J. Endocrinol. Invest. *25:* 773-778, 2002

Somatostatin analogs in the treatment of medullary thyroid carcinoma

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ABSTRACT. The medical therapy for advanced or metastatic medullary thyroid carcinoma has not been fully established. Somatostatin analogs have been used with variable success in the therapy of a few patients with medullary thyroid carcinoma. In the present study, we evaluated the effects of somatostatin analog therapy on calcitonin (ct) and carcinoembryonic antigen in patients with advanced medullary thyroid carcinoma. Five patients (2 men and 3 women, aged 35-57 yr) with post-operative recurrent medullary thyroid carcinoma received somatostatin analog therapy for 12 weeks. All had been previously treated with total thyroidectomy and lymphadenectomy. Four of them showed positive uptake in ^{111}In-pentetreotide scanning. One patient was treated with sc octreotide (100 µg/8 h), 3 patients received im slow release lanreotide (30 mg/14 days), and a further one received im octreotide LAR (30 mg/28 days). Serum samples for ct and carcinoembryonic antigen were obtained at 0, 1, 2, 4, 8 and 12 weeks of therapy. Therapy was well-tolerated in general, with minimal side-effects. One patient died after the first month of therapy because of advanced disease. Another patient showed normalization of his ct and carcinoembryonic antigen concentrations at the second week of therapy, maintaining elevated values thereafter. No clinically relevant changes in serum concentrations of ct and carcinoembryonic antigen were observed in the rest of the patients. One patient with positive ^{111}In-pentetreotide scan, showed no uptake after somatostatin analog therapy. No significant decrease in the size of metastases was evident in the remaining patients. In conclusion, therapy with different formulations of octreotide and lanreotide does not seem to modify serum concentrations of ct and carcinoembryonic antigen in patients with recurrent medullary thyroid carcinoma.

(J. Endocrinol. Invest. *25:* 773-778, 2002)

INTRODUCTION

Medullary thyroid carcinoma (MTC) is derived from the parafollicular cells (C cells) of the thyroid and accounts for as many as 10% of all thyroid malignancies. Tumor C cells release calcitonin (ct), carcinoembryonic antigen (CEA) and several other peptides. The majority of MTC are sporadic, with a 20% inherited as an autosomal dominant form. Tumors are multifocal in 20% of sporadic cases and 90% of familial. Metastases usually occur in lymph nodes of the neck and mediastinum, but may also be found in the lung, bone and liver (1).

Therapy for MTC requires total thyroidectomy and removal of the central lymph nodes and all involved nodes (1, 2). Post-operative high serum concentrations of tumor markers, ct and CEA, suggest persistence or recurrence of the disease. Recurrences are usually evaluated by US, CT and scanning with radiotracers such as ^{123}I-metaiodobenzylguanidine (MIBG). The medical treatment of recurrences and that of advanced or metastatic disease has not been well established. Repeated surgery is indicated in cases of disease recurrence with compromise of structures in the neck. Radiotherapy and chemotherapy have also been suggested, although results seem to be of little benefit (2).

Therapy with somatostatin analogs (SSA) has become a new therapeutic approach in patients with MTC with the rationale that these tumors may express somatostatin receptors (3). Octreotide and lanreotide, the available somatostatin analogs for clinical use, have shown to be safe and effective treatments for GH-secreting pituitary adenomas,

Key words: Octreotide, lanreotide, medullary thyroid carcinoma.

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Accepted May 21, 2002.

