

Clinical Efficacy of Octreotide in the Treatment of Metastatic Neuroendocrine Tumors

A Study by the Italian Trials in Medical Oncology Group

Maria Di Bartolomeo, M.D.
 Emilio Bajetta, M.D.
 Roberto Buzzoni, M.D.
 Luigi Mariani, M.D.
 Carlo Carnaghi, M.D.
 Luisa Somma, M.D.
 Nicoletta Zilembo, M.D.
 Angelo Di Leo, M.D.
 ITMO Association*

Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.

Presented in part at the 19th Congress of the European Society for Medical Oncology, Lisbon, Portugal, November 18 to 22, 1994.

The authors thank SANDOZ, Inc. S.p.A. Pharmaceuticals, Basel, Switzerland, for kindly supplying the octreotide, and the Data Management Service of Italian Trials in Medical Oncology for its editorial assistance.

* The following investigators should be considered as coauthors of this paper: Vittorio Gebbia, M.D., Policlinico, Palermo; Graziella Pinotti, M.D., Ospedale di Circolo, Varese; Carla Rabbi, M.D., Ospedale Civile C. Poma, Mantova; Tiziano Franceschi, M.D., Ospedale Civile Maggiore, Verona; Salvatore Tumolo, M.D., Centro Riferimento Oncologico, Aviano (PN); Marilena Visini, M.D., Ospedale di Lecco; Fabrizio Artioli, M.D., Ospedale Ramazzini, Carpi (MO); Paolo Ballatore, M.D., Ospedale San Camillo, Roma; Sandro Barni, M.D., Ospedale San Gerardo, Monza; Vito Lorusso, M.D., Istituto Oncologico, Bari; Salvatore Mazzotta, M.D., Ospedale Vito Fazzi, Lecce; and Alberto Rosa Bian, M.D., Ospedale Civile, Thiene (Vicenza), Italy.

Address for reprints: Emilio Bajetta, M.D., Division of Medical Oncology B, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via Venezian 1, 20133 Milano, Italy.

Received April 19, 1995; revisions received July 27, 1995, and September 22, 1995; accepted September 22, 1995.

BACKGROUND. The unsatisfactory control of neuroendocrine tumor growth with chemotherapy and/or interferon (IFN-2a) stimulated us to investigate the role of the somatostatin analogue octreotide (SMS 201.995), which is reported to be highly effective in controlling carcinoid syndrome symptoms. Octreotide has been used in a wide range of doses, and it was postulated that higher doses might lead to an objective response.

METHODS. The aim of the present multicenter Phase II study was to determine the safety and efficacy of SMS 201.995 in controlling carcinoids and other neuroendocrine tumors. Fifty-eight patients were treated subcutaneously with 2 sequential doses of the drug (Sandostatina®, Sandoz, Inc., S.b.A. Pharmaceuticals, Basel, Switzerland). The first 23 patients received 500 µg 3 times a day and the remaining 35 patients received 1000 µg 3 times a day. The treatment was continued until the tumor progressed.

RESULTS. All of the patients were adequately treated and evaluated. The predominant histotype was carcinoid, although there were instances of medullary thyroid carcinoma, pancreatic islet cell tumors, and Merkel cell carcinoma. Carcinoid syndrome was documented in 16 patients and abnormal urinary 5-hydroxyindoloacetic acid excretion in 15. The median treatment duration was 5 months (range, 2–31 months). The responses were evaluated in three categories: tumor regression for tumor growth control, symptom response, and biochemical response. There was an effect on tumor growth in two patients with carcinoids. Symptomatic control was achieved in 73% of patients and a biochemical response in 77% of patients. In twenty-seven patients, the disease stabilized for at least 6 months (range, 6–32+). The median survival time for all patients was 22 months (range, 1–32+).

CONCLUSIONS. In terms of tumor regression, octreotide is disappointing (partial response: 3%); symptomatic response and biochemical control are satisfactory. These data confirm that somatostatin analogues are comparable to interferons in the treatment of carcinoid syndrome, although other efforts are necessary to control tumor regression. *Cancer* 1996; 77:402–8. © 1996 American Cancer Society.

KEYWORDS: somatostatin analogue, octreotide, neuroendocrine tumor, carcinoid.

Carcinoids and pancreatic islet cell tumors include a group of heterogeneous neoplasms that are derived from neuroendocrine cells scattered throughout the gastrointestinal system and the body. They have a number of histopathologic characteristics in common with medullary thyroid carcinoma (MTC) and Merkel cell carcinoma.¹

When possible, radical surgical resection is used as the initial treatment; when this is not possible, hormones are used to control symptoms. The natural history of these tumors is usually characterized by slow and indolent growth, but they may also present a phase of more accelerated

progression with a more aggressive clinical course. In this phase, their natural history is characterized by continued growth, with a median patient survival of approximately one to two years.² At the time the disease is progressing, chemotherapy is the standard treatment for relieving the symptoms deriving from the production of hormones or increased tumor bulk. In carcinoids, the tumor regression induced by chemotherapy is modest and no clear impact on survival has been demonstrated. The response rate is higher in patients with islet cell carcinomas, but a survival advantage has rarely been reported.³⁻⁵ Reports concerning MTC and Merkel cell carcinoma are inconclusive.⁶

There are currently a number of new and experimental treatment approaches. Some studies confirm the efficacy of interferon in controlling carcinoid syndrome.⁷⁻⁹ Oberg et al reported a response in 41% of patients when using human leukocyte IFN, but they observed tumor mass regression in only 11% of cases.¹⁰ We have recently treated 49 patients with carcinoids and other neuroendocrine tumors with recombinant IFN alpha-2a and obtained good symptomatic control but only a limited reduction in tumor mass.^{11,12}

Somatostatin (SMS) is a tetradecapeptide-releasing factor with a powerful inhibiting action against several endocrine systems.³ It also affects exocrine and other gut functions by inhibiting motility and absorption and decreasing gut blood flow. Somatostatin has been investigated as a continuous intravenous infusion for the treatment of symptoms associated with a variety of conditions, and the inhibition of tumor secretion has been reported in patients