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ORIGINAL REPORT

Phase II Study of Clofarabine in Pediatric Patients With Refractory or Relapsed Acute Myeloid Leukemia

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ABSTRACT

Purpose
To determine the efficacy and safety of clofarabine in pediatric patients with refractory or relapsed acute myeloid leukemia (AML).

Patients and Methods
A phase II, open-label, multicenter study was conducted with single-agent clofarabine in pediatric patients with refractory or relapsed AML. Clofarabine was administered intravenously over 2 hours at the pediatric maximum-tolerated dose (MTD) of 52 mg/m^2 daily for 5 consecutive days. Cycles were repeated every 2 to 6 weeks. Responses determined by an independent response review panel.

Results
The 42 patients treated on the study had a median age of 13 years (range, 2 to 22 years) and had received a median number of two (range, one to five) prior regimens. The response rate was 26% and included one complete response without platelet recovery and 10 partial responses. The median duration of response was 20 weeks (range, 2 to ≥ 156 weeks). Six of 28 patients who were refractory to the immediately preceding therapy achieved response. Thirteen patients (31%), including seven responders, proceeded to hematopoietic stem-cell transplantation (HSCT) after treatment with clofarabine and survived between 24 to ≥ 160 weeks. Five patients (12%) remain alive post-transplantation at ≥ 63, ≥ 71, ≥ 86, ≥ 114, and ≥ 130 weeks. The most common grade 3 or greater adverse events without regard to causality were febrile neutropenia, catheter-related infection, epistaxis, hypotension, nausea, and fever. Transient elevation of liver enzymes and hypokalemia occurred frequently. Five patients died within 30 days of clofarabine administration secondary to progressive disease, and another five died as a result of an adverse event.

Conclusion
Clofarabine is active in pediatric patients with multiply relapsed or refractory AML. Responses allowed several refractory patients to proceed to HSCT. The toxicity profile was expected in this patient population.

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INTRODUCTION

Acute myeloid leukemia (AML) accounts for approximately 20% of all childhood leukemia. Although greater than 80% of children with AML achieve remission with current treatment regimens, 50% still succumb to the disease despite intensive therapy and aggressive supportive care.[1-6] Response rates and overall survival are dismal for refractory patients and for those with short first remission. Little improvement in overall survival has been observed during the last decade.[7-11]

Clofarabine is a second-generation purine nucleoside analog that contains two halogens within its molecule, which thereby distinguishes it from drugs with similar chemical structures, such as fludarabine and cladribine.[12-15] The additional fluoride on the carbohydrate moiety protects the glycosidic linkage against phosphorolysis and acid hydrolysis, which thus improves the bioavailability of clofarabine and prevents its metabolism to the neurotoxic, halogenated adenine base.[16] Clofarabine is a prodrug that requires step-wise phosphorylation to the triphosphate form for activity. The mechanism of action of clofarabine involves inhibition of ribonucleotide reductase and DNA polymerase that produces inhibition of DNA synthesis and repair, as well as induction of apoptosis through direct and indirect actions on mitochondria by release of cytochrome C and other proapoptotic factors.[12-15]

Clofarabine has significant activity against pediatric and adult leukemia.[17-19] Phase I studies have shown that the maximum-tolerated dose (MTD) is 52 mg/m^2/d for 5 days in children and is 40 mg/m^2/d for 5 days in adults with hematologic malignancies. Dose-limiting toxicities (DLTs) were reversible hepatotoxicity and skin rash. Clofarabine received accelerated approval by the US Food and Drug Administration (US FDA) for use in pediatric patients age 1 to 21 years with relapsed or refractory acute lymphoblastic leukemia (ALL) who have failed two prior regimens. We have previously published the results of the phase II, pediatric ALL study that led to this approval.[20]

