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Treatment of Hairy-Cell Leukemia with Recombinant Alpha$_2$-Interferon

Z.N. BERNEMAN,* G. GASTL,† D. GANGJI,‡ B. VAN CAMP,§ K. JOCHMANS,§ W. AULITZKY,† J. FLAMENT,‖ M.E. PEETERMANS* and C. HUBER†

**Department of Hematology, Universitair Ziekenhuis Antwerpen, University of Antwerp (UIA), Belgium; †Clinical Immunobiology, Department of Internal Medicine, University Hospital, Innsbruck, Austria; ‡Section of Hematology, Department of Medicine, and ‖Department of Immunology, Hematology and Transfusion, Hôpital Erasme, Université Libre de Bruxelles, Belgium; §Department of Hematology, Akademisch Ziekenhuis, Vrije Universiteit Brussel, Belgium*

Abstract—*Eleven patients with hairy-cell leukemia (eight with progressive and three with non-progressive disease) were treated with low dose recombinant human alpha$_2$-interferon. After a* 3-month *treatment period, nine patients showed an improvement and one patient a partial remission. By then, transfusions were not required any more and serious infections were no longer encountered. Four patients were further treated: three for a total period of* 9 months *and one for* 6 months; *all of them reached a partial or complete remission. The treatment was equally effective in patients with both progressive and non-progressive disease. Previous absence of response to splenectomy did not preclude a positive effect of IFN therapy. In two patients, IFN dose reduction was necessary due to unremitting flu-like symptoms.*

INTRODUCTION

HAIRY-cell leukemia (HCL) is a neoplastic disorder, involving the proliferation of B lymphoid cells with typical cytoplasmic hairy projections. Until now it has been treated with splenectomy; chemotherapy only had a limited success or was accompanied by severe and prolonged myelosuppression [1]. Recently, the introduction of interferon (IFN) has been a major breakthrough in the treatment of the disease.

Therapy with partially purified alpha-(leucocyte) IFN has resulted in a complete or partial remission in the first reported cases [2]. Response to therapy with leucocyte alpha-IFN was also reported in another series of patients in a more advanced stage of the disease; after 6 months of treatment, 1 and 6 of 10 patients achieved respectively a complete and partial remission [3]. In addition a complete remission has been described in a patient treated with a relatively high dose of recombinant human alpha$_2$-IFN [4]. More recently, three studies reported marked clinical and biological improvement in all patients treated with low doses of recombinant alpha$_2$-IFN [5,6] or human lymphoblastoid alpha-IFN [7], although no or few complete remissions were observed in these series. We present the data of a collaborative phase II study on the efficacy of various recombinant alpha$_2$-IFN treatment schemes in HCL.

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Address all correspondence to: Dr. Z. Berneman, Dienst Hematologie, Universitair Ziekenhuis Antwerpen, Wilrijkstraat 10, B-2520 Edegem, Belgium.

MATERIALS AND METHODS

Patients

Eleven patients (nine male, two female), aged 31–57 yr (mean: 45.4 yr) entered the study. The diagnosis of HCL was based in all cases on the presence of hairy cells (HC) in the bone marrow (BM) and in all but one case in the peripheral blood (PB); diagnosis was established 0–45 months prior to entering the study (mean: 20.2 months).

At diagnosis, six patients were in Stage I, three in stage II and two in stage III of the disease, according to the staging system of Jansen *et al.* [8]. All but two patients had been splenectomized 0–7 months after diagnosis (mean: 2.5 months) and 6–38 months (mean: 22.3 months) before IFN treatment. Three months after splenectomy, three patients were in stage A, two in stage B and four in stage C according to the criteria of the post-splenectomy prognostic staging system [8]. Other treatments were administered to six patients after splenectomy: chlorambucil (four patients), corticosteroids and leukapheresis (one patient), lithium and oxymetholone (one patient), without any beneficial effect on HC infiltration or on cytopenia. After splenectomy, six patients suffered from recur-

rent infections: dermatitis, sinusitis, angina, pneumonia; three patients had suffered from life-threatening infections, all of them pneumonias.

