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].

1. Edwards CW. Alveolar carcinoma: a review. *Thorax* 1984, **39**, 166–174.
2. Singh G, Katyal SL, Torikata C. Carcinoma of type II pneumocytes. Immunodiagnosis of a subtype of 'bronchioloalveolar carcinomas'. *Am J Pathol* 1981, **102**, 195–208.
3. Nobel TA, Perk K. Animal model of human disease. Bronchioloalveolar cell carcinoma. *Am J Pathol* 1978. **90**, 783–786.
4. Gutterman J. Overview of advances in the use of biological proteins in human cancer. *Semin Oncol* 1988, **15** (suppl 5), 2–6.
5. Jett JR. Is there a role for interferon in the treatment of small cell lung cancer? *Lung Cancer* 1990 (in press).
6. Jones DH, Bleehen NM, Slater AJ, George PJM, Walker JR, Dixon AK. Human lymphoblastoid interferon in the treatment of small cell lung cancer. *Br J Cancer* 1983, **47**, 361–366.
7. Leavitt RD, Duffey P, Aisner J. A phase II study of recombinant leukocyte-A interferon in non-small cell carcinoma of the lung. *Proc ASCO* 1984, **3**, 52.
8. Olesen BK, Ernst P, Nissen MH, Hansen HH. Recombinant interferon A (IFL-rA) therapy of small cell and squamous cell carcinoma of the lung. A phase II study. *Eur J Cancer Clin Oncol* 1987, **23**, 987–989.
9. Bocci V. Evaluation of routes of administration of interferon in cancer: a review and a proposal. *Cancer Drug Deliv* 1984, **1**, 337–351.
10. Bocci V, Pessina GP, Pacini A, Paulesu L, Muscettola M, Mogensen KE. Pulmonary catabolism of interferons: alveolar absorption of ^{125}I-labelled human interferon alpha is accompanied by partial loss of biological activity. *Antiviral Res* 1984, **4**, 211–219.
11. Douglas RM, Moore BW, Miles HB *et al.* Prophylactic efficacy of intranasal alpha 2-interferon against rhinovirus infections in the family setting. *N Engl J Med* 1986, **314**, 65–70.
12. *WHO Handbook of Reporting Results of Cancer Treatment.* WHO Offset Publication No. 48, 1979.
13. Walker JR, Nagginton J, Scott GM, Secher DS. An immunoradiometric assay of serum interferon using a monoclonal antibody. *J Gen Virol* 1982, **62**, 181–185.
14. Kinnula V, Cantell K, Mattson K. Effect of inhaled natural interferon-alpha on diffuse bronchioalveolar carcinoma. *Eur J Cancer* 1990, **26**, 740–741.
15. Maluish AE, Urba WJ, Longo DL *et al.* The determination of an immunologically active dose of interferon-gamma in patients with melanoma. *J Clin Oncol* 1988, **6**, 434–445.

Acknowledgements—We thank Dr K. Cantell, Wellcome Research Laboratories and Schering Corporation for providing interferon-alpha, and Dr W. Bakker and Prof. J.H. Dijkman for their help and cooperation.

Eur J Cancer, Vol. 26, No. 6, pp. 740–741, 1990.
Printed in Great Britain

0277–5379/90$3.00 + 0.00

Effect of Inhaled Natural Interferon-alpha on Diffuse Bronchioalveolar Carcinoma

Vuokko Kinnula, Kari Cantell and Karin Mattson

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.
Eur J Cancer, Vol. 26, No. 6, pp. 740—741, 1990.

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.

Correspondence to: Karin Mattson, Department of Pulmonary Medicine, Helsinki University Central Hospital, Haartmaninkatu 4, 00290 Helsinki, Finland.
V. Kinnula, K. Mattson are at the Department of Pulmonary Medicine, Helsinki University Central Hospital and K. Cantell is at the National Public Health Institute, Helsinki, Finland.

PATIENTS AND METHODS

Eligibility criteria included: confirmed diagnosis of diffuse BAC confined to the thorax, no previous radiotherapy to the reference lesions, age under 70, Karnofsky score of at least 60% and pulmonary function adequate to undergo inhalation therapy (forced vital capacity 50% or more of predicted). Natural IFN-alpha (Finnferon-alpha, Finnish Red Cross) was administered with a dosimeter-equipped jet nebulizer delivering particles with a mass median diameter of 1.6 μm (Spira Electro 4, Hämeenlinnan Työkeskus) after dilution in 1 ml 0.9% NaCl (pH 7.4). 1 ml of the solution was nebulized during the first 0.6 s of consecutive inspirations during normal breathing. The dose of IFN was 1 or 6 MU three times a day and treatment was continued until the tumour progressed or toxicity was unacceptable.

Patients were evaluated for response by chest X-rays and computerized tomography monthly. Toxicity was graded according to WHO guidelines. Pulmonary and other toxicities were monitored by serial measurements of peak expiratory flow rate (PEFR) three times a day and spirometric indices; diffusing capacity; electrocardiagram (ECG); weekly blood counts and blood biochemistry. Serum interferon levels were measured by vesicular-stomatitis virus plaque reduction in HEp2 culture. Measurements were done before the start of treatment, at least every fourth week during treatment and once after discontinuation. Quality of life was assessed on a visual analogue scale [4].

