Cancer Chemother Pharmacol (1986) 18: 54–58

Cancer Chemotherapy and Pharmacology

A phase II study of human rDNA alpha-2 interferon in patients with low grade non-Hodgkin's lymphoma

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Summary. Thirty five patients with a diagnosis of non-Hodgkin's lymphoma of low histological grade were treated with $2 \times 10^6/m^2$ of human rDNA alpha 2 IFN-a_2 by subcutaneous injection. Treatment was continued until progressive disease was documented or one year of therapy had been given. None of the patients had to stop treatment because of toxicity and no treatment delays or suspensions of therapy were necessary as a consequence of myelosuppression. Thirty four patients were evaluable and seventeen (50%) obtained an objective response (2 CR, 15 PR) with a median duration of eleven months. Sixteen patients were untreated prior to receiving interferon but were felt to need some form of therapy rather than be suitable for a watch policy. Eleven of these patients responded (69%) with 95% confidence limits lying between 41% and 89%. No other pretreatment factors appeared to affect the liklihood of response. Single agent IFN-α_2 has significant activity in the low grade non-Hodgkin's lymphomata and warrants further investigation in this disease.

Introduction

The non-Hodgkin's lymphomas (NHL) of low histological grade are a group of malignancies whose management is currently the subject of controversy. The disease usually follows an indolent course with the median survival time lying between 3 and 10+ years. Treatment policies have included single agent chemotherapy, intensive combination chemotherapy, total nodal radiotherapy and combined modality treatments. All these therapeutic strategies produce high response rates, but none is superior in terms of relapse-free or overall survival [1, 3, 4, 6, 8, 11, 14, 15, 17, 19, 20, 21, 23, 24, 27]. Indeed, the outlook for this group of patients has not changed over the last two decades. Recently the result of operating an initial watch policy has demonstrated that about a quarter of such patients will undergo a spontaneous remission and that the average patient will not require chemotherapy for at least 3 years [13].

It is clear therefore that for improvements to be made in the management of patients with low-grade NHL new and novel therapies will be required. It is with these points in mind that molecules which exert a controlling influence upon the immune system are attracting attention. One such family of substances is the interferons (IFNs).

Early preparations of IFN were scarce, of variable purity and potency and were prohibitively expensive. The recent cloning of the human IFN gene and the application of recombinant DNA technology to the production of biological molecules has allowed the manufacture of highly pure forms of human IFN for the first time. Sufficient quantities of IFN are now available allowing properly conducted clinical trials to be undertaken. In this paper we present the results of using rDNA human IFN-a_2 (Intron) in patients with advanced low grade NHL.

Patients and methods

In all, 35 with a histologically confirmed and centrally reviewed diagnosis of low grade NHL were entered into this study. Patients had stage III or IV disease (Anne Arbor convention), with measurable lesions and documented disease progression prior to study entry. Some patients had received chemotherapy or radiotherapy previously. For previously untreated patients to be eligible some form of active therapy must have been deemed necessary. In other words, a watch policy was not considered appropriate in this group of patients. The indications for treatment were: bulky disease (> 5 cm), systemic symptoms or life threatening organ involvement. In patients in whom the diagnosis had been made more than 3 months previously a repeat lymph node biopsy was performed where possible, to confirm that there had not been transformation to a high-grade histology. The histological groups considered for inclusion (using the Rappaport system) were: nodular lymphocytic poorly differentiated (NLPD), nodular mixed lymphocytic/histiocytic (NM), nodular histiocytic (NH), nodular and diffuse lymphocytic poorly differentiated (NDLPD) and diffuse lymphocytic well differentiated (DLWD).

Prior to commencing therapy patients had a full clinical examination, including measurement and charting of disease. Full blood count, coagulation screen, and biochemical profile were performed. All these investigations were repeated at monthly intervals during IFN therapy. Bone marrow aspirate and trephine biopsy, chest X-ray and abdominopelvic CAT scan were done initially, at 3 months, and after 12 months of therapy. Other radiological and radioisotopic investigations were performed where

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clinically indicated. Blood was taken at monthly intervals for measurement of serum IFN neutralisation factors.

