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Treatment of Hairy-cell Leukaemia with α-Interferon (α-IFN)

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Abstract—*Twenty-three patients with hairy-cell leukaemia (HCL), six of whom were previously splenectomized, were treated with α-interferon (α-IFN) 3 MU per day for 3–6 months and then with 3 MU three times per week for at least 3 further months. Seven patients (two splenectomized) showed a complete response (CR), 11 patients achieved a partial response (PR) and the remaining five experienced only a minor response (MR). All seven patients who achieved a CR are still in CR after 10–21 months from the onset of the disease. Among the 11 PRs, five showed an increase in the number of circulating hairy cells during the follow-up; they were re-started on α-IFN and an improvement of the haematological values was again obtained. One patient who achieved only a MR died after 1 month therapy because of severe infection. Following treatment with α-IFN, the improvement or normalization of the peripheral blood counts was paralleled by an improvement of the immunologic surface markers, as determined by monoclonal antibodies, and by an improvement of the response to PHA and of the natural killer activity. These findings, coupled to the mild drug-related toxicity observed, confirm that treatment with α-IFN represents a safe and effective therapeutic approach for both splenectomized and non-splenectomized HCL patients.*

INTRODUCTION

HAIRY CELL LEUKAEMIA (HCL) is a B-cell chronic lymphoproliferative disorder characterized by splenomegaly frequently associated with a marked mono- or pancytopenia [1–3]. In addition to the well-known clinico-haematological features, different phenotypic and functional immunological abnormalities have also been reported in HCL [4], namely a reduction in the natural killer (NK) activity [5, 6]. Splenectomy has represented the standard therapeutic approach to these patients capable of restoring to normal the haematologic values [7]. However, following splenectomy, most of the patients relapse with recurrent disease and cytopenia(s), scarcely improved by chemotherapeutic agents. On the contrary, recent reports have documented, in patients with HCL, an important clinical and haematological response following treatment with α-interferon (α-IFN) [8–13].

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In this study we have evaluated the clinical, haematological and immunological findings in 23 HCL patients treated with leucocyte α-IFN.

PATIENTS AND METHODS

Twenty-three patients, 18 males and 5 females, with HCL entered the study. The clinical characteristics are reported in Table 1. The age ranged between 36 and 78 years; 14 of the 23 patients had a newly diagnosed disease, whereas the remaining nine had been under care for 1–5 years. All patients showed typical hairy cells (HC) in the peripheral blood and bone marrow and were tartrate-resistant acid phosphatase (TRAP) positive. Two patients had no palpable spleen when they started α-IFN treatment, six had undergone splenectomy and the remaining 15 were splenomegalic (Table 1). Fifteen patients had never been treated, and the remaining eight had not received chemotherapy over the 3 months prior to entering this study.

α-IFN was provided by Wellcome (Wellferon) (a partially purified α-IFN obtained from a human lymphoblastoid cell line). All patients but one received 3 × 10 units (3 MU) daily i.m.; in the

Table 1. Clinical and haematological results before and after treatment with α-IFN in 23 patients with HCL