PATIENTS AND METHODS

Patients

A multicenter, phase II trial of clofarabine was conducted in pediatric patients with refractory or relapsed AML who were not eligible for therapy of higher curative potential. Informed consent was obtained from parents or guardians, and assent was obtained from patients 7 years of age or older. Eligible patients had histologically proven AML according to the French American British classification, with at least 25% blasts in the bone marrow. Patients had to be in first or subsequent relapse and/or refractory, and they had to be 21 years of age or younger at the time of original diagnosis. Patients were also required to have a Karnofsky performance status (KPS) of 50% or greater; this was amended to 70% or greater before enrollment of the last eight patients. Other inclusion criteria was adequate organ function within 2 weeks of registration; this criteria included renal (ie, serum creatinine $<$ two times the upper limit of normal [ULN] for age) and hepatic (ie, serum bilirubin $\leq 1.5 \times$ ULN; AST and ALT $\leq 5 \times$ ULN) function measurements. Patients with active, uncontrolled, systemic infection, with severe concurrent organ dysfunction, or with symptomatic central nervous system involvement were excluded. Prior chemotherapy had to be completed at least 2 weeks before study entry. Pregnant or lactating women were excluded, and women of childbearing potential were asked to use appropriate measures to prevent pregnancy.

Dose and Treatment Plan

Patients were treated with clofarabine monotherapy 52 mg/m^2 by intravenous (IV) infusion over 2 hours for 5 consecutive days. Cycles were repeated every 2 to 6 weeks for up to 12 cycles, depending on the status of the leukemia and the recovery of normal hematopoiesis (ie, absolute neutrophil count $\geq 0.75 \times 10^9$/L) and organ function. Dosage calculations were based on the patient body-surface area, which was determined from the actual height and weight obtained before each cycle. Dose adjustments were required for certain toxicities. Grade 3 nonhematologic, noninfectious events from which the patient recovered within 14 days required a 25% dose reduction. Grade 3 nonhematologic, noninfectious events from which the patient did not recover within 14 days and all grade 4 nonhematologic, noninfectious events required withdrawal from study. Grade 2 neurologic or cardiac events necessitated discussion with the medical monitor. Routine prophylactic use of a colony-stimulating factor was not permitted. Prophylaxis for central nervous system leukemia was not allowed during the first two cycles of treatment. The prophylactic use of antibiotics, antifungal agents, and antiviral agents was recommended.

Evaluation During Study

Pretreatment evaluations included the following: history and physical examination, KPS assessment, CBC with differential, biochemical profile, echocardiogram (ECHO) or multigated acquisition (MUGA) scan, bone marrow aspirate and/or biopsy, and diagnostic lumbar puncture. Evaluation of past medical history was performed at screening. During treatment, physical examination was performed weekly; CBC and a biochemical profile were repeated one to two times per week, as clinically indicated. Physical evaluation, KPS, CBC, biochemical profile, and bone marrow aspirate were obtained before each cycle. A patient's best response was determined as the best individual response after each cycle of chemotherapy. Initially, ECHO or MUGA were repeated every cycle until amendment six, when they were repeated at every cycle to closely monitor ventricular function and to screen for pericardial effusions. In addition, according to amendment six, more frequent cardiac assessments (ie, ECHO/MUGA on days 1, 3, and 5 of each cycle; 12-lead ECG on day 1 of each cycle) were performed in eight patients at select study sites.

Response Criteria

Confirmation of diagnosis was obtained from an independent pathologist with expertise in hematologic malignancies. In addition, an independent response review panel comprised of three pediatric oncologists who were not participants in the study determined the response for each patient. Complete remission (CR) was defined as follows: no evidence of circulating blasts or extramedullary disease, an M1 marrow (ie, $<$ 5% bone marrow blasts), and recovery of peripheral counts (platelets $\geq 100 \times 10^9$/L and absolute neutrophil count $\geq 1.0 \times 10^9$/L).[21] A CRp required all of the criteria for a CR with the exception of platelet recovery. A partial remission (PR) had to meet the following criteria: complete disappearance of circulating blasts, an M2 marrow (ie, $\geq$ 5% and $<$ 25% bone marrow blasts), and appearance of normal progenitor cells; or an M1 marrow that did not qualify for CR or CRp.