IFN was provided by the Schering-Plough Corporation. Formulated IFN-a_2, dissolved in phosphate-buffered saline (Ph 7.2), was freeze-dried in sterile vials and stored at 4 °C. It was reconstituted immediately before injection by adding 1 ml sterile pyrogen-free water. A dose of 2.0 megaunits/m^2 was administered by SC injection on 3 days per week (Monday, Wednesday and Friday). Treatment was given on an outpatient basis, with the IFN being administered either by the district nurse or by the patients themselves. Patients were seen at two and four weeks after starting therapy and then at monthly intervals. Therapy was continued until there was documented disease progression or 1 year of treatment had been completed. Following withdrawal of any patient from the study alternative treatment was given at the discretion of the treating physician.

A complete response (CR) was defined as complete disappearance of all evidence of disease clinically and the return to normal of all abnormal investigations. A partial response (PR) was a reduction of 50%, maintained for at least four weeks, in the product of two perpendicular diameters of a measureable lesion. No new lesions should have appeared, but not all the lesions need have regressed by 50% in order for a result to qualify as PR. Stable disease (SD) was a change in the product of two perpendicular diameters by between +25% and −50%. Progressive disease (PD) meant that new lesions had appeared or there was a 25% increase in the product of two perpendicular diameters of any measurable lesion. The duration of response was measured from the date of first documentation of remission, and survival from the date of the first IFN injection.

Results

The study was activated in October 1982, and the last patient entered in January 1985. Four patients are sill receiving IFN but have had at least 5 months' treatment. The median number of IFN injections given was 37 (4-158). In all, 35 patients have been entered, and their characteristics are shown in Table 1. One patient is not evaluable for response. She was known to have ischaemic heart disease and had a history of cardiac arrythmias. She received four doses of IFN and was admitted to another hospital with an intractable cardiac arrythmia, from which she died.

All of the patients experience influenza-like symptoms after the first few injections of IFN. These were mild and tachyphylaxis occurred. By 1 month of treatment patients were either not recording these symptoms or they had abated and become intermittent. Most of the patients described feeling rather more tired than before starting the IFN therapy. This was mild and did not interfere with the life style of any of the patients. WHO grade I haematological toxicity occurred with a fall in the white blood count during the 1st month of treatment. This haematological toxicity did not worsen after the 1st month, and no patients had to have the IFN suspended or dose modified because of it. No patient developed abnormal liver function as a result of IFN, and there was no renal toxicity. Neither was there any evidence of peripheral neuropathy, even in those patients who had previously been exposed to vinca alkaloids. Reactivation of latent herpes labialis was seen in 5 of the 35 patients, with positive electron microscopy for virus on smears of vesicle fluid. In 6 patients red patches developed around the sites of IFN injection. These patches developed 24 hours after the injection and lasted 2 to 3 days. They were not painful or pruritic. A skin biopsy from one of these showed a mild dermal infiltrate with lymphocytes and eosinophils.

Of the 34 evaluable patients, 17 responded (CR = 2, PR = 15) giving a response rate of 50% with 95% confidence limits of 32%–68%. The median duration of response was 11 months. Four other patients had SD when the IFN was stopped. One of these patients was the first patient entered in the study. At that time our intention was to escalate the dose of IFN after 3 months in patients with

Table 1. Patient characteristics

		Number	%
Sex	Male	17	49
	Female	18	51
Age (years)		median 57	(49–70)
Performance status		median 80	(60–90)
Histology	DLWD	11	31
	Follicular	24	69
Stage	III	10	29
	IV	25	71
Symptoms	A	27	77
	B	8	23
Bulky disease (≥5 cm)	Yes	22	63
	No	13	37
No prior chemotherapy		16	46

Table 2. Phase II results with human IFN-a_2 in patients with low grade NHL treated in Manchester: response by prior chemotherapy

	CR + PR (%)	95% confidence limits
None	11/16 (69)	41–89
Relapsed >2 months after chemotherapy	5/13 (38)	14–68
Relapsed ≤2 months after chemotherapy	1/5 (20)	1–81