Patients	Age/ sex	Before α-IFN treatment: Spleen size	Hb g/dl	PMN ×10⁹/l	Plat. ×10⁹/l	HC ×10⁹/l	Start of α-IFN (date)	After 6 months of α-IFN treatment: Spleen size	Hb (g/dl)	PMN ×10⁹/l	Plat. ×10⁹/l	HC ×10⁹/l	12 months of α-IFN treatment: Spleen size	Hb g/dl	PMN ×10⁹/l	Plat. ×10⁹/l	HC ×10⁹/l	Response	Maintenance treatment (3 MU/ week)	Survival from onset of therapy (months)	Current status
1	59/M	Splen.	11.0	0.37	234	3.8	12/84	/	13.5	1.4	326	0.06	/	14.0	0.9	339	0.5	PR	No	27	Well. Increase of HC during follow-up
2	52/M	Splen.	9.8*	0.98	35	5.7	4/85	/	13.6	3.1	230	0	/	15.2	3.2	290	0	PR	Yes	3	Well. No progression
3	52/M	Splen.	8.5*	0.10	60	7.2	4/85	/	11.9	1.8	126	1.1	/	11.8	1.4	120	0.9	PR	Yes	23	Well. Increase of HC during maintenance
4	47/F	13cm	13.9	1.94	247	44.2	4/85	4cm	11.3	1.4	128	0.8	1cm	14.0	1.7	174	0.1	PR	Yes	23	Well. Increase of HC during maintenance
5	36/M	8cm	13.2	0.25	57	0.1	6/85	0	15.1	1.6	170	0	0	15.4	1.8	158	0	CR	No	21	Well in CR
6	61/M	10cm	9.7	0.28	39	0.1	6/85	0	10.8	1.4	45	0	0	10.9	0.9	58	0	MR	Yes	21	Alive with stable disease
7	56/M	Splen.	13.6	3.69	231	28.8	6.85	/	11.8	10.2	214	0	/	14.8	5.8	408	0	CR	Yes	21	Well in CR
8	70/M	0cm	10.1	0.21	37	0.6	10/85	0	13.3	1.2	133	0	0	15.0	0.9	140	0	PR	No	17	Well. No progression
9	54/M	3cm	15.0	5.22	131	8.8	10/85	0	13.5	2.4	110	5.4	0	15.5	3.5	102	3.6	MR	No	17	Well with stable disease
10	78/M	0cm	8.8*	1.05	70	0.1	10/85	0	12.3	4.0	150	0	0	15.1	3.3	130	0	CR	No	17	Well in CR
11	55/M	10cm	8.3*	0.10	70	4.0	10/85	/	/	/	/	/	/	/	/	/	/	MR	No	1	Dead with infection and disease
12	38/M	2cm	13.4	1.4	94	12.0	10/85	0	14.8	4.5	10	0	/	14.4	1.6	169	0.2	PR	No	17	Well. Increase of HC during follow-up
13	73/F	30cm	9.6	0.14	66	6.2	12/85	20	10.6	3.2	41	2.4	20	11.6	2.2	41	4.1	MR	Yes	12	Well with stable disease
14	70/F	3cm	8.6	0.10	28	0.8	12/85	0	12.3	1.3	135	0	0	14.9	2.0	196	0	CR	Yes	15	Well in CR
15	62/M	20cm	8.4	0.10	50	0.3	2/86	0	13.3	2.4	110	0	0	15.2	2.7	97	0	PR	Yes	13	Well in stable PR
16	55/M	Splen.	9.1*	0.42	32	0.1	2/86	/	14.0	2.8	220	0	0	14.3	3.1	197	0	PR	No	13	Well in stable PR
17	56/F	2cm	13.0	0.47	74	0.8	3/86	0	13.5	1.0	180	0	0	14.1	1.2	194	0.2	PR	No	12	Well. Increase of HC during follow-up
18	46/M	3cm	11.5*	0.32	85	0.1	5/86	0	13.9	1.8	126	0	/	/	/	/	/	CR	Yes	10	Well in CR
19	53/M	5cm	12.2	0.37	74	0.3	5/86	0	14.8	1.7	151	0	/	/	/	/	/	CR	Yes	10	Well in CR
20	61/M	14cm	9.8	2.8	141	181	5/86	10	10.1	2.2	181	68	/	/	/	/	/	MR	No	10	Splenectomized
21	50/M	Splen.	9.0	2.37	109	3.0	5/86	/	14.1	4.6	200	0	/	/	/	/	/	CR	Yes	10	Well in CR
22	41/M	5cm	8.6	0.44	110	0.1	6/86	0	11.5	1.3	130	0	/	/	/	/	/	PR	Yes	9	Well with stable disease
23	46/F	4cm	7.6*	0.40	107	0.1	6/86	0	12.4	2.7	180	0	/	/	/	/	/	PR	Yes	9	Well with stable disease

*Patients requiring blood transfusions; Hb = haemoglobin; PMN = neutrophils; Plat. = platelets; HC = hairy cells; CR = complete response; PR = partial response; MR = minor response.

