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TREATMENT OF GASTROINTESTINAL ENDOCRINE TUMOURS WITH INTERFERON-α AND OCTREOTIDE

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Abstract

This paper reports on the results of two controlled therapeutic trials on patients with endocrine tumours of the gastrointestinal tract. Seventeen patients were treated up to 18 months with recombinant interferon-α2c (2×10^6 IU/m^2 s.c. daily) and 16 patients are treated in an ongoing study with octreotide (3×200 μg daily). Objective response (>50% reduction of hormone secretion) was observed in one of 15 evaluable patients on IFN-α and in 12 of 16 patients on octreotide. Reduction of tumour size was not observed in these two trials. However, the majority of patients had stable tumour size during IFN-α and octreotide treatment despite progressive disease before. Subjective improvement due to reduction of symptoms such as flushing, diarrhea, and dermatitis was significantly more frequent after octreotide than after IFN-α. Of five endocrine tumour patients with progressive disease on IFN-α, three responded to subsequent treatment with octreotide while one had stable disease and one progressed. Two cases are reported from the authors' series of patients treated with octreotide before start of these trials. Complete remission of the tumour by low-dose (2×100 μg daily) octreotide was observed in one carcinoid patient. This remission has now lasted for four years. In one patient with liver metastasis of a VIPoma, who had become resistant to streptozotocin, his watery diarrhoea is now completely controlled with 100 μg octreotide s.c. every second day.

Key words: Endocrine GI-tumours, interferon-α, octreotide, somatostatin-analogue, carcinoid, gastrinoma, VIPoma.

Interferons belong to a class of proteins termed biological response modifier. Besides their antiviral activities, growth inhibition and immunomodulation are their most relevant biological effects. Interferons have demonstrated significant antitumour activity in several hematologic malignancies such as hairy cell leukemia, myeloproliferative syndromes and in low-grade non-Hodgkin's lymphomas (1). Since 1983 there have appeared several reports indicating a beneficial influence of natural and recombinant interferon-α on clinical symptoms and tumour size in patients with metastatic carcinoid syndrome (2–4). However, the existing data are still controversial and the definite role of interferons in the treatment of metastatic endocrine gastrointestinal tumours has yet to be established.

Somatostatin, a peptide hormone with 14 amino acids, was first isolated from sheep hypothalamus and named SRIF (somatotropin release inhibiting factor) according to the inhibitory effect on growth hormone secretion (5). Very soon an inhibitory effect of somatostatin was observed on peptide hormone secretion from nearly all endocrine organs together with an inhibition of fluid secretion from the stomach, the pancreas, and the gut (6–9). In several animal experiments a growth inhibiting effect on several organs was described. In addition to the central nervous system somatostatin has been demonstrated in nerves and in epithelial cells of many organs of the gastro-entero-pancreatic system (10).

Due to the short half-life of the natural somatostatin, its therapeutic use was limited to hospitalized patients due to the need for continuous intravenous infusion. The long-acting somatostatin analogue octreotide (Sandostatin), however, can be given subcutaneously and used

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Table 1

Clinical data of patients with endocrine GI-tumours treated with rIFN-α2c

Males (n)	11
Females (n)	6
Mean age (range)	57.6 y (44–68 y.)
Metastatic carcinoid tumour (n)	10
Gastrinoma	2
Neuroendocrine tumour without hormone hypersecretion	5
Previous treatment	
surgical	14/17
hormones	2/17
cytostatics	1/17
radiation	1/17
Localization of metastases	
liver	15/17
lung	1/17
bone	1/17

for long-term treatment (11). Several studies of patients with endocrine gastrointestinal tumours treated with octreotide have now been reported (12–15).

In the present phase II study on patients with advanced endocrine tumours of the gut we have compared the effects of interferon and octreotide. Some of the patients were first treated with interferon and thereafter the treatment was continued with octreotide.

Patients, Material and Methods

Interferon-α therapy

From October 1987 to September 1989, 17 patients (11 males, 6 females) with metastatic endocrine tumours were treated with recombinant human interferon-α2c (rIFN-α2c, produced by Boehringer Ingelheim, Germany and provided by Thomae, Biberach, Germany) after giving informed consent. The patient characteristics are summarized in Table 1. Ten patients with metastatic carcinoid tumours, two with gastrinoma and five with neuroendocrine tumours without hormone hypersecretion were treated for a duration of between 14 and 662 days (mean 270 days). The mean time from diagnosis to start of IFN-α2c therapy was 22 months (range 0–137). Nine of the 17 patients had significantly elevated 24-h excretion of 5-hydroxyindole acetic acid (5-HIAA) before entering the study and 6/9 patients with elevated urinary 5-HIAA excretion were treated for more than 4 months and, therefore, the 5-HIAA excretion could be used as a response parameter. The predominant site of metastasis was the liver (15 of 17 patients), one patient had bone, and one lung metastasis.