Fisher's exact test: p = 0.09

Table 3. Response to IFN-a_2 by histology, stage, bulk of disease and symptoms

		CR + PR (%)	p value
Histology	DLWD	4/11 (36)	0.46
	Follicular	13/23 (57)	
Stage	III	6/10 (60)	0.71
	IV	11/24 (46)	
Symptoms	A	13/26 (50)	0.69
	B	4/8 (50)	
Bulk (≥5 cm)	Yes	11/21 (52)	0.69
	No	6/13 (46)	

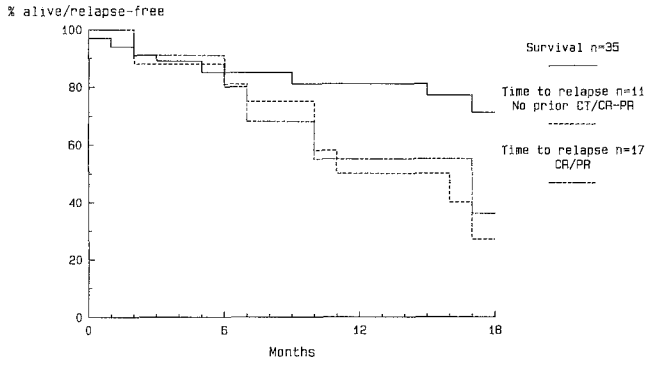

Fig. 1. The survival and time to relapse curves for patients with stages III and IV low grade non-Hodgkin's lymphoma treated with rDNA human alpha 2

SD disease. Accordingly this patient was given 30 megaunits/m^2 IV daily for 5 days after the 3 months of low-dose treatment. He had severe toxicity and declined further IFN treatment. Following this we did not continue with the policy of dose escalation. The second of these patients developed pneumonia after 3 months therapy and subsequently developed renal failure and died. The third patient stopped IFN after 5 months because of lethargy and tiredness thought to be due to IFN. She rapidly developed progressive disease after stopping IFN, and it became clear that her symptoms were due to NHL and not IFN. The final patient received 12 months therapy, after which her disease remained static for a further 6 months. She subsequently required chemotherapy. The progression-free survival curves and the overall survival curve are shown in Fig. 1. Response by prior treatment is given in Table 2, and response by histology, stage and symptoms in Table 3.

The 16 patients who had not received chemotherapy previously are all alive but 11 of the remaining 19 patients have died, 8 of NHL, 1 of pneumonia, and 2 from cardiac causes. Both of the last 2 patients had a prior history of cardiac problems; 1 of them has been discussed above. The other had a history of angina and died in hospital of a myocardial infarction.

Discussion

There are eight published reports detailing the results of treating low grade NHL with IFN (Table .4). Most of these studies have used leucocyte or fibroblast IFN and have been conducted almost exclusively in patients who had received chemotherapy previously. Among a total of 151 patients reported on, the response rate of 38% indicates a significant degree of activity for IFN.

In this study the results of treating a cohort of previously untreated patients who were not suitable for an initial watch policy are presented. The response rate of 69% appears higher than that seen in previously treated patients, although the difference does not reach statistical significance at the 5% level ($P=0.1$, Fisher's exact test). This degree of activity is similar to that which would be expected with single alkylating agents.

One other study [7] reported was conducted in series of previously treated patients with low grade NHL given a recombinant IFN (rDNA, IFN-a_2). In this study a dose of 50 million units/m^2 was administered three times per week by IM injection. This regimen was toxic, requiring initial hospitalization of the patients, and all but one patient had to have the dose reduced by at least 50%. Although the response rate of 54% appears higher than that seen in the current series (38% in previously treated patients) this is not a significant difference (raw $Chi^2=1.059$ with 1 df: $p=0.3$). It therefore remains unclear whether there are dose or schedule effects for IFN in low grade NHL. Rand-

