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SOMATOSTATIN ANALOGUE PHASE I TRIALS IN NEUROENDOCRINE NEOPLASMS

LOWELL ANTHONY, DAVID JOHNSON, KENNETH HANDE, MAX SHAFF, SHEILAH WINN, MARY KROZELY and JOHN OATES

To further investigate the antineoplastic efficacy and safety of somatostatin analogues, 2 trials were performed. Octreotide, SMS 201–995 (Sandostatin), was escalated in doses ranging from 1 500 μg to 6 000 μg daily in 14 patients with carcinoid. Somatuline, (BIM 23014C, Angiopeptin, Lanreotide) was given in doses ranging from 2 250 μg to 9 000 μg daily to 13 neuroendocrine patients (6 carcinoid, 2 atypical carcinoid, 3 pancreatic islet cell and 2 small cell lung cancer patients). All patients successfully completed dose escalations without significant adverse effects and were evaluable for toxicity. The dose limiting side-effect of octreotide was the injection volume. No dose limiting adverse effects have been observed with somatuline. Carcinoid syndrome symptoms were better controlled with higher octreotide doses. Thirteen patients were evaluable for octreotide's antitumor efficacy with a partial response observed in 4 (31%), stable disease in 2 and progressive disease in 7 patients. Radiographic changes of increased tumor necrosis occurred in 5 patients and was independent of response. Somatuline resulted in a partial response in 4 patients (2 carcinoids, 1 gastrinoma and 1 small cell lung cancer) (31%), stable disease in 1 atypical carcinoid, and progressive disease in 8 (4 carcinoid, 1 atypical carcinoid, 2 islet cell and 1 multi-drug resistant small cell lung cancer). Six of the 8 carcinoid patients had radiographic changes of increased necrosis. Dose escalation of somatostatin analogues is well tolerated and may be associated with antitumor activity in some neuroendocrine neoplasms.

Neuroendocrine tumors can produce distressing symptoms related to the release of serotonin and/or peptide hormones. Controlling these symptoms may diminish the physical and emotional consequences of cancer and improve quality of life, patient compliance and survival. Biotherapy for neoplastic diseases has markedly advanced over the last decade and now includes somatostatin analogs as effective agents in managing some hormonally active tumors (1). These analogues are not only effective in controlling the symptoms of gastroenteropancreatic tumors but can also influence cell growth and differentiation (2).

The spectrum of hormonal suppression by somatostatin and its analogues is broad and includes growth hormone, thyroid stimulating hormone, insulin, glucagon, gastrin, somatomedin C (IGF-1) and other gastrointestinal and growth factor peptides (3, 4). Somatostatin is also effective in controlling the symptoms of hormonal release from neoplastic diseases (5, 6). Due to pharmacologic limitations with the native hormone, octreotide, a somatostatin analogue, was developed and shown to be effective at doses ranging from 50 to 150 μg two or three times a day in controlling carcinoid syndrome (1, 7). These octreotide doses resulted in a 15–20% partial response rate in carcinoid tumor (1). Somatuline, RC-160 and other peptide analogs have been synthesized and are investigational (Fig. 1).

Somatostatin's inhibitory action on cell growth and its receptor's presence in many tumors suggest the potential usefulness of somatostatin analogues in cancer treatment

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From the Department of Medicine and Radiology, Vanderbilt University and Nashville Veterans Affairs Medical Center, Nashville, TN, USA.
Correspondence to: Dr Lowell Anthony, Room 1956, The Vanderbilt Clinic, Vanderbilt University, Nashville, TN 37232-5536, USA.
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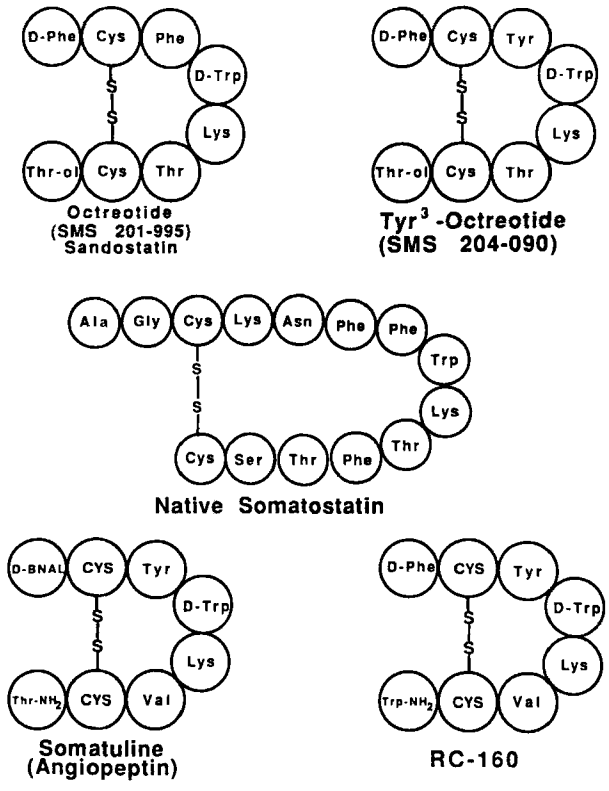