RESULTS

Table 1 shows the clinical characteristics of the patients, IFN doses and duration of treatment. With the exception of patient 3, all were smokers or ex-smokers, had chronic bronchitis and had had bronchodilator treatment before the beginning of IFN therapy. In patient 1 no side-effects were observed, but treatment was discontinued after 5 weeks because of progressive disease. In patient 2, the thrice daily dose of 1 MU was increased to 6 MU after 16 weeks and discontinued after 2 days because of dyspnoea, wheezing and decrease in PEFR. Tumour response was classified as stable disease at discontinuation of IFN. Patients 3–6 inhaled an initial dose of 6 MU but treatment had to be stopped due to progression and side-effects after 2–4 weeks.

Side-effects of inhaled IFN included coughing and dyspnoea starting within 3–6 h of inhalation. PEFR decreased from pretreatment recordings, especially in patient 3 (Fig. 1). Variations over 15% in daily PEFR were recorded in the other

Table 1. *Clinical characteristics of patients, IFN doses and duration of IFN treatment*

Patient No. (sex/age)*	IFN (MU thrice daily)	Duration of treatment (weeks)
1 M (54)	1	5
2 M (60)	1	
	6	16.3†
3 F (60)	6	4
4 M (55)	6	4
5 M (64)	6	2
6 F (50)	6	3.5

*Patients 2 and 4–6 also had chronic obstructive pulmonary disease and patient 4 also had diabetes mellitus.
†1 MU thrice daily for 16 weeks and 6 MU thrice daily for 2 days.

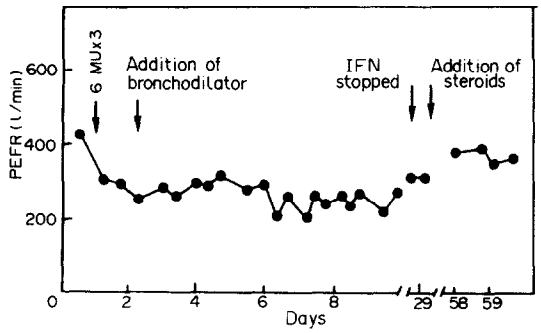

Fig. 1. PEFR during and after inhaled IFN-alpha (patient 3).

patients, irrespective of ongoing bronchodilator treatment. In patient 3 forced expiratory volume in 1s decreased from 2.2 l (80%) before treatment to 1.6 l (59%) after treatment, increasing to 2.0 l (75%) during oral steroid therapy started after the discontinuation of IFN. None of the patients experienced fever or chills. No changes occurred in white blood cell count, platelet count or liver transaminase or creatinine levels. No significant ECG changes were observed. IFN was never detected in the serum.

The administration of IFN by inhalation with our device was feasible on an outpatient basis and was well accepted by the patients.

DISCUSSION

Previous clinical single-agent studies of parenteral IFN-alpha or IFN-beta for non-small cell lung cancer have been negative [5]. In combination therapy IFN-alpha has enhanced radiation effects in the treatment of small cell lung cancer [6]. Inhaled natural IFN-alpha was not active against diffuse BAC in our patients.

The dose-limiting toxicity in our study was bronchial hyperreactivity and/or bronchoconstriction despite the physiological pH of the inhaled solution and optimal particle size. Impurities of the natural crude IFN preparation may be the cause of the local toxicity. Although we consider this unlikely, similar investigations should be done with recombinant pure interferons, possibly combined with prophylactic supportive bronchodilator treatment. Inhaled IFN may have a role in the prophylaxis or treatment of lower respiratory tract virus infection. A nasal IFN spray had a prophylactic effect in rhinovirus infection.

1. Malik R, Keating RJ, Valdivieso M. Bronchoalveolar lung cancer. *Semin Resp Med* 1982, **4**, 64–75.
2. Bocci V, Pessina JP, Pacini A, Paulesu L, Muscettola M, Mogensen KE. Pulmonary catabolism of interferons: alveolar absorption of ^{125}I-labeled human interferon-alpha is accompanied by partial loss of biological activity. *Antiviral Res* 1984, **4**, 211–220.
3. Kinnula V, Mattson K, Cantell K. Pharmacokinetics and toxicity of inhaled human alpha interferon in patients with lung cancer. *J Interferon Res* 1989, **9**, 419–423.
4. Selby PJ, Chapman J-AW, Etazadi-Amdi J *et al.* The development of a method for assessing the quality of life of cancer patients. *Br J Cancer* 1984, **50**, 13–22.
5. Sarna G, Figlin R, Callaghan M. α-(Human leucocyte)-interferon as treatment for non-small cell carcinoma of the lung: a phase II trial. *J Biol Resp Med* 1983, **2**, 343–347.
6. Holsti LR, Mattson K, Niiranen A *et al.* Enhancement of radiation effects by alpha interferon in the treatment of small cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys*, 1987, **13**, 1161–1166.
7. Scott GM, Phillpotts RJ, Wallace J *et al.* Purified interferon as protection against rhinovirus infection. *Br Med J* 1982, **284**, 1822–1825.