Table 1 - *Clinical characteristics of studied patients.*

#	Sex, age (yr)	Mutation	Clinical presentation	Previous therapy	Metastases at diagnosis	Duration of disease (yr)
1	M, 35	Exon 11, TCG(634)TAG	Thyroid nodule, palpable lymph nodes in the neck	Surgery (1) Radioiodine (80 mCi)	Cervical lymph nodes	1
2	M, 38	None	Nodular goiter	Surgery (3) Radioiodine (100 mCi) External radiotherapy	Unknown	12
3	F, 57	None	Nodular goiter, palpable lymph nodes in the neck	Surgery (2)	Cervical lymph nodes	2
4	F, 44	None	Nodular goiter, palpable lymph nodes in the neck	Surgery (3) Radioiodine (130 mCi)	Cervical and subman dibular lymph nodes	0.5
5	F, 45	Exon 15, TCG(891)GCG	Nodular goiter, palpable lymph nodes in the neck	Surgery (1) Radioiodine (100 mCi) External radiotherapy	Cervical and supra-clavicular lymph nodes	1

M=male; F=female.

carcinoid tumors, as well as some other neuroendocrine tumors with somatostatin receptors (4). Several authors have reported on the effectiveness of octreotide (5-8) or the combination of SSA with interferon (9, 10) in patients with MTC. Results have been variable, with clinical improvement in many cases, although no evidence of reduction of metastases or tumor mass has been reported so far. In the present study, we evaluated the effects of different formulations of SSA, octreotide and lanreotide, on serum concentrations of ct and CEA in 5 patients with post-operative recurrent MTC.

SUBJECTS AND METHODS

We studied 5 patients (2 men and 3 women, Table 1) ranging in age from 35-57 yr (mean±SD, 44±8 yr), with histologically proven MTC and with post-operative recurrence of the disease as demonstrated by elevated serum levels of ct and CEA. Three patients had sporadic MTC and 2 had the familial form of MTC. None had clinical or laboratory evidence of hyperparathyroidism or pheochromocytoma. All patients had been treated previously with total thyroidectomy in combination with lymphonodal dissection as primary therapy of their disease. Radioiodine therapy was employed in 4 of them, and external radiotherapy was used as adjunctive therapy in 2 cases. Surgical excision of recurrences was performed in 3. All patients were on replacement doses of LT_4 and were euthyroid.

All patients showed high serum concentrations of both ct (112-2158 pg/ml) and CEA (29.8-194.9 ng/ml), thus indicating the persistence of malignant parafollicular tissue (Table 2). Total body CT revealed metastases in 2 patients (number 2 and 4), whereas scintigraphy with ^{123}I-MIBG showed pathological uptake in one case (number 2). Four patients showed *in vivo* somatostatin receptors, as visualized after iv administration of ^{111}In-diethylenetriamine-pentacetic acid-D-Phe^{1}-octreotide (pentetreotide) (Table 2).

All patients gave written informed consent before starting therapy with SSA. One patient (number 1) was treated by sc administered octreotide, 100 µg/8 h, three patients (number 2-4) were given im injections of slow release lanreotide, 30 mg every 14 days, and a further patient (number 5) was treated with octreotide LAR, 30 mg every 28 days, by im route. Duration of therapy with SSA was 12 weeks. They were evaluated at monthly intervals for registering clinical evolution and adverse effects. Baseline blood samples were drawn before starting therapy with

Table 2 - *Biochemical and imaging techniques results of the studied patients before starting somatostatin analog therapy.*

#	ct (pg/ml)	CEA (ng/ml)	CT	^{123}I-MIBG scintigraphy	^{111}In-pentetreotide scintigraphy
1	358	17.3	No metastases	Negative	Not done
2	2158	175.5	Local recurrence, metastases in dorsal column	Positive uptake in mediastinum and dorsal column	Positive uptake in dorsal column
3	1365	53.7	No metastases	Negative	Positive uptake in neck and mediastinum
4	891	194.9	Cervical lymph nodes	Negative	Positive uptake in dorsal column, sacroiliac joint, femur and iliac crest
5	112	29.8	No metastases	Negative	Positive uptake in sternoclavicular joint

CEA: carcinoembryonic antigen; MIBG: metaiodobenzylguanidine.

