Phase I and Extension Study of Clofarabine Plus Cyclophosphamide in Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia

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Abstract

Clofarabine has activity in children with relapsed/refractory acute lymphoblastic leukemia (ALL). To evaluate its activity in adults, we performed a phase I study in 50 patients using clofarabine in combination with cyclophosphamide. Dose-limiting toxicity (DLT) included diarrhea, transaminase elevations, and skin rashes. The response rate was 14%. The combination of clofarabine and cyclophosphamide at the evaluated doses and schedule showed only moderate clinical activity.

Background: Clofarabine is a nucleoside analogue with activity in children with acute lymphoblastic leukemia (ALL). Based on the hypothesis that clofarabine inhibits DNA repair after exposure to DNA-damaging agents, we designed a phase I and extension study to evaluate the combination of clofarabine and cyclophosphamide in adult patients with relapsed/refractory ALL. **Methods:** The continual reassessment method (CRM) was used to define the maximum tolerated dose (MTD). **Results:** Fifty patients with a median age of 30 years (range, 21-72 years) were enrolled, 30 of whom were part of the phase I group. Clofarabine 40 mg/m^2 intravenously daily $\times$ 3 days and cyclophosphamide 200 mg/m^2 intravenously every 12 hours $\times$ 3 days were established as the MTDs. Dose limiting toxicity (DLT) included diarrhea, transaminase elevations, and skin rashes. The response rate of the whole study group was 14%, including 10% of patients who achieved complete remission (CR) or CR without platelet recovery (CRp). Three responses occurred in patients with primary refractory disease. Early mortality ($<$ 30 days) was 6%. The median duration of response was 69 days (range, 5-315 days). Median overall survival was about 3 months. Compared with day 1 (cyclophosphamide alone), H2AX phosphorylation was increased on day 2 when clofarabine and cyclophosphamide were administered as a couplet (n = 8). **Conclusion:** The combination of clofarabine plus cyclophosphamide at the doses used in this study in a group of heavily pretreated patients with ALL is only moderately effective. Other doses, alternative schedules, or a more favorable patient population may achieve better results.

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Introduction

Outcomes of patients with relapsed and/or refractory acute lymphoblastic leukemia ALL remain poor, with response rates of $<$ 30% depending on previous therapy and duration of first remission. Median disease-free survival is in the range of 2 to 7.5 months, and long-term survival remains exceptional.[1] No effective salvage strategies except stem cell transplantation exist. Clofarabine, a second-generation deoxyadenosine analogue, is one of the most recently approved drugs for children with ALL relapse.[2] In a study

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of 61 children (median age, 12 years; range, 1-20 years) with a median number of 3 previous therapies (range, 2-6), the overall response rate was 30%, including 20% of children who achieved either complete remission (CR) or CR with incomplete platelet recovery (CRp).[3] Median response duration was 29 weeks (range, 1-48 weeks), and 9 children were able to proceed with a stem cell transplantation.

The role of clofarabine in adult patients with ALL is less well defined. Limited experience from single-agent phase II studies indicates less activity than seen in children.[4] Combination therapies may help to improve the activity of clofarabine in adults with ALL. Clinical and laboratory observations suggested synergistic activity between clofarabine and cyclophosphamide.[5] Cyclophosphamide causes DNA interstrand crosslinks, which are rapidly repaired, limiting its activity.[6] We hypothesized that in addition to its intrinsic anti-ALL activity, pretreatment with clofarabine would inhibit repair of cyclophosphamide DNA strand breaks, thus augmenting the activity of cyclophosphamide. In a phase I clinical and laboratory study of clofarabine followed by cyclophosphamide, Karp et al reported responses in 4 of 6 (67%) patients with refractory ALL using a timed sequential approach in which treatment was delivered on days 1 to 3 and again on days 8 to 10, albeit at the cost of significant toxicity.[7] We designed a daily up to × 5 days schedule of both drugs in a phase I study for patients with relapsed and refractory ALL followed by an expansion cohort to assess activity of the combination further.

Patients, Materials, and Methods

Study Group

Patients aged 21 years and older with a diagnosis of previously treated ALL (including Burkitt leukemia/lymphoma and lymphoblastic lymphoma) whose disease had either relapsed or who were refractory to induction therapy were eligible for the study. The study was later amended so that the duration of the first remission of patients who were in first relapse had to be < 12 months. Patients were required to have discontinued previous therapy for at least 2 weeks by the time of study enrollment. Concurrent treatment for relapse in the central nervous system (CNS) or CNS prophylaxis with intrathecal chemotherapy was permitted. Other eligibility criteria included (1) performance status of at least 3 (Eastern Cooperative Oncology Group scale), (2) adequate organ function (serum total bilirubin level ≤ 2.5 mg/dL, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] levels ≤ 3 × the upper limit of normal, and glomerular filtration rate ≥ 60 mL/min), (3) absence of active heart disease (New York Heart Association class 3 or greater) based on history and physical examination, and (4) a cardiac ejection fraction that was at least 45% (based on multigated acquisition scan [MUGA] or echocardiogram). Informed consent was obtained from every participant according to institutional guidelines. Approval for the study was granted from the Institutional Review Board of The University of Texas MD Anderson Cancer Center. The study was conducted in accordance with the basic principles of the Declaration of Helsinki.

Treatment Design

Four dose levels were defined. A dose-limiting toxicity (DLT) was defined as any grade ≥ 3 drug-related nonhematologic toxicity that occurred within the first 14 days after start of treatment. Patients in dose levels 1 and 2 received clofarabine 40 mg/m^2 as a 1-hour intravenous infusion daily for 3 consecutive days starting on day 2 (Fig. 1). Cyclophosphamide 200 mg/m^2 (dose level 1) and 300 mg/m^2 (dose level 2), respectively, was given as a 3-hour intravenous infusion every 12 hours for 6 doses on days 1 to 4. The first dose of cyclophosphamide was given by itself (without accompanying clofarabine) and then continued about 2 hours after the start of the clofarabine infusions with subsequent doses. For dose levels 3 and 4, the number of days was extended to 4 and 5, translating into 4 and 5 doses of clofarabine and 8 and 10 doses of cyclophosphamide, respectively. Patients could receive up to 2 induction cycles and a maximum of 6 consolidation cycles depending on leukemia response and resolution of toxicities. To continue in the study, achievement of at least a partial response was required. Consolidation cycles were to be administered at a 25% lower dose than the

Figure 1 Treatment Design