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RECOMBINANT INTERFERON GAMMA TREATMENT IN NON-SMALL CELL LUNG CANCER

Antitumour effect and cardiotoxicity

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Abstract

Fifteen patients with previously untreated, inoperable non-small cell lung cancer were treated with r-IFN-gamma 2 mg/m^2, on alternate days three times a week for a maximun of 12 weeks. After IFN treatment patients with stage III a + b disease received radiotherapy (55 Gy/44 F/32 d b.i.d.), and 4/5 patients with stage IV disease received chemotherapy (cisplatin-vindesine). Ten patients were evaluable for response at 4 weeks; 9 had stable disease and one had progressive disease. At 12 weeks 7 patients were evaluable; one had a partial response, and 6 had stable disease. Of 10 patients subsequently given radiotherapy 2 achieved CR, 5 PR, and 3 SD. Of the 3 evaluable patients receiving chemotherapy 1 PR, 1 SD and 1 PD were observed. IFN-gamma treatment was discontinued due to toxicity in 7/15 of patients. Main toxicities were the 'flu'-like syndrome (in 15 patients) and cardiovascular events (in 13 patients). Three patients were withdrawn because of cardiotoxicity. Our results suggest that high dose r-IFN-gamma might have some biological activity in NSCLC and does not interfere with subsequent conventional therapies given with a curative intent.

Key words: Lung cancer, non-small cell, interferon-γ, recombinant, radiotherapy, chemotherapy.

Interferons (IFNs) act on solid tumours by other mechanisms than conventional cytotoxic agents. The optimal therapeutic dose as well as the scheduling and duration of IFN therapy in cancer treatment cannot be derived by the same principles as adopted for cytotoxic chemotherapy.

Results from experimental and clinical studies suggest that IFNs are biologically active against small cell lung cancer (SCLC) (1, 2). Natural alpha interferon (n-IFN-alpha) induced class I histocompatibility antigens on SCLC cells both in vitro and in vivo (3). Recombinant gamma interferon (r-IFN-gamma) and granulocyte macrophage colony-stimulating factor (GMSF) inhibited growth and induced antigens characteristic of myeloid differentation in SCLC cell lines (4). In a clinical study, promising preliminary results indicated that n-IFN-alpha maintained a response achieved with chemoradiotherapy (5).

Non-small cell lung cancer (NSCLC) on the other hand was refractory to alpha IFNs in several studies (6, 7). Data on the activity of r-IFN-gamma against this disease are scarce. r-IFN-gamma shares many of the properties of IFN-alpha but has also several specific modes of action (8). To obtain data on the efficacy of r-IFN-gamma on NSCLC and its spectrum of clinical toxicity, we performed an open study in patients with previously untreated inoperable NSCLC using i.v. high-dose r-IFN-gamma as a single agent, before conventional therapies.

Material and Methods

Fifteen patients with previously untreated, inoperable NSCLC entered the study. Entry criteria were as follows: Measurable disease with a Karnofsky performance status > 70% (ECOG 0, 1 or 2) and no evidence of cerebral metastases; age 18–72 years; WBC $> 3 \times 10^9$/l; platelet count $> 75 \times 10^9$/l; and haemoglobin > 95 g/l. None had renal disease, chronic hepatic disease or respiratory failure.

Cardiovascular status was evaluated using resting 12 lead ECG and exercise ECG. Patients with evidence of cardiac arrhythmias, congestive heart failure, hypertension

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or a recent (<3 months) myocardial infarction were excluded. However, patients with cardiovascular disease, clinically stable and controlled by appropriate medication, were included. Informed consent was obtained from all patients.

r-IFN-gamma (specific activity of >95% pure material was 24×10^6 U/mg protein) was given as a 4 h IV infusion in 5% dextrose at a dose of 2 mg/m^2 3 times a week, on alternate days up to a maximum of 12 weeks. Thereafter patients with M0 disease received radiotherapy (55 Gy/44 F/32 d) and patients with M1 disease received chemotherapy (cisplatin 90 mg/m^2 q 28 days × 3 and—vindesine 3 mg/m^2 q 14 days × 6). Vital signs (temperature, pulse, respiration, and blood pressure) were measured immediately before treatment, during infusion, and 1 h after infusion.

Patients were evaluated for tumour response every 4 weeks whilst receiving r-IFN-gamma. Response and toxicity evaluations were made according to the WHO criteria (9). Patients who had received a minimum of 4 weeks of r-IFN-gamma were considered evaluable for treatment efficacy. All patients receiving r-IFN-gamma were evaluable for treatment toxicity. The duration of any response was measured from the date of the first documentation of remission.

Haematology, blood chemistry, and urine analysis were performed before entry into the study, weekly for the first 4 weeks of the study, every 4 weeks thereafter, and at cessation of treatment.