All patients received 2×10^6 IU/m^2 recombinant IFN-α2c s.c. daily. Diagnostic procedures with complete blood chemistry, profile of gastrointestinal hormones, CT-scan, ultrasound and x-ray were made before start of rIFN-α2c treatment and at three-month intervals. A minimal treatment period of three months was requested for assessing of response. Objective response (OR) was defined as a $\geqslant 50\%$ reduction of either pathologically elevated hormone parameter (hormone plasma levels or urinary 5-HIAA excretion) and/or bidimensional size of measurable tumour lesions; $\leqslant 50\%$ reduction and $\leqslant 25\%$ increase of these parameters were stated as no change (NC). Significant reduction of symptoms (flush, diarrhoea, pain) was characterized as subjective improvement (SI). According to these criteria 15/17 patients were evaluable for response, in two patients the time of treatment was <3 months.

Octreotide therapy

When octreotide became available for treatment of patients with severe syndromes of endocrine gastrointestinal tumours in 1985, we were advised to use this substance in doses up to 2×50 μg daily. With this low-dose regimen we have, for 3 days, studied the effect of octreotide on flushing in patients with midgut carcinoids and the carcinoid syndrome (16). Five patients with metastatic carcinoids were treated long-term (two to nine months) with 3×50 μg daily (17). In addition, octreotide was applied in single cases with gastrinoma, VIPoma, and glucagonoma.

Recently, 16 patients were treated with octreotide, 3×200 μg s.c. daily according to a protocol of the German octreotide multicentre study for treatment of endocrine gastrointestinal tumours initiated in 1988 by Prof. R. Arnold, Marburg, and one of the authors (W. Creutzfeldt). This study is still ongoing and the results presented here are preliminary. According to the protocol the octreotide dose is increased to 3×500 μg s.c. daily when the tumour is found to progress. Inclusion criteria were as follows: Confirmation of diagnosis by histology; screening for elevated plasma levels of gastrointestinal regulatory peptides; demonstration of tumour by at least one imaging procedure; progression of tumour growth during a prephase of three to four months or severe clinical symptoms, such as diarrhoea, flushing, and hypoglycaemia. The data of these patients are given in Table 2.

The duration of treatment of our 16 patients enrolled in this ongoing study until now ranges from 3–12 months. The response is being evaluated for each three-month period separately. The diagnostic procedures and evaluation of response were the same as described for the interferon study group. Five of our 16 patients had previously been treated with interferon which allows a direct comparison of the effects of the two treatment protocols.

Table 2

Clinical data of patients with endocrine GI-tumours treated with octreotide

Males (n)	8
Females (n)	8
Mean age (range)	58.3 y. (46–71 y.)
Metastatic carcinoid tumour	10
Gastrinoma	1
Insulinoma	2
Glucagonoma	1
Neuroendocrine tumours without hormone hypersecretion	2
Previous treatment	
surgical	11/16
cytostatics	4/16
rIFN-α2c	5/16
Localization of metastases	
liver	16/16
lung	1/16
bone	4/16

Results

Interferon

The treatment with recombinant interferon-α2c was tolerated without any severe side-effects by the majority of patients. Only one patient refused therapy after two weeks due to subjective toxicity (anorexia, nausea, fatigue). At the beginning of therapy the dose of rIFN-α was increased from $1.5 \cdot 10^6$ U/day up to the maximum individual dose within five days. Therefore, flu-like symptoms and fever did not seriously impair the patients' condition. There was no grade III or grade IV toxicity documented throughout the study period. In 4/17 patients mild hair loss, and in 7/17 patients anorexia appeared during the time of treatment. One-third of the patients complained about chronic fatigue, but no symptomatic therapy was necessary. No neurologic/psychiatric side-effects were noted in our patients. The decrease of haemoglobin, leukocytes and platelets were significant after one year of therapy ($p < 0.01$). At that time also a decrease of cholesterol and an increase of triglycerides reached significant levels ($p < 0.01$). There were no other significant metabolic changes in any patient.

