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Somatostatin Analog Sandostatin and Inhibition of Tumor Growth in Patients with Metastatic Endocrine Gastroenteropancreatic Tumors

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A prospective study was performed to determine the efficacy of octreotide (Sandostatin®; SMS 201-995) 200 μg tid in controlling tumor growth. The study included 21 patients with metastasized endocrine GEP tumors: 6 gastrinomas, 8 carcinoid syndromes, 7 nonfunctioning tumors. Treatment was performed for 3 to 59 months (median 15 months). Evaluation of the response to octreotide was facilitated in 12 patients by a pretreatment observation period of 3 to 47 months (median 17 months) during which the natural growth behavior was determined. Based on the presence or absence of a control period prior to treatment, 5 patients were considered to be responders, 7 as questionable responders (no pretreatment phase available), and 9 as nonresponders. None of the 21 patients had documented shrinkage of the tumor mass. The most favorable response was tumor standstill. In all but one responder an escape to an initially favorable response occurred after 6 to 28 months (median 14 months). Proved inhibition of growth was paralleled by a reduction of serum and urine hormone parameters, whereas unaltered progression of tumor growth was observed also in the presence of hormone suppression. Tumor growth and hormone release was inhibited in the absence and presence of somatostatin receptors on the tumor. It is concluded that octreotide exerts a limited effect on metastatic GEP tumor growth. The evaluation of a response to octreotide is facilitated by an observation period prior to the drug that provides information on growth characteristics of the tumor. The presence of octreotide receptors does not predict the success of therapy.

Therapeutic strategies for the management of patients with metastatic endocrine gastroenteropancreatic (GEP) tumors have been supplemented recently by the availability of somatostatin and its analogs, which demonstrated impressive efficacy on symptoms resulting from excessive hormonal hypersecretion resistant to standard therapy. Somatostatin was originally detected in the hypothalamus acting as a growth hormone release-inhibiting hormone [1, 2] and has been later demonstrated to be present throughout the central nervous system and the gastrointestinal tract [3, 4]. It inhibits the release of gastrointestinal regulatory peptides and (directly) pancreatic and gastric exocrine secretion [5]. Basically, therapeutic availability of this peptide is hampered by its short half-life of 1 to 3 minutes in humans. Applying step-by-step modification of the molecule, half-life was considerably prolonged, which resulted in an elimination half-life of 113 minutes. The central essential moiety of somatostatin consisting of the four amino acids Phe-Trp-Lys-Thr was preserved and is part of the stable octapeptide analog octreotide acetate (Sandostatin®, SMS 201-995) [6, 7]. More recently, additional octapeptide analogs with higher potency and longer duration of action have been synthesized utilizing solid-phase methods and designed for antiproliferative activity [8].

Octreotide was first introduced for treatment of disabling acromegaly [9] and later for malignant endocrine GEP tumors to suppress hormone secretion and thereby improve hormone-mediated clinical symptoms [9–11]. Currently, subcutaneously administered octreotide is the therapeutic drug of choice for reliable control of the flushing, wheezing, and diarrhea of patients with carcinoid syndrome [12–14], the watery diarrhea of patients with Verner-Morrison syndrome [15–18], and the necrolytic migratory erythema in patients with glucagonoma syndrome [19]. In contrast, there is no need for octreotide in the control of gastric acid hypersecretion of gastrinoma patients, which can be completely suppressed by oral omeprazole [20, 21]. The beneficial effect of octreotide in inhibiting insulin release from insulinomas is as unpredictable as it is for diazoxide [22], thus limiting its therapeutic usefulness for preventing hypoglycemia to a small number of patients [22, 23].

In addition to its inhibitory effect on endocrine and exocrine secretion, octreotide and some of its many analogs reveal antiproliferative properties [24]. Evidence for this assumption arises from in vitro studies using tumor cell lines. These findings are supported by in vivo data from immunocompetent rats, Syrian gold hamsters, and nude mice that strongly support an antiproliferative effect of octreotide analogs for a variety of solid tumors including cancers of the breast, prostate, lung, colon, and exocrine pancreas [24]. In addition to these limited experiences from animal studies, there are several reports regarding the effect of octreotide on tumor size in patients with functionally active metastatic GEP tumors [10, 11, 14, 22, 25, 26].

In a recent NIH report, results of octreotide treatment on

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Table 1. Clinical status of 25 patients with metastatic GEP tumors.