There was evidence of progressive disease in 8 of 11 patients. Progression was defined by the following criteria: increase of the percentage HC in the BM and/or of the absolute count of the HC in the PB by at least 25%, associated with at least one of the following parameters: 1° decrease of the hemoglobin (Hb) value, causing transfusion requirement; 2° decrease of the absolute neutrophil count (PMN) below $0.5 \times 10^9/l$; 3° decrease of the thrombocyte count (TRC) below $100 \times 10^9/l$; 4° recurrent infections. In 3 of 11 patients, there was no evidence of progressive disease: two were treated with IFN at diagnosis without previous splenectomy, and the third was treated respectively 21 and 17 months after diagnosis and splenectomy.

Treatment

All patients were treated with intramuscular injections of recombinant human IFN, type alfa-2c; the substance has a specific activity of 3.2×10^8 IU/mg and a degree of purity of 98%. It was kindly provided by Boehringer Ingelheim International. All patients were treated for at least 3 months; three of them were treated for a total period of 9 months and one for a total period of 6 months (Table 1).

Evaluation and definition of response to IFN treatment

All patients were evaluated before and 3, 6 and 9 months after initiation of treatment with PB and BM (biopsies and smears of the bone marrow biopsy) examinations. Quesada's criteria for remission [2] were used with some modifications. Complete remission (CR) was defined as follows: 1° no more detectable HC in BM and PB; 2° Hb $\geq$ 12 g/dl; 3° PMN $\geq 1.5 \times 10^9/l$; 4° TRC $\geq 100 \times 10^9/l$; and disappearance of organomegaly and lymphadenopathy. Partial remission (PR) was defined as: 1° decrease of HC in BM and PB by at least 50%; 2°Hb $\geq$ 12 g/dl; 3° PMN $\geq 1.5 \times 10^9/l$; 4° TRC $\geq 100 \times 10^9/l$; and 5° decrease of organomegaly and lymphadenopathy by at least 50%. An additional response category, improvement (I) was defined as follows: 1° reduction of HC infiltration in BM or PB by at least 25%; and 2° one of the following: Hb $\geq$ 12 g/dl, or PMN $\geq 1.5 \times 10^9/l$, or TRC $\geq 100 \times 10^9/l$ or reduction of organomegaly and lympnadenopathy by at least 25%. The absence of CR, PR or I was defined as no response (NR).

RESULTS

Within 3 months of starting IFN treatment, a clear effect on the HCL was evident (Table 2). Morphologically recognizable HC had disappeared from the PB, except in cases of non-progressive HCL. Improvement of blood cell counts was associated with a marked clinical improvement in cases with progressive HCL; at 3 months therapy, transfusions were not required any more and serious infections were no longer encountered. Although the number of patients in each treatment arm was small (Table 2), there seemed to be no significant differences in the efficacy of the different dose schedules on the evolution of the hematological parameters. PMN counts were an exception and tended to normalize more rapidly with the higher dose schedule (5×10^6 U/day). However it should be pointed out that, even with lower dose or lower frequency schedules, the PMN count always normalized within 6 months of starting treatment.

Treatment periods of 6 and 9 months resulted in remissions (partial or complete) in all the evaluable cases (Table 3). Three patients with progres-

Table 1. Dosage, duration and result of the IFN treatment

Number of patients	Dosage	Duration	Result
3	3×10^6 U/day	3 months	2/3 I, 1/3 PR
6	5×10^6 U/day	3 months	5/6 I, 1/6 NR
of whom:			
4 further	No treatment		
1 further	5×10^6 U/thrice/week	3 months	CR
1 further	5×10^6 U thrice/week	2 months	
	then 2×10^6 U twice/week	4 months	CR
2	5×10^6 U/day	1 month	
	then 5×10^6 U thrice/week	2 months	1/2 I, 1/2 NR
	then 5×10^6 U thrice/week	6 months	2/2 PR

Table 2. Mean hematologic values before and after 3 months IFN therapy in the different treatment groups