Statistical Considerations

All patients who received any amount of study drug were included in the safety and efficacy analyses. The primary objective of this study was to determine the efficacy of clofarabine in pediatric patients with refractory or relapsed AML by determining the overall remission rate (defined as CR plus CRp) in this patient population. Secondary objectives included documentation of the rate of CR, CRp, and PR; duration of remission (ie, from IRRP-assessed date of response to date of first objective documentation of disease relapse or death); overall survival (ie, date of first dose of clofarabine to the date of death); and evaluation of the safety and tolerability of this dosing regimen in this patient population. In addition, transplantation and post-transplantation data were collected and analyzed. Point estimates and corresponding 95% CIs were used to summarize response rates. Kaplan-Meier methodology was used to summarize time to event variables.[22] CIs were constructed by using a significance level of $\alpha = .05$. Safety was evaluated on the basis of incidence, severity, duration, causality, seriousness, and type of adverse events (AEs), in addition to changes in the patient's physical examination, vital signs, and clinical laboratory results. Investigators graded the severity of AEs by using the National Cancer Institute Common Toxicity Criteria version 2.0.

RESULTS

Patient Characteristics

Forty-three patients were entered onto the study, but only 42 received any amount of study drug and were included in the analysis. Patient characteristics and French-American-British classification subtypes are listed in Table 1. The median age was 13 years (range, 2 to 22 years); 64% were men; and the majority of patients had intermediate or adverse cytogenetics at the time of relapse.[23] Patients had received a median number of two prior induction regimens since initial diagnosis, and 18 patients (43%) had at least one prior hematopoietic stem-cell transplantation (HSCT). The median interval between prior transplantation and first dose of clofarabine was 28 weeks (range, 6 to 117 weeks).

The median duration of first remission in patients who had CR as the best response to the initial induction therapy was 28 weeks (range, 11 to 103 weeks). Thirteen patients (31%) were refractory to the first induction regimen, and 28 patients (67%) were refractory to the most recent therapeutic regimen received before enrollment in this trial. The median percentage of bone marrow blasts at study enrollment for all patients was 62.5% (range, 12% to100%).

The median number of clofarabine cycles patients received in this study was two (range, one to five cycles). The median interval between

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	No. of Patients (N = 42)
Age, years	
Median	13
Range	2-22
Sex	
Male	27
Female	15
FAB classification subtype	
M0	4
M1	3
M2	7
M3	0
M4	11
M5	4
M6	0
M7	4
Unknown	9
Cytogenetics*	
Favorable	1
Intermediate	23
Adverse	14
Unknown	4
No. of prior induction regimens	
1	6
2	16
3	9
4	5
5	6
Refractory to most recent regimen	28
Most recent refractory regimen	
Cytarabine + anthracycline	7
Fludarabine-based	3
Cladrabine-based	3
Other cytarabine-based	3
Gemtuzumab ozogamicin	3
Other	9
No. of prior transplantations	
1	13
2	5
Clofarabine cycles per patient	
Median	2
Range	1-5

Abbreviation: FAB, French-American-British.
*On the basis of classification according to the Medical Research Council (Grimwade et al[23]).

cycles, defined as the number of days from the first dose of a cycle to the first dose of the next cycle, for patients who received at least two cycles of treatment was 24 days (range, 13 to 53 days).

Efficacy

The overall remission rate as determined by the IRRP was 2%, which included no CRs and one CRp, and 10 patients (24%) achieved a PR; these responses provided an overall response rate of 26%. Six (21%) of 28 patients who were refractory to their most recent chemotherapy regimen and four (22%) of 18 patients who had received prior HSCT had a response to clofarabine. Characteristics of the patients who responded to clofarabine are listed in Table 2. Patients who achieved PR had a median of 9.5% (range, 0.0% to 20.0%) blasts in the marrow at the time of response assessment, compared with 57.5% (range, 31.0% to 95.0%) at enrollment. The median duration of remission for the 11 responding patients was 20 weeks (range, 2 to $\geq$ 156 weeks), and the median survival was 32 weeks (range, 8 to $\geq$ 160 weeks).