Patient no.	Sex	Age	Clinical syndrome	Primary tumor	Metastases			Surgical therapy	Length of history until 8/91 (month)
					Local	Liver	Elsewhere		
1	F	67	Gastrinoma	Lig. hepatoduodenal	+	+	Bone	Enucleation of primary	31
2	F	33	Gastrinoma	Duodenum	+	+	–	Enucleation of primary	68
3	F	44	Gastrinoma	Pancreas	–	+	–	Whipple's procedure, total gastrectomy	64
4	F	65	Gastrinoma	Pancreas	+	–	–	Unresectable primary	66
5	M	54	Gastrinoma	Pancreas	+	+	–	Unresectable primary	21
6	F	64	Gastrinoma	Pancreas	+	+	–	Unresectable primary	8
7	F	55	CS	Unknown	–	+	–	—	27
8	M	48	CS	Unknown	–	+	–	—	18
9	F	54	CS	Jejunum	+	+	–	Unresectable primary	106
10	M	46	CS	Ileum	+	+	–	Resection of primary	69
11	F	64	CS	Ileum	+	+	Pleura	Ileocolectomy	30
12	F	47	CS	Ileum	+	+	–	Ileocolectomy	47
13	M	48	CS	Jejunum	+	+	–	Resection of primary	9
14	F	38	CS	Pancreas	+	+	Skin, mamma	Unresectable primary	10
15	M	63	CS	Jejunum	+	+	–	Resection of primary	50
16	M	52	CS	Ileum	–	+	–	Ileocolectomy	48
17	F	63	CS	Ileum	+	+	Ovary	Resection of primary	18
18	M	34	Nonfunctioning	Pancreas	+	+	–	Whipple's procedure	80
19	M	25	Nonfunctioning	Pancreas	+	+	–	Unresectable primary	28
20	M	45	Nonfunctioning	Pancreas	+	+	–	Unresectable primary	20
21	F	62	Nonfunctioning	Bronchus	+	–	Pancreas, skin, retroperitoneal space	Lobectomy	30
22	F	41	Nonfunctioning	Duodenum	+	+	Adrenal mediastinum	Whipple's procedure, debulking	79
23	M	27	Nonfunctioning	Jejunum	+	+	Brain, lung	Unresectable primary	4
24	F	44	Nonfunctioning	Stomach	+	+	Lung	Unresectable primary	6
25	F	25	Nonfunctioning	Pancreas	+	+	—	Unresectable primary	240

CS: carcinoid syndrome.

tumor size were summarized from 94 patients (48 with carcinoid syndrome, 16 with gastrinoma, 10 with Verner-Morrison syndrome, 8 with glucagonoma, 5 with insulinoma, 4 with nonfunctioning or other islet cell tumors, and 3 with growth hormone-releasing hormone-producing tumors). Among these 94 patients, the size of metastases increased during therapy in 24%, remained unchanged in 63%, and decreased in 13% [10]. These promising results should be critically viewed, however, as patients who were included in this report had not been standardized with respect to spontaneous growth behavior before initiation of octreotide therapy, its dosage, and to the criteria that indicate how tumor growth was estimated.

The purpose of this report is to address these questions by studying the effect of standardized octreotide therapy on tumor growth and symptoms during a long-term follow-up in 21 patients with metastatic endocrine GEP tumors. Spontaneous tumor growth was evaluated in 16 patients during an observation period prior to octreotide therapy in which patients either received no antiproliferative therapy or the antiproliferative therapy was ineffective.

Patients and Methods

Patient Population

There were 25 patients with endocrine GEP tumors and extended metastatic disease enrolled in this prospective study: 6 with gastrinoma, 11 with carcinoid syndrome, and 8 with nonfunctioning tumors. The characteristics of the study sample and surgical procedures prior to octreotide therapy are detailed in Table 1. Diagnosis was based on the clinical history, the immunohistologic or ultrastructural characterization on biopsy specimens obtained during laparotomy or ultrasound-guided fine-needle biopsies [27], markedly elevated gastric acid hypersecretion and serum gastrin levels in patients with gastrinoma, elevated 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) in patients with carcinoid syndrome, and the lack of measurable serum hormone parameters or urinary 5-HIAA in patients with nonfunctioning tumors.

Clinical presentation of nonfunctioning tumors included obstructive jaundice (patients 22 and 23), intestinal obstruction (patient 18), abdominal pain (patient 25), gastric bleeding (patient 24), or cough (patient 21), or it was found incidentally (patients 19 and 20).

