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# Recombinant Interferon A (IFL-rA) Therapy of Small Cell and Squamous Cell Carcinoma of the Lung. A Phase II Study

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**Abstract**—*Recombinant interferon A* ($50 \times 10^6$ U/m$^2$ *three times weekly*) *was given to* 17 *patients with SCCL and* 13 *patients with SQL. The minimal scheduled duration of therapy was* 12 *weeks. Fifteen and* 11 *patients, respectively, were evaluable for response. All* 15 *patients with SCCL showed progressive disease after a period of* 2.5 *weeks (median; range* 1–13). *One patient with SQL obtained a partial remission lasting* 14 *months and six patients showed no change for* 14–20 *weeks, while the remaining patients showed progression during the initial* 12 *week period.*

*Toxicity was shown to be significant and only one patient completed therapy without dose reduction. The major cause of dose reduction was fatigue and anorexia* (18 *patients). Fourteen patients experienced a median weight loss of* 6%. *Haematological and hepatological toxicity was found in six and* 19 *patients, respectively. In most cases parameters of marrow and liver function were reversible in spite of continuing interferon treatment.*

## INTRODUCTION

INTERFERONS are glycoproteins with antiviral, antiproliferative and immunomodulating activity [1, 2]. Following the development of gene technology, interferon has been produced by cloning the human gene for interferon in *E. coli* bacteria resulting in the procurement of larger amounts of interferon with a purity around 80–90%.

As a part of this development a prospective study was undertaken testing the efficacy and tolerance of recombinant interferon A† in patients with small and squamous cell carcinoma of the lung refractory to conventional treatment.

## MATERIALS AND METHODS

Patients with histologically proven small cell or squamous cell carcinoma of the lung having measurable disease according to WHO criteria [3], aged between 18 and 70 years and with a performance status above 50 (Karnoffsky) were included in the study. No patients had received chemotherapy or radiation within the preceding 4 weeks. None of the patients had previously received interferon. All patients with small cell lung carcinoma (SCCL) showed progressive disease on intensive combination chemotherapy. All patients with squamous cell lung cancer were found to have a non-resectable tumour.

Before entering the study, patients underwent physical examination including measurement of tumour markers, chest X-ray, ECG and bone marrow aspiration and biopsy. During the study physical examination was repeated initially once a week and later every 2 weeks. Chest X-ray and measurement of marker lesions were done monthly. The following laboratory values were measured before and during the study: hepatitis B antigen, haemoglobin, platelet counts, white blood and differential counts, s-alkaline phosphatase, s-GOT, s-bilirubin, s-calcium, s-uric acid, s-glucose and s-creatinine. A urine specimen was analysed for protein, blood and sugar. Recombinant leucocyte A interferon was given at a dose of $50 \times 10^6$ units per square metre (U/m$^2$) intramuscularly (i.m.) three times weekly. The minimal scheduled treatment period was 12 weeks. Before the administration of interferon, 1 g of paracetamol was given to ameliorate fever and chills. Dose reduction was carried out according to the WHO grading of toxicity in such a way that the dosage of interferon remained unchanged for grades I–II, while the dose was descalated for grade III in a stepwise fashion

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*Table* 1. *Results (antineoplastic effect)*

| | Evaluable patients | Duration of treatment (weeks) median (range) | Number of injections median (range) | Total amount of interferon median (range) | Response PD | NC | PR | CR |
|---|---|---|---|---|---|---|---|---|
| SCCL | 15 | 2 1/2 (1–13) | 8 (2–32) | 644 × $10^6$ U (136–1466) | 14 | 1 | | 0 |
| SQL | 11 | 15 (2–73) | 40 (5–115) | 1650 × $10^6$ U (429–3440) | 4 | 6 | 1 | 0 |

to 50 and 10% of the original dose. If grade IV occurred, the patient was withdrawn from the study. Definitions of treatment responses followed criteria as recommended by WHO. Patients showing progressive disease during the treatment were removed from the study. If a complete remission, partial remission or no change was documented after 12 weeks of therapy, the treatment was continued until progression of the disease was demonstrated.