Table 4. Interferon in patients with low grade non-Hodgkin's lymphoma

Non recombinant IFNs			No.	CR+PR	Follicular	DLWD+CLL
HuIFN-α (le)	Louie et al. 1981 [18]	5 mega IM × 2/day 30 days	8	4	4/8	–
HuIFN-α (le)	Gutterman et al. 1980 [10]	3 mega IM/day 28+ days	10	5	3/6	2/4
HuIFN-α (le)	Hornings 1983 [12] ACS study	9 mega IM/day 28 days	28	6	6/18	0/10
HuIFN-β (F)	Siegert et al. 1982 [22]	4.5–9 mega IV/day 42 days	10	2	2/10	–
			56	17 (30%)	15/42 (36%)	2/24 (14%)
Recombinant IFNs						
HuIFN-αA	Foon et al. 1984 [7]	50 mega IM × 3/week	24	13	Insufficient data given	
HuIFN-α_2	Leavitt et al. 1985 [16]	2 mega SC × 3/week 12+ weeks	28	9	9/21	0/7
HuIFN-α_2	Wagstaff et al. 1985 this paper)	2 mega SC × 3/week 12+ weeks	34	17	13/21	4/11
HuIFN-α_2	Wagstaff et al. 1985 [25]	Various	9	2	2/9	–
			95	41 (43%)	24/51 (47%)	4/18 (22%)
Overall results for all cases			151	58 (38%)	39/93 (42%)	6/32 (19%)

omised trials or singlearm studies with larger numbers of patients will be necessary to answer this question. Low-dose therapy, however is much more acceptable from the patients' point of view, and it appears, on the evidence available at present, that this would be the preferred regimen.

In our series of 35 patients there were 3 patients who developed cardiac problems. All 3 patients had a history of cardiac disease. Whilst we do not feel that IFN is directly cardiotoxic, it may be that the "stress" induced by IFN therapy can exacerbate an underlying cardiac problem. We therefore counsel caution in administering IFN to patients with a history of cardiac disease.

As a consequence of the small numbers of patients treated in the trials summarised in Table 4 we must be circumspect about drawing too many conclusions concerning factors, which might predict a greater likelihood of a response to IFN. However, it appears that patients with a follicular histology (CR + PR = 42%) have a higher response rate than those with DLWD (CR + PR = 19%: raw Chi-square = 4.594, $p = 0.03$). In our series we observed responses in 4 of 11 patients with DLWD histology and 9 of these had received chemotherapy previously. This was not a significantly lower response rate than we observed in our patients with follicular histology (36% vs 57%: $p = 0.5$). This may constitute evidence that IFN-a_2 is more active in patients with DLWD histology than the older preparations of leukocyte IFN, although once again larger numbers of patients will need to be treated to confirm this.

It seems clear that recombinant IFNs have substantial activity in low grade NHL, and thought now needs to be given to the problem of how to integrate IFN into the management of these patients. Three startegies could be entertained. Firstly at diagnosis patients could be divided into two groups, those in whom an initial watch policy is appropriate and secondly those who require immediate therapy. In this latter group low dose IFN could be used. In this way it may be possible to delay the time when more toxic and possibly carcinogenic chemotherapy would be required.

A number of workers have now demonstrated that synergy exists between other chemotherapeutic agents including alkylating agents and IFN [2, 5, 9, 26, 28]. Since the toxicity profiles of IFN and alkylating agents are different it is an attractive proposition to combine these two classes of drug in an attempt to exploit the possible synergy between them in a clinical setting. A randomised multicentre trial comparing chlorambucil alone with chlorambucil plus IFN has been started in the UK in an attempt to answer this question.

Low grade NHL patients have a continously relapsing course following induction chemotherapy/radiotherapy. It may be possible to prevent or delay recurrence by giving IFN maintenance therapy once a remission has been induced. Several randomised trials have been started, both in Europe and the USA, in order to explore this scenario.

Over the coming few years we will learn much more about the biology of the IFN family and how to apply this knowledge to a clinical setting. As I have indicated above many important questions concerning the optimum way to administer IFN remain unanswered. Indeed other IFN species such as gamma (immune) IFN may prove superior, in a clinical context, to the IFN's already available. The results of the clinical trials described above will soon begin to appear and we will be able decide for the first time whether IFN has a significant role to play in the management of patients with NHL.

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Received October 10, 1985/Accepted January 22, 1986