Treatment Schedule

After informed consent, all patients subjected to therapy received octreotide (Sandostatin®, SMS 201-995; Sandoz, Basel, Switzerland) in an initial dose of 50 μg tid SQ. The dosage was increased to 100 μg every 8 hours on day 4 and to 200 μg every 8 hours on day 7. Although, in general, flushing and wheezing in patients with carcinoid syndrome were controlled by 50 or 100 μg octreotide, the every 8 hour dosage was increased arbi-

Table 2. Tumor growth in 6 patients with metastatic gastrinoma before and during therapy with octreotide (200 μg tid).

Patient no.	Before treatment		During treatment				
	Observation period (months)	Growth behavior	Observation period (months)	Growth behavior	Response	Months	Escape to initial response
1	17	Progression	14	For 6 months slow progression; later standstill for 8 months	Yes	14	No
2		Unknown	42	For 28 months standstill; later progression	Quest. yes	28	Probably yes
3		Unknown	36	For 24 months slow progression; later fast progression	Quest. yes	24	Probably yes
4		Unknown	33	For 6 months standstill; later slow progression	Quest. yes	6	Probably yes
5	6	Standstill	15	For 6 months standstill; later fast progression	Quest. no	6	Probably yes
6		Unknown	3	Tumor progression (death)	No		—

trarily to 200 μg every 8 hours. Subcutaneous injection was facilitated by use of an automatic injection device (D-PEN U40/2, Disetronic GmbH, FRG).

Patients with gastrinoma received omeprazole 40 to 60 mg/day PO; the dosage was individually titrated based on basal gastric acid secretion, which was below 10 mmol l^{-1} in all patients before the next dose [28]. Octreotide therapy induced further reduction of basal acid secretion. During octreotide treatment patients received neither chemotherapy, interferon, nor other antiproliferative therapy. However, patients did receive supplements of pancreatic enzymes whenever steatorrhea was present either before octreotide treatment or if changes in bowel habit developed suggestive of malabsorption during therapy.

According to the study design, octreotide treatment was intended for at least 12 months. It was discontinued after 3 to 6 months, however, if patients showed rapid tumor progression during treatment. Otherwise therapy was continued as long as patients wished to receive it (mean 15 months; range 3–59 months) and had evidence of clinical or biochemical improvement or of stable disease. Patients 15, 16, 17, and 25 remained untreated but were included in the study to visualize no or extremely slow tumor growth during observation periods up to 240 months. Their follow-up demonstrated the difficulty of assessing response to therapy in some patients with metastatic GEP tumors with standstill of growth during specific treatment but no tumor growth during the pretreatment phase.

Follow-up Investigations

Patients were hospitalized for follow-up at 3-month intervals and, if necessary, were controlled over shorter intervals in the outpatient clinic. Follow-up investigations included physical examination, complete blood count, measurement of serum electrolytes, renal and liver functions, estimation of gastrointestinal hormones, and 24-hour urine specimens for 5-HIAA assay. To evaluate clinical symptoms, patients kept a diary regarding the number, extent, and severity of flushing episodes, the frequency and consistency of bowel movements, and their well-being.

Tumor growth was assessed at 3-month intervals by abdominal ultrasonography and abdominal CT. CT was performed with and without intravenous contrast enhancement after orally administered contrast material. It started at the end of the dome of the liver and extended caudally to the pelvis at 0.8-cm intervals. The number of metastases within the liver, ligamentum hepatoduodenale, mesenterium, paraaorta, or elsewhere was estimated, as was the size of two or three reference metastases determined by measuring the perpendicular diameters of each metastasis. Planimetry during ultrasonography and volumetry during CT of reference metastases was performed if possible. Ultrasonography and CT were performed by independent investigators.

Evaluation of Response

Tumor Growth. Progression was defined as an increase in tumor growth of more than 25% within 3 months assessed by the sum of two perpendicular diameters estimated in two metastases by planimetry or volumetry, or by the appearance of new metastases. *Slow progression* was defined as an increase of tumor growth by more than 25% within 6 to 12 months. Standstill was assumed if less than 25% increase or decrease of tumor growth was observed within the observation period indicated in Tables 2, 3, and 4. *Regression* was defined as a decrease in tumor growth by more than 25% within the observation period.

Response to octreotide was defined as standstill or a decrease in tumor growth after documented progression prior to treatment or a decrease in tumor growth following standstill within the pretreatment period. A *questionable response* was assumed if growth behavior prior to octreotide treatment was unknown but during octreotide therapy standstill occurred followed by

Table 3. Tumor growth in 11 patients with carcinoid syndrome before and during therapy with octreotide (200 μg tid).