Urinary 5-HIAA excretion was measured after four months of rIFN-α therapy in 6 patients and the mean values of the 3-day urine collections compared with the pretreatment values. As demonstrated in Fig. 1, only in one patient the 5-HIAA excretion had decreased >50%. In three patients the decrease was smaller and in two cases an increase of more than 100% occurred (progressive disease). There was no reduction in measurable tumour size in any patient which could qualifiy as partial remission (PR). The overall results are summarized in Table 3, from which it appears that the majority of patients had stable disease during IFN-α treatment. Only one patient could be classified as objective response (>50% decrease of 5-HIAA excretion). Some patients reported subjective improvement.

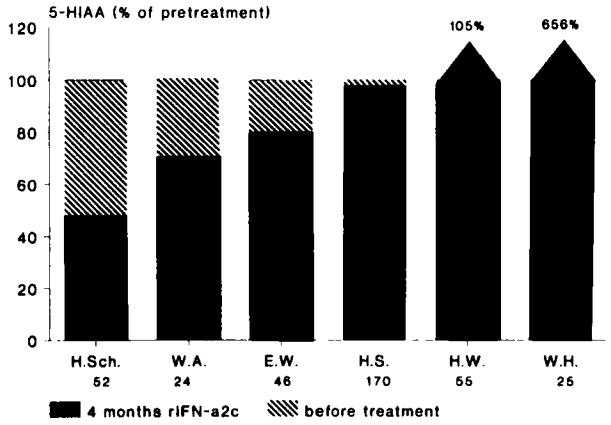

Fig. 1. Histogram of the change in percentage of 5-hydroxyindoleacetic acid (5-HIAA) urinary excretion in 6 carcinoid patients before and after 4 months treatment with recombinant interferon-α2c (rIFN-α2c) in the dose of 2×10^6 IU/m^2 s.c. daily. Below the initials of the patients are listed the absolute values of the 24-h 5-HIAA excretion in mg (mean of 3 days) before treatment. The black columns represent the change in percentage of pretreatment.

Table 3

Results of treatment with rIFN-α2c (2×10^6 IU/m^2 s.c. daily) in 17 patients with endocrine GI-tumours

Time (months)	3 n	6 n	9 n	12 n	15 n	18 n
OR	1	–	–	–	–	–
NC	10	9	8	6	4	2
PD	4	3	–	1	2	–
NE	2	–	–	–	–	–
SI	4	3	3	3	3	–
n	17	12	8	7	6	2

OR = Objective response (≥ 50% reduction of tumour size or 5-HIAA excretion or serum levels of gastrin)
NC = No change
PD = Progressive disease (≥ 25% increase of tumour size or 5-HIAA excretion or serum levels of gastrin)
NE = Not evaluable due to less than 3 months' treatment
SI = Subjective improvement

Octreotide therapy

In a first phase octreotide was given only to patients with symptomatic endocrine tumours in order to influence the clinical symptoms (especially flushing and diarrhea). In this phase a low-dose treatment regimen ($2-3 \times 50\ \mu g$ daily) had been recommended. We found this dose effective in reducing the frequency and intensity of flushing in six of eight patients with the carcinoid syndrome but not on watery diarrhoea (16).

