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Splenectomy vs. Alpha Interferon: A Randomized Study in Patients With Previously Untreated Hairy Cell Leukemia

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Twenty patients with previously untreated hairy cell leukemia were randomized to undergo either splenectomy or to receive interferon alfa-N1, a highly purified natural alpha interferon, as primary therapy. A response in the peripheral blood elements to a hemoglobin greater than 110 gm/l, a granulocyte count greater than 1×10^9/l, and a platelet count greater than 100×10^9/l (Catovsky criteria) was noted in all ten patients receiving alpha interferon but in only three of the patients undergoing splenectomy ($P = < .01$). Median time to response was longer in the ten interferon patients (153 days) than in the three splenectomy responders (20 days). Median time to treatment failure was significantly greater in the alpha interferon patients (> 18 months) than in the splenectomy patients (< 1 month). Survival was no different since patients relapsing following splenectomy subsequently responded to alpha interferon. A significant decrease in leukemic bone marrow infiltration was observed in seven of ten patients receiving alpha interferon and in none of the patients undergoing splenectomy. Side effects, primarily infections, were more frequent in patients receiving interferon. Alpha interferon is preferable to splenectomy as initial treatment for hairy cell leukemia. © 1992 Wiley–Liss, Inc.

Key words: hairy cell leukemia, alpha interferon, splenectomy

INTRODUCTION

Hairy cell leukemia (HCL) is a lymphoproliferative disorder that occurs primarily in middle-aged men. It is characterized by infiltration of the spleen and bone marrow with the so-called hairy cell, a malignant B lymphocyte. HCL was first well characterized and described by Bouroncle in 1958 in her classic description of 26 patients with "leukemic reticuloendotheliosis" [1].

Patients typically present with splenomegaly, pancytopenia, and infiltration of the bone marrow [2,3]. They usually also have a history of serious infections and a requirement for red cell transfusions. Until recently, the treatment of choice has been splenectomy, following which nearly all patients obtain some clinical benefit [4]. Splenectomy eliminates the site for preferential growth of the neoplastic cell and alleviates hypersplenism, a contributing factor to pancytopenia. Splenectomy improves both neutropenia and the hemorrhagic diathesis in most patients, but frequently the neutrophil count does not become normal, and over the duration of illness the incidence of infection is not altered by splenectomy [5]. Nearly all patients eventually relapse following splenectomy.

In 1984 Quesada et al. reported therapeutic efficacy in seven patients using a partially purified natural human alpha interferon [6]. He and co-workers have subsequently expanded their experience with both the Finnish Red Cross natural alpha interferon and recombinant human interferon alfa-2a [7,8]. Many others have demonstrated efficacy with a variety of recombinant alpha and beta interferons and with the highly purified natural alpha interferon, human interferon alfa-N1 [9–15].

Following Quesada's demonstration of activity with alpha interferon, a study was organized to compare the effectiveness of splenectomy with that of interferon alfa-N1 in previously untreated patients with HCL. We

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have compared the response rate as defined by peripheral hematologic response, by bone marrow response, and by the time to treatment failure obtained from these two approaches and report here the results of that study.

PATIENTS AND METHODS

In this multi-institutional study patients with active HCL, previously untreated, were randomized centrally by telephone between alpha interferon and splenectomy. Before randomization all patients were required to have a morphologic diagnosis of HCL with leukemic infiltration of the bone marrow and peripheral cytopenia defined as a granulocyte count less than 0.5×10^9/l, a platelet count less than 50×10^9/l, and/or a hemoglobin less than 90 g/l. Additional eligibility criteria included adequate renal function defined as a serum creatinine less than 2 mg/dl; an ECOG performance status of 0–3; splenomegaly by either physical exam, CT scan, or isotope scan; and no prior treatment. Ineligibility criteria included a contraindication to splenectomy; an active infectious process; pregnancy; significant cardiovascular disease (defined as New York Heart Association functional class III or IV); other pulmonary, gastrointestinal, or renal conditions which might have impaired tolerance to the acute pyrexial reaction associated with interferon administration; or a known sensitivity to neomycin or polymyxin B.