SSA and at 1, 2, 4, 8 and 12 weeks for determination of ct and CEA. In these samples we also assessed complete blood cell count, and serum concentrations of glucose, creatinine, cholesterol, triglyceride, calcium, phosphorus, total protein, aspartate aminotransferase, alanine aminotransferase, ALP, and lactic dehydrogenase, TSH and free T_4. Total body CT and scintigraphy with ^{111}In-pentetreotide were repeated 1-3 months after finishing therapy with SSA.

Serum ct concentrations were determined by using an IRMA assay (BioSource Europe, Nivelles, Belgium). Maximal intra- and inter-assay coefficients of variation were 3.4% and 5.4%, respectively. The sensitivity of the assay was 0.8 pg/ml. ct concentrations in healthy people without hyperplasia of C cells or MTC were less than 10 pg/ml. CEA levels were measured by using an enzymoimmunoassay (AxSYM CEA, Abbott, Wiesbaden, Germany). The normal concentration for healthy subjects was less than 5 ng/ml. Maximal intra- and inter-assay coefficients of variation were 7.0% and 6.9%, respectively. The sensitivity of the assay was 0.5 ng/ml.

RESULTS

Three patients (number 2, 3 and 5), who were asymptomatic at the start of the study, did not report any clinical change in their general state. Patient 1 complained of impairment of his pre-existing diarrhea at the third month of therapy. Patient 4, who had multiple bone metastases at the start of the study, suffered a dramatic impairment of her general condition and lastly died after the first month of the study. SSA therapy was in general well tolerated. Diarrhea and loose stools were reported by patients (number 1 and 2). Patient number 3 reported a 2-day duration fever episode after the fourth injection of lanreotide. Patient number 5 complained of transitory local pain at the site of injection of octreotide LAR.

Individual values of serum concentrations of ct and CEA are shown in Figure 1. Patient number 2 exhibit a dramatic fall in tumor markers at week 2, reaching normal values for serum concentrations of both ct (1.6 pg/ml) and CEA (1.9 ng/ml). However, these values returned to high levels at weeks 4 to 12. The remaining patients did not show any clinically relevant change in their values of both ct and CEA. After 12 weeks, the percentages of serum ct levels variation in patients 1, 2, 3 and 5 were, respectively, +25.1%, -14.3%, -22.4% and +4.1% from the initial levels. Values of percent variation for CEA concentrations in the same patients were -21.5%, -47.8%, +47.3% and +2.4%, respectively. We did not observe any significant variation of hematological and biochemical tests throughout the study period. Thyroid function tests also remained unchanged.

Post-therapy CT was negative in patients 1 and 5.

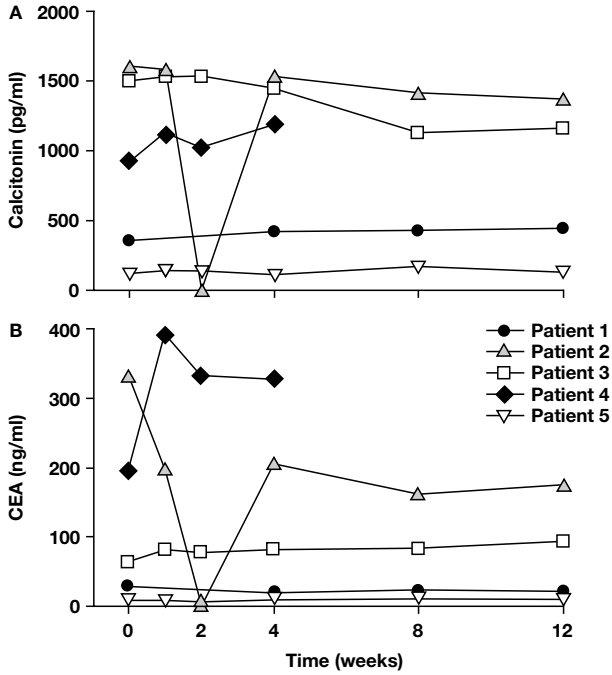

Fig. 1 - *Evolution of individual values of serum concentrations of ct (A) and carcinoembryonic antigen (B) in 5 patients with medullary thyroid carcinoma treated with somatostatin analogs for 12 weeks (sc octreotide in patient 1, im slow release lanreotide in patients 2-4, and im octreotide LAR in patient 5). CEA: carcinoembryonic antigen; ct: calcitonin.*

