Clinical Trials

Fludarabine Therapy in Hairy Cell Leukemia

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This study evaluated the efficacy of fludarabine, a new adenine nucleoside analogue, in typical and variant forms of hairy cell leukemia (HCL). Two patients with HCL and one patient with a variant form of HCL (HCL-variant) with resistant or progressive disease with prior treatments were studied. Fludarabine (30 mg/m^2) was administered intravenously over 30 minutes daily for 5 days every month. Two patients (one with HCL and one with HCL-variant) achieved partial responses; the third patient had a minor response. This is the first report of encouraging activity of fludarabine in typical and variant forms of HCL. Further experience with fludarabine in these disorders is indicated. *Cancer* **67:1291–1293, 1991.**

HAIRY CELL LEUKEMIA (HCL) is a chronic lymphoproliferative B-cell disorder characterized by infiltration of the bone marrow, spleen, and liver, resulting in peripheral pancytopenia, splenomegaly, and various immunologic deficits.[1] Splenectomy is the mainstay of therapy resulting in clinical and hematologic improvement in 75% of cases.[2] Several agents have shown promising antileukemic efficacy in HCL including alpha-interferon, 2'-deoxycoformycin (DCF), and 2-chlorodeoxyadenosine.[3–5] DCF is also active in patients with HCL resistant to alpha-interferon.[6] Variant forms of HCL (HCL-variant) are generally resistant to currently available treatments.[7]

Fludarabine monophosphate, an adenine nucleoside analogue, has demonstrated significant antitumor efficacy in chronic lymphocytic leukemia and other indolent lymphomas.[8,9] Fludarabine has a structure similar to DCF and 2-chlorodeoxyadenosine, and may act through inhibition of the adenosine deaminase enzyme. We report our encouraging experience with fludarabine in three patients with either HCL (two patients) or HCL-variant (one patient). This is the first demonstration of the activity of fludarabine in these diseases.

Methods, Patients, and Results

Patients with documented diagnoses of HCL (two patients) or HCL-variant (one patient) were treated with fludarabine (30 mg/m^2) intravenously over 30 minutes daily for 5 days every month. Response criteria were as previously published.[3]

The diagnosis of HCL in the first two patients was confirmed by morphologic evaluation by light microscopic study, tartrate-resistant acid phosphatase (TRAP) positivity in the cells, and characteristic hairy cells seen on electron microscopic study. This showed a population of small lymphocytes exhibiting abundant "hairy" cytoplasmic extensions, an irregular nuclear configuration with folds and indentations, a coarse nuclear chromatin with moderate peripheral margination, inconspicuous nucleoli, active cytoplasm with abundant polyribosomes, and increased Golgi's complex and pinocytotic activities. The diagnosis of HCL-variant was confirmed by two institutional pathologic reviews. The diagnosis was based on the presence of atypical lymphoid cells by light and electron microscopic study in the marrow and spleen. The cells were larger than typical hairy cells, and showed TRAP positivity in only occasional cells (<10%). Electron microscopic study showed large lymphoid cells with numerous microvillous-like projections and a moderate

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TABLE 1. Treatment Results in Three Patients Receiving Fludarabine

Patient no. (disease)	Evaluation post course no./mo of therapy	Response variable: Hemoglobin (g/dl)	Leukocyte ($\times 10^3/\mu l$)	% polys	Platelets ($\times 10^3/\mu l$)	Marrow (%) cellularity/ abnormal cells	Other	
1 (HCL)	Pretherapy	10.4	2.6	26	79	60/57		
	2/2	11.8	0.6	50	94	10/30		
	4/4	13.0	2.1	45	217	10		
	4/7	13.9	3.1	79	188	10/9		
2 (HCL)	Pretherapy	8.6	1.9	64	107	85/94	Lymph nodes (1.5 cm)	
	3/6	13.5	3.0	66	290	60/95	0	
	5/9	12.1	1.1	60	246	10/95	0	
	5/23	13.1	2.0	47	162	90/75	0	
							Peripheral abnormal lymphocytes (%)	Liver (cm)
3 (HCL variant)	Pretherapy	12.5	7.0	20	174	65/56	52	11
	3/5	10.5	4.9	86	198	20/0	0	0
	3/18	13.5	3.8	42	293	30/45	0	0
	9/24	9.8	2.4	88	137	30/0	0	0
	12/27	10.7	3.8	76	162	30/0	0	0

HCL: hairy cell leukemia.

number of organelles. Ribosome-lamellar complexes were not found. The nucleus was irregular with a prominent large nucleolus. Immunophenotyping showed these cells to be CD25 negative, but $CD11_c$ and CD22 positive.