After giving informed consent, patients were randomly assigned using a permuted block with ten patients per block to receive a standard dose of interferon alfa-N1 or to undergo splenectomy. This randomization procedure allowed for an equal number of patients to be randomized to each treatment after every ten entries. The blocks were designed and the sequences assigned by Clinical Statistics of Burroughs Wellcome Co. No stratification procedures were performed. Patients randomized to interferon were to receive 2.0 mega units (MU) per square-meter body surface area of human interferon alfa-N1 (1 MU = 10^6 IU) daily subcutaneously (SC) for 28 days followed by a three times a week (tiw) schedule for 22 weeks. Patients randomized to splenectomy underwent surgery and then received no further treatment. A complete blood count and serum chemistry evaluation was to be obtained weekly for the first 4 weeks and then every 4 weeks thereafter. At 3, 6, and 12 months following randomization, patients were evaluated for therapeutic efficacy. At the time of progressive disease following randomization, patients were to be considered off study.

Treatment efficacy was primarily assessed by a peripheral blood hematologic evaluation, by time to treatment failure as defined by peripheral blood parameters, and by bone marrow evaluation. Peripheral blood hematologic evaluation was performed using two sets of criteria: the Catovsky criteria which have been used to evaluate results following splenectomy [16] and the Golomb criteria which have been used to evaluate the response to alpha interferon [10]. Patients were considered to have obtained a peripheral blood response using the Catovsky criteria if the hemoglobin exceeded 110 g/l, the granulocyte count exceeded 1×10^9/l, and the platelet count exceeded 100×10^9/l. Patients were considered to have obtained a response by the Golomb criteria if the hemoglobin exceeded 120 g/l, the granulocyte count exceeded 1.5×10^9/l, and the platelet count exceeded 100×10^9/l. Curves were constructed evaluating the time to treatment failure using the technique of Kaplan-Meier and were compared using the Logrank test. The time to treatment failure was considered as the time from the day on study to the time of the first of two consecutive abnormal peripheral blood counts using the Catovsky criteria. In addition, but secondarily, treatment efficacy was evaluated by a bone marrow biopsy evaluation as interpreted by the individual investigator and an evaluation of overall response. A complete bone marrow response was defined as the loss of leukemic infiltration with the presence of adequate hematopoiesis, and a partial bone marrow response was defined as a decrease of at least 50% in the leukemic infiltrate by subjective impression and comparison coupled with the presence of adequate hematopoiesis. For the evaluation of overall response, a complete response (CR) was defined as a normal peripheral blood count (as defined by Golomb), a normal bone marrow, and a normal physical and radiologic examination; a partial response (PR) was defined by a bone marrow with a 50% decrease in leukemic infiltrate plus hematologic and physical exam criteria as defined under CR; and a partial response hematologic (PRH) was defined as a normalization of peripheral blood as defined under complete response but with less than a 50% decrease in the leukemic infiltrate plus hematologic and physical exam as defined under CR [10]. All three degrees of response, CR, PR, and PRH, were considered a major overall response. Patients in whom all three peripheral blood elements failed to improve to normal were categorized as either stable (on treatment for 12 months) or treatment failure (within 12 months of initiating therapy). The need for red cell and platelet transfusions and the incidence of infection were recorded. Fisher's exact test, two-tailed was used for determining differences between various responses; a two-tailed Logrank test was used for comparing the Kaplan-Meier plots in Figure 1.

Interferon alfa-N1 (Wellferon^R, Wellcome Biotechnology, UK) is a natural, highly purified preparation of human alpha interferons obtained from the supernate of cultured human lymphoblastoid cells stimulated with Sendai virus. Extensive experimental work has demonstrated that this preparation contains at least 16 human alpha interferon subtypes [17]. The induced alpha interferons are purified to a specific activity of 2×10^8 international units (IU) per mg protein [18]. Biological activ-