## RESULTS

Thirty patients were included in the study, 17 patients with small cell carcinoma (SCCL) and 13 with squamous cell carcinoma (SQL). All patients had measurable lesions consisting of either lung infiltrates, lymph nodes or cutaneous metastases. The median ages of the patients with SCCL and SQL were 63 and 58 years, with a median performance status of 80 and 90, respectively. Two SCCL and two SQL were disqualified from the study for the following reasons: (a) one patient received a too low initial dose of interferon; (b) one patient refused further treatment after 2 weeks of therapy; (c) one patient had severe hypercalcaemia before treatment; (d) one patient had no measurable lesion. Thus concerning antineoplastic effect and tolerance, 26 and 27 patients, respectively, were evaluable.

*Antineoplastic effect* (*Table* 1)

Of the 15 patients with SCCL 14 patients developed progressive disease after a median of eight injections (range 2–32) administered during a median period of 2.5 weeks (range 1–12). Only one patient completed the scheduled 12 weeks of treatment without change in the measurable lesion. Among 11 evaluable patients with SQL, four patients showed progressive disease. Six patients showed no change. One patient showed normalization of a marker lesion on chest X-ray, but a bronchoscopy revealed persistent tumour. This patient received therapy for a total of 16 1/2 months after which radiographic relapse occurred. In the intervening period the bronchial tumour was demonstrable by repeated bronchoscopies.

*Toxicity*

Twenty-seven patients were evaluable for toxicity. The majority of the patients suffered from fatigue, chills and fever accompanying injections lasting from 2 to 24 hr in spite of prophylactic paracetamol administration. As treatment continued, increasing fatigue was the reason for dose reduction in 18 patients. In contrast to the observation that fatigue represented an increasing problem, fever and chills, which were significant during the initial phase of the treatment, showed a tendency to disappear with continuous treatment. Eighteen patients experienced anorexia, and in 14 patients a median weight loss of 6% (4–12%) of pre-treatment body weight was observed. Seven patients experienced muscle pain and "flu-like" symptoms. Diarrhoea, nausea, vomiting, dryness of mouth and eyes, and loss of smell sensation were sporadically registered. No patient developed significant neurological symptoms. Six patients showed leucopenia grade II–III, but it resulted in dose reduction in one patient only. Usually the WBCs spontaneously normalized in spite of continuous treatment. Four patients developed thrombocytopenia grade II–III, with the lowest value being 38 × $10^9$/l. Bone marrow examination was normal in this patient and following dose reduction partly because of fatigue and partly because of thrombocytopenia, the platelet count nomalized suggesting that interferon was the factor causing thrombocytopenia. In the remaining cases, platelet counts increased in spite of continuous interferon therapy. Haemoglobin concentration remained stable during the treatment period.

Alkaline phosphatase and SGOT were elevated in 15 and 19 patients, respectively, during interferon treatment. In most cases the elevation was concomitant with progressive disease, but in some patients the values normalized after discontinuing treatment, indicating that the changes were caused by interferon. No other changes in biochemical parameters were noted.

## DISCUSSION

Few studies have been published evaluating the efficacy of interferon in the management of lung

cancer. Figlin and Sarna [4] using leucocyte interferon, reported no response in 13 cases of SQL. Similarly, Krown [5] saw no effect of human leucocyte interferon in two cases of SQL. Jones *et al.* [6] treated 10 patients with SCCL with human lymphoblastoid interferon and registered no response. In the present study, all patients with SCCL showed progressive disease while on interferon therapy, and only one patient with SQL obtained a partial remission lasting 14 months.

In the present study the major side effects of interferon, such as flu-like illness and fatigue, were significant and in the majority of cases necessitated a dose reduction. Several of the patients included in the present trial had failed on intensive chemotherapy. Although their initial performance status was relatively good, they represent a prognostic high risk group and after a median of 2 1/2 weeks of treatment, progressive disease was registered with a rapid decline in performance status. In spite of this, only two patients refused continuing interferon treatment. The quality of life, however, must be estimated as poor for the majority of patients.

Altogether, based on the results from this and other studies and the toxicity observed, interferon does not appear to have a role as a single antineoplastic agent in the treatment of SQL and SCCL.

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