Fig. 1. Structural formulas of native somatostatin and several clinically important analogues.

(2, 8–14). The presence of somatostatin receptors in neuroendocrine tumors is variable and ranges from 40% in small cell lung cancer (SCLC) to 80–90% of carcinoid tumors (15, 16). Even though somatostatin's anti-proliferative effect includes the inhibition of hormone secretion and the interference with the release and/or action of growth factors, the direct effect of somatostatin may contribute significantly to its antitumor activity. Somatostatin receptor stimulation activates protein tyrosine phosphatase enzymes resulting in protein dephosphorylation (2, 17, 18). For a human pancreatic cell line, the stimulation of protein tyrosine phosphatase is linear between somatostatin concentrations of 5 and 150 nM suggesting a higher plasma somatostatin concentration may result in a stronger negative counter-regulatory signal influencing cell growth (18).

Because of the broad inhibitory action of somatostatin and the occurrence of the somatostatinoma as a unique pancreatic islet cell neoplasm, toxicity from these peptides used as therapeutic agents could include diabetes mellitus, hypoglycemia, steatorrhea, abdominal cramping, gall stones, cachexia, malaise, weight loss and secondary hypothyroidism (19–21). Since doses in the 50–150 μg range were effective in serotonin and peptide hormone suppression, doses above 500 μg three times daily have been considered to be unnecessary and potentially toxic.

Carcinoid syndrome symptoms may become less well controlled by octreotide as the tumor mass increases. Titrating the somatostatin analogue dose to that required to block more receptors and control breakthrough symptoms could result in unacceptable drug toxicity. Identifying the dose limiting toxicity of these peptides is necessary to not only safely use these drugs for supportive care but to determine whether higher doses may result in a greater antitumor response. We herein report two phase I trials of somatostatin analogues, octreotide and somatuline, in neuroendocrine neoplasms.

Material and Methods

Octreotide phase I trial in carcinoid. Fourteen patients (Table 1) underwent octreotide (Sandostatin, Sandoz Pharmaceutical Corporation, East Hanover, New Jersey) dose escalation between July 1990 and October 1991. The duration of carcinoid disease from first symptoms to the start of treatment was variable and ranged from 17 years to 6 months. Octreotide therapy had been previously initiated at doses ranging from 150 to 300 μg q 8 h in all 14 patients. The duration of prior octreotide therapy ranged from 3.5 years to 1.5 months. All patients had pathologically confirmed carcinoid tumors of foregut, midgut or hindgut origin and had elevation of their urinary 5-HIAA. The majority of patients had liver metastases.

On a 6-week interval, these patients were admitted to the Vanderbilt Clinical Research Center (CRC) and evaluated for signs of toxicity and antitumor efficacy. Twenty-four

Table 1

Characteristics of patients entered into the trials

Patient characteristic	Octreotide trial	Somatuline trial
n	14	13
Age (years)		
Range	46–79	35–70
Median	64	49
Sex		
Male	7	6
Female	7	7
Performance status		
100–80%	10	5
79–60%	4	8
Carcinoid syndrome	14	5
Cancer type		
Typical carcinoid	14	6
Foregut	3	
Midgut	11	4
Hindgut		1
Unknown primary		1
Atypical bronchial carcinoid		2
Insulinoma		1
PPoma		1
Gastrinoma		1
Small cell lung		2
Liver metastases	12	12
Bone metastases	3	3
Abdominal metastases	5	3

hours prior to discharge, the octreotide dose was escalated. Octreotide doses studied were 500 μg, 750 μg, 1 000 μg, 1 500 μg, 2 000 μg q 8 h. Patients were evaluated on each occasion with either an abdominal CT scan or ultrasound, thyroid function tests, fasting and postprandial blood sugars, 72-h fecal fat collection, serum carotene measurement, 24-h 5-HIAA repeated 3 times, serum chemistries (including hepatic and renal function measurements), and quality of life assessments including a measure of flushing and diarrhea severity using a 10 cm visual analog scale. Gall bladder ultrasound was done prior to octreotide dose escalation and repeated every 6 months. Except for one patient who received concomitant 5-FU, no other treatment was allowed except for loperamide for diarrhea.