Patient no.	Before octreotide: Observation period (months)	Before octreotide: Growth behavior	During octreotide: Observation period (months)	During octreotide: Growth behavior	Response	Months	Escape to initial response
7	5	Progression	18	Standstill	Yes	18	No
8	6	Progression	12	For 6 months standstill; later progression	Yes	6	Yes
9	36	Standstill	18	Standstill	Quest. no	18	No
10	47	Slow progression	12	Standstill	Quest. yes	12	No
11		Unknown	30	For 9 months standstill; later progression (death)	Quest. no	9	Probably no
12	17	Progression	16	Progression (death)	No		—
13	3	Progression	6	Progression	No		—
14		Unknown	5	Progression (death)	No	—	
15	50	Standstill or minimal progression (< 25% in 4 years)			No therapy		
16	48	Standstill			No therapy		
17	18	Standstill			No therapy		

Table 4. Tumor growth in 8 patients with metastatic nonfunctioning GEP tumors before and during therapy with octreotide (200 μg tid).

Patient no.	Before octreotide: Observation period (months)	Before octreotide: Growth behavior	During octreotide: Observation period (months)	During octreotide: Growth behavior	Response	Months	Escape to initial response
18	48	For 43 months postop. no tumor detectable, later fast progression	32	For 6 months slow progression; for 18 months standstill; later progression	Yes	24	Yes
19	16	Progression	9	For 6 months standstill; later progression (death)	Yes	6	Yes
20		Unknown	12	For 6 months standstill; later progression (death)	Quest. yes	6	Probably yes
21	30	Progression	3	Progression (death)	No		—
22	20	Slow progression	59	Slow progression	No		—
23		Unknown	3	Progression (death)	No		—
24		Unknown	6	Progression	No		—
25	240	Extremely slow progression			No therapy		

later progression or there was slow progression followed by later fast progression. A questionable response was further assumed if growth behavior prior to octreotide therapy was assessed as slow progression followed by standstill during therapy (patient 10). If a questionable growth response was paralleled by a decrease of hormone parameters, patients were categorized as "questionable yes" otherwise "questionable no." All patients with progression of tumor growth during therapy were considered *nonresponders*.

Escape to initially successful therapy was defined as progression of tumor growth during octreotide therapy despite an ascertained or assumed response to the drug at the beginning of therapy.

Gastrin and 5-HIAA. Response to octreotide treatment was defined as a decrease of at least 50% compared to pretreatment values and a duration of response of at least 3 months. Nonresponders were those with less than 50% improvement and a duration of response of less than 3 months.

Flushing. Clinical symptomatology was assessed in patients with carcinoid syndrome based on the patients' diaries and by interview. Episodes of flushing were graded for their frequency and duration.

Octreotide Receptor Status

Octreotide receptors were visualized either in vitro by autoradiography using SDZ 204-090, the stable Tyr^3 analog of SMS 201-995, as specific radioligand [29] or by in vivo scintigraphy using indium-labeled octreotide (Octreoscan 111; Mallinckrodt Diagnostika, Holland) [30].

Table 5. Effect of octreotide (200 μg tid) on serum gastrin[a] in patients with metastatic gastrinoma.

Patient no.	Before sandostatin	During octreotide								
		10 Days	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months	36 Months	48 Months
1	673	58	123	127	130	270				
2	630	22	129	80		125	140	51	870	710
3	2,100	270	78	480	290	912	7,200	11,800	135,000	1,200,000
4	590	303	210	820	410	1,290	1,194	1,730	3,475	2,800
5	374		630		1,345	2,580	1,060			
6	25,500	18,500	40,000							

[a]Serum gastrin is indicated as picograms per milliliter (upper normal range is > 60 pg/ml). Blood was sampled 8 hours after the octreotide injection.

Table 6. Effect of octreotide (200 μg tid) on urinary 5-HIAA[a] in patients with carcinoid syndrome.

Patient no.	Before octreotide	During octreotide							
		10 Days	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months	36 Months
7	121	38	39	55	45	22			
8	1410	964	676	971	1712	2331			
9	68	64	73	43	138	96	90	50	
10	319	165	257		315				
11	1119		1315	1000	1265	1234	1285	965	1325
12	1018	507	1061	860	773	950	1218		
13	1644	659	570						
14	84	86	152						
15	63–110								
16	460–960								
17	40–95								

[a]5-HIAA is indicated as micromoles per day (upper normal range > 47).