The first patient was a 33-year-old man who received alpha-interferon (3×10^6 units daily for 4 months) for HCL and achieved a minor response. At that time the physical examination was negative for palpable hepatosplenomegaly or lymphadenopathy. The pretreatment characteristics are shown in Table 1. After four courses of fludarabine, the patient achieved a complete remission (CR) in the peripheral blood and a partial response (PR) in the marrow. Hematologic improvement was noticeable after two courses (Table 1). The first course was complicated by a febrile episode of unknown origin (FUO) requiring intravenous antibiotics. The patient is currently in remission for 13+ months from the start of therapy.

The second patient was a 40-year-old man with HCL for 5 years before starting fludarabine. The diagnosis was made in December 1982, at which time the patient underwent a splenectomy. With disease progression in June 1983, he was started on alpha-interferon for 12 months, achieving a PR. At relapse in June 1985, he was treated with alpha-interferon and prednisone for 3 months but obtained only a minor response. In February 1987, he received DCF for 4 months without a response, followed by 2 months of alpha-interferon therapy with progressive disease. In October 1987, he was started on fludarabine. In April 1988, after three cycles of chemotherapy, he had an improvement in the peripheral counts. He received two additional courses of fludarabine. In July 1988, his leukocyte count had decreased, and the repeat marrow studies showed 10% cellularity with 95% hairy cells (Table 1). He achieved a minor response (improvement in peripheral blood variables), and therapy was discontinued. Reevaluation 14 months later, without further therapy, documented stable disease. Fludarabine courses were uncomplicated except for the fifth course during which herpes zoster developed.

The third patient was a 69-year-old woman diagnosed with HCL-variant who initially underwent splenectomy. The spleen weight was 3875 g. Six months later, because of disease progression, the patient was treated with alpha-interferon (3×10^6 units daily for 6 months) without a response. Reevaluation 22 months after diagnosis demonstrated palpable hepatomegaly 11 cm below the costal margin and a leukocyte count of $7.0 \times 10^3/\mu l$ with 20% granulocytes, 19% lymphocytes, 9% monocytes, and 52% abnormal lymphoid cells (Table 1). The marrow cellularity was 65% with 56% variant hairy cells; the TRAP stain was positive in less than 10% of cells. Immunophenotyping confirmed that the cells were positive for immunoglobulin (Ig) M heavy chain and lambda light chain. They were also CD25 negative, but $CD11_c$ and CD22 positive. The patient received three courses of fludarabine, after which the palpable hepatomegaly disappeared and she achieved a CR in the peripheral blood. The bone marrow was in remission except for occasional atypical lymphoid cells (marrow PR). The first course was complicated by an FUO, and the third course was complicated by myelosuppression-associated FUO and moderate nose and gum bleeding. Therapy was withheld and the patient remained

in remission for 18 months from the start of therapy. Relapse was documented by reappearance of 45% variant hairy cells in the bone marrow concomitant with development of increased fatigue. There was no palpable hepatomegaly and the peripheral counts were normal. The patient was restarted on fludarabine and received eight additional courses. She achieved a second PR after three courses (morphologic remission with rare atypical lymphoid cells). Her second remission has now lasted for 15+ months.

Discussion

Recent advances in the therapy of HCL have dramatically improved the outcome of affected patients. Currently, alpha-interferon and DCF induce high response rates and improve survival in HCL. A third agent, 2-chlorodeoxyadenosine, has shown promising results with a small number of patients treated. Because of the availability of these agents, it will be difficult to extensively evaluate the efficacy of fludarabine in patients with a similar stage of disease and extent of prior therapy. Our preliminary experience suggests that fludarabine may be effective in HCL. Demonstration of a lack of cross-resistance between fludarabine and other agents by administering fludarabine to patients failing alpha-interferon, DCF, or 2-chlorodeoxyadenosine therapy may establish a role for fludarabine in this disease. This could lead to comparative studies of the effectiveness and toxicities of each agent among populations.

HCL-variant is generally resistant to alpha-interferon therapy,[7] and is poorly responsive to DCF. The impressive response obtained in our patient with HCL-variant warrants further investigation of fludarabine in this disease subset.

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