Somatuline phase I trial in neuroendocrine neoplasms. Thirteen patients (Table 1) were enrolled into the study between May 1991 and June 1992. The duration of carcinoid disease ranged from 7 years to 2 months. All patients had histologically confirmed neuroendocrine tumors including carcinoid arising from the foregut, midgut and hindgut, atypical carcinoid and small cell lung cancer. Patients' initial somatuline (BIM 23014C, Angiopeptin, Lanreotide, Henri Beaufour Institute, Washington, D.C.) dose was 750 μg q 8 h. The dose was doubled on 2 occasions a week apart and 3 000 μg q 8 h maintained indefinitely. No concomitant antitumor therapy was allowed. A similar surveillance for toxicity and efficacy as performed with octreotide was done.

Methods. The response to therapy for the carcinoid patients was monitored by measurements of urinary 5-HIAA in triplicates and abdominal or chest CT scans. Other markers were followed according to the clinical circumstances and included gastrin, pancreatic polypeptide or fasting blood sugar. A partial tumor response was defined as a 50% reduction in the product of perpendicular tumor diameters without any signs of new metastases. Stable disease occurred when there was less than a 50% reduction but no greater than a 25% increase in the product of perpendicular diameters. Progressive disease was defined as more than a 25% increase in the product of perpendicular diameters.

Results

Octreotide phase I trial in carcinoid

All patients successfully completed octreotide dose escalation as planned. The dose limiting side-effect was the subcutaneous injection volume of 2 ml required to administer 2 000 μg. One patient had the octreotide dose reduced to 750 μg q 8 h because of insufficient subcutaneous tissue needed for the 2 ml q 8 h injections. Two patients died of progressive disease 15 and 16 months respectively, after octreotide dose escalation. Both patients had cardiac valvular insufficiencies and widely metastatic disease either to bone or retroperitoneum in addition to the liver. Both patients received palliative clinical benefit and no signs of toxicity. An autopsy on one patient revealed no biliary sludge or gall stones after a total of 4 years on octreotide. One patient noticed less dietary discretion while receiving 1 000 μg q 8 h and after 3 months on 2 000 μg q 8 h, her dose was decreased to 1 000 μg q 8 h.

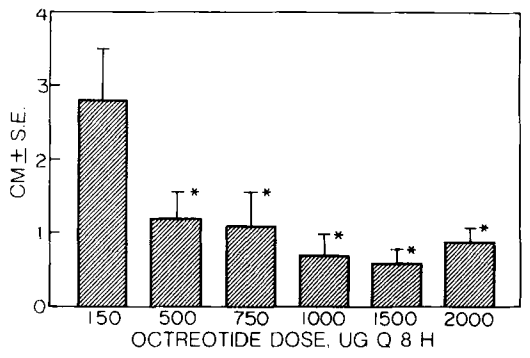


Fig. 2. Flushing severity at various octreotide doses in 14 carcinoid patients. 0 = none; 10 = severe; *p < 0.05.

A visual analog scale was used to quantify flushing in the patients with carcinoid syndrome (see Fig. 2). Flushing was significantly reduced with higher octreotide doses but leveled off after the first dose escalation. Fecal fat and serum