Evaluation of Side Effects

In addition to general clinical nonspecific side effects and sensations at the octreotide injection site, patients were evaluated with respect to the development of steatorrhea, gallstones, and vitamin B_{12} deficiency.

Results

Spontaneous Growth of Metastatic GEP Tumors

Data on the length of the history in this study sample, i.e., from the first symptom(s) related to the tumor until now, are depicted in Table 1. Information on spontaneous tumor growth during the period prior to octreotide treatment was gained from CT scans and ultrasound investigations (available in 16 of 25 patients): 2 with gastrinoma, 9 with carcinoid syndrome, and 5 with nonfunctioning tumors (Tables 2–4). A wide range of spontaneous growth features were documented: fast progression (i.e., increase of tumor size by more than 25% during 3 months), slow progression (i.e., increase of tumor size by more than 25% during 6–12 months), and growth standstill up to 50 months. Whether the higher number of patients with tumor standstill or slow progression within the carcinoid syndrome group reflects a real effect, indicating slower malignant potential, cannot be answered from the present study. Because of the slow progression of tumors in patients 15 and 25 and the long-lasting tumor standstill in patients 16 and 17, we were obliged to leave these patients untreated. Flushing in patients 15, 16, and 17 was mild and required no treatment. In patient 15 it appeared 38 months after the incidental diagnosis of a metastatic endocrine tumor, which was originally classified as nonfunctioning because of the lack of symptoms.

Octreotide and Tumor Growth

An observation period prior to treatment of at least 3 months (range 3–47 months) was available for 12 of 21 patients subjected to octreotide. According to this preobservation period, an ascertained response to octreotide was assumed in 5 patients, a questionable response in 7 patients, and a clear treatment failure in 9 patients.

The 5 patients identified as definite responders (patients 1, 7, 8, 18, and 19 of Tables 2–4) showed progression during the pretreatment phase followed either by standstill during treatment (patients 7, 8, and 19 of Tables 3 and 4) or by slower progression and later standstill (patients 1 and 18 of Tables 2 and 4). Seven patients have been evaluated as questionable responders. In 5 of these patients (patients 2, 3, 4, 11, and 20 of Tables 2–4) no observation period prior to giving octreotide was available. In these patients no tumor growth or only little progression was found during treatment for 6 to 28 months. However, this initial standstill was followed by later fast progression. The assumption of an at least temporary questionable response was further substantiated by serum gastrin levels obtained during treatment (Table 5). In patients 2, 3, and 4, gastrin decreased significantly for at least 9 months. Therefore these patients have been evaluated as "questionable yes" responders. Because urinary 5-HIAA in patient 11 did not

Table 7. Tumor growth, serum gastrin, urinary 5-HIAA, escape to initial response and somatostatin receptor status in patients with metastatic GEP tumors treated with octreotide (200 μg tid).

Patient no.	Tumor growth		Hormone suppression		Somatostatin receptor status[a]
	Inhibition	Escape	Inhibition	Escape	
1	Yes	No	Yes	No	+ (S)
2	(Yes)[b]	(Yes)	Yes	Yes	ND
3	(Yes)	(Yes)	Yes	Yes	+ (S)
4	(Yes)	(Yes)	Yes	Yes	+ (SA)
5	(No)	(—)	No	—	ND
6	No	—	No	—	+ (A)
7	Yes	No	Yes	No	ND
8	Yes	Yes	Yes	Yes	+ (SA)
9	(No)	No	No	—	+ (S)
10	(Yes)	No	Yes	No	ND
11	(No)	(No)	No	—	+ (A)
12	No	—	Yes	Yes	ND
13	No	—	Yes	No	+ (A)
14	No	—	No	—	+ (SA)
18	Yes	Yes			+ (S)
19	Yes	Yes			− (A)[c]
20	(Yes)	(Yes)			ND
21	No	—			− (A)
22	No	—			+ (SA)
23	No	—			− (A)
24	No	—			+ (A)

ND: not done.
[a]Somatostatin receptor status was evaluated by in vitro autoradiography (A) or scintigraphy with OctreoScan 111 (S).
[b]Parentheses indicate questionable inhibition or probable escape.
[c]Somatostatin receptor status was estimated during escape after initial growth response from tumor metastasis.

decrease in response to octreotide (Table 6) he was considered as "questionable no" responder (Table 7). In patients 9 and 10, standstill or slow tumor progression was found during the observation period prior to octreotide. Patient 10 has been assessed as "questionable yes" because standstill of tumor growth continued for another 6 to 9 months and was paralleled by a decrease in urinary 5-HIAA (Table 3). Later, this tumor showed fast progression. Whether a similar assessment is also true for patient 9 is difficult to say, as tumor standstill during the period prior to treatment and during octreotide was not followed by a decrease in urinary 5-HIAA during treatment (Tables 3, 6, and 7). Possibly growth standstill in this patient during treatment reflected spontaneous growth.