A full physical examination, with evaluation of performance status, was carried out at the end of each treatment week. Cardiovascular status was evaluated before and after treatment by chest x-ray with measurement of heart volume, a resting 12 lead ECG and a bicycle exercise test with ECG and blood pressure recordings. Further ECGs were also performed if clinically indicated. Early in the study ECG examinations were extended to cover r-IFN-gamma administration, ECGs being taken before treatment, during infusion and 1 h after infusion.

EEG with psychometric tests was performed before and after treatment and at any time during treatment if clinically indicated. All patients received acetaminophen at high doses (1 g qds) to cover the infusion of r-IFN-gamma. Some patients also received indomethacin for the same reason.

Results

The study began in January 1985 and the last patient entered in January 1986. Fifteen patients received r-IFN-gamma and their characteristics are given in Table 1. Seven completed the 12-week course of treatment (8 patients did not complete 12 weeks). Ten out of 15 patients with stage III disease initially were subsequently given radiotherapy, and 4/5 patients with stage IV disease initially received 2–3 cycles of combination chemotherapy.

Table 1

Characteristics of 15 patients with inoperable non-small cell lung cancer treated with r-IFN-gamma

No. of patients	15
Male/Female	12/3
Age, years, median (range)	63 (50–71)
Karnofsky	
>80%	12
60–70%	3
Diameter of primary tumor	
≥5 cm	9
<5 cm	6
Cell type	
Epidermoid	10
Adeno	3
Large cell	2
Stage	
III a + b	10
IV	5

Table 2

Tumour response to r-IFN-gamma and subsequent radio- or chemotherapy in patients with non-small cell lung cancer (n = 15)

Time of assessment	Number of patients	Tumour response
r-IFN-gamma		
4 weeks	10	1 MR, 8 SD, 1 PD
12 weeks	7	1 PR, 3 MR, 3 SD
After radiotherapy	10	2 CR, 5 PR, 2 MR, 1 SD
After chemotherapy		
1 cycle	3	2 SD, 1 PD
2 cycles	3	2 SD, 1 PD
3 cycles	1	1 PR

Abbreviations: CR = complete response; PR = partial response; MR = minor response; SD = stable disease; PD = progressive disease.

Ten patients were evaluable for response to single r-IFN-gamma therapy at 4 weeks and 7 patients were evaluable at 12 weeks (Table 2). Of the 3 patients with minor response, two had epidermoid carcinoma and one adenocarcinoma. The only patient with a PR had epidermoid carcinoma (clinical stage T3N2M0) and received radiotherapy (RT) immediately after r-IFN-gamma therapy and achieved a complete response (CR), with survival for 22 months. Median survival in the entire group of 15 patients was 15 months (4–46 months). One-year survival was 67% and 2-year survival 20%.

All patients developed a 'flu'-like syndrome with fever, tachycardia, chills, malaise, headache and muscle pain during the course of each infusion. No patient displayed any signs or symptoms of neurotoxicity despite systematic

monitoring by EEG and psychometric tests. Hypotension (defined as > 30 mm Hg fall in systolic blood pressure) was seen in 6 patients. In 5 of them the observation was isolated, requiring no treatment or dose reduction. One patient developed orthostatic hypotension, but was able to complete the 12 weeks' course without any dose reduction or interruption. In the 7 patients completing the study (12 weeks of treatment) there were changes in ECG, all patients exhibiting sinus tachycardia at most infusions of r-IFN-gamma. Prolongation of the QT interval and QU changes were prominent features and they were accompanied by ST/T wave changes. However, the ECG changes were not accompanied by symptoms, nor did they require treatment or dose reduction. Two of the patients completing the study had premature ventricular beats recorded during their treatment. One patient has also a sinus tachycardia on entry to the study and had episodes of hypocalcaemia during the study. The ECG changes are consistent with this finding. One patient had aortic stenosis on entry. Premature ventricular beats were observed early in the study, and continued intermittently throughout. The patient had no recorded electrolyte abnormalities.

Of the 8 patients who did not complete the study, 3 dropped off due to the 'flu'-like syndrome, one after 5 weeks, another after 7 weeks and the third after 3 weeks, despite high doses of acetaminophen. One patient was withdrawn because of progressive disease at 4 weeks, and one had an anaphylactic reaction to the first dose of r-IFN-gamma, with severe bronchoconstriction at the end of the first infusion. Three patients were withdrawn due to cardiovascular events. One patient had a previous history of myocardial infarction and coronary artery by-pass grafting some years prior to entry in the study. The pre-entry ECG showed intermittent right bundle branch block (RBBB), which became constant after 10 days. The r-IFN-gamma dose was reduced from 3 mg to 1.5 mg but a complete A-V block developed, and the patient was withdrawn from the study and a pacemaker was installed. Three months after leaving the study the patient died following another myocardial infarction. The second patient received only 2 doses of r-IFN-gamma. The pretreatment ECG showed a sinus tachycardia, and atrial fibrillation developed the day after the first injection of r-IFN-gamma. Cardiac monitoring over the next few weeks revealed intermittent atrial fibrillation. The patient died 8 months after discontinuation of r-IFN-gamma therapy, and at post-mortem there was evidence of pericardial invasion by the tumour. In the third patient the infusion was discontinued since ventricular premature beats began after infusion of 1.5 mg IFN. The pretreatment resting ECG was normal but the exercise ECG pretreatment showed ventricular ectopic beats with RBBB. The arrhythmia persisted and the patient was withdrawn. This patient had a CR with radiotherapy. His overall survival was 10 months.