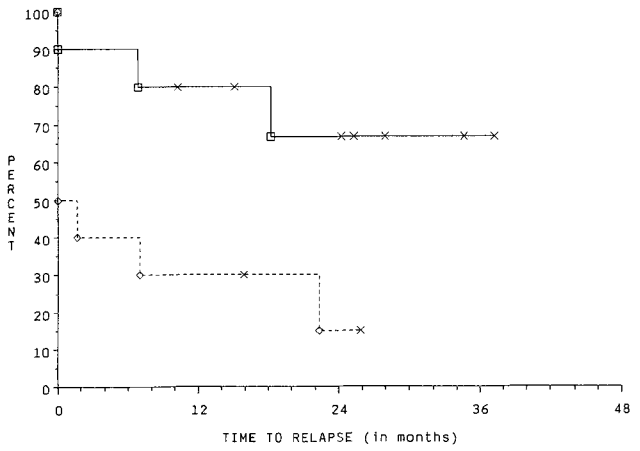

Fig. 1. Kaplan-Meier curves of the time to hematologic progression for the interferon patients (open square) and for the splenectomy patients (open diamond). The time to progression is significantly longer for the interferon treatment patients (P = .02).

ity is expressed in megaunits as determined in a viral cytopathic effect inhibition assay standardized against the international alpha interferon standard MRC-69/19. Interferon alfa-N1 was supplied to the United States patients by Burroughs Wellcome Co., Research Triangle Park, NC and to the Canadian patients by Pacific Isotopes and Pharmaceuticals, Ltd., Vancouver, BC.

RESULTS

Twenty patients were entered on study: ten were randomized to splenectomy and ten to receive interferon alfa-N1. Patient demographics are listed in Table I. For two patients in each treatment group the time from diagnosis to treatment was between 12 and 18 months. In all remaining patients but one, the time from diagnosis to treatment was within 2 months. The two treatment groups were well balanced.

Table II presents a summary of the response data. All patients receiving interferon alfa-N1 obtained a hematologic response by the Catovsky criteria while eight of ten obtained a response by the Golomb criteria. All responses were obtained within 8 months of the initiation of treatment. Of the ten patients who underwent splenectomy, three obtained a hematologic response by either Golomb or Catovsky criteria. The response rate was statistically significantly different between the two groups using the Catovsky criteria ($P < .01$) and of borderline statistical significance using the Golomb criteria ($P < .07$). The mean time to response was shorter for the three splenectomy responders (20 days) than it was for the interferon responders (153 days).

The ten interferon patients received a mean of 13 months of interferon alfa-N1 therapy. Two patients received interferon alfa-N1 for 6 months; one continued on interferon at last contact after 9 months of treatment, still in response; five patients received approximately 12 months of treatment; and two were continued on treatment for 21 and 22 months. Two interferon treated patients were considered treatment failures (although both had just barely obtained a peripheral blood response by Catovsky criteria) after 6 and 12 months of treatment and then underwent splenectomy. Seven of the eight remaining interferon treated patients remain in remission 10+ to 25+ months after initiating therapy. One patient relapsed (Catovsky citeria) 18 months after initiating and 6 months after discontinuing interferon treatment.

The median time to treatment failure for the interferon patients has not been reached (> 18 months), whereas the median time to treatment failure for the splenectomy patients was less than one month. Figure 1 presents Kaplan-Meier curves of the time to treatment failure and demonstrates a statistically significant longer time to treatment failure for the interferon group (P = .02).

Adequate data were available for evaluation of bone marrow response in seven of the patients receiving interferon alfa-N1 and in eight undergoing splenectomy. Leukemic infiltration was observed to decrease significantly within 3 months of initiating interferon therapy, and all seven evaluated interferon patients obtained significant clearing of leukemic infiltrate, six of them complete, after a median of nine months of treatment (range 3–18 months). Marrow specimens were available for eight of the patients undergoing splenectomy. None of the marrows in these eight patients demonstrated significant change ($P < .01$). Eight interferon treatment patients obtained a major overall response (two CR, four PR, and two PRH) compared to two splenectomy treated patients, both of whom attained a PRH (P = .02).

Splenectomy treatment failures were removed from study and, by individual choice of the investigator, were crossed over to alpha interferon therapy. Table III provides the baseline and time of treatment failure hematologic parameters for these patients. Five subsequently obtained a hematologic response to interferon therapy. Two interferon treated patients, barely in peripheral blood response by Catovsky criteria, underwent splenectomy following 6 and 12 months of treatment with further additional improvement.