In the remaining patients (patients 6, 12, 13, 14, 21, 22, 23, and 24 of Tables 2–4) no growth response to octreotide could be demonstrated. This finding is in accordance with unchanged serum gastrin levels in patient 6 (Table 5). In contrast, a tendency to lower 5-HIAA levels in patient 12 and a clear decrease of 5-HIAA in patient 13 were in contrast to the fast progression in tumor growth.

Tumor growth, serum gastrin, and urinary 5-HIAA in response to octreotide treatment are summarized in Table 7. There is remarkable agreement between tumor growth assessed as unequivocal "yes" or "no" and the hormone response to octreotide (patients 1, 6, 7, 8, and 14). Only in patients 12 and 13 was tumor progression during octreotide treatment not mirrored by a failure of the drug to inhibit urinary 5-HIAA excretion. Because a favorable growth response was always paralleled by inhibition of serum gastrin or urinary 5-HIAA we believe it is justified to assume that a favorable growth response to octreotide occurred also in some patients with unknown growth behavior or with tumor standstill prior to octreotide treatment. Therefore we judged patients 2, 3, 4, and 10 as "questionable yes," as hormone secretion was initially suppressed and later showed an escape reflected in both initial favorable growth behavior (standstill, slow progression) and later fast progression. Interestingly, only 2 patients with nonfunctioning tumors had an unequivocally favorable response.

Receptor Status and Escape to Therapy

As indicated in Table 7, an escape to an initially favorable response was a frequent finding and was observed in 7 patients. In only 3 patients did a favorable response continue for 14 months (patient 1), 18 months (patient 7), or 12 months (patient 10). Escape to therapy always corresponded to tumor growth and hormone parameters. Interestingly, positive somatostatin receptor status is not a good predictor for efficacy of octreotide therapy. In the presence of somatostatin receptors, both favorable and no response with respect to inhibition of tumor growth and suppression of serum gastrin or urinary 5-HIAA have been observed (Table 7). There was one patient (patient 19) with a negative receptor status, as shown on tumor tissue obtained during laparotomy, who responded to octreotide with growth standstill for 6 months after proved progression prior to treatment. Receptors in this patient have been estimated during the phase of escape to initially favorable response. It is possible that receptors disappeared during dedifferentiation, though similar events have not been observed in other tumors (Table 7). With the questionable exception of patient 19, no favorable growth response occurred in the absence of somatostatin receptors.

Flushing

In all patients, flushing was alleviated, with a clear decrease in the frequency and severity of symptoms. We observed no indication of resistance or tachyphylaxis to the drug. Flushing remained less even in patients in whom the urinary 5-HIAA did not drop or who showed an escape to initial favorable response with respect to tumor growth and hormone levels.

Side Effects

Major side effects were not observed in our patients. Some reported a burning sensation at the site of the injection that improved spontaneously or after administration of 0.1 ml of 0.1% lidocaine. One patient reported dizziness and nausea if the morning octreotide dose was administered before breakfast, but it disappeared with postcibal injections. None developed gallstones or vitamin B_{12} deficiency. As a regular finding patients experienced loose stools and steathorrhea that were marked after previous total gastrectomy or the Whipple procedure. Oral administration of pancreatic enzymes alleviated the steathorrhea in some but not all patients; loperamide was ineffective.

Table 8. Receptor status versus tumor growth response.

	Receptor status		
Tumor growth response	+	−	Not done
Yes	3	1[a]	1
Questionable	4		3
No	5	2	2

[a]Parentheses indicate questionable inhibition or probable escape.

Table 9. Hormone suppression versus tumor growth response.