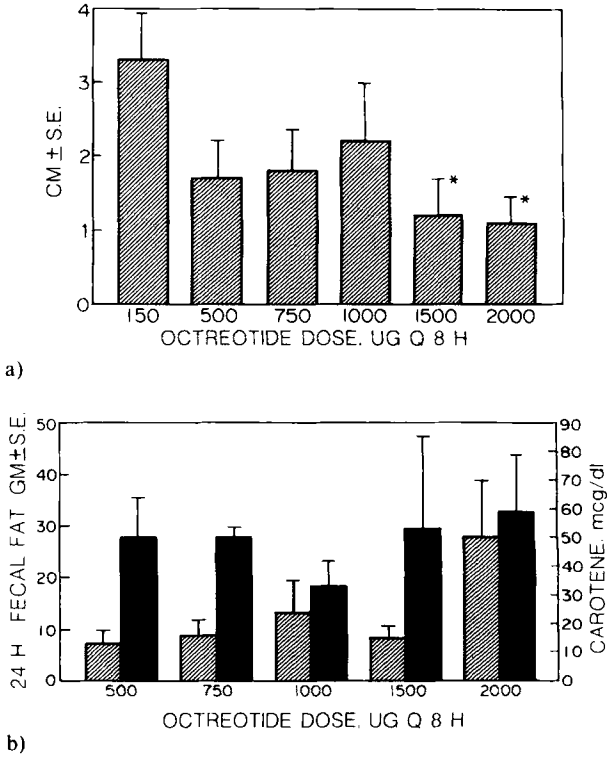


Fig. 3. Effect of octreotide dose escalation on fat absorption. a) visual analog scale measure of patients' perception of diarrhea severity. 0 = none; 10 = severe; *p < 0.05. b) objective measurements of fecal fat and blood carotene concentration. ▨: fecal fat; ■: carotene.

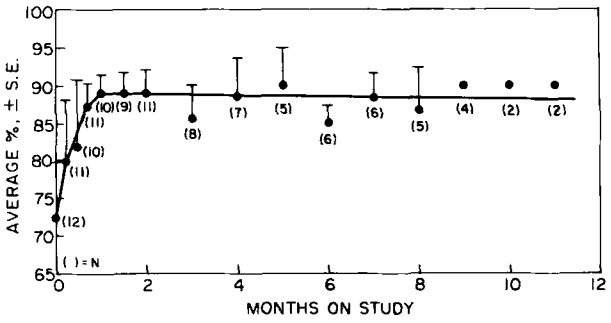


Fig. 4. Somatuline's effect on patients' performance status (Karnofsky scale).

carotene measurements (see Fig. 3) assessed exocrine pancreatic function. Even though steatorrhea was documented, its occurrence was sporadic and proved not to be dose limiting. No incidence of gall stones has been documented. Patients with existing gall bladder disease have not required surgical intervention.

With higher octreotide doses there were no dose limiting side-effects of abdominal cramping, steatorrhea, weight loss, malaise, hypoglycemia, hypothyroidism or gall stones but discomfort at injection sites and bruising did occur in the majority of patients. Symptomatic hyperglycemia occurred in only one patient and 2 were started on oral hypoglycemics when their post-prandial blood sugars were consistently greater than 400 mg/dl.

The biochemical response as determined by changes in 5-HIAA is represented in Table 2. The overall trend was stability in the 5-HIAA. Correcting for creatinine did not significantly alter the urinary 5-HIAA results.

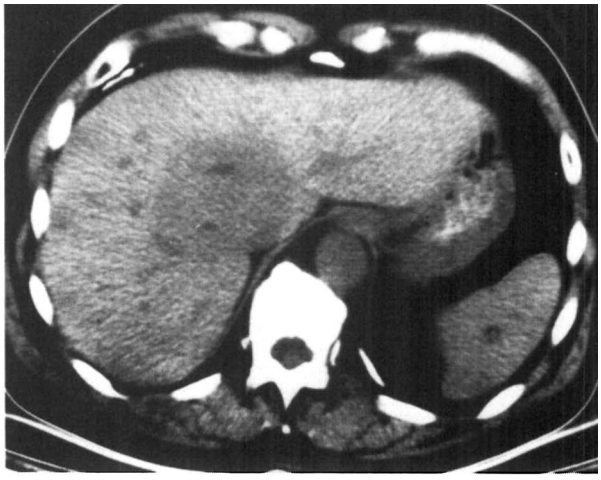
Of 13 evaluable patients (one patient received concomitant 5-FU as the octreotide dose was escalated), a partial radiographic response (see Table 3) occurred in 4 patients;

Table 2

Urinary 5-HIAA response to somatostatin analogue dose escalation

Dose μg/24 h	5-HIAA mg/24 h (Mean ± SE)
Octreotide	
Baseline	123 ± 29
450	60 ± 14*
1500	83 ± 18
2250	75 ± 15
3000	89 ± 22
4500	84 ± 20
6000	93 ± 6
Somatuline	
Baseline	93 ± 35
2250	81 ± 38
4500	72 ± 36
9000	72 ± 13*