absence of clinical and haematological toxicity, the dose could be increased to 6 MU daily if the peripheral blood counts had not improved after 4 weeks. Patients usually self-administered α-IFN. After 3 months, if the patients showed either a complete remission (CR, see below) or a stable partial remission (PR), the administration schedule was reduced to 3 times a week (except for two patients who stopped treatment after 3 months), otherwise α-IFN was maintained on a daily schedule. After 3 or more further months, if the patients were in CR or in stable PR, they were randomized to either no therapy or 3 MU α-IFN weekly. All patients were evaluated clinically and haematologically on a weekly basis for the first 3 months and then monthly. The effects of treatment were measured by standard haematological counts, bone marrow studies (6 weeks, 3, 6 and 12 months) and by immunological assessments. The distribution of lymphoid subpopulations was assessed by flow cytometry (Ortho Spectrum III) using a panel of monoclonal antibodies (MoAbs) directed against cell surface antigens. The following MoAbs were used: T3 (CD3), T4 (CD4), T8 (CD8), M1 (CD11) (Ortho), Leu 1 (CD5), LeuM5 (CD11), Leu-7 (HNK-1), Leu-11 (CD16), Leu-12 (CD19) (Becton-Dickinson) and anti-Tac (CD25) (kindly donated by Dr. Waldmann, NIH, Bethesda, U.S.A.). The response to phytohaemagglutinin (PHA) and the natural killer (NK) activity, as well as the changes in surface markers, were monitored on peripheral blood cells prior to starting therapy and every 6–8 weeks. NK function was measured in a 4-h Cr release assay using the K562 cell line as a target, at effector–target ratios of 25:1, 12:1 and 6:1. Details of the functional assay procedures have been extensively described elsewhere [4].

Complete response (CR) was defined as the absence of HC in the bone marrow aspirate, bone biopsy and peripheral blood, disappearance of the splenomegaly, when present, and recovery of the haemoglobin level to more than 12 g/dl, absolute granulocyte count to 1.5×10^9/l or more and platelet count to 100×10^9/l or more. Partial response (PR) was defined as decrease in the HC infiltrate in the bone marrow and peripheral blood of more than 50% of the pre-treatment values coupled to the restoration of the peripheral blood values (as defined for CR) for at least 1 month. Minor response (MR) was defined a restoration of at least one of the peripheral blood values, as indicated above.

RESULTS

All 23 patients have completed at least 8 months of therapy except two (Cases 1 and 10). Of the six splenectomized patients, two obtained a CR and four a PR (Table 1). Among the 17 non-splenectomized patients five achieved a CR and seven a PR. In all splenomegalic patients the spleen was no longer palpable or showed a marked reduction. The last five patients achieved only a MR and one of them deceased after 1 month of therapy due to severe cutaneous infection, pneumonia and liver failure. Following treatment, of the seven complete responders, two are in unmaintained remission 21 and 17 months from the onset of therapy and four are in maintained CR after 21, 15, 10, 10 and 10 months from the onset of therapy. Five patients, who had achieved a PR, experienced an increase in the HC count and were subsequently restarted on full dose (3 MU/daily) of α-IFN.

The phases of response usually followed a predictable sequence. The first detectable response to α-IFN was a reduction in the spleen size and then in the circulating HC. After 6 months, HC were present only in six cases who started with 3.8, 7.2, 44.2, 8.8, 6.2 and 181.0 HC 10^9/l, respectively. The platelet counts began to improve within the first week of therapy and, after 3 months, only one patient had less than 100×10^9/l platelets. Sixteen patients were anaemic (12 g/dl) at the start of therapy and seven of them were transfusion-dependent; after 3 months of therapy, all but one improved the Hb level and no further transfusions were required. The granulocyte and monocyte counts were the slowest to recover and although 15 patients were severely neutropenic (less than 0.5×10^9/l of neutrophils) before starting treatment, after 3 months of therapy, all patients had more than 1.0×10^9/l. Following treatment, bone-marrow biopsy specimens demonstrated a gradual but consistent improvement in all the patients with evidence of response. Only seven showed a complete disappearance of the HC from the bone marrow, indicative of a CR.

Surface marker studies, evaluable in 17 patients, demonstrated a marked improvement mainly in patients with a high number of circulating HC (Table 2). In 10 patients there was an evident increase of T3 (CD3) and T4 (CD4) positive cells with a normalization of the T4 (CD4)/T8 (CD8) ratio. Figure 1 and Table 2 report the NK activity and PHA response, before and after treatment; in the majority of the cases studied a good recovery was observed. The improvement of the cytotoxic function was generally gradual, starting at 3 months and further increasing at 6–9 months. A normalization of the NK activity was documented in 10 out of 16 cases. In four cases the normalization of the NK activity was achieved within 6 months of α-IFN therapy and in six after more than 6 months. Despite treatment and despite stable haematological recovery, in six patients the NK function was still reduced after more than 6 months therapy.