In patient 2, who have residual tumor in the neck and bone metastases, second examination also showed lung nodules and lymph nodes in the mediastinum. Patient 3, who had no lesions before starting the study, showed local recurrence with lymph nodes in the neck. ^{111}In-pentetreotide scintigraphy performed after the study period was positive in patients 2 and 3, and negative in patient 1. Patient 5, who had a positive uptake in the first examination, was negative on this second occasion.

DISCUSSION

All studied patients showed elevated serum levels of tumor markers and 4 of them had evidence of metastases in imaging techniques. No significant change in clinical state was recorded in 3 asymptomatic patients (2, 3 and 5). Patient 1 reported an impairment of his diarrhea in the third month of therapy. Patient 4, with advanced disease at the start of the study, progressively impairs and died. Our results clearly show that SSA therapy for 3 months does not modify serum concentration of ct

and CEA in patients with recurrent MTC. We only observed a frank decline with normalization of both tumor markers in one patient treated with lanreotide, but this effect was transitory. We have no clear explanation for this finding, but a similar phenomenon was observed in 1 of the patients studied by Lupoli *et al*. (9) after 3 months of therapy with octreotide in combination with interferon.

A number of investigators have been interested in the use of SSA in the treatment of advanced MTC (Table 3). Most of them reported an improvement in symptoms (5, 7, 11, 14-16, 19, 20, 22, 25, 27, 28), whereas others did not observe any significant clinical improvement (12, 21). The effects of octreotide therapy on ct concentration have been variable and contradictory (Table 3). Reduction of ct levels below 50% of basal values have been reported in isolated patients (8,19). Guliana *et al.* (6) reported a decrease in ct levels in 10 out of 18 patients treated with octreotide, however, only 5 of these patients show a decrement of 20% or more. In many cases, octreotide administration appears to have no effect on ct levels in both acute administration (6, 22, 29) and chronic therapy (11, 12, 14-16, 22, 23). Other investigators have found a decrease of ct levels in some patients and an increase in other patients under the same protocol (5, 6, 20, 21, 24, 28). In some occasions, an initial decrease in ct levels followed by a subsequent rise has been reported (13, 19, 27). CEA concentrations have been found to be unmodified by octreotide therapy (5, 20, 21, 24). The high variability of results may be accounted for the wide range of doses of octreotide, the different duration of therapy and the diverse disease staging of the patients. A decrease in ct levels

Table 3 - *Reported results on the effects of somatostatin analogue therapy on serum ct concentrations in patients with medullary thyroid carcinoma.*

