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Aerosol Application of Interferon-alpha in the Treatment of Bronchioloalveolar Carcinoma

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10 patients with locally advanced bronchioloalveolar carcinoma were treated with interferon-alpha as an inhaled aerosol. Initial doses ranged between 1 and 10 MU daily or thrice weekly and were then increased to 20 MU daily. Treatment was continued until disease progression or excessive toxicity occurred. 9 patients were evaluable for toxicity. In 1 case treatment had to be stopped after 2 weeks due to fever, fatigue and progressive dyspnoea. 2 patients developed fever, 1 had malaise, fatigue and loss of appetite and 2 had dose-dependent transient dyspnoea. According to standard criteria no tumour responses could be detected. In 6 out of 8 evaluated for response to interferon, radiological stabilisation of disease for 7–43 weeks (median 15) was observed. These results point to the feasibility of aerosol inhalation of interferon-alpha, but also to its limited antitumour activity in locally advanced bronchioloalveolar carcinoma.
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INTRODUCTION

BRONCHIOLOALVEOLAR CARCINOMA is a rare chest malignancy, accounting for 1–9% of all forms of lung carcinoma [1]. This tumour is less related to smoking than other types of lung cancer. Intranuclear virus-like inclusions in bronchioloalveolar carcinoma [2] as well as a similarity to 'Jaagsiekte', a contagious disease in sheep [3], suggest a viral aetiology. Patients with localised tumour may be treated successfully with surgery, but prognosis in advanced disease is poor because the tumour is resistant to radiotherapy and chemotherapy.

Interferon has antineoplastic activity in malignant melanoma and renal carcinoma [4]. Small and non-small cell lung cancers are resistant to treatment [5–8] but the modest antitumour efficacy of interferon may have been due to suboptimal doses and routes of administration [6]. The most frequent routes (intravenous, intramuscular, and subcutaneous) led to considerable toxicity and it is possible that rapid filtration of the drug by the kidneys decreases its concentration in target or effector cells [9].

Inhaled aerosol forms of drugs have been used in many lung disorders and aerosol administration of interferon may have therapeutic advantage [10]. Prophylactic intranasal application of interferon reduced the frequency of rhinoviral infection [11]. There are no clinical data, however, on this route of interferon application in patients with lung cancer. A feasibility study of inhaled interferon treatment in patients with bronchioloalveolar carcinoma has therefore been done. This type of lung cancer was chosen because its presumed viral aetiology may make it amenable to treatment with interferon. Moreover, it was hoped that topical administration of interferon would enable delivery of high drug dose at the tumour site with low systemic toxicity.

PATIENTS AND METHODS

Patients with locally advanced, inoperable bronchioloalveolar carcinoma entered this study between November 1981 and June 1989. Eligibility criteria included: Karnofsky performance status of 60% or more, age up to 70, lung function enabling satisfactory inhalation of aerosols, no cytostatic therapy within the previous 6 weeks, no therapy with immunosuppressives or antipyretics, no local or systemic infection and no fever. All patients gave informed consent. The following were assessed before treatment: history, physical condition, Karnofsky performance status, haemoglobin, haematocrit, erythrocyte sedimentation rate, white blood cell count and differential count, serum electrolytes, creatinine, aminotransferases, gamma GT, alkaline phosphatase. Chest radiograph, ventilation/perfusion scan, chest computerised tomography and lung function tests (total lung capacity, residual volume, forced expiratory volume in 1s, vital capacity and carbon monoxide diffusing capacity) were done. During the first week of treatment temperature was recorded daily and leucocytes were counted every second day. Thereafter leucocyte counts were done every second week and all other tests every 4 weeks during treatment. Treatment effects were evaluated by serial radiological chest examinations and by lung function tests. Response to treatment followed standard WHO criteria [12]. Time to progression and survival were computed from the start of treatment.

Lyophilised human lymphoblastoid (leucocyte-type) interferon was supplied by Dr Kari Cantell, Helsinki and 'recombi-

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Table 1. Patients' characteristics

Patient No. (sex/age)	Karnofsky score	Previous treatment
1 (M/64)	80	Lobectomy, interferon subcutaneously
2 (M/64)	40	—
3 (M/48)	90	Pneumonectomy
4 (M/40)	80	Bilobectomy, chemotherapy
5 (M/56)	70	Chemotherapy
6 (M/64)	80	—
7 (F/31)	90	Chemotherapy
8 (F/65)	100	—
9 (M/52)	100	Lobectomy, chemotherapy
10 (F/42)	60	—

Table 2. Results of treatment

Patient No.	IFN type	IFN dose (MU)	Treatment duration (weeks)	Toxicity	Response (weeks)	Survival (weeks)
1	H	3×3	54	Fever (38°C)	NC (43)	72
		2	13			
2	H	3×3	1	NE	—†	1
3	R	3×3	4	—	PD	3
		10×3	4			
		10	3			
4	R	3×3	5	—	NC (17)	42
		10×3	4			
		10	3			
5	R	10	6	Malaise, loss of appetite	NC (8)	15
		20	6			
6	R	10	5	—	PD	41
7	R	10	2	Fever (39°C), dyspnoea, malaise	NE	10
8	R	1	11	Dyspnoea	NC (16)	>48
		2	7			
		10	2			
9	R	10	2	Dyspnoea	NC (7)	>41
		20	11			
10	R	3×3	11	Fever (<38°C)	NC (15)	48
		10	8			
		2	6			

*All daily except × 3 = thrice weekly.
†Ineligible.
H = human and R = recombinant interferon, NC = no change, PD = progressive disease, NE = not evaluable.

nant' interferon by Wellcome Research Laboratories and Schering Corporation. Aerosol with a particle median diameter of less than 5 μm and a flow rate of more than 5 l/min was generated with a 'Turret' jet nebuliser by forcing compressed oxygen through a narrow orifice. A valve was used to prevent unnecessary loss of drug.