Toxicity was only a minor problem for most of the patients in this study. One patient who started

Table 2. Surface marker studies and immunological function before and after 6 (+) and 12 months with α-IFN in 17 patients with HCL

Patients	Lymphocytes × 10⁹/l Pre	Post	T3 (CD3) % Pre	Post	T4 (CD4) % Pre	Post	T8 (CD8) % Pre	Post	Leu-7 (HNK-1) % Pre	Post	Leu-11 (CD16)% Pre	Post	PHA (cpm) × 10⁹/l Pre	Post	NK* Pre	Post	Result
1	1.8	2.2	3	60	1	38	2	18	42	12	37	10	10	72	4	20	PR
2	2.4	1.9	28	40	7	23	20	14	19	13	14	6	6	13	7	14	PR
3	0.5	2.5	10	50	10	35	4	16	14	11	76	4	38	57	6	10	PR
4	1.2	1.7	60	68	39	38	29	23	12	8	7	6	90	70	50	42	CR
5	2.2	1.5	9	24	7	16	3	14	6	5	6	2	18	30	5	46	MR
6	1.8	1.0	47	70	29	42	16	22	6	5	7	3	10	45	0	12	PR
7	1.4	1.8	70	73	34	39	28	25	31	11	4	2	30	40	2	24	CR
8	1.1	1.2	55	82	33	48	20	20	19	24	7	7	47	42	5	24	CR
9	2.9	1.3	13	76	5	30	10	45	30	18	7	8	8.5	9.7	5	5	CR
10	5.4	3.1	2	7	1	3	1	2	0	4	0	2	28	19	1	8	MR
11	2.0	1.2	15	62	10	45	6	26	18	17	20	21	70	75	5	35	PR
12+	1.7	2.2	21	46	11	23	10	26	19	16	9	1	/	/	20	56	CR
13+	1.7	2.1	75	68	55	44	16	21	11	8	5	7	/	/	12	18	CR
14+	1.7	1.9	48	73	26	44	21	26	12	7	2	1	/	/	10	14	PR
15+	1.9	1.3	80	50	45	32	55	42	21	13	10	7	/	/	7	33	PR
16+	1.2	0.7	78	52	58	38	38	15	30	35	14	32	/	/	6	15	PR
17+	1.6	1.3	40	88	24	54	16	30	40	21	32	20	/	/	/	/	CR

*% of cytotoxicity (effector:target 25:1 ratio); CR = complete response; PR = partial response; MR = minor response.

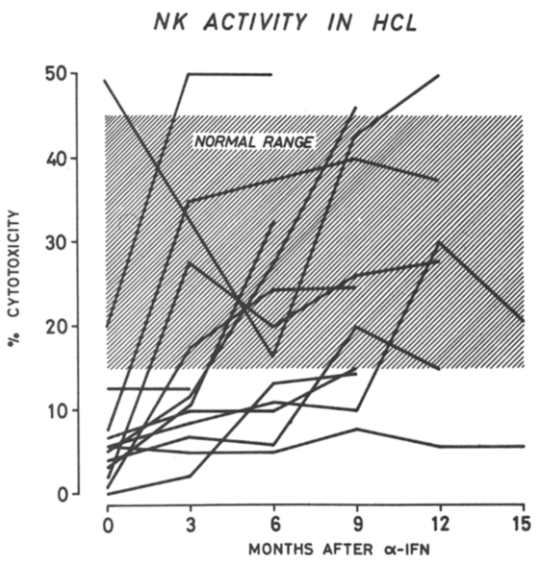

Fig. 1. Natural killer activity of the peripheral blood mononuclear cells from 13 patients with HCL before and during treatment with α-IFN.

treatment whilst febrile and with a severe cutaneous infiltrate died with infection 1 month later. Another patient, after 3 weeks of therapy, developed pneumonia that was successfully treated with antibiotics without stopping α-IFN. Fever was seen, as expected, only at the time of the initial administrations of α-IFN; in four patients, weight loss was documented in two hair loss.

DISCUSSION

This study documents the beneficial effect of treatment with α-IFN on the clinico-haematological course and immunological status of both splenectomized and non-splenectomized patients suffering from HCL. Of the 23 cases studied, seven achieved a CR, 11 a good PR, while only five patients experienced a MR, including one who deceased after 1 month of therapy.

