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Octreotide and Interferon Alfa: A New Combination for the Treatment of Malignant Carcinoid Tumours

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24 patients with malignant carcinoid tumours received octreotide and interferon alfa (IFN-α). All the patients initially received octreotide 50–100 μg, twice daily. When progressive symptoms or increasing biochemical markers were observed, the daily dose was raised to a median 300 μg. If the initial dose proved ineffective or if no improvement was seen after escalation, IFN-α was added (median 9 MU subcutaneously per week). After the addition of IFN-α, 17 of the 22 patients (77%) with elevated urinary 5-hydroxyindoleacetic acid showed a significant (> 50%) reduction. Only 1 patient progressed and 4 had continuously stable biochemical disease. No significant reduction in tumour size was noted; in 5 patients, the tumour continued to grow despite decreasing hormone levels. 18 patients had carcinoid syndrome when IFN-α was added, in 10 (56%) symptoms ameliorated. Thus, the addition of IFN-α is beneficial for patients with malignant carcinoid tumours that progress and/or who do not respond to octreotide.
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INTRODUCTION

THE CARCINOID syndrome has been a therapeutic challenge for clinicians for many years. Since surgery seldom cures these patients in the advanced stages of the disease, different medical treatment modalities have been tried. Medical treatment of malignant carcinoid tumours has to be continued for long periods of time since these tumours are usually slow growing, despite widespread disease. Chemotherapy has produced poor results, i.e. response rates of between 10 and 30% for the different combinations used, and accompanied by severe adverse reactions [1, 2].

During the past decade major advances in the treatment of the carcinoid syndrome have been made. Octreotide [3, 4] and interferon alfa (IFN-α) [5–8] have both been used with promising results. Biochemical responses to octreotide have been noticed in 40–72% of patients while response rates of 39–50% have been seen for IFN-α. These drugs have provided a possibility for patients suffering from carcinoid tumours to achieve a good quality of life for extended periods of time.

Recently, octreotide has been used by many clinicians as first line therapy for the carcinoid syndrome. However, most patients develop "tachyphylaxis", i.e. decreased sensitivity after a certain period of treatment with octreotide [9]. This can be reversed initially by dose escalation but, after varying periods of time, a further dose escalation can no longer control the clinical symptoms. This is an increasing problem in the long-term management of these patients.

Treatment with IFN-α is accompanied by dose-dependent adverse reactions such as the chronic fatigue syndrome, malaise and weight loss. It is thus of great importance to keep the dose of IFN-α as low as possible.

In the present study, we included patients with malignant carcinoid tumours who failed to respond to octreotide treatment. These patients were administered IFN-α in addition to the initial octreotide treatment, in order to investigate whether the addition of a low dose of IFN-α could induce a clinical response. We also wanted to see if resistance to octreotide meant a concomitant lack of response to IFN-α. The tolerability to the combination therapy was also evaluated.

PATIENTS AND METHODS

All patients in this study were required to have a histologically confirmed metastatic carcinoid tumour and to have at least one clearly measurable lesion in the liver, seen on either computed tomography or ultrasonic investigation. Patients had been treated with octreotide prior to inclusion in this study and had either not responded clinically to the recommended starting dose (50–100 μg two times a day) or had after an initial phase of response begun to develop resistance to octreotide. The daily octreotide dose had been raised in these patients to a median of 300 μg.

The IFN-α was administered at doses which were individually titrated according to the age and performance status of the patient. Elderly patients started on a dose of 3 MU 3 times per week, while younger patients usually began at one of 5 MU 3 times per week. The dose was escalated after 3 months if there were no side-effects and if the leucocyte count was $> 4 \times 10^9/l$ in a non-responding patient. The dose was decreased if intolerable side effects occurred. The median dose of IFN-α was 9 MU/week (3 MU × 3/week) administered subcutaneously (range 4.5–21 MU/week).

Patients were monitored by routine haematology, liver and kidney function tests, serum electrolytes and blood glucose every third month. The tumour marker urinary 5-hydroxyindoleacetic acid (U-5HIAA) (determined according to the method described

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Table 1. Patients' characteristics

No. of patients	24
Males/females	13/11
Median age (years)	66 (39–77)
Liver metastases	24/24
Increased U-5HIAA	22/24
Median U-5HIAA (μmols/24 h)*	440 (40–1842)
Carcinoid syndrome	18/24

*Normal range 10–80 μmols/24 h.

previously [10]), was measured every 3 months and calculated as the mean of two 24 h periods of collection. Tumour size was monitored by ultrasound and computed tomography after 3 and 6 months, respectively.

A complete biochemical response was defined as a normalisation of U-5HIAA, while partial biochemical response was considered to have occurred when U-5HIAA was reduced by 50% or more. An increase in U-5HIAA of 25% or more was regarded as tumour progression.

