductase and DNA polymerases can potentially overcome drug resistance to conventional cytotoxic agents in patients with relapsed lymphoma. Further studies could explore combinations of clofarabine with other novel agents in relapsed T- and B-cell lymphomas.

### RESPONSES TO CLOFARABINE

Patient	Disease	Dose cohort (dose)	Number of cycles received	Best response
1	CTCL, stage III erythroderma	1 (10 mg/m <sup>2</sup> )	3	Stable disease
2	CTCL, stage III erythroderma	1 (10 mg/m <sup>2</sup> )	11	Nodal CR by PET; PR skin
3	SLL with Richter's transformation	1 (10 mg/m <sup>2</sup> )	1 (2/3 doses)	No response
4	CTCL, stage IVA	1 (10 mg/m <sup>2</sup> )	3	Stable disease
5	CTCL, stage IIB	2 (15 mg/m <sup>2</sup> )	1	No response
6	Follicular transformed to DLBCL	2 (15 mg/m <sup>2</sup> )	1	No response
7	DLBCL	2 (15 mg/m <sup>2</sup> )	1 (1/3 doses)	No response
8	Mycosis fungoides, stage III	2 (15 mg/m <sup>2</sup> )	3	Stable disease
9	Mycosis fungoides, stage IIA	3 (20 mg/m <sup>2</sup> )	5	Stable disease
10	PTCL	3 (20 mg/m <sup>2</sup> )	3	Stable disease
11	Mycosis fungoides, stage IIA	3 (20 mg/m <sup>2</sup> )	1	No response
12	PTCL	4 (30 mg/m <sup>2</sup> )	1	No response
13	CTCL with large cell transformation	4 (30 mg/m <sup>2</sup> )	1	No response

Abbreviations: CR, complete response; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; PET, positron emission tomography; PR, partial response; PTCL, peripheral T-cell lymphoma; SLL, small lymphocytic lymphoma.

### TRIAL INFORMATION

Disease	Lymphoma – non-Hodgkin
Stage of Disease/Treatment	Metastatic/Advanced
Prior Therapy	More than two prior regimens
Type of Study - 1	Phase I
Type of Study - 2	Modified Fibonacci
Primary Endpoint	Tolerability
Secondary Endpoint	Efficacy

#### Additional Details of Endpoints or Study Design

##### Trial Design and Objectives

In this phase I dose escalation trial, clofarabine was evaluated in patients with relapsed or refractory, low-grade or intermediate-grade, B-cell or T-cell lymphoma. The starting dose of 10 mg/m<sup>2</sup> per week was administered IV for 3 consecutive weeks every 28 days. The study objectives were to determine the MTD, characterize and quantify the toxicity profile, and determine the overall response rate of clofarabine administered once a week for 3 weeks and repeated every 4 weeks.

##### Eligibility Criteria

Eligible patients were over the age of 18 and had a histologically confirmed low-grade or intermediate-grade B-cell or T-cell lymphoma with measurable disease defined by the Cheson lymphoma criteria [13]. All enrolled patients must have failed at least one standard chemotherapy regimen, excluding single-agent rituximab. Patients had to demonstrate an adequate Eastern Cooperative Oncology Group (ECOG) performance status of <2 and have a life expectancy of >12 weeks, normal cardiac function (ejection fraction >45%), and appropriate organ function (absolute neutrophil count >1000 × 10<sup>9</sup>/L, white blood cell count >2.5 × 10<sup>9</sup>/L, platelet count >75 × 10<sup>9</sup>/L, hemoglobin >9.0 g/dL, total bilirubin <2.0 mg/dL, aspartate and alanine transaminase <3 × upper limit of normal, and creatinine <2.0 mg/dL).