With the exception of an increased incidence of infection during the first 3 months of treatment in the interferon treated patients, there was no significant (grade 3–4) toxicity observed in either treatment group. Two of the patients receiving interferon alfa-N1 became neutropenic and febrile during the third week of therapy, and two others developed a staphylococcal folliculitis (associated with grade 3 chills and fever) and a presumed granulomatous infection, respectively. One patient undergoing splenectomy developed a post-operative sub-

TABLE I. Patient Demographics*

PT #	Sex	Age	Race	PS	PLAT.	WBC	Institution	Investigator
IFN ALFA N-1								
202	F	46	W	1	80	5.3	U Colorado	Robinson
204	M	59	W	1	48	2.5	U Colorado	Robinson
205	F	39	W	0	58	2.0	U of Penna.	Cassileth
207	M	40	W	1	65	1.4	Wash. U	Denes
209	F	55	W	1	89	2.6	U of Penna.	Cassileth
210	F	49	W	0	57	4.6	Ft. Gordon	Troxell
214	M	55	W	1	42	3.0	Duke U	Huang
216	M	76	W	0	63	2.7	Wash. U	Denes
218	M	54	W	1	64	1.1	U Colorado	Robinson
302	M	41	W	0	88	16.1	CCA/BC	Connors
Splenectomy								
201	M	47	W	0	104	1.8	U Cincinnati	Martello
203	M	32	W	1	47	0.9	Emory U	Vogler
206	M	37	W	1	37	2.9	Duke U	Laszlo
208	M	33	W	0	20	1.7	U Colorado	Robinson
211	M	30	W	0	82	3.4	U Colorado	Robinson
212	M	52	W	1	84	8.4	U Florida	Weiner
213	M	47	W	0	44	1.5	U Colorado	Robinson
215	F	Unk	W	0	59	1.1	U of Penna.	Cassileth
217	F	46	W	Unk	53	1.9	Emory U	Vogler
301	F	55	W	1	43	6.0	CCA/BC	Connors

*PS, ECOG performance status at baseline; Unk, unknown.

TABLE II. Response*

Hematologic	C	G	TTR
ALPHA IFN	10	8	153 d
Splenectomy	3	3	20 d
P value	<.01	<.07	

Bone marrow	PR	CR	NE
ALPHA IFN	1	6	3
Splenectomy	0	0	2
P value		<.01	

Overall	TF	SD	PRH	PR	CR
ALPHA IFN	2	0	2	4	2
Splenectomy	6	2	2	0	0
P value			.02		

*C, Catovsky criteria; G, Golomb criteria; TTr, time to response; PR, partial response; CR, complete response; NE, not evaluated; TF, treatment failure; SD, stable disease; PRH, partial response, hematologic.

TABLE III. Hematologic Values for Splenectomy Treatment Failures at Baseline and at Time of Failure*

PT ID	Post Op Day of TF	HGB (GM/L) B	HGB (GM/L) TF	GRAN (10^9/L) B	GRAN (10^9/L) TF	PLAT (10^9/L) B	PLAT (10^9/L) TF
203	87	122	79	.441	1.050	47	88
206	103	114	119	.290	.648	37	92
208	50	75	125	.289	.492	20	40
211	106	97	89	.986	1.332	82	58
212	321	120	87	.420	.812	84	56
301	131	42	84	.900	.468	43	117

*TF, treatment failure; B, baseline.

phrenic abscess. A fifth patient receiving interferon alfa-N1 developed septicemia during the seventh month of treatment not associated with neutropenia. Only one other patient developed grade 3–4 toxicity; a patient receiving interferon developed severe splenic pain during the first week of treatment. Interferon was generally well tolerated long term without any acute or chronic grade 3–4 toxicity. There was no evidence in this small group of patients of the chronic fatigue syndrome and no indication that interferon interfered with the ability of any patient to function normally.

All patients randomized to alpha interferon remain alive as of last follow up (mean 21.9+ months; range 10+–32+ months). Nine of the ten splenectomy patients remain alive (mean 25.9+ months; range 7+–36+ months). One patient's leukemia progressed eight months following splenectomy and he died 12 months after initiating interferon alfa-N1 therapy of lung cancer. There is no difference between the two treatment approaches in their effect on survival.