	Progressive HCL				Non-progressive HCL			
	3×10^6 U/day for 3 months (three patients)		5×10^6 U/day for 3 months (three patients)		5×10^6 U/day for 1 month then 3 ×/week for 2 months (two patients)		5×10^6 U-day for 3 months (three patients)	
	Before	After	Before	After	Before	After	Before	After
Hb (g/dl)	10.1	12.2	8.1	10.7	9.6	12.2	13.2	13.8
PMN ($\times 10^9$/1)	0.6	0.8	0.2	2.0	0.4	0.9	1.5	1.4
TRC ($\times 10^9$/1)	117	359	108	218	90	270	124	164
PB HC ($\times 10^9$/1)	23.0	0	32.7	0	11.9	0	0.6	0.3
BM HC (%)*	78	42	68	36	92.5	30	58	40

*In 7/11 cases, this percentage was determined on BM smears and it corresponded to the picture of the histology slides. In 4/11 cases, the smears were not contributive (i.e. hypocellular) and/or showed a different (usually lower) HC percentage, when compared to the BM biopsies; this percentage was then determined on the histology slides.

Table 3. Result of the IFN treatment for progressive and non-progressive HCL patients at 3, 6 and 9 months of treatment

Duration of treatment	Progressive HCL (eight patients)	Non-progressive HCL (three patients)
3 months	7/8 I, 1/8 PR	2/3 I, 1/3 NR
6 months	1/4 CR, 1/4 PR, 1/4 n.e.*	1/1 PR
9 months	2/2 PR	1/1 CR

*n.e.: not evaluable

sive HCL, showing an improvement after 3 months treatment, achieved CR or PR after 6–9 months IFN. One patient with non-progressive HCL, showing no response after 3 months therapy, achieved PR after 6 months and CR after 9 months of treatment with IFN.

Previous responses to splenectomy were not predictive for response to IFN treatment (Table 4). I, PR and CR categories were evenly distributed among the A, B and C post-splenectomy stages.

Fibrosis was still present in the BM of the two patients achieving CR after respectively 6 and 9 months of treatment. Further therapy of these patients (data not shown in Table 1) for respectively 3 and 9 months, was accompanied by a marked reduction of the fibrosis. In one case — the patient with non-progressive HCL achieving CR after 9 months of treatment — BM fibrosis has completely disappeared after 12 months of therapy with IFN.

As for the toxicity, 9 out of 11 patients initially developed a flu-like syndrome, consisting of fever, chills, fatigue and/or myalgias, as a result of the IFN treatment. In general, these symptoms were mild and disappeared completely within the first 4 weeks of treatment. In seven patients they did not require a dose reduction. In two patients, however, the reactions were more severe and required an IFN dose reduction (to 5×10^6 U twice or thrice/week). Two of 11 patients complained of itching, without developing a skin rash; in one patient, this symptom was only relieved by stopping the IFN.

Four patients, treated for 3 months and having achieved I (3 cases) or PR (1 case), were followed after stopping IFN therapy. Within 1–3 months, morphologically recognizable HC reappeared in the PB, and PMN and TRC counts started dropping in all four cases. In three patients the Hb level

Table 4. Response to IFN treatment in the splenectomized and non-splenectomized patients

Duration of IFN therapy	Splenectomy: Post-splenectomy responses			No splenectomy
	A (three patients)	B (two patients)	C (four patients)	(two patients)
3 months	2/3 I, 1/3 NR	1/2 I, 1/2 PR	4/4 I	2/2 I
6 months	1/1 PR	1/1 PR	1/2 CR, 1/2 n.e.*	–
9 months	1/1 CR	1/1 PR	1/1 PR	–

*n.e.: not evaluable

started to drop respectively after 1, 6 and 12 months; the Hb level of the fourth patient, who presented with non-progressive disease, continues to remain normal for so far more than 1 yr after stopping treatment.

