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Antitumour Effect and Symptomatic Control with Interferon α_{2b} in Patients with Endocrine Active Tumours

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26 patients with progressive neuroendocrine tumours received 3 × 10^6U/m² interferon alfa (IFN-α_{2b}) subcutaneously thrice weekly, until progression, as outpatients with moderate toxicity. 4/16 carcinoids and none out of 10 endocrine pancreatic tumours showed objective regression. Another 17 patients (68%) had no change. For a median of 34 weeks symptom control was excellent: 9 of 17 patients had major relief from pain, 11 of 13 from diarrhoea, and 7 of 7 from flushing. Thus, low-dose INF-α_{2b} given thrice weekly might be as effective as daily treatment with higher dosages. Treatment was only administered to patients with progression or major symptoms and this did not seem to adversely affect remission quality and survival.
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INTRODUCTION

ENDOCRINE GUT tumours are relatively rare but they are of great interest to oncologists because their survival even in metastatic disease can be long even with little or no therapy. Subjective symptoms arising from ectopic hormone activity could become deleterious [1, 2]. Therefore, subjective response and 50% decrease of hormone levels were judged as the aims of treatment [3].

Systemic treatment with cytotoxic agents has been disappointing. In vipomas it offers the prospect of long-lasting remissions [4]. Antiproliferative treatment with the hormone-like peptide somatostatin [3, 5] or interferons are promising alternatives.

Updated results from OBERG with intermediate dosage of interferon in 32 patients with endocrine pancreatic tumours gave an overall response rate of 22% [3]. In a review of the literature, patients with carcinoid tumours achieved only 10/111 (9%) remissions defined by WHO criteria [3, 6–16]. Subjective

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control and decline of hormone secretion was between 43 and 63% with acceptable toxicity.

The optimal schedule, dose and treatment duration have not yet been defined. No clear cut dose-response relationship could be demonstrated. Ultra high doses of interferon alfa (IFN-α) applied by MOERTEL did not seem to increase response rates but acute toxicity was remarkable [11]. Furthermore, the patient group who will profit most probably from interferon treatment is not characterised.

To avoid overtreatment, the need for therapeutic intervention might best be defined by progressive and/or symptomatic disease during an observational period prior to start of therapy.

The aim of this study was to test the feasibility of this approach and to further evaluate activity and toxicity of low-dose recombinant IFN-α_{2b} given thrice weekly in neuroendocrine tumours until progression.

PATIENTS AND METHODS

Patients with the diagnosis of an advanced and progressive neuroendocrine tumour (confirmed by immunostaining or hormone activity) were eligible. Progression was defined as a > 25% increase in tumour size or new evolving metastases or severe tumour-related symptoms between two separate evaluations termed every 4 weeks prior to start of treatment.

Interval to previous treatment had to be more than 4 weeks. No other severe co-morbidities should have been encountered. Toxicity, objective remission, defined according to WHO criteria as shrinkage of tumour lesions of greater than 50%, objective response, defined by OBERG as 50% decrease in hormone levels and symptomatic control, were judged with a questionnaire and evaluated every 4 weeks. Progression-free and overall survival were calculated from the start of therapy.

Statistical analysis was performed if indicated with the Wilcoxon test for paired values. Comparison of survival data were analysed by the logrank test.

Therapy protocol

IFN-α was given weekly on days 1, 3 and 5 at 3×10^6U/m^2 subcutaneously. Treatment was scheduled for at least 8 weeks unless rapid tumour progression or undue toxicity was observed. In case of objective tumours, stabilisation treatment continued until progressive disease occurred. In patients who suffered toxicities > WHO grade 3, individual dose adjustments were allowed.

Patients' characteristics

From May 1987 to September 1991 26 patients entered this study (12 male, 14 female) with a median age of 53 (range 19–71) years, median Karnofsky performance status 80 (60–100). Of the 16 carcinoids, nine were hormone active. Of the 10 endocrine pancreatic tumours, four had signs of hormonal activity including one glucagonoma and one vipoma. 5 patients remained unclassified, 1 patient had NSE-positive undifferentiated carcinoma. Most of the patients had advanced disease, 19 had two or more metastatic sites at presentation. Only 7 patients had surgery with curative intent, 14 patients had one or more preceding therapy other than surgery, 3 were in partial remission and 1 stable disease following chemoembolisation, 7 patients relapsed or were refractory to 5-fluorouracil or ciplatin-based chemotherapy (the prior response to therapy was: 1 PR, 5 NC, 1 P). 2 patients had good symptomatic control after radiation for bony lesions, 1 patient had adjuvant mediastinal radiation.