Exclusion criteria included a previously untreated B-cell or T-cell lymphoma, previous treatment with clofarabine, chronic use of oral high-dose corticosteroids greater than 20 mg/day prednisone for any medical condition, and prior radiotherapy to the only site of measurable disease. Additional standard exclusion criteria were implemented, including known AIDS-related or human immunodeficiency virus-positive lymphoma, active or untreated central nervous system lymphoma, autologous bone marrow or stem cell transplant (within the previous 6 months), and autoimmune thrombocytopenia. Patients were also ineligible

if they used an investigational agent within 30 days or any anticancer therapy 3 weeks before study entry, had an active systemic infection, an active secondary malignancy, or were pregnant or lactating.

#### Treatment Plan

In this phase I trial, patients were enrolled in cohorts of three at a starting dose of clofarabine 10 mg/m<sup>2</sup> per week for 3 weeks repeated every 28 days. The dose was escalated for subsequent cohorts if no DLT was observed. Please see table for dose escalation design. If a DLT was observed in one of three patients in the cohort, three additional patients were enrolled at that dose level. Dose escalation was then allowed if none of the additional three patients experienced a DLT. If one or more of the additional patients experienced a DLT, the MTD was considered to be exceeded and three additional patients would be treated at the next lower dose if only three patients were treated at that dose level. The MTD was defined as the dose at which fewer than one of six patients experienced a drug-related DLT, with the next higher dose provoking a DLT in two of six or two of three patients. Additional patients were enrolled if data obtained from previous patients were inadequate because of early death from an unrelated drug toxicity. Patients were treated for a maximum of two cycles before response assessment and were continued on clofarabine until disease progression, unacceptable toxicity, or patient withdrawal.

#### Supportive Care

Patients were premedicated with acetaminophen 650–1,000 mg orally 30 minutes prior to each dose of clofarabine. Patients received antiviral and *Pneumocystis jiroveci* prophylaxis. Allopurinol was given at the discretion of the treating physician for patients with extensive tumor bulk at the initiation of treatment. Hematopoietic growth factors were given based on institutional practice. Other supportive care included antiemetics, antibiotics, antidiarrheals, hydration, and blood products as clinically indicated. If patients developed evidence of systemic inflammatory response syndrome or cytokine release, corticosteroids, histamine blockade, and acetaminophen could be administered at the treating physician's discretion.

#### Dose-Limiting Toxicity

Dose-limiting toxicities were defined as any grade 4 neutropenia or grade 3 febrile neutropenia that lasted >7 days; grade 4 thrombocytopenia; grade 3 or 4 nonhematologic toxicity and/or grade 3 or 4 nausea, vomiting, or diarrhea in patients who received optimal treatment with antiemetics and antidiarrheals; grade 4 elevations in alanine, aspartate transaminase, or bilirubin; or treatment delay >2 weeks because of unresolved toxicity in patients who experienced at least grade 3 thrombocytopenia, grade 4 neutropenia, or any grade 3 nonhematologic toxicity.

#### Response Assessment

Responses were assessed every two cycles using the 1999 National Cancer Institute (NCI) response criteria [13]. All patients who achieved a complete response (CR), complete response unconfirmed, or partial response (PR) had their response confirmed at least 2 months after the first documented response. Patients underwent a computed tomography scan if they had a CR or PR at the end of therapy assessment. Bone marrow biopsy and aspirate were obtained in all patients after 2 months and in those who achieved a CR.

#### Statistical Analysis

The primary objectives included in statistical analyses were MTD, toxicity, and ORR. All patients who entered the study and received at least one dose of clofarabine were evaluated for the safety analyses and determination of MTD. Descriptive statistics were used to summarize safety parameters, including the incidence of adverse events and serious adverse events. Toxicity grading was according to the NCI Common Terminology Criteria for Adverse Events, version 3.0. All patients who enrolled in the study and received at least one dose of clofarabine were evaluated for efficacy using the 1999 NCI International Working Group response criteria for lymphoma.