A reduction in tumour size, calculated as the product of two perpendicular diameters of the two largest metastases, of more than 50% was considered partial response while an increase of more than 25% was designated progression.

Response duration was calculated from the date IFN-α treatment was started until progression was noted. Survival was calculated according to Kaplan–Meier analysis.

RESULTS

24 consecutive patients, 11 women and 13 men were included in this study (see Table 1). The median age was 66 years (range 39–77). 23 patients had mid-gut carcinoid tumours and one had a lung carcinoid tumour. 22 patients had increased levels of U-5HIAA while 2 had normal hormone levels. 18 patients presented with a carcinoid syndrome with flushes and/or diarrhoea. The median U-5HIAA was 440 μmol/24 h (range 40–1842 μmol/24 h, normal range 0–80 μmols/24 h). 10 patients were previously untreated, while 14 had been treated with chemotherapy and/or interferon before they started the octreotide treatment. The median duration of the initial octreotide treatment was 8 months (range 3–36 months) and the median dose of octreotide when IFN-α was supplemented was 250 μg/day (range 100–1000 μg/day). The median disease duration before the start of IFN-α treatment was 35 months (range 3–204 months).

10 of the 24 patients had initially shown objective biochemical response to octreotide for a median of 12 months (range 3–29 months). Dose escalation in these patients up to a median of 300 μg/day could not control the disease. The other 14 patients had not shown any significant reduction (> 50%) in U-5HIAA levels or symptoms after 3 months of octreotide therapy.

When IFN-α therapy was added, 4 (18%) of the 22 patients with increased U-5HIAA levels demonstrated a complete biochemical response and 13 (59%) a partial one, giving a total biochemical response rate of 77%. This response lasted for a median of 12 months (range 5–46 months). Of these 17 responding patients, 9 had previously, before the start of this study, been treated with IFN-α at a median dose of 3 MU three times a week, but had discontinued this treatment either due to tumour progression or to intolerable toxicity.

Only 1 patient continued to progress biochemically after the addition of IFN-α while the rest of the patients (n = 4) showed continuous stable U-5HIAA levels for a median of 14 months (range 7–26 months).

Of the 18 patients presenting with the carcinoid syndrome 3 (17%) experienced a complete relief of their symptoms and signs, while 5 patients (28%) experienced a complete relief of one of the symptoms. 2 patients (11%) showed a reduction in their symptoms. 1 patient experienced a worsening of her carcinoid syndrome while 7 patients remained unchanged.

Tumour size remained unchanged in 15 patients, while there was an increase in 5. In 4 patients, tumour size could not be evaluated due to technical problems. Of the 5 patients with an increase in tumour size, 4 had a concomitant biochemical response with > 50% decrease in U-5HIAA levels, while the fifth patient also demonstrated biochemical progression.

Adverse reactions due to IFN-α included flu-like symptoms during the initial 3–5 days of treatment in 18 of the patients (75%), tiredness in 15 (62%), a slight weight loss, anorexia and dryness of skin each in 6 patients (25%). None of these adverse reactions was more severe than WHO grades I and II. Although leukopenia with a leucocyte count below 3×10^9 was seen in 5 patients and thrombocytopenia with counts below 100×10^9 in 1 patient, this was not considered to be of any clinical importance since none of the patients suffered from infections or bleeding. Only 1 patient showed a moderate increase in liver enzymes up to twice the upper reference value.

During the follow-up of a median of 19 months (range 3–72), 8 patients died after a median of 10 months on IFN-α therapy, half of them due to tumour progression, 2 because of cerebral haemorrhage, one from pericarditis and one from carcinoid heart disease. 3 patients discontinued octreotide treatment, 1 due to cholangitis, and in 2 cases due to difficulties in tolerating the frequent injections. A total of 5 patients discontinued their IFN-α treatment. Of these, 2 patients developed vasculitis which was suspected to be related to the interferon treatment. 2 patients had problems with weight loss and tiredness and therefore discontinued treatment. In 1 patient, the interferon was withdrawn since the patient experienced social problems regarding the injections. The IFN-α treatment was interrupted for 5, 4 and 2 months in 3 patients because of tiredness and weight loss,but in these patients IFN-α was reintroduced later at lower doses without any severe adverse reactions.

In each of the 8 patients where IFN-α was withdrawn or interrupted we could see an immediate increase in symptoms as well as in U-5HIAA levels. In the 3 patients where IFN-α was reintroduced, a prompt new biochemical as well as symptomatic response was seen (Fig. 1).

The estimated survival had a median value of 58 months from the start of the IFN-α treatment (Fig. 2 upper panel) and the median survival from the initial time of diagnosis was 108 months (Fig. 2 lower panel).