	Hormone suppression	
Tumor growth response	Yes	No
Yes	3	0
Questionable	4	2
No	2	3

Discussion

This study is the first to prospectively investigate, as its main purpose, the growth of metastatic endocrine GEP tumors in response to octreotide. Tumor growth was followed at 3-month intervals by CT and ultrasonography. For final evaluation CT scans of every patient covering the entire observation period were reevaluated by an expert not familiar with the clinical response. This step is mandatory, as routine examinations frequently resulted in either "no change" or even "regression" but rarely "progression" if compared to the CT performed 3 months earlier. In contrast, thorough evaluation of scans covering the whole observation period including the time prior to octreotide treatment frequently led to a divergent assessment. Different types and generations of scanners from different hospitals, CTs performed with and without intravenous contrast enhancement, different section thickness, the occasional appearance and disappearance of a fatty liver, and other factors may bias the assessment of a scan. Importantly, results obtained by ultrasonography frequently contribute to the evaluation of CT scans if metastases are first detected by ultrasonography and are recognized on CT scans during a "second look." In this report every statement on tumor growth is based on combined evaluation of CT and ultrasonography. This protocol was possible because the patients enrolled in this study have been investigated and followed up at a single institution.

This study differs from previous reports in that it included patients with known growth behavior prior to treatment. Information on spontaneous tumor growth before specific antiproliferative therapy is important because endocrine GEP tumors and their metastases sometimes remain unchanged in size for months or even years without therapy, grow slowly, or show rapid progression. Because GEP tumors are rare, estimates on the frequency of rapidly or slowly growing tumors are not available. There are no measures to predict growth in an individual tumor. Patients included in this report confirmed this wide range of growth behavior. Standstill or minimal progression up to 20 years could be documented in a few patients (patients 15, 16, 17, and 25 in Tables 3 and 4), which encouraged us not to recommend treatment with chemotherapy (and its serious side effects), octreotide, or interferon α. Known growth behavior in 12 of 21 patients prior to the initiation of octreotide treatment, on the other hand, enabled us to assess the efficacy of treatment. Furthermore, experiences with these patients uncovered the difficulty of evaluating the treatment response of those whose tumor growth behavior was unknown prior to therapy.

According to our preconditions, we found an unequivocally favorable response to octreotide in 5 of 21 treated patients (Table 8). Tumor masses never decreased in size but revealed standstill after documented previous progression. An ongoing response was observed in only 2 patients; 3 patients escaped after 6 to 24 months with respect to both tumor growth and hormone levels. A questionably favorable response to octreotide was assumed in 7 patients in whom tumor growth prior to treatment was unknown (4 patients) or in whom standstill or slow progression was seen. In these patients standstill (4 patients) or slow progression (1 patient) lasted 6 to 28 months and was followed by later fast progression. The assumption of a favorable response was further based on a decrease of gastrin or 5-HIAA during the period of assumed growth response. However, it must be admitted that there is no proof for the assumption that octreotide influenced growth favorably, as none of these patients responded with a decrease in tumor mass. Therefore the observed standstill could equally continue as standstill during the pretreatment phase and thus mirror spontaneous growth behavior. This observation underlines the importance of an observation phase prior to therapy. Nine patients had been identified as definite treatment failures based on tumor progression during octreotide treatment.

Proved and assumed inhibition of tumor growth in all patients was paralleled by inhibition of serum gastrin and urinary 5-HIAA (Table 9). In patient 12 tumor showed rapid progression during octreotide treatment, whereas 5-HIAA excretion was suppressed. Therefore hormone suppression does not predict a possibly favorable growth response. The divergent action of octreotide is further substantiated by its overall favorable effect on flushing. In this study no patient with

carcinoid syndrome was refractory to octreotide with respect to flushing, whereas urinary 5-HIAA dropped in only 5 of 8 patients and tumor growth responded unequivocally in 2 patients. This finding strongly suggests different mechanisms of action of octreotide on the tumor.

It has been suggested by several groups that the effect of octreotide on symptoms, hormone release, and tumor growth is mediated by octreotide receptors present in large numbers on endocrine tumors [8, 9, 30–32]. In accordance with previous findings [32, 33] we demonstrated somatostatin receptors on most tumors. However, the presence of these receptors seems to be an independent phenomenon that predicts neither a favorable growth response nor hormone suppression during octreotide treatment (Table 8). Three tumors in this study were receptor-negative, and all were functionally inactive. Nevertheless, one of these tumors (No. 19) responded to octreotide with standstill for 6 months after ascertained progression prior to therapy. Later the tumor escaped to initially favorable response. If confirmed, this observation indicates that the mechanism of how octreotide affects tumor growth may be indirect and not necessarily mediated by receptors on the tumor. In accordance with this assumption it has been suggested that changes in tumor size are secondary to changes in hemodynamics due to reduced splanchnic blood flow [5, 34].