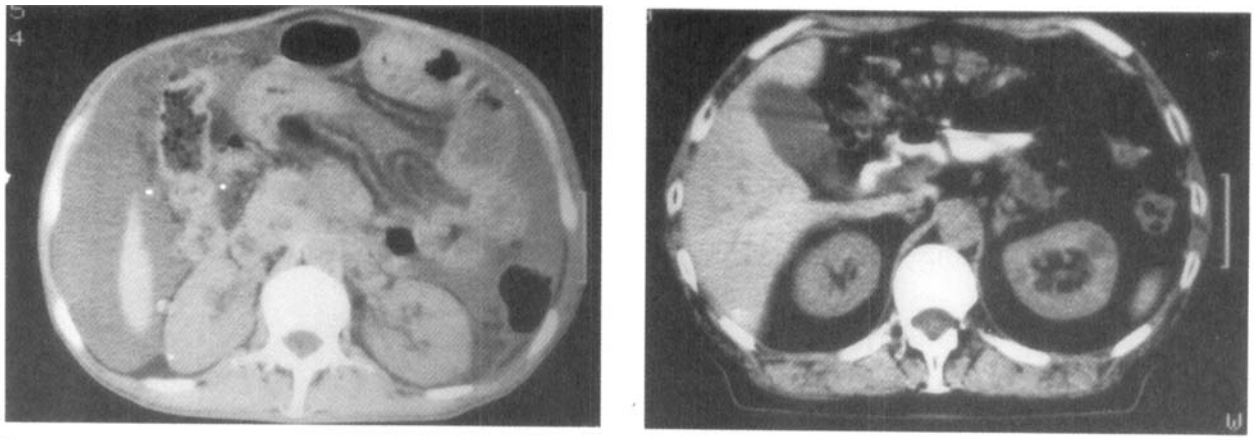

Fig. 2a. CT-scan of patient W.S. with a metastatic carcinoid tumour and total duodenal stenosis before (left) and after (right) 12 months' treatment with octreotide 2 × 100 μg s.c. daily. The tumour mass and the ascites have disappeared in the control scan.

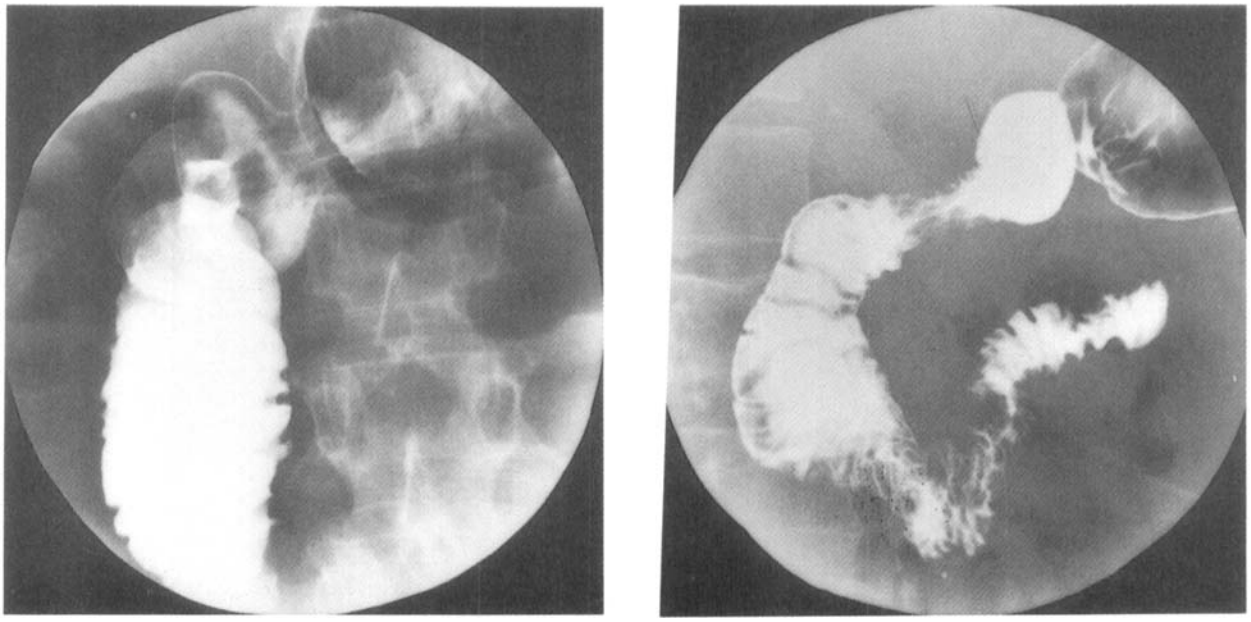

Fig. 2b. Barium meal of patient W.S. with metastatic carcinoid tumour and total duodenal obstruction before (left) treatment with octreotide 2 × 100 μg s.c. and control after (right) 12 months. A duodenal stenosis cannot be demonstrated in the control investigation.

One patient with mild carcinoid symptoms but complete duodenal stenosis, requiring permanent parenteral nutrition, received very successfully 2 × 100 μg octreotide in order to decrease reflux of salivary and gastric fluid. After one year the duodenal stenosis and the pancreatic tumour had disappeared as documented by CT scan, barium meal, (Fig. 2a and b) and sonography. The patient has now eaten normally for about four years and is fully rehabilitated. Since six months the tumour is again slowly growing. Therefore, the octreotide dose has been increased to 3 × 200 μg daily. However, the complete remission of the tumour occurred during the low-dose regimen (2 × 100 μg daily).