DISCUSSION

By introducing IFN-α into the treatment regimen of patients with malignant carcinoid tumours failing to respond to octreotide treatment, we could induce a significant biochemical response in more than two thirds of the patients. These results should be related to the advanced stages of the disease as indicated by the median time from diagnosis of about 3 years, high U-5HIAA levels, multiple liver metastases and earlier treatment with various drugs. The addition of IFN-α induced a response for a median of 12 months with considerable variations in time (5–46 months). 9 of the 17 responding patients had previously been treated with IFN-α but showed progression or experienced

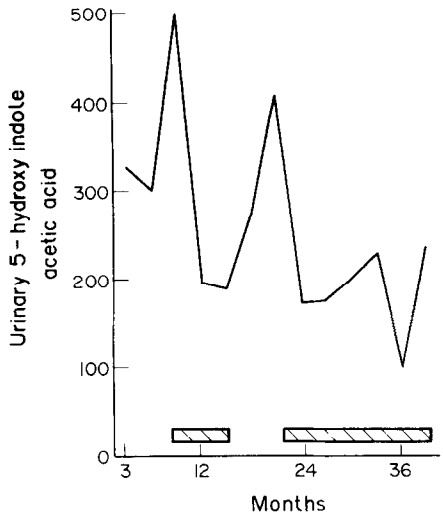

Fig. 1. This is an example of the biochemical response in patients treated with a combination of octreotide and IFN-α. Note the immediate increase in U-5HIAA levels when IFN-α is withdrawn, and the prompt biochemical response when IFN-α is reintroduced. ▨ indicates period of IFN-α treatment.

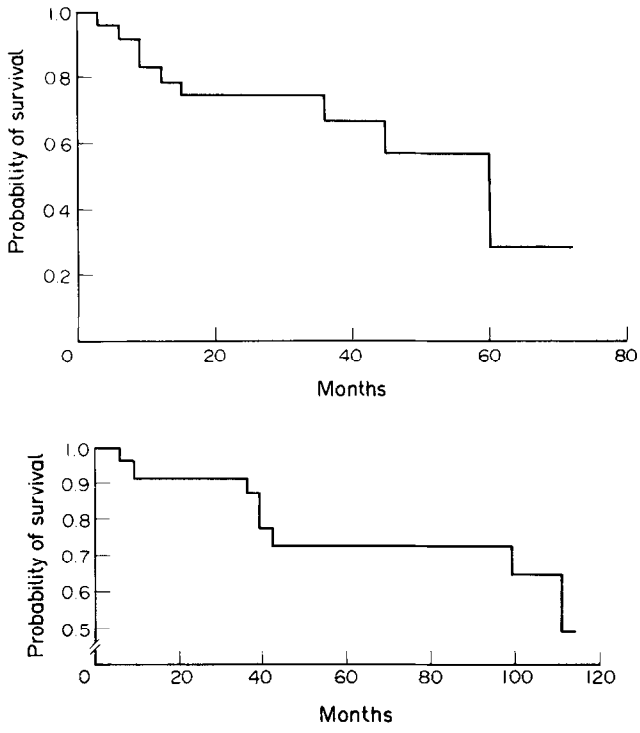

Fig. 2. Survival calculated according to Kaplan–Meier analysis from the start of IFN-α treatment (upper) and from initial diagnosis (lower).

intolerable adverse reactions. In these 9 patients, IFN-α given in combination with octreotide could induce a biochemical response. This might indicate that tumours resistant to IFN-α can respond to the combination and it also indicates that patients who cannot tolerate IFN-α alone may tolerate the same dose when it is given in combination with octreotide.

We believe that the high biochemical response rate depends on the combination of IFN-α and octreotide and not only the addition of IFN-α. The reason for this conclusion is that such high response rates (77%) for IFN-α alone (median 44%) have never been reported.

The beneficial value of adding IFN-α to patients on initial octreotide treatment is further underlined by the observation that when IFN-α was withdrawn for some reason, an immediate increase in biochemical markers occurred concomitantly with the return of clinical symptoms. In 3 of these patients, we were able to reintroduce IFN-α and this was followed by biochemical and clinical improvement (Fig. 1). Our results indicate that no cross resistance exists between the two biotherapies, i.e. a patient who is unable to respond to one drug can be expected to respond to the other. Another important observation is that IFN-α can be withdrawn for a short period of time and then reintroduced with good biochemical and clinical effects.