Table 1. Objective responses in 25 patients by (a) WHO criteria and (b) judged as major symptomatic control and/or 50% decline of 24-h excretion of 5-hydroxy-indole acetic acid (5-HIAA)

(a)

WHO criteria	PR	NC	P
Carcinoids	4	10	2
Endocrine/pancreatic tumours	0	7	1
Undifferentiated NSE positive carcinoma	0	0	1
Total	4(16%)	17(68%)	4(16%)

(b)

Symptoms	No. of patients/patients with symptom
> 50 decrease in 5-HIAA/serotonin 24-h excretion	8/12 (66%)
Flushing	7/ 7 (100%)
Diarrhoea	11/13 (85%)
Pain	9/17 (53%)

Percentages are given in parentheses. 95% confidence limits.
PR = partial response; NC = no change; P = progression

RESULTS

25 patients were evaluable for toxicity and response (1 patient stopped therapy after the first dose because of subjective symptoms). The overall response rate was 16% (95% confidence limit 2–30%). 1 patient with carcinoid of the bronchus experienced remission of liver metastases and recalcification of bony lesions, 3 additional carcinoid patients responded with remission of liver metastases, 2 of them in additional to abdominal indicator lesions. Regressions lasted for 25+, 25+, 88 and 155 weeks. All regressions were seen in patients with hormonally active carcinoid tumours. Symptomatic relief and decrease of hormone levels were parallel in these 4 patients. Direct tumour progression was observed in only 4 patients (Table 1a).

Although there was no objective regression in endocrine pancreatic tumour patients, duration of progression-free survival and overall survival did not differ significantly from carcinoids. Median time to progression for the whole study population was 34 weeks.

Median expected overall survival was 92 weeks (Fig. 1). In contrast to the low response rate there was good symptomatic control (Table 1b). Only 3 out of 17 patients had progressive pain. Diarrhoea was a symptom in 13 patients and daily frequency was reduced in 11 of them from a prestudy median of 6 (2–20) to 1 (0–8) ($P < 0.01$); in all 7 patients with flush syndrome the median number of episodes per day was lowered from 3 (1–6) to an on treatment median of 1 (0–3) ($P < 0.05$).

Hormone activity measured as the 24-h urinary excretion of hydroxy-indole-acetic acid declined in 8 out of 12 patients (66%).

Toxicity was relatively mild and comparable with other reports. 2 patients had to have interferon reduced to 2×10^6 U/m^2 because of subjective symptoms, 1 patient stopped therapy because of lethargy.

DISCUSSION

The treatment of malignant tumours of the so-called APUD system is a great challenge to oncologists because the course of the disease is typically indolent. Nevertheless, some patients will survive without any or only minimal therapy for a long period of time. Therefore, toxicity of treatment has to be adjusted to its palliative intent and the need to treat a patient has to be better defined.

With interferon, objective responses were documented in about 10–20% with symptomatic control in nearly 70% and acceptable toxicity [3, 6–16].

The effects on symptoms and hormone activity might suggest interferon receptors as mediators of cell activity by second messengers or growth factor inhibitor activity of interferon rather than direct cytotoxic properties [17].

There seems to be no clear cut dose–response relationship with interferon treatment in these diseases. Therefore, the intent of this study was to demonstrate the effectiveness of low-dose IFN-α_{2b} given subcutaneously only to patients with symptomatic or established progressive disease. Despite these strict entry criteria, objective responses and remissions were as high as known from the literature. Thus, treatment delay and dose-reduction does not transform into a disadvantage for the patients followed with this strategy. In this context, control of hormonal excess in 66% of patients and tumour stabilisation (PR, NC) in 84% of patients might be judged as positive treatment results.

The selection of patients with only progressive disease was supposed to create a bad prognostic subgroup with a clearly defined need for intervention with a potentially toxic approach. Thus, survival data might not be directly comparable to the data from the literature, but at least the duration of progression-free survival seems to be comparable. Data on long-term follow-up are scarce. A 50% survival at 2 years achieved with low-dose interferon scheduled to be given until tumour progression described in this report might be inferior to the data achieved by OBERG [3]. Typically, this group treated their patients for life, which due to delay of tumour growth might have had a positive influence on survival. Compared with chemotherapeutic regimens advocated for these patients [4] and high-dose interferon treatment, subjective tolerance was excellent.

Although the question of which would be the optimal dose of interferon is still open, treatment thrice weekly subcutaneously at intermediate dosages might prove beneficial for patients' compliance because of its low toxicity and reasonable activity. Competitive results concerning symptomatic control were reported with the use of long acting somatostatin analogues [5] though tumour reductions were not often reported. Comparative studies of these different and relatively atoxic approaches are still unable to define the optimal sequence of these drugs and to determine cross resistance.

Further improvements of interferon scheduling and dosing are needed as well as combination studies with effective cytostatic drugs, which *in vitro* showed synergism to interferons [18].

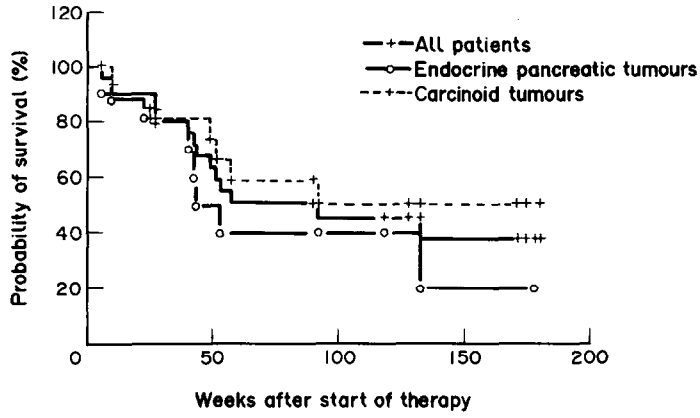

Fig. 1. Probability of overall survival in 25 evaluable patients with neuroendocrine tumours treated with IFN-α_{2b}, 3 × 10^6 U/m^2 subcutaneously thrice weekly.

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