#### Investigator's Analysis

Drug tolerable, hints of efficacy

### DRUG INFORMATION FOR PHASE I CLOFARABINE

#### Drug 1

Generic/Working Name	Clofarabine
Trade Name	Clolar
Company Name	Sanofi
Drug Type	Small molecule
Drug Class	Antimetabolite
Dose	Milligrams (mg) per square meter (m <sup>2</sup> )
Route	IV
Schedule of Administration	Weekly

### PATIENT CHARACTERISTICS FOR PHASE I CLOFARABINE

Number of Patients, Male	8
Number of Patients, Female	6
Stage	Not collected
Age	Median (range): 66 (52–87)
Number of Prior Systemic Therapies	Median (range): 5 (2–8)
Performance Status: ECOG	0 – 3 1 – 10 2 – 1 3 – Unknown –

PRIMARY ASSESSMENT METHOD FOR PHASE I CLOFARABINE	
CTCL	
Number of Patients Screened	8
Number of Patients Enrolled	8
Number of Patients Evaluable for Toxicity	8
Number of Patients Evaluated for Efficacy	8
Evaluation Method	Cheson criteria for patients with nodal disease and the modified Severity-Weighted Assessment Tool and Global Assessment for patients with cutaneous T-cell lymphoma
Response Assessment PR	$n = 1$
Response Assessment SD	$n = 4$
Response Assessment PD	$n = 3$

Diffuse Large B-Cell Lymphoma	
Number of Patients Screened	4
Number of Patients Enrolled	4
Number of Patients Evaluable for Toxicity	4
Number of Patients Evaluated for Efficacy	4
Response Assessment PD	$n = 4$

Peripheral T-Cell Lymphoma	
Number of Patients Screened	2
Number of Patients Enrolled	2
Number of Patients Evaluable for Toxicity	2
Number of Patients Evaluated for Efficacy	2
Response Assessment SD	$n = 1$
Response Assessment PD	$n = 1$

Total Patient Population	
Number of Patients Screened	14
Number of Patients Enrolled	14
Number of Patients Evaluable for Toxicity	14
Number of Patients Evaluated for Efficacy	14
Response Assessment PR	$n = 1$
Response Assessment SD	$n = 1$
Response Assessment PD	$n = 1$

PHASE I CLOFARABINE ADVERSE EVENTS			
Toxicity	All, $n$	Grade 3, $n$	Grade 4, $n$
Hematologic			
Anemia	3	2	0
Leukopenia	5	4	0
Neutropenia	5	0	3
Thrombocytopenia	2	0	1
Neutropenic fever	1	0	1
Nonhematologic			
GI: N/V, diarrhea	2	0	0
Insomnia	1	0	0

Infectious episode (CMV, HSV)	2	1	0
Hypotension/tachycardia	1	1	0
Fatigue	2	1	0
Erythema multiforme	1	0	1
Anorexia	1	0	0

Abbreviations: CMV, cytomegalovirus; GI, gastrointestinal; HSV, herpes simplex virus; N/V, nausea and vomiting.

Dose level	Dose of drug: clofarabine	Number enrolled	Number evaluable for toxicity	Number with a dose-limiting toxicity
1	10 mg/m <sup>2</sup>	4	4	none
2	15 mg/m <sup>2</sup>	4	4	none
3	20 mg/m <sup>2</sup>	3	3	none
4	30 mg/m <sup>2</sup>	2	2	none
5	40 mg/m <sup>2</sup>	1	1	none

## ASSESSMENT, ANALYSIS, AND DISCUSSION

<b>Completion</b>	Study terminated before completion
<b>Terminated Reason</b>	Funding ended
<b>Investigator's Assessment</b>	Drug tolerable, hints of efficacy

Estimates are that in 2017, 72,240 individuals will be diagnosed with non-Hodgkin lymphoma and that 20,140 will die of the disease [1]. Analysis of the Surveillance, Epidemiology, and End Results program database suggests that 5-year overall survival will reach 73% for non-Hodgkin lymphoma, compared with 51% in 1989. Improvements in chemotherapy and the addition of biological therapy account for this change. Efforts to find good salvage therapies have been underway since the 1980s [2–4]. In this study we assessed the tolerability and feasibility of an alternative schedule for the antileukemia drug clofarabine as a salvage treatment in non-Hodgkin lymphoma.