Another patient with a VIPoma syndrome was successfully treated with pancreatic resection in 1975 and, after recurrence of diarrhoea due to liver metastasis, in 1981 with six cycles of streptozotocin and 5-FU. In 1988, diarrhoea recurred and new liver metastases were found. Octreotide treatment was started. The diarrhoea is since two years under complete control with 100 μg octreotide s.c. every second day and no change of the liver metastases has been observed yet.

The results of octreotide treatment (200 μg 3 × daily) in the 16 patients in Table 2 were as follows. Most impressive was the effect on the subjective improvement, especially in the ten patients with carcinoid syndrome. These patients experienced marked improvement or disappearance of flushing and improvement of watery diarrhoea despite continuing or even new steatorrhea. These results are summarized in Table 4. Urinary excretion of 5-HIAA in 24 h (mean of three days) and pathologically elevated plasma hormone levels were reduced by more than 50% in

Table 4

Effect on clinical symptoms during treatment with octreotide (3 × 200 μg/day) of 16 patients with endocrine gastrointestinal tumours

	Positive effect n
Carcinoid syndrome	
flushing	10/10
diarrhoea (frequency and volume of stool)	7/10
steatorrhea	
before	5/10
during	8/10
Insulinoma	
hypoglycemia	2/2
Glucagonoma	
exanthema, pruritus, anaemia	1/1

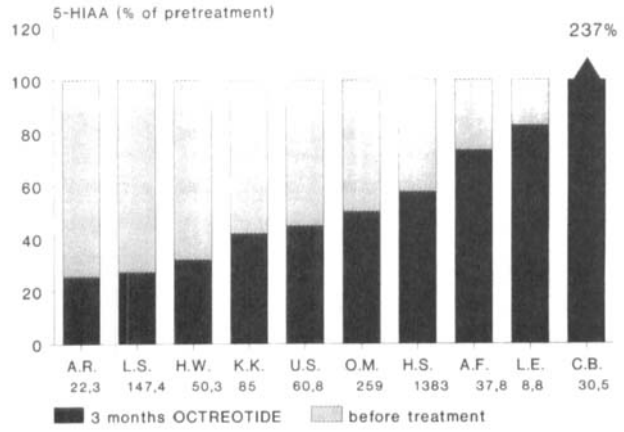

Fig. 3. Histogram of the change in percentage of 5-hydroxyindoleacetic acid (5-HIAA) urinary excretion in 10 carcinoid patients before and after 3 months' treatment with octreotide (3 × 200 μg s.c. daily). Below the initials of the patients are listed the absolute values of the 24-h 5-HIAA excretion in mg (mean of 3 days) before treatment. The black columns represent the change in percentage of pretreatment. Note that patients H.W. and H.S. are listed in Figs 1 and 3 and responded only to octreotide.

the majority of patients (Fig. 3 and Table 5). A reduction of measurable tumour size was not observed. However, unchanged tumour size was found in 2/3 of the cases. The preliminary results of this ongoing prospective controlled study with 3 × 200 μg octreotide are summarized in Table 6.

It thus appears that the favourable effect of the octreotide treatment is mainly due to the effect on hormone secretion and improvement of subjective symptoms. While no tumour regression was observed, stable disease was found in the majority of patients.

Of the five patients who showed progressive disease (> 25% increase of tumour size and/or of the pathological hormone levels) after 6–12 months' treatment with IFN-α, three responded to octreotide (> 50% decrease of urinary 5-HIAA excretion, disappearance of flushing, and improvement of diarrhoea in two carcinoid patients and of plasma gastrin levels in one gastrinoma patient). One patient with bone metastases from a carcinoid failed to respond on octreotide in respect of tumour growth and 5-HIAA excretion. The fifth patient had no pathological hormone secretion. His tumour progressed on IFN-α but has not grown further on octreotide now for 12 months.