* $p < 0.05$



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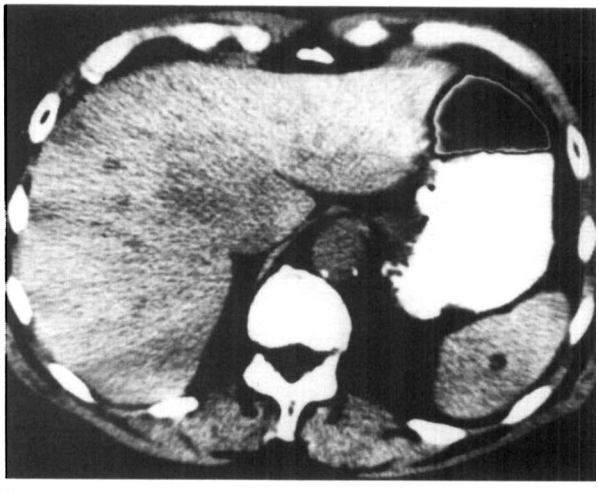


b)

Fig. 5. Effects of octreotide on the size of liver metastases in a patient with midgut carcinoid tumor. a) Three months after octreotide initiation and while receiving 500 μg q 8 h. b) Eighteen months later on octreotide 2 000 μg q 8 h.

stable disease was seen in 2 patients; 7 patients had progressive disease. Eleven patients continue to receive 6 000 μg/day with a duration between 1 and 2 years. One subject continues to receive weekly 5-FU in addition to octreotide with a partial response. No additional toxicities have been observed as the treatment duration has increased or when combined with 5-FU.

Somatuline phase I trial in neuroendocrine neoplasms

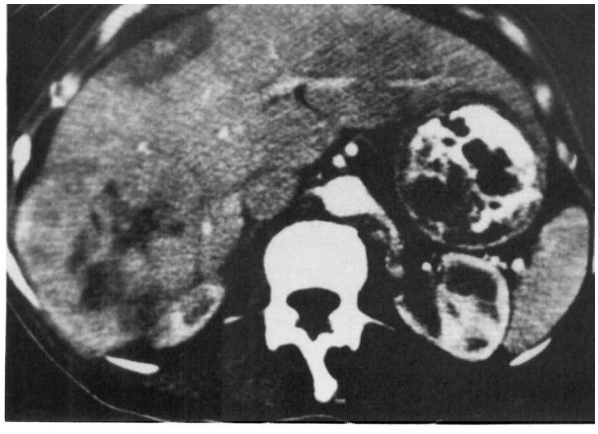
Thirteen patients were enrolled over 12 months. Various neuroendocrine tumor types were represented (see Table 1). All patients completed the scheduled somatuline dose escalation. One patient with multi-drug resistant SCLC progressed during the 4th week of treatment. Eight patients had a clinical and/or a biochemical response. Of the six carcinoid patients, all experienced consistent reduction

Table 3

Response rate by treatment

Response	Octreotide		Somatuline	
	n	%	n	%
PR	4	31	4	31
SD	2	15	1	8
PD	7	54	8	62
Total assessable	13		13	
Increased necrosis	5	38	6	46

Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease



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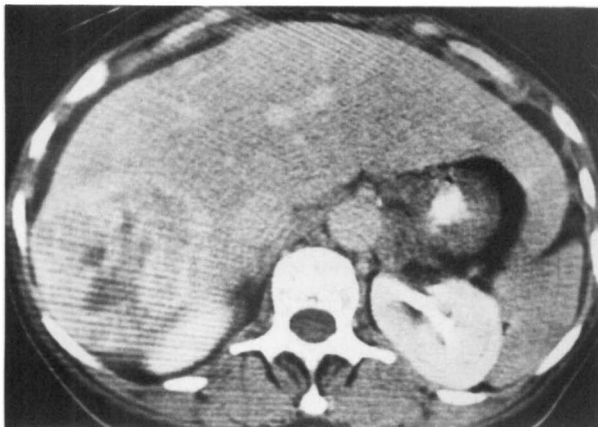

b)

Fig. 6. Effects of somatuline on the size of liver metastases in a patient with midgut carcinoid tumor. a) Before treatment. b) Sixty days after somatuline treatment.

in the urinary 5-HIAA. The onset of 5-HIAA suppression began during the second week of therapy with the magnitude of reduction varying between 17 to 70%. This decrease in 5-HIAA reached statistical significance at weeks 2 and 4 when the sample size was 5 or more.

A biochemical response in the insulinoma patient could not be documented consistently using insulin as a marker. However, during the fourth month of somatuline treatment, this patient had consistently elevated fasting blood sugars above 60 and was able to skip meals without becoming symptomatic. Radiographically the patient had a stable pancreatic mass but increased necrosis of her multiple hepatic lesions developed after 4 months.