While the favourable results obtained in the splenectomized group are largely confirmatory of other recent studies [9, 10], it is instead important to underline the excellent response achieved in non-splenectomized patients. In fact, of the 17 untreated and non-splenectomized patients, five obtained a CR, seven a PR and only five a MR. In all splenomegalic patients a complete disappearance or a marked reduction of the spleen size was observed. Though splenectomy is still considered by some authors the best initial therapeutic choice for patients with HCL, relying on α-IFN for relapsed post-splenectomy cases [9, 10], on the basis of the experience of our group and of others [11, 12], it appears that α-IFN is a very effective treatment also in patients with a large spleen at the onset of the disease. The average time for obtaining the clearance of the HC from the peripheral blood and the recovery of normal peripheral blood values was similar in the splenectomized and non-splenectomized groups. Despite these favourable results, several aspects still need to be clarified and within these the optimal duration time of treatment with α-IFN in order to obtain an increased CR rate, as well as a prolonged CR. In our series, treatment was stopped early in one patient who remained in PR for 11 more months before relapsing. In 11 patients treatment was discontinued and five (who

achieved a PR) showed signs of progression. The patients were re-started on α-IFN treatment and an improvement of the haematological values was obtained, suggesting that this form of therapy can be successfully repeated. All patients who achieved a CR are still in CR including two who stopped α-IFN treatment. Only the long-term follow-up of splenectomized and non-splenectomized cases treated with α-IFN will help to clarify whether splenectomy or α-IFN should be the first-line treatment for splenomegalic patients. In view of the complete disappearance of the spleen in all patients but two, we at present favour the primary use of α-IFN for patients with a moderately enlarged spleen. Though this specific point needs to be further clarified, it is instead possible that splenectomy may be the most appropriate approach to patients with a large splenomegaly, particularly because this procedure may lead to a prolonged remission which may last for several years.

Numerous biologic effects have been ascribed to α-IFN, some of which may also influence the clinical results. The direct antitumour effect of α-IFN on the malignant cells is well recognized and its selective effect in patients with HCL, whilst being little beneficial in other lymphoproliferative disorders, namely chronic lymphocytic leukaemia [14], is intriguing. Interestingly, the disappearance or reduction of the neoplastic clone following treatment with α-IFN, also documented at the DNA level [15], is generally followed by the repopulation of the bone marrow precursor cells. This is never observed in other diseases. The possibility that HC may produce a factor capable of inhibiting the growth of bone marrow precursor cells has been considered. While Richman and Golomb [16] reported that a HC conditioned medium was ineffective on the growth of bone marrow myeloid progenitors, we have recently documented that HC may release a factor(s) which inhibits the growth of myeloid, erythroid and megakaryocytic colony forming units [17]. The disappearance of HC following treatment with α-IFN may therefore lead to the removal of this inhibitor factor(s).

With regard to the effect of α-IFN on the immune system, in agreement with previous data [11, 18, 19], a marked restoration of the immunological status parallelled the clinico-haematological parameters. This was documented by an improvement of the T-cell subset distribution following the disappearance of circulating HC and the haematological recovery. More strikingly, the often depressed NK function observed in HCL [4, 5, 6] and confirmed in our patients, improved following α-IFN therapy. This was often a slowly progressive effect, which led to a normalization of the cytotoxic function in the majority of patients, particularly after the third month of treatment. The possibility that the enhanced NK function may be simply due to the direct effect of α-IFN, rather than to the improvement and most often normalization of the haematological parameters is unlikely in view of the evidence of the late restoration of the cytotoxic activity which parallels the haematological modifications and which often persists in patients off-therapy. In many patients the enhanced NK activity was coupled to a normalization in the percentage of Leu7 (HNK-1) positive cells, while the proportion of Leu11 (CD16) positive cells often tended to decrease below normal following treatment. In view of the role of NK cells against infection and tumour aggression [20] it is suggestive to hypothesize that the improvement of the cytotoxic function in HCL patients treated with α-IFN may play a role in controlling the disease.

In conclusion, α-IFN is in our experience highly effective in the clinical management and immunological status of splenectomized and non-splenectomized patients with HCL. Further studies are necessary to compare the long-lasting effects of α-IFN with those obtained with other forms of treatment. In particular, the promising results recently observed with deoxycoformycin [21] need to be taken into account, and the possibility of rotating drugs in resistant patients will have to be considered.

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