Patients were admitted for the initial period of treatment and therapy was continued on an ambulatory basis whenever possible. Patients received detailed instructions on the use and cleaning of the apparatus. Initial doses of interferon ranged between 1 and 10 MU delivered daily or thrice weekly. The dose was then increased up to 20 MU daily. Treatment was continued until there were radiological or functional signs of disease progression or excessive toxicity occurred.

In one patient, serum levels of interferon were measured. Serum samples were collected during the 3 days before inhalation, at the end of inhalation and after 15 and 30 min. Interferon levels were measured with an immunoradiometric assay [13].

RESULTS

10 patients entered the study (Table 1). Treatment lasted between 1 and 67 weeks (median 12) (Table 2). 1 patient (No. 2) was retrospectively judged ineligible due to low performance status (40%) and poor lung function. He died from disease progression 6 days after interferon treatment had been started. 9 patients were evaluable for toxicity (Table 2). In one patient (No. 7) treatment was stopped after 2 weeks due to excessive toxicity, including temperature up to 39°C, fatigue, and progressive dyspnoea. These symptoms disappeared soon after withdrawal of therapy. In the remaining 8 patients there was no or only mild toxicity: 2 patients had temperatures up to 38°C, one had malaise, fatigue and loss of appetite, and 2 had dose-dependent transient dyspnoea and deterioration of lung function tests. In both patients dyspnoea and pulmonary function improved shortly after stopping therapy. Leukopenia, thrombocytopenia and biochemical abnormalities never occurred.

None of the 8 patients fully evaluable for response had an objective clinical response (Table 2). In 6 patients radiological stabilisation for 7–43 weeks (median 15) of previously progressive disease was observed. This included patient No. 1 who had previously shown evidence of progressive disease during subcutaneous injections of interferon; aerosol application of the drug resulted in an apparent stabilisation of disease for 43 weeks. In 3 patients interferon slowed deterioration of lung function. 2 patients progressed during therapy after 5 and 6 weeks, respectively. Median time to progression for the whole group was 8 weeks (range 5–43) and the median survival time was 41 weeks (1–72). 2 patients are still alive including one (No. 9) leading a normal life.

In patient No. 10 serum levels of interferon were measured during treatment with a daily dose of 20 MU. At no time was interferon detected.

DISCUSSION

Our results demonstrated that aerosol application of interferon is a safe and tolerable method of treatment, in contrast to intramuscular or intravenous use of interferon, which is often accompanied by serious and dose-limiting side-effects. Interruption of treatment due to toxicity was necessary in one patient only, while in all other patients inhalation was well tolerated and allowed administration on an ambulatory basis.

The limited number of patients did not allow firm conclusions to be drawn on the antitumour activity of inhaled interferon in bronchioloalveolar carcinoma. This malignancy is refractory to any known systemic therapy. The lack of tumour response noted in our series suggests that inhaled interferon-alpha as a single agent is also of limited value. Similarly, no response to inhaled interferon in bronchioloalveolar carcinoma was observed in a Finnish study [14]. The slowing of disease progression for up to 43 weeks observed in a few patients in our study suggested some

antineoplastic activity by this agent, however. The effect was achieved without the side-effects that usually accompany aggressive systemic therapy of cancer.

In view of the limited experience of aerosolised interferon in malignant disease, dose and schedule was chosen based on experience in non-neoplastic disorders. Good tolerance suggests that higher doses of interferon could be used. However, there is no convincing evidence of dose-dependency of tumour effects for interferon [15].

The rationale of topical administration of interferon is to deliver high doses directly at that tumour site. There is no evidence that this aim is achieved by inhalation. Interferon was not detected in the serum of 1 patient. In another study of bronchioloalveolar carcinoma, interferon could be detected in serum only after the inhalation of doses of 18 MU or more [14]. This suggests absorption and probably use of interferon in lung tissue. High absorption of inhaled interferon in lung mucosa has been demonstrated experimentally [10].

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Effect of Inhaled Natural Interferon-alpha on Diffuse Bronchioalveolar Carcinoma

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Six patients with diffuse bronchioalveolar carcinoma confined to the thorax were treated with interferon-alpha by inhalation. The dose was 1 or 6 MU thrice daily. Therapy was continued until the tumour progressed or bronchial hyperreactivity became unacceptable. The treatment was not effective.
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INTRODUCTION

BRONCHIOALVEOLAR CARCINOMA (BAC) is a subtype of adenocarcinoma of the lung originating from alveolar type II pneumocytes and/or bronchiolar Clara cells. The common diffuse bilateral form is beyond curative surgery, radiotherapy or chemotherapy [1]. Results with combined radiation and chemotherapy are poor and progression, which most often occurs within the thorax, is not prevented. Interferon (IFN) has both antiviral and antitumoral activity. By inhalation, IFN reaches the target cells of BAC directly, maximizing local tumour effect and minimizing systemic side-effects. IFN-alpha is partly absorbed after bronchial instillation in perfused rabbit lung [2] and after single high-dose (60 MU) inhalation in man [3]. In a pilot study we have evaluated the antitumour effect, toxicity and feasibility of using inhaled natural IFN-alpha in patients with diffuse BAC.

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