One carcinoid patient had objective tumor progression in the setting of known high tumor somatostatin receptor concentration and a biochemical response as measured by 5-HIAA. This one patient presented with widespread peritoneal studding and omental involvement but no hepatic disease. Another metastatic carcinoid patient, not benefited symptomatically or biochemically by octreotide, responded clinically and had a lowering of the 5-HIAA with increased hepatic tumor necrosis on CT scan during somatuline therapy. An atypical carcinoid patient has had stable disease for 13 months as measured by CT scans of a hepatic lesion; 3 carcinoid patients have had a 50% or greater response in their hepatic lesions (see Fig. 6); one carcinoid patient has demonstrated stable disease but with increased tumor necrosis while 2 carcinoid patients experienced disease progression during the first 4 months.

Side-effects related to somatuline were minimal and not dose-related. Reported toxicities included discomfort at injection sites, mild abdominal cramping during the first week of therapy, lower extremity edema not requiring intervention, and one patient developed gall stones after 13 months on somatuline. Changes in blood sugar, hepatic or renal function have not been documented.

Discussion

Using somatostatin analogues to target cell membrane growth control pathways for therapeutic purposes represents an additional approach to cancer management. The results of these trials demonstrate that chronic 'high-dose' octreotide and somatuline are safe and do not cause the somatostatinoma syndrome. Octreotide doses greater than 500 μg three times daily resulted in improved carcinoid syndrome control and exhibited a greater response rate (31%) as compared to historical controls (20%). The optimal octreotide dose remains undefined. Somatuline demonstrated effective carcinoid syndrome control and antitumor activity in several different neuroendocrine neoplasms. Somatuline dose initiation at 2 250 μg daily is well tolerated and 9 000 μg daily appears as a safe dose for chronic administration. Dose limiting toxicity has not been identified.

Minimal side-effects were observed in both trials. Hyperglycemia requiring treatment occurred in 3 octreotide subjects. Steatorrhea occurred intermittently and was not perceived as severe by the majority of patients. Dietary preferences may account for the lack of predictability of this well-documented side-effect of octreotide. Pain at the injection site related to the volume required to administer octreotide appeared to be dose limiting.

Preclinical studies suggest the therapeutic benefit of high-dose somatostatin analog therapy. Dose-related tumor responses to octreotide and somatuline have been demonstrated in a variety of tumor models including pancreatic, breast, prostate and lung cancers (8, 10–14). These models suggest dose dependence and somatostatin receptor presence for an antitumor response. In a mouse breast cancer model, infusional octreotide (10 μg/kg/h) resulted in blood octreotide levels of 5–6 ng/ml which inhibited tumor growth (10). In a somatuline dose ranging study in lung cancer using NCI-H69 cell line, 31.25, 6.25 and 1.25 mg/kg/injection were administered every 12 h (theoretical human equivalent total daily dose of 1 562, 312 and 62 μg respectively). The highest somatuline dose had an antitumor effect which began after 6 days of treatment. The middle dose had a therapeutic effect occurring after 9 days of treatment. The lowest somatuline dose was not associated with any tumor inhibition suggesting a dose response and threshold effect (11).

Additional preclinical data in neuroendocrine lung tumors suggests a dose-related response. In cell culture, somatuline inhibited SCLS proliferation in a dose-dependent (1–1 000 nM) manner during a 24-h exposure (12). In in vivo experiments, NCI-H69 cells, a human SCLC line, were implanted subcutaneously into 15 athymic nude female mice without disaggregation of the cellular lumps. Newly xenografted mice were treated with somatuline, 500 μg/injection, given subcutaneously or intraperitoneally twice daily (equivalent to a 1 250 μg theoretical total daily dose for humans) for 40 days. There was a prolongation of lag time until measurable tumors appeared and a marked inhibition of tumor growth rate. The subcutaneous administration of somatuline in the area surrounding the tumor resulted in a complete regression of the NCI-H69 tumor (12).

Based on our findings, 'high-dose' octreotide and somatuline can be chronically administered safely and may be preferred in some patients for carcinoid symptom control. To understand the intersubject variability and the significance of increasing tumor necrosis on radiologic evaluation, somatostatin receptor data as obtained by direct tumor measurement and/or by using the Iodine or Indium radiolabeled peptides could provide more predictive information. The presence of several subtypes of somatostatin receptors suggests that these two analogues may have unique characteristics which could explain why some patients might respond to one peptide and not another. Additional studies are needed to clarify the optimal doses of these peptides. Further investigation is also required to evaluate biotherapy with other cytoreductive measures.

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