Thirteen patients (which included one CRp, six PR, three responses not evaluable, and three treatment failures) proceeded to HSCT after clofarabine treatment, and the interval between the last dose of clofarabine and HSCT ranged from 21 to 75 days (median, 38 days). No other therapy was given to any of these patients before the HSCT after clofarabine treatment. Post-transplantation survival was between 17 to $\geq$ 130 weeks. Five patients remain alive post-transplantation at $\geq$ 63, $\geq$ 71, $\geq$ 86, $\geq$ 114, and $\geq$ 130 weeks (Table 3). The duration of remission for the patients who achieved a PR and who did not receive transplantation ranged from 2 to 20 weeks, and survival ranged from 8 to 25 weeks.

Eight patients were considered not evaluable or were not assessed for response by the IRRP. Of these, four patients died before response assessment could be performed, two patients were considered responders by the investigator but had less than 25% marrow blasts at study entry, one patient refused additional treatment after two doses, and one patient proceeded to transplantation before count recovery.

Safety

The most common grade 3 or greater nonhematologic AEs that occurred in $\geq$ 15% of the patients, regardless of causality, included febrile neutropenia (55%), catheter-related infection (17%), epistaxis (17%), hypotension (17%), nausea (17%), and fever (17%). Grade 3 or 4 hepatobiliary abnormalities commonly developed during the study and included ALT elevation (43%), AST elevation (34%), and hyperbilirubinemia (12%). No instances of hepatic veno-occlusive disease were observed on this study. Other grades 3 to 4 postbaseline laboratory abnormalities included hypokalemia (40%) and grade 3 elevation in serum creatinine (2%, or only one patient). As expected with cytotoxic chemotherapy, clofarabine administration was commonly associated with nausea, vomiting, fatigue, anemia, neutropenia, and thrombocytopenia. A large number of the AEs seen in this study were present at baseline in many of the patients. The most frequent pre-existing conditions other than abnormal blood counts included tachycardia (38%), nausea (26%), fatigue (26%), anorexia (24%), and vomiting (21%).

Sixty-seven percent of patients experienced grade 3 or greater infections during the study. One instance of systemic inflammatory response syndrome (grade 3) and two instances of transient tumor lysis syndrome (grade 3) also were observed. Ten patients died within 30 days of clofarabine administration or as a result of an AE that occurred during the study. Of these 10 deaths, five were due to progressive disease, three were due to sepsis, and two were considered drug-related by the investigator (one as a result of shock and multiorgan failure, and one as a result of cardiopulmonary arrest secondary to sepsis).

Eleven (39%) of the 28 patients evaluated were noted to have minimal to small pericardial effusions during the study. In addition, nine patients (32%) had some evidence of deterioration of left ventricular systolic function. There was a greater than 10% decrease of shortening fraction within the normal range in two patients, deterioration of left ventricular systolic function from normal to below-normal limits in four patients, and additional deterioration of shortening fraction from abnormal baseline studies in three patients. Evidence of

Table 2. Demographic and Clinical Characteristics of Patients Who Had a Response to Clorafabine