Clofarabine (2-chloro-2-fluoro-deoxy-9-D-arabinofuranosyladenine) is a nucleoside analog that was synthesized with halogenation at the 2-position of adenine and substitution of a fluorine group at the C-2 position of the arabinofuranosyl moiety [5]. It has high affinity for deoxycytidine kinase, and its mechanisms of action are multiple, including inhibition of ribonucleotide reductase, inhibition of DNA synthesis, and incorporation of clofarabine monophosphate into DNA. Clofarabine is a second-generation purine nucleoside analog that inhibits DNA synthesis and repair. It is currently approved for the treatment of pediatric patients with relapsed or refractory acute lymphoblastic leukemia [5, 6]. In adults, clofarabine has been investigated in several phase I and II trials as a single agent and in combination for relapsed or refractory acute leukemia [7–11]. These studies have shown that clofarabine has activity and an acceptable safety profile in patients with hematological malignancies.

However, clofarabine use in lymphoproliferative disorders has been limited because of myelosuppression and inability for dose escalation. For example, in a phase I/II trial evaluating

clofarabine in relapsed or refractory non-Hodgkin lymphoma, the maximum tolerated dose (MTD) was noted to be 4 mg/m<sup>2</sup> based upon the dose-limiting toxicity of myelosuppression [12]. This dose is significantly less than the doses used in the acute leukemia trials in which myelosuppression was considered acceptable. Therefore, a phase I clinical trial was conducted to investigate the safety and efficacy of clofarabine starting at a dose of 10 mg/m<sup>2</sup> per week.

Clofarabine was approved by the U.S. Food and Drug Administration for the treatment of pediatric acute lymphoblastic leukemia in 2004. Subsequent studies showed that clofarabine triphosphate can increase levels of intracellular ara-CTP, leading to combination trials with ara-C in patients with myeloid leukemias. In phase I studies, the maximum tolerated dose of clofarabine given as a 1-hour infusion daily for 5 days was 40 mg/m<sup>2</sup> per day. The dose-limiting toxicity was hepatotoxicity.

Clofarabine continues to play a major role in the treatment of acute myeloid leukemias. Induction regimens containing clofarabine are associated with a high complete response rate and lower morbidity, and the drug is active in the salvage setting in both young and elderly patients. Additionally, clofarabine is used as a conditioning regimen prior to transplantation. The most frequently used dosing regimen for acute myeloid lymphoma is 30 mg/m<sup>2</sup> weekly for 5 consecutive days.

In this study, clofarabine was dosed on a once-weekly basis. There was no MTD seen with this schedule. There was no demonstrated activity for B-cell lymphomas when dosed on this schedule, although the number of patients treated was small and all were refractory to other therapies. A signal of activity was seen in T-cell lymphomas, with one

partial response in a patient with cutaneous T-cell lymphoma and several patients with T-cell lymphomas who achieved stabilization of their disease. Based on this study enrolling a small number of patients with refractory disease and using a weekly dosing schedule, it is unclear whether clofarabine has meaningful clinical activity in T-cell lymphomas. Activity was also observed by Mulford et al., who reported results from 29 patients with aggressive T-cell lymphomas, including 4 with transformed mycosis fungoides treated with clofarabine for 3 consecutive days at doses ranging from 4–20 mg/m<sup>2</sup> [14]. Pleural effusion and prolonged cytopenias were seen at the MTD of 28 mg/m<sup>2</sup>. Five of 29 (17%) patients responded, including 1 with transformed mycosis fungoides, and 7 patients had disease

stabilization. Tumor reductions were reported at all dose levels.

This study enrolled a heterogeneous group of patients with refractory disease. The median was five prior regimens. A signal of activity was seen in patients with cutaneous T-cell lymphomas—but only a single partial response. There was no response in patients with B-cell lymphomas. There was no apparent dose response relationship, and the sole response occurred at the lowest dose. Clofarabine may be an active drug in T-cell lymphomas and could be further explored in patients who have not had extensive prior therapy.

#### DISCLOSURES

The authors indicated no financial relationships.

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