4 patients demonstrated an increase in tumour size during the period of biochemical response. This is a new observation and indicates the need for frequent radiological follow-up. In previous studies we have shown that biochemical responses during IFN-α therapy have always been accompanied by a stabilisation of or reduction in tumour size [6, 7]. This is also supported by the fact that in previous studies with IFN-α treatment of patients with malignant carcinoid tumours, 10–20% of the patients with biochemical responses showed a significant reduction in tumour size [6–8]. This was not observed in the present study despite a high biochemical response rate.

Only 8 patients died during the observation period of 19 months (median). The estimated median survival from the start of IFN-α therapy was 58 months which is considerably longer than historical controls [11–13]. Adverse reactions showed the same frequency as that expected from each drug used alone, but by keeping the dose of IFN-α in the low range these could be significantly reduced. Autoimmune reactions have been observed previously in patients during single IFN-α treatment [7]. The patient who died from pericarditis had recently been operated with a replacement of the valves on the right side of the heart, and the death was not related to IFN-α treatment.

Our aim to reduce the dose of IFN-α in order to keep the adverse reactions as low as possible but still be able to demonstrate an antitumoral effect could be achieved in this study. It seems that the dose of IFN-α can be kept in the very low dose range of about 3 MU 3 times per week subcutaneously, when combined with octreotide.

In conclusion, our data show that IFN-α is of beneficial value when administered to patients with malignant carcinoid tumours who do not respond to or who demonstrate progression during octreotide treatment. These effects will be further explored in a forthcoming study where both these drugs are combined directly from the start of treatment.

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Treatment of Metastatic Carcinoid Tumour with Recombinant Interferon Alfa

Heikki Joensuu, Eero Kumpulainen and Pentti Gröhn

14 patients with metastatic carcinoid tumour were treated with recombinant interferon alfa 6–30 × 10^6 IU weekly for 3–25 (median 6.5) months. A decrease in the 24-h urinary 5-hydroxyindoleacetic acid (5-HIAA) level to less than 50% of the pretreatment value was observed in 5 of the 10 cases with an elevated urinary 5-HIAA level. In 4 of the 5 remaining patients, the 5-HIAA level decreased 30–50% from the pretreatment value. 5 of the 9 evaluable patients with carcinoid syndrome experienced symptomatic relief, but none became symptom-free. Severe toxicity was not observed. The median time to progression was 4.5 months, and, in patients with a greater than 50% decrease in 24-h urinary-5-HIAA, it was 17 months. Objective regression in tumour size could not be demonstrated in any of the patients.
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INTRODUCTION

SURGICAL REMOVAL of carcinoid tumour is often curative when the disease is detected at an early stage, but advanced carcinoid tumours with distant metastases are incurable. Symptoms caused by carcinoid tumour may be similar to those caused by other types of neoplasms, but the carcinoids typically secrete biologically active substances, such as serotonin, tachykinins, and bradykinins, which may cause the carcinoid syndrome with flushing, diarrhoea, asthma and cardiac failure. Carcinoid tumour is usually a slowly advancing neoplasm, but the median survival with the malignant carcinoid syndrome is 38 months from the time of the first flush, and only 11 months with clinical evidence of carcinoid heart disease [1]. Metastatic disease may not require treatment for months or even years in patients whose disease is not seriously interfering with their lifestyle [2]. The treatment options include surgical debulking, ligation or embolisation of the hepatic artery, cytostatic therapy, palliative irradiation, the long-acting somatostatin analogue octreotide, and interferons.

In 1983, Öberg *et al.* introduced human leucocyte interferon in the treatment of malignant carcinoids [3]. They observed objective tumour regression in 4 (11%) of 36 patients, at least a 50% reduction of elevated urine 5-hydroxyindoleacetic acid (5-HIAA) levels in 15 (50%) of 30 patients, and 64% of the patients had subjective improvement. The median duration of either objective or biochemical response was 34 months [4]. These results have recently been challenged by Moertel *et al.* [5], who found hormonal improvement to last for a median of only 1 month in 9 out of 23 patients (39%), and by Välimäki *et al.* [6], who found a clear-cut and continuing decrease in urinary levels of 5-HIAA in only 1 out of 8 patients, and carcinoid symptoms improved in only 2 out of 7 evaluable patients. Neither group recommended interferon for routine treatment of the carcinoid tumour syndrome. In the present article, we describe the results of 14 patients with symptomatic metastatic carcinoid tumour treated with recombinant interferon alfa.

PATIENTS AND METHODS

Patients

14 patients with histologically verified metastatic carcinoid tumour were included in the study. 11 were treated in University Central Hospital of Turku, and 3 in University Hospital of Kuopio, Finland, between November 1987 and January 1992. In both hospitals, consecutive patients with disease causing symptoms and considered to require treatment were included. 7 patients were male, and the mean age was 54 years (median 57; range 20–72 years, Table 1). The primary tumour was of

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