Recombinant IFN-α in Lymphomas

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The effectiveness of interferon (IFN) therapy in malignant lymphoma is analyzed in this review. Although various treatment regimens including IFN at various dose levels have so far not proved to have curative potential, a substantial palliative effect has been noted in hairy-cell leukemia and in some non-Hodgkin lymphomas of low-grade malignancy. Early stages of lymphoma disease are more responsive to IFN therapy, and this holds true also for chronic lymphocytic leukemia, in which IFN treatment is usually not effective in progressed disease after chemotherapy. Concepts of early-phase treatment and of remission maintenance by using IFN therapy are discussed on the basis of the data from several studies. *J Invest Dermatol 95:213S–215S, 1990*

Interferon (IFN) therapy in oncology was initiated using natural IFN, induced in human blood leukocytes. Patients with osteosarcoma experienced an increased survival after treatment. The dramatic effect of IFN in this disease, although not confirmed in later studies, gave rise to a major effort for the evaluation of IFN in oncology, including hematologic malignancies. These studies by and large showed little benefit to patients in most entities studied. A major breakthrough, however, was the discovery of the effectiveness of IFN in hairy-cell leukemia (HCL) [1–6]. In these patients, low doses of IFN at 3×10^6 U 3 times per week were found sufficient to reduce the number of detectable HCL cells in blood and bone marrow and to increase hemoglobin, platelets, neutrophils, and monocytes into the normal range. Complete hematologic responses were reported for 14% of the HCL patients (Table I), but this does not necessarily imply that all malignant cells have been destroyed. In fact, IFN treatment does not eradicate the disease, because after discontinuation of treatment the HCL cells reappear and bone-marrow function deteriorates again [7]. Hence, we face the possibility of life-long treatment of HCL patients with IFN either continuously or intermittently. With this long-term treatment, the minimal side effects of IFN gain importance, because phenomena like chronic fatigue may substantially impair the quality of life.

The success rate of IFN therapy in other leukemias/lymphomas initially proved less convincing. Except for CTCL, only few complete or partial responses were noted for chronic lymphocytic leukemia (CLL), Hodgkin's disease (HD), multiple myeloma, or high-grade non-Hodgkin lymphoma (NHL) (Table II). The success rate was, however, higher in low-grade NHL where a CR of 10% was reported (Foon, 1989), and the overall response rate was found to be 48% (Table III). This included patients treated with high doses (50×10^6 U), but also with low doses (2×10^6 U) of IFN.

Furthermore, response rates were considerably higher in previously untreated compared to pretreated patients that were refractory to standard chemotherapy. In multiple myeloma, for instance, the response rate in refractory patients was 15%, but it increased to 50% in previously untreated patients (Table II). The same applies to CLL where studies on pretreated patients resulted in an overall response rate of 6%, whereas previously untreated patients had a response rate of 73% (Table IV). The reason for the greater resistance in the pretreated patients may be threefold: 1) Extensive chemotherapy induces tumor-cell variants that are no longer sensitive to the direct effects of IFN. 2) Extensive chemotherapy may affect the immune system, such that the indirect effects of IFN through activation of lymphocytes and monocytes are no longer effective. 3) Patients with previous chemotherapy form a group of patients with later stages of disease and with higher tumor-cell burden.

While these postulated mechanisms may contribute to the failure of IFN therapy in pretreated patients to a variable degree, it is obvious that patients in an early stage do substantially benefit from the treatment (Table IV). The benefit of IFN treatment in such patients can be documented both with respect to tumor-cell depletion and with respect to immune activation by IFN. In our studies on early-stage B CLL patients, we noted a clearcut reduction of lymphocyte numbers in every patient that was largely due to a reduction of the leukemic B cells in that B1-positive cells decreased in average from 14,300 to 4,000 cells/mm^3 [8]. On the other hand, IFN appeared to activate the immune system in that, in some patients, serum immunoglobulins were increased and monocytes exhibited a higher class II antigen density.

At this point, we do not know whether these effects will result in an improved survival in these patients; this question will be answered in a controlled study currently being conducted. Hence, it appears that early-stage B CLL patients may be successfully treated with IFN. Given the fact that many CLL patients have an indolent course of the disease and may not require any treatment in the future years. The question is: which patients do we treat? In early B CLL prognostic markers like rapid lymphocyte doubling, high thymidine kinase activity in serum and non-nodular bone-marrow pattern correlates with a rapid course of disease. We believe that such patients are eligible for treatment at a point in time when tumor burden is still low and the immune response is still intact. Similar

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Abbreviations:
CLL: chronic lymphocytic leukemia
CTCL: cutaneous T-cell lymphoma
HCL: hairy-cell leukemia
HD: Hodgkin's disease
IFN: interferon
NHL: non-Hodgkin lymphoma

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Table I. Activity of rIFN-Alpha in Hematologic Malignancies[a]

Type	Number of Patients	Response Rates			% of Total Response
		CR[b]	PR	MR	
Hairy-cell leukemia	158	22	86	44	68 (96 with MR)
Cutaneous T-cell lymphoma	42	8	14	3	50
Chronic lymphocytic leukemia	73	0	12		16
Multiple myeloma	224	3	41		17
Non-Hodgkin's lymphoma, intermediate and high grade	61	1	8	2	15

[a] For references see [16].
[b] CR, complete response; PR, partial response; MR, minor response; % of total response, (CR + PR) number of patients.

Table II. Activity of IFN in Hematologic Malignancies According to Disease State[a]

Type of Tumor		Complete and Partial Response (%)
Non-Hodgkin's lymphoma	Low grade	40–50
	Intermediate/ high grade	10–15
Multiple myeloma	Untreated	50
	Refractory	15
T-cell lymphoma	Untreated	90
	Refractory	45

[a] According to [20].

Table III. Treatment Results with rIFN-Alpha-2 in Low-Grade NHL[a]

Reference	Patients	Dose ($\times 10^6$/week)	Response	
			n	%
[14]	24	3 × 50	13	54
[15]	34	3 × 2	17	50
[10]	9	varying	2	22
Total	67		32	48

[a] CLL excluded.

Table IV. Comparison of Treatment Results in CLL with rINF-Alpha

	n	IFN	Dose ($\times 10^6$/week)	Responder	
Pretreated patients					
[17]	18	alpha 2a	3 × (50–5)	2	Response rate: 6% (2 of 31)
[18]	5	alpha 2b	3 × 10	0	
[11]	8	alpha 2	3 × 20	0	
No previous treatment early phase					
[11]	4	alpha 2a	3 × 20	2	Response rate: 73% (27 of 37)
[10]	4	alpha 2a	3 × 12	1	
[19]	9	alpha 2b	3 × 5	9	
[8]					
[12]	10	alpha 2a	3 × 2	10	
[13]	10	alpha 2b	3 × 3	5	

concepts have been discussed by Rozman et al [9] and may be applicable to other forms of leukemia/lymphoma possibly also in an adjuvant setting.

Taken together, we have summarized herein data that indicate a good effectiveness of IFN treatment in certain forms of leukemia/lymphoma. As we learn more about the mechanisms of action of IFN and about the biology of the various types of leukemia/lymphoma, we may finally end up with a selected group of entities where IFN treatment can be successfully applied.

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