Although our study sample of 21 patients treated with octreotide to inhibit tumor growth is small and permits only preliminary conclusions, it is in variance with recent reports indicating shrinkage of malignant GEP tumors and their metastases [35–40]. We found standstill to be the most favorable response after previously documented progression; there was never regression. Most importantly, this response lasted 24 months in 1 patient only; in others it was of shorter duration and was followed by later escape. In other patients of this study the difficulty of assessing the treatment response resulted mainly from the absence of a reliable pretreatment period with which the spontaneous tumor growth could be compared. Presently, a prospective German multicenter trial is being performed in cooperation with the authors in which more than 100 patients with metastatic endocrine GEP tumors are under treatment with octreotide 200 μg tid for at least 1 year. For most of the patients enrolled in this study, an observation period prior to treatment is available, which hopefully facilitates more precise evaluation of tumor growth. The data of this new study must come to a more definitive conclusion on the value of octreotide treatment for controlling the growth of malignant endocrine GEP tumors.

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Résumé

Par une étude prospective chez 21 patients, on a déterminé l'efficacité de 200 μg de sandostatine (SMS 201-995) pour contrôler la croissance tumorale d'une tumeur endocrine du pancréas-GEP métastasée: 6 gastrinomes, 8 tumeurs carcinoïdes et 7 tumeurs non-fonctionnelles. Le traitement a été donné pendant une médiane de 15 (3–59) mois. La réponse au traitement a été comparée à l'évolution naturelle des tumeurs endocrines chez 12 de ces patients avant tout traitement pendant une médiane de 17 (3–47) mois. Selon qu'il y a eu une période d'observation avant le traitement ou pas, on a considéré 5 patients comme des "répondeurs possibles", 7 comme des "répondeurs douteux" et 9 comme des "non répondeurs". Chez aucun des patients, la tumeur n'a diminué de volume. La réponse la plus favorable a été une stabilisation de la croissance tumorale. Chez tous les "répondeurs" sauf un, une réponse initiale favorable s'est soldée par un échec après une médiane de 14 (6–28) mois. Parallèlement à l'inhibition de la croissance, on a observé une réduction hormonale dans le sang et dans les urines. La croissance tumorale n'a pas été altérée même en cas de suppression hormonale. La croissance tumorale et le largage hormonal n'ont pas été corrélés avec la présence ou l'absence de récepteurs de la somatostatine sur la tumeur. On conclut que la sandostatine exerce un effet tout à fait éphémère sur la croissance métastatique des tumeurs GEP. L'évaluation de la réponse au traitement a été grandement facilité par la période d'observation pré-traitement. La présence de récepeurs à la somatostatine ne prédit pas le succès de la thérapeutique par la sandostatine.

Resumen

Se emprendió un estudio prospectivo con el propósito de determinar la eficacia de 200 ug de sandostatina (SMS 201-995) tres veces al día en el control del crecimiento tumoral. El estudio incluye 21 pacientes con tumor gastroenteropancreático (GEP) metastásicos: 6 gastrinomas, 8 síndromes carcinoides, 7 tumores no funcionantes. El tratamiento tuvo una duración de 3–59 meses (media 15 meses). La evaluación de la respuesta a la sandostatina se facilitó en 12 pacientes por un periodo de observación anterior al tratamiento de 3–47 meses (media 17 meses), del cual se dedujo el comportamiento natural de su crecimiento. Con base en la presencia o ausencia de un periodo de control anterior al tratamiento, 5 pacientes fueron calificados como de respuesta positiva, 7 como de respuesta cuestionable (no hubo fase pretratamiento disponible) y 9 como de respuesta negativa.

Ninguno de los 21 pacientes exhibió disminución de la masa tumoral. La respuesta más favorable fué un estancamiento en el crecimiento del tumor. En todos los pacientes con respuesta positiva, menos en uno, se produjo un escape a una respuesta inicialmente favorable a los 6–28 meses (media 14 meses). La comprobada inhibición del crecimiento tumoral tuvo paralelismo en una reducción en los niveles séricos y urinarios de parámetros hormonales, en tanto que la inalterada progresión del crecimiento tumoral fue observada también en presencia de supresión hormonal. El crecimiento tumoral y la liberación hormonal fueron inhibidos tanto en ausencia como en presencia de receptores de somatostatina en el tumor.

Nuestra conclusión es que la sandostatina ejerce un efecto de corta duración sobre el crecimiento de tumores GEP metastásicos. La valoración de la respuesta a la sandostatina se facilita por un periodo de observación previo a la administración de sandostatina, el cual provee información sobre las características del crecimiento del tumor. La presencia de receptores de somatostatina no es factor de predicción del éxito de la terapia con sandostatina.

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