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CASE REPORT

Efficacy of Low Dose Clofarabine in Refractory Precursor T- Acute Lymphoblastic Leukemia

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Refractory T-lymphoblastic leukemia in adults has a poor prognosis in patients who relapse after allogeneic stem cell transplantation, and relatively few new agents have demonstrated activity. Clofarabine is a novel nucleoside analog that has been associated with significant clinical activity in relapsed pediatric B-ALL. We used low dose clofarabine and induced a remission in a patient who relapsed in the skin and marrow after allogeneic transplant and was refractory to nelarabine and report a near complete response, suggesting significant activity for low intermittent dose clofarabine in patients with relapsed T-cell leukemias.

INTRODUCTION

Of the 4,000 cases of acute lymphoblastic leukemias (ALL)[†] diagnosed in the United States every year, one third occur in adults. Adult ALL remains a difficult disease to cure in contrast with the cure rate of almost 80 percent in children and adolescents [1]. Front-line protocols often call for aggressive therapy for high-risk patients during induction, consolidation, and maintenance therapy. Allogeneic hematopoietic stem cell transplantation is offered to eligible patients with the promise of a prolonged leukemia free survival [1]. For patients who relapse after transplantation or who are not eligible for stem cell transplant due to lack of an appropriate donor or comorbid medical conditions, novel salvage therapies are desperately needed [2]. Recently, two nucleoside analogs, nelarabine and clofarabine, have been FDA approved for patients with relapsed or refractory T-cell and B-cell lymphocytic leukemia respectively [3-7].

Clofarabine is a novel purine nucleoside analog that has shown promise in early phase II studies for pediatric patients with B-ALL. The product of rationally designed improvements to two older adenine nucleosides, clofarabine is taken up into cells by an active nucleoside transporter [8] and is subsequently phosphorylated into nucleotide analogues clofarabine 5'-mono-, di-, and triphosphate, with clofarabine triphosphate being the active metabolite [9]. Clofarabine has been shown to have three mechanisms of action in leukemia cells: first, it is incorporated into DNA and impairs DNA elongation and repair; second, it is a potent inhibitor of ribonucleotide reductase, depleting the nucleotide pool primarily

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†Abbreviations: ALL, acute lymphoblastic leukemias; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome.

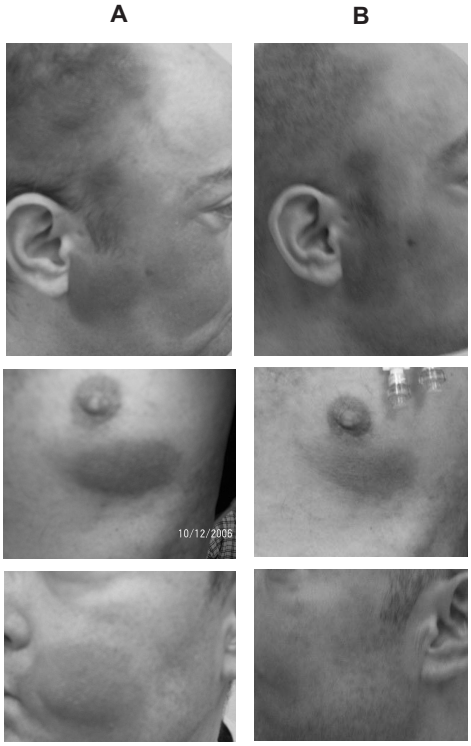
of dCTP and dATP; and third, it may directly induce apoptosis by altering the mitochondrial membrane and subsequently enabling release of cytochrome c [4].

In a phase II study of clofarabine in a pediatric population with refractory B-ALL, the response rate was 30 percent [5]. In the adult population, an initial phase I study showed that two of 13 patients responded [7]. In a subsequent phase II study in patients with refractory or relapsing ALL, acute myelogenous leukemia (AML), and myelodysplastic syndrome (MDS), two of 12 patients with ALL had responses [6]. In this report, we describe a case wherein low-dose weekly administration of clofarabine induced a response in a patient with refractory T cell ALL with primarily cutaneous disease.

CASE REPORT

JK is a 35-year-old male with precursor T-lymphoblastic leukemia diagnosed in 2001 with a bone marrow blast immunophenotype of CD2+CD7+CD3+ cells with aberrant expression of CD13 and negative staining for TdT and myeloperoxidase. His karyotypic analysis was indicative of a 4;11 translocation involving the MLL gene at 11q23. He was induced and underwent allogeneic stem cell transplantation (SCT) from his HLA-identical fraternal twin brother in April 2002. He was in remission with limited skin chronic graft-vs.-host disease until January 2003, when he relapsed and was treated with ICE chemotherapy followed by a donor lymphocyte infusion. He remained in remission until February 2005, when he developed nodular violacious skin lesions which on biopsy revealed T-cells consistent with his original leukemia. Full restaging including bone marrow biopsy and cerebrospinal fluid analysis were negative, indicating an isolated skin recurrence. Reinduction therapy was initiated with cyclophosphamide and gemcitabine but was complicated by significant myelosuppression and renal insufficiency. He received a brief course of systemic retinoid therapy with bexarotene and spot electron beam irradiation for symptomatic improvement of nodular disease on his face with rapid recurrence at the completion of radiation. He then was treated with nelarabine in February 2006 and responded but developed worsening renal insufficiency.