Characteristic											
Age (years)	FAB Classification Subtype	Cytogenetics	No. of Prior Regimens	Most Recent Prior Therapy	Response to Most Recent Therapy	Prior HSCT	Response to Clofarabine	No. of Clofarabine Cycles Received	No. of Clofarabine Cycles to Response	HSCT Post-Clofarabine	Duration of Remission (weeks)
4	M5	46, XY, der (11) t(1;11) (q21;q23)	5	Ara-C	CR	Yes (n = 1)	CRp	5	1	Yes	≥ 156
4	M0	NA	2	Ara-C/Mito	PR	No	PR	2	2	Yes	≥ 89
11	M4	47, XY, +8	2	2-CDA/Ida	Refractory	No	PR	1	1	Yes	≥ 75
3	M2	Clone 1: 47, XY, +8 Clone 2: 46, XY, t(3;12) (p14;p13)	2	Ara-C	PR	No	PR	4	2	Yes	30
5	Unknown	N/A	3	Tipifarnib	Refractory	Yes (n = 2)	PR	3	3	Yes	21
15	M1	47, XY, t(1;5;7) (p36;q15;q32), add (8) (q22), add (11) (p13; q15), add (12) (q22), del (16) (q22), der (21) t(12;21) (p13; p11.2)	5	Ara-C	Refractory	Yes (n = 1)	PR	2	1	Yes	20
22	M2	46, XX	1	Ara-C/DNM/TG	CR	Yes (n = 1)	PR	2	2	Yes	12
16	Unknown	Clone 1: 48, XY, +8, +13 Clone 2: 48, XY, +8, del (11) q(13), +13 Clone 3: 49, XY, +6, +8, +13	4	TG	Refractory	No	PR	2	2	No	20
8	Unknown	45, XY, −7	2	Ara-C/ASP	Refractory	No	PR	2	1	No	6
12	Unknown	43-47, XX, der (7) t(8;7;21) (q22; q22;q22), t(7;9) (p13;q22), ins (7;21) (p13;q22), der (9) t(7;9) (p12; q21), +13	1	Ara-C/DNM/TG	CR	No	PR	2	1	No	5
10	M0	44-46, XY, −7, del (13) (q12;q14)	4	Dex/MP	Refractory	No	PR	3	2	No	2

NOTE. Response included complete remission, complete remission without platelet recovery, and partial remission. Total No. of patients = 11.
Abbreviations: FAB, French-American-British; HSCT, hematopoietic stem-cell transplantation; Ara-C, cytarabine; CR, complete remission; CRp, complete remission without platelet recovery; NA, not applicable; Mito, mitoxantrone; PR, partial remission; 2-CDA, cladribine; Ida, idarubicin; DNM, daunomycin; TG, thioguanine; ASP, asparaginase; Dex, dexamethasone; MP, mercaptopurine.

new congestive heart failure was noted in two patients (one with a normal baseline study and that ultimately returned to normal, and one with an abnormal baseline study). In some patients, the cardiac changes were transient. Because of concurrent conditions, such as infection and disease progression, as well as because of the recent treatment of these patients with cardiotoxic agents before treatment with clofarabine, it was difficult to accurately assign causality for the deterioration of cardiac function observed.

Table 3. Demographic and Clinical Characteristics of Patients Who Underwent Transplantation

Characteristic							
Age (years)	Sex	No. of Prior Regimens	No. of Clofarabine Cycles	IRRP Response	Days to Transplantation Post-Clofarabine*	Survival From Start of Clofarabine (weeks)†	Survival Post-Transplantation (weeks)‡
4	M	5	5	CRp	53	≥ 160.1	≥ 130.0
4	F	2	2	PR	39	≥ 94.7	≥ 85.7
11	M	2	1	PR	65	≥ 80.9	≥ 71.0
3	M	2	4	PR	21	49.1	36.6
22	F	1	2	PR	25	39.0	32.7
5	M	3	3	PR	48	32.1	16.9
15	M	5	2	PR	38	30.3	21.3
2	M	4	1	TF	30	38.0	33.1
18	M	5	2	TF	23	28.7	22.3
17	F	1	1	TF	NA	NA	≥ 62.7
11	F	1	2	NAS	50	≥ 125.3	≥ 114.4
21	M	3	4	NAS	75	92.4	65.4
17	M	2	1	NAS	37	24.4	18.7

NOTE. No. of patients = 13. Seven patients had prior transplantation. The interval between prior transplantation and first dose of clofarabine was 151 to 568 days (median, 274 days). The interval between prior transplantation and transplantation after clofarabine was 194 to 675 days (median, 355 days).
Abbreviations: IRRP, independent response review panel; M, male; CRp, complete remission without platelet recovery; F, female; PR, partial remission; TF, treatment failure; NA, data not available; NAS, not assessable.
*Defined as time from the date of last dose of clofarabine to date of transplantation.
†Defined as time from the date of first dose of clofarabine to death or last follow-up.
‡Defined as time from the date of transplantation to death or last follow-up.