DISCUSSION

Our data confirm the effectiveness of recombinant human alpha$_2$-IFN in HCL. After 3 months of therapy, all but one patient showed an objective improvement of their hematological and clinical condition; only one patient reached PR at this stage. This contrasts with the results of Quesada *et al.* [2], who reported that the proportion of BM HC was 5% or less in six of his seven patients, within 8–12 weeks after starting treatment with partially purified alpha-IFN. On the other hand, our results are comparable with those of the other groups using low dose recombinant alpha-IFN [5,6] or human lymphoblastoid alpha-IFN [7]: while improvement was seen within the first 3 months of treatment, most of the remissions only occurred after 6 months of therapy or more. In order to explain the difference in results between Quesada's study using partially purified IFN [2] and the other studies using recombinant ([5,6], present study) or lymphoblastoid IFN [7], the possibility was raised that the partially purified preparation may contain additional substances other than IFN with an effectiveness against HCL. However this possibility must be challenged by a recent study also using leucocyte alpha-IFN [3]. The results obtained in this series were similar to those seen in the groups treated with low dose recombinant ([5,6], present study) and lymphoblastoid alpha-IFN [7], regarding the proportion of patients achieving PR or CR and regarding the time needed to reach these targets. The differences between the treatment results are then most probably due to differences in patient populations rather than IFN preparation. The patients treated with the leucocyte [3], recombinant ([5,6], our study) or lymphoblastoid IFN [7] were apparently in a more advanced stage of the disease, with more extensive bone marrow HC infiltration and/or more pronounced cytopenias than those in Quesada's study [2].

It should be stressed that meeting the remission treatment response criteria was not a prerequisite for improving the quality of life of the patients. Within three months of treatment the down-hill course of progressive HCL was reversed, even without first obtaining a PR or CR.

The IFN therapy also seems to be effective in reducing the disease in non-progressive HCL and in non-splenectomized patients. Whether it will become the first choice treatment of HCL before splenectomy is still not settled; the present data however suggest this possibility.

Our data do not indicate a decreased therapeutic efficacy for lower dose (3×10^6 U vs. 5×10^6 U/day) or lower frequency treatment schedules (twice or thrice/week vs. once/day). The main feature to achieve and improve a therapeutic response is the duration of treatment; indeed, most of the PR or CR were seen after 6–9 months of treatment. The clinical course in the four patients treated for 3 months and followed after stopping therapy, indicates that recurrence of HCL is rapid. However, some patients remained in a rather stable clinical condition for several months up to a year after stopping the IFN therapy. Thus, a major area of future investigation will be the optimal duration of IFN treatment, in order to achieve and maintain remission of HCL.

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REFERENCES

1. Cawley JC, Worman CP. Hairy-cell leukaemia. *Br J Haemat* 1985, **60**, 213–218.
2. Quesada JR, Reuben J, Manning JT, Hersh EM, Gutterman JU. Alpha interferon for induction of remission in hairy-cell leukemia. *N Engl J Med* 1984, **310**, 15–18.
3. Hagberg H, Alm G, Björkholm M *et al.* Alpha interferon treatment of patients with hairy-cell leukaemia. *Scand J Haematol* 1985, **35**, 66–70.
4. Janssen JTP, de Pauw BE, Holdrinet RSG. Treatment of hairy-cell leukaemia with recombinant human α_2-interferon. *Lancet* 1984, **i**, 1025–1026.
5. Ratain MJ, Golomb HM, Vardiman JW, Vokes EE, Jacobs RH, Daly K. Treatment of hairy cell leukemia with recombinant alpha$_2$ interferon. *Blood* 1985, **65**, 644–648.
6. Jacobs AD, Champlin RE, Golde DW. Recombinant α_2-interferon for hairy cell leukemia. *Blood* 1985, **65**, 1017–1020.
7. Worman CP, Catovsky D, Bevan PC *et al.* Interferon is effective in hairy-cell leukaemia. *Br J Haemat* 1985, **60**, 759–763.
8. Jansen J, Hermans J. Clinical staging system for hairy-cell leukemia. *Blood* 1982, **60**, 571–576.