Figure 1: Clinical response to clofarabine in patient with precursor T-ALL with cutaneous involvement. A: At study entry; B: After 2 cycles of clofarabine.



He quickly developed recurrent nodular tumors over his brow, around his right ear, on his chest, and on his back and chest (Figure 1). On restaging in October 2006, the patient had no evidence of lymphadenopathy or involvement of liver or spleen by CT scan. A bone marrow biopsy revealed relapse of known precursor-T lymphoblastic leukemia involving 40 percent of the marrow. The cells were CD2+ CD7+ CD34+ HLA-DR+ CD3-. Flow cytometry of the blood was negative for blasts with only occasional reactive lymphocytes. At that time, his leukocyte count was 2.0 with 64 percent neutrophils and 35 percent lymphocytes, the hematocrit was 24.5 and platelets were 52 x 10^3/dl. He initiated therapy with clofarabine at 10 mg/m2 weekly for three consecutive weeks every 28 days. Treatment schedule

Table 1. Dose and toxicity of weekly clofarabine.

	WBC (10^3/mm3)	Creatinine (mg/dl)	Clofarabine dose
C1D1	2.5	1.8	10 mg/m2
C1D8	2.0	2.2	10 mg/m2
C1D15	0.3	2.2	held
C2D1	3.7	2.2	10 mg/m2
C2D8	2.2	2.1	10 mg/m2
C2D15	1.0	2.0	held
C3D1	1.4	1.9	10 mg/m2
C3D8	0.4	2.0	held
C4D1	1.9	2.3	10 mg/m2

and toxicities are shown in Table 1. There was no hepatic toxicity, and only mild fluctuations of the creatinine were noted. Treatment was held on the third week of the first two cycles due to neutropenia.

After two cycles of clofarabine, the patient's lesions regressed significantly as shown in Figure 1. Cycle 3 was delayed due to a hospitalization for herpetic esophagitis, which resolved with acyclovir therapy. He remains on weekly low-dose clofarabine with ongoing response after three months. His platelet count has been stable at 99,000/mm^3. An unrelated donor has been identified, and the patient will undergo a second allogeneic stem cell transplant.

DISCUSSION

In this case report, we demonstrate the efficacy and safety of weekly low dose clofarabine in a patient with relapsed and refractory precursor T-ALL. Because clofarabine is renally excreted, it has been dosed with caution in patients with renal or hepatic insufficiency [4]. In this case, clofarabine was successfully administered, albeit at a reduced dose, without worsening of renal function or evidence of disproportionate drug-related toxicity.

The observed response in this patient is surprising, given the low dose and intermittent scheduling [4]. Pharmacokinetics studies showed that intracellular concentrations did not become saturated at doses less than 20 mg/m^2; furthermore, despite an estimated half-life of 24 hours, there was no evidence of accumulation in doses less than 40 mg/m^2/day. *In vitro* studies demonstrated that breakthrough DNA synthesis occurs in leukocytes derived from patients receiving systemic doses less than 40 mg/m^2, suggesting suboptimal effect [10]. Consistent with the predictions made by the *in vitro* data and the pharmacokinetics of the drug, the clinical trials have suggested better results with higher doses. In particular, patients with relapsed CLL were treated with 2 mg/m^2 without any responses observed (ILEX Products Inc., personal communication). Nevertheless, it may be reasonable in patients with more rapidly proliferating disorders to administer clofarabine at a lower dose using this weekly schedule.

Lastly, we present this case report as the first evidence for the efficacy of clofarabine in treating primary or secondary cutaneous lymphoma/leukemia. As mentioned above, this patient had extensive involvement of the skin with his T-cell leukemia. The cutaneous

response was brisk with this low dose of clofarabine. One possible explanation for the sensitivity of the patient's tumor to low-dose clofarabine is localization of the drug in the skin, as was demonstrated in murine pharmacokinetic models by Lindemalm et al. Skin rash and palmoplantar erythrodysesthesias have been reported in the clinical trials in which clofarabine is administered on a five-day schedule at higher doses, perhaps related to retention of the drug in skin. Based on this experience, it may be worthwhile to further investigate the efficacy of low dose clofarabine in primary and secondary cutaneous malignancies.

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