DISCUSSION

Long-term survival rates after first recurrence of childhood AML are poor and range from 21% to 34%.[7,8,10,24-26] Initial remission durations less than 1 year and allogeneic HSCT during first remission are associated with inability to achieve second remission and with a particularly dismal outcome. Little data are available on the outcome of patients with AML beyond first relapse, as most are enrolled on phase I trials or are given palliative care. The overall response rate of 26% observed in this study is encouraging, considering the heavily pretreated population enrolled; 86% of patients were in greater than first relapse, and 43% of patients had received prior HSCT. Most responders were in second or higher AML relapse, and six of the 11 responders were refractory to the last salvage regimen received immediately before enrollment. Resistance to other nucleoside analogs, including cytarabine and cladribine, did not preclude response to clofarabine. One patient with relapsed acute myelomonocytic leukemia who was refractory to reinduction with cladribine and idarubicin achieved a PR with clofarabine, which allowed the patient to proceed to HSCT. This patient remained in remission at 71 weeks post-transplantation. Similar responses have been previously reported in phase I and II trials with clofarabine in patients with AML and ALL, in whom leukemia was refractory to fludarabine and high-dose cytarabine, including a patient with AML refractory to this regimen who declined transplantation and who maintained CR during a year with single-agent clofarabine.[27]

The toxicity profile observed was as expected in this heavily pretreated patient population, as febrile neutropenia and infections were commonly observed. The serious AEs, including sepsis-related deaths, emphasize the need for close clinical monitoring and optimal supportive care during treatment with clofarabine in this patient population. Concerns regarding the association of cardiac toxicity with clofarabine arose during the conduct of this study but were not substantiated with close monitoring of cardiac function.

Allogeneic HSCT is associated with significant improvement in survival in patients with refractory or recurrent AML. As such, some investigators proceeded with HSCT as soon as the refractory patients enrolled on this study achieved a PR with clofarabine. Of the 13 patients who underwent transplantation, six survived longer than a year, and three were still in remission at last follow-up. These results underscore the favorable safety profile of clofarabine, as patients with AML recurrence typically have variable degrees of organ dysfunction. Although elevation in liver enzymes is dose limiting for clofarabine, there was no increased incidence of post-transplantation liver toxicity or hepatic veno-occlusive disease in patients who proceeded to HSCT after clofarabine treatment, even in patients with history of prior transplantation. Several patients appeared to have longer durations of remission after clofarabine and transplantation than with their prior therapies. These observations, along with the lack of neurotoxicity that has been observed with other similar nucleoside analogs, have led to ongoing trials to explore the role of clofarabine in preparative HSCT regimens.

The ultimate test for any antileukemia agent is its effective incorporation into standard regimens. Because clofarabine inhibits both DNA synthesis and repair, several trials are exploring the benefits of combining clofarabine with DNA-damaging agents. A phase I study of clofarabine followed by cyclophosphamide in adults with refractory acute leukemias showed increased DNA damage with clofarabine and cyclophosphamide compared with cyclophosphamide alone.[28] In an ongoing, phase I/II pediatric study of clofarabine in combination with etoposide and cyclophosphamide, five (100%) of five children with AML achieved a CR (n = 1) or CRp (n = 4), and 55% of 20 patients with ALL achieved a CR (n = 9) or CRp (n = 2) on the basis of investigator assessment.[29] Clofarabine also has been studied in combination with cytarabine, which optimizes ara-CTP accumulation in blast cells.[30] The activity and tolerability of this regimen have been demonstrated in adults with relapsed AML and myelodysplastic syndrome and in elderly patients with untreated AML who are at high risk of anthracycline toxicity.[31,32] A pediatric Children Oncology Group (COG) study currently is exploring this combination in children with recurrent leukemia.

In conclusion, clofarabine as a single agent is active and well tolerated in heavily pretreated patients with refractory and recurrent AML, including leukemias refractory to other nucleoside analogs. Additional development of this agent in pediatric patients with AML is focusing on incorporation of clofarabine in standard regimens.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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