Author and year	Num. of patients	Dose (μg/day)*	Duration (months)	Changes in ct levels	Changes in measurable lesions
Geelhoed *et al*., 1986 (11)	1	200-500	3	No change	No change
Schrezenmeir *et al*., 1986 (12)	3	100-150	5 days	No change	Ns.
Berkelhammer *et al*., 1986 (13)	1	100-1500	1	Dec & Inc	Ns.
Alhman *et al*., 1987 (14)	1	100-200	3	No change	Ns.
Jerkins *et al*., 1987 (15)	1	50-100	7	No change	No change
Keeling *et al*., 1988 (16)	1	100	N.E.	Inc	Inc
Modigliani *et al*., 1989 (5)	18	300-1500	1-2	Dec 11, Inc 7	Dec 5
Guliana *et al*., 1989 (6)	18	300-1500	1-2	Dec 10, Inc 8	Ns.
Sagman *et al*., 1989 (17)	2	200	3	No change	Ns.
Libroia *et al*., 1989 (7)	2	300	3	Dec 1	Ns.
Libroia *et al*., 1990 (8)	2	200-300	1-3	Dec 2	Ns.
Somlo *et al*., 1990 (18)	1	300	6	No change	Ns.
Mahler *et al*., 1990 (19)	3	600-2000	3-17	Dec & Inc	Ns.
Fugazzola *et al*., 1991 (20)	5	150-900	0.5-7	Dec 1, Inc 2	Inc 2
Modigliani *et al*., 1992 (21)	14	500	3	Dec 4, Inc 7	No change 7, Dec 1, Inc 6
Smid *et al*., 1992 (22)	1	300	12	No change	Inc
Kvols *et al*., 1992 (23)	3	1500	1-8	No change	Inc 3
Frank-Raue *et al*., 1993 (24)	6	200-1000	3-9	Dec 1, Inc 5	No change 3, Inc 3
Frank-Raue *et al*., 1995 (25)	7	300-600	3-9	Dec 2	Dec 1
Ronga *et al*., 1995 (26)	5	300-600	3-9	Dec	Dec 3
Sanabria *et al*., 1995 (27)	1	300-500	6	Dec & Inc	Inc
Di Bartolomeo *et al*., 1996 (28)	12	1500-3000	5	Dec & Inc	No change 4, Inc 8
Lupoli *et al*., 1996 (9)	6	150-300**	12	Dec 6	No change
Vitale *et al*., 2000 (10)	7	***	12	Dec 6, Inc 1	No change 3, Dec 2, Inc 2

Dec: decrease in ct levels or in lesion size; Inc: increase in ct levels or in lesion size; N.E.: not established; Ns.: not studied. *All doses refer to sc octreotide. **In combination with interferon α-2b. ***Lanreotide (30 mg/10-14 days), in combination with interferon α-2b.

seems to be more frequent in patients with normal or minimally elevated CEA levels (5, 6), and in those with slowly evolving MTC (21). Lack of effects in some patients might be due to insufficient dose or to desensitization of somatostatin receptors. Besides, some of the reported patients had extensive disease and somatostatin receptor status could not be established in most of them.

A modest reduction of volume in cervical nodes or liver metastases was reported in 5 patients studied by Modigliani *et al.* (5) under therapy with 3 daily injections of octreotide, and subsequently in one of these patients under continuous infusion of octreotide (21). No tumor regression with octreotide therapy was observed by most of the authors (11, 15, 16, 20-22, 24, 28), and in some studies metastases continued to grow (21, 24). Our results have also been disappointing. Only one of our patients (number 5) showed a negativization of her uptake of ^{111}In-pentetreotide in the second exploration, thus suggesting a possible reduction in tumor mass. However, one patient (number 3) without normal images in basal CT developed local recurrence, and another patient (number 2) exhibited lung metastases at the end of the study period. These data suggest that octreotide therapy does not stop the progression of disease.

Some Authors have reported beneficial effects of the combination of SSA with interferon α-2b. Lupoli *et al.* (9) reported an alleviation of symptoms and a reduction in ct and CEA levels in 6 patients treated with octreotide plus interferon. No significant change in tumor lesions was observed. The combination of SR lanreotide and interferon was also investigated in a group of 7 patients with advanced and symptomatic MTC. Symptoms improved in these patients, although no major tumor regression was recorded (10). Ct levels decreased in 6 of these patients. These authors conclude that the combination of SSA and interferon may have synergistic effects in therapy of advanced MTC. However, a significant reduction of primary tumor or metastases has not been demonstrated.

In conclusion, we could not demonstrate any clinical, biochemical or morphological beneficial effects of octreotide or lanreotide in patients with MTC. Although some data of the literature suggest that symptomatic improvement can be obtained in at least some patients with MTC, especially in combination with interferon, our disappointing results do not allow us to recommend therapy with SSA in patients with recurrent or metastatic MTC, neither in the case of pentetreotide scan-positive patients.

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