There were no significant changes in haematological parameters, and serial examinations of neutralising antibodies to r-IFN-gamma were negative. There were some changes in biochemical parameters, including marked reductions in serum calcium and serum potassium. These occurred sporadically in most patients, hypocalcemia being more frequently seen.

Discussion

The greatest degree of antitumour activity of any type of IFN when used as single agent therapy has been observed in hairy cell leukemia (10). Clinical responses have also been seen in several other malignancies (11, 12), notably those usually refractory to cytotoxic chemotherapy such as melanoma and renal cell carcinoma. In our study, the activity of r-IFN-gamma on NSCLC was tested.

Previous studies performed in NSCLC with any type of IFN alone have been negative (6, 7, 13). However, when interferons were combined in experimental studies with radiotherapy (14) or chemotherapy (15), a synergistic effect was obtained. Clinical studies supporting this synergism have recently been reported (16). The results of our study with sequential therapies gave a median survival of 15 months, with 67% of patients surviving for 1 year and 20% for 2 years, which compares favourably with previous reports. Current studies are investigating the optimal way of combining interferons with conventional therapies. In our study IFN was given first followed by either radio- or chemotherapy. This allowed us to obtain clear information on the efficacy of r-IFN-gamma as a single agent in NSCLC.

We selected patients with a good prognosis, who had received no previous treatment. There were 6 patients with stable disease and one with a partial response after 12 weeks of treatment with r-IFN-gamma. Within the stable disease category 3 patients had minor responses i.e. some reduction in tumour size but insufficient for a PR rating. However, when single agent biological response modifiers are used, the concept of requiring partial or complete tumour response as the criterion for efficacy may not be valid; maintenance of stable disease may well demonstrate biological activity. Again, biological response modifiers are known to produce late rather than early responses. This protocol, activated in January 1985, selected high-dose short duration treatment believed at that time to be optimal, as opposed to a lower dose, longer duration treatment which is the current practice. Furthermore we did not want to delay potentially curative conventional therapies.

The characteristic acute toxicity, typical of IFNs when given in high doses, was seen in this study, with all patients developing fever, tachycardia, malaise, headache and muscle pain during the infusions of IFN. Contrary to our experience with n-IFN-alpha the patients did not develop tachyphylaxis, the degree of fever and tachycardia

remaining constant throughout the study. This 'flu'-like syndrome was clearly relieved by acetaminophen doses up to 1 g qds which was routinely used. We also used diazepam and indomethacin for symptom treatment during and after the infusion.

This particular group of patients with NSCLC were mostly heavy smokers all their lives; thus they had a background of pulmonary and cardiovascular illness needing treatment. The acute 'flu'-like syndrome, with its accompanying tachycardia, may impose a strain on the cardiovascular system and exacerbate an underlying problem. Early in the course of the study we saw minor prolongation of the PQ (PR) interval in two patients. This had no clinical significance for the patients with both patients completing the 12-week study. For this reason we increased the frequency of ECG recordings during and after the IFN infusion and detected clinically significant arrhythmias in 5 patients. In these 5 cases of arrhythmias, we have to consider the role played by r-IFN-gamma. In the first 2 cases, the atrial fibrillation and the AV block, it is probable that these events were directly related to r-IFN-gamma treatment. Another reason could be progression of an underlying disease state. In the other 3 cases, all having premature ventricular beats, the effect was also probably related to the administration of r-IFN-gamma. However, only one of these 3 failed to complete the study and was withdrawn. None suffered any clinical symptom as a result of the arrhythmia. The clinical background of this particular group of patients can create a potential for arrhythmogenesis, and it may be that r-IFN-gamma was exacerbating an underlying condition rather than causing a direct effect. This interpretation is supported by a study by Steiner et al. (17) reporting myocardial infarction in 2 out of 7 patients treated with low-dose r-IFN-gamma. Both patients had a pretreatment diagnosis of mild ischemic heart disease.

We conclude that r-IFN-gamma showed some biological activity in NSCLC. To our knowledge such activity has not been seen using other interferons. High i.v. doses of r-IFN-gamma in this group of patients exacerbated underlying cardiovascular disease. It should therefore be used with caution in this type of patients. Close monitoring of ECG and electrolyte levels, particularly calcium, is recommended to further clarify the real spectrum of cardiotoxicity.

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