DISCUSSION

Until the demonstration by Quesada et al. of the efficacy of alpha interferon, splenectomy was the treatment of choice for patients with HCL. Although the majority of patients undergoing splenectomy obtained clinical benefit, it has been difficult to document a decrease in the

incidence of infection and an improvement in overall survival following this procedure [5]. Using the criteria first proposed by Catovsky, 40–46% of patients obtained a peripheral blood response following splenectomy in three reasonably sized series [4,19,20]. In the present study, three of the ten patients undergoing splenectomy obtained a response (while a fourth fell just short) using these criteria. The results in this small study are comparable to the previously published experience with splenectomy as primary treatment. Six of the splenectomy patients ultimately required a change in therapy (all were treated with interferon) within 3 to 8 months of undergoing splenectomy.

All ten interferon treated patients improved following the initiation of interferon alfa-N1 therapy and obtained a peripheral blood response as defined by Catovsky although it required several months of treatment to obtain maximal benefit. Seven patients receiving interferon obtained either a partial or complete response (significant decrease in leukemic infiltrate) in their marrow and all ten patients had a significant decrease in splenomegaly. In three of the interferon patients the initial response was considered clinically inadequate; two were taken off study after 6 and 12 months of treatment and underwent splenectomy while in the third the dose of interferon alfa-N1 was escalated five-fold in order to improve the quality of response.

When first initiated, alpha interferon can cause further suppression of myelopoiesis. Two patients, who had marginally normal neutrophil counts at the initiation of therapy, developed neutropenic fever within 3 weeks of initiating treatment. In a companion study of alpha interferon therapy in patients previously splenectomized or unable to be splenectomized, we compared the effects of the standard dose of 2 MU/m^2 with a dose of 0.2 MU/m^2 and demonstrated the ability of either dose to induce a peripheral blood response within several months of initiating therapy [11]. That study also demonstrated a tendency for the higher dose of interferon alfa-N1 to induce clinically significant neutropenia within 2 to 3 weeks of initiation of therapy which contributed to the recommendation that patients initiate therapy with alpha interferon at a dose of 0.2 MU/m^2 and escalate to a higher dose once improvement in the peripheral blood count is observed.

Other methods of treatment for HCL need to be considered. Some patients randomized to alpha interferon in this study responded less than optimally and continued to show some degree of hypersplenism. This also was true in our study comparing the effects of two doses of alpha interferon [11]. After months of interferon therapy, splenectomy may improve the quality of response initiated by interferon. Additionally, two other agents, deoxycoformycin and 2-chlorodeoxyadenosine, have recently been shown to be highly effective therapy for HCL [21–24]. The optimal approach to the treatment of patients with HCL is currently unknown. As recently as 10 years ago there was no medical treatment for this disease, whereas at present there are at least three effective agents. Based on the results from this study and our companion study of two doses alpha interferon [11], we recommend initiating treatment with a low dose (0.2 MU/m^2) daily of alpha interferon, increasing this dose to a standard dose of 2.0 MU/m^2 tiw once improvement in both neutrophil and platelet counts is observed. Treatment with alpha interferon should then be continued until the patient's bone marrow and peripheral blood have normalized. Splenectomy might be considered subsequently in patients whose peripheral blood may have improved but not normalized within 6 to 9 months of initiating treatment. Alternatively, following the induction of a response by alpha interferon, deoxycoformycin might be appropriate consolidation therapy. This latter approach would need to be subjected to a randomized trial. This study demonstrates the superiority of alpha interferon over splenectomy as initial therapy, but additional studies need to be performed to determine the optimal approach to using one or more of the effective medical treatments.

CONCLUSIONS

Only two of ten patients randomized to interferon subsequently underwent splenectomy (although in neither case had the patient failed by Catovsky criteria) compared with six of ten splenectomized patients crossed over to interferon. This, along with the prolonged TTF induced by interferon and the significant anti-leukemic effect of interferon on the bone marrow, strongly suggests that medical treatment is the recommended initial therapy for patients with hairy cell leukemia.

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