Table 5

> 50% decrease of pathologically elevated hormone secretion in 16 patients with endocrine gastrointestinal tumours during treatment with octreotide (3 × 200 μg/day)

Urinary excretion of HIAA in 24-h urine (mean of 3 days)		
Response	1 week	10/10
	3 months	9/10
	6 months	5/8
	9 months	6/7
	12 months	2/5
Fasting plasma pancreatic polypeptide		
Response	1 week	4/5
	3 months	4/5
	9 months	1/2
Fasting plasma gastrin		
Response	1 week	1/1
	3 months	1/1
	6 months	1/1
	9 months	1/1
	12 months	1/1
Fasting plasma insulin/ C-peptide		
Response	1 week	1/2
	3 months	1/2
	6 months	1/2
Fasting plasma glucagon		
Response	1 week	1/1
	3 months	1/1
	6 months	1/1

Table 6

Results of treatment with octreotide (3 × 200 μg s.c. daily) in 16 patients with endocrine GI-tumours (ongoing study)

Time (months)	3 n	6 n	9 n	12 n
OR	12	8	7	3
NC	1	0	3	3
PD	3	5		2
SI	12	8	9	6
Total	16	13	10	8

OR = Objective response (≥ 50% reduction of tumour size or 5-HIAA excretion or serum levels of gastrin, insulin, glucagon)
NC = No change
PD = Progressive disease (≥ 25% increase of tumour size or 5-HIAA excretion or serum levels of gastrin)
SI = Subjective improvement

Discussion

If surgery cannot be performed in patients with endocrine gastrointestinal tumours due to extensive liver metastases, effective medical treatment is needed, especially in case of a functioning endocrine tumour. Cytostatic treatment is only indicated for a few tumours, such as VIPoma and insulinoma, which usually respond to streptozotocin alone or in combination with 5-fluoruracil and doxorubicin. However, the most frequent endocrine gastrointestinal tumour, the carcinoid (especially the midgut carcinoid), responds to chemotherapy in less than 10% (18). The same is true for the metastatic gastrinoma and glucagonoma. Therefore, chemotherapy with its serious side-effects is hardly justified as first-line treatment in these cases. Non-functioning endocrine tumours should be treated by chemotherapy only in case of rapid growth. Some patients will benefit by this. However, these tumours usually grow slowly and the patients often survive many years without any treatment.

In case of functioning endocrine tumours, hormone production and the clinical syndromes related to hypersecretion of various peptide hormones and/or amines, constitute indication for medical treatment. For these patients less aggressive forms of treatment than chemotherapy are needed and have recently been successfully applied, such as interferon-α by Öberg et al. (2, 18) and the long-acting somatostatin analogue octreotide by Kvols et al. (12, 13) and others. The treatment results with both drugs are not uniform (2–4, 12–15, 18). Therefore, the experiences of one institution with both drugs have been presented in this paper and the results are compared.

Both drugs had a remarkably low rate of side-effects which was thus rarely the reason for stopping treatment. The objective response (>50% reduction of tumour growth or hormone secretion) was very low during IFN-α treatment (only one of 15 patients) and high with octreotide (12 of 16 patients). This difference is due to the dramatic effect of octroeotide on hormone hypersecretion and clinical symptoms.

The effect is understandable since somatostatin is well known to inhibit secretion of all regulatory peptides and amines of the gastroenteropancreatic system (6). Octreotide has been shown to have similar effects already at the low dose of 25 μg daily (19). Since IFN-α does not have this dramatic effect on hormone secretion, the rate of subjective improvement was much lower after IFN-α than after octreotide. Significant regression of tumour growth did not occur in our two prospective studies. Several authors have seen tumour regression in a few cases after octreotide and such a dramatic effect has been observed in our institution too in one patient (Fig. 2).

The rare occurrence of true tumour regression makes it difficult to understand its mechanism. Somatostatin has been shown to inhibit the growth of gastrointestinal organs (20) and also the growth of different tumour cell lines in vitro (21) and in vivo (22). The demonstration of somatostatin receptors on endocrine tumours (23) may be the explanation for this, offering new perspectives in oncology (24). Another explanation could be mediation of the octreotide effect via suppression of paracrine or autocrine growth factors.

This study, as well as previous studies (18, 12), has shown that during IFN-α and octreotide treatment no tumour progression occurs in 30–50% of the treated cases. This should be regarded as a therapeutic success, especially since the side-effects of both drugs are minimal. The dramatic effect of octreotide on the hormone hypersecretion of functional endocrine tumours and thereby on the clinical symptoms is an advantage of this drug and explains why octreotide was objectively and subjectively superior to IFN-α in the five patients who were first included in the IFN-α and later on in the octreotide study.

The different pattern of response to IFN-α and octreotide suggests a different mechanism of action of the two and, therefore, combined treatment of endocrine gastrointestinal tumours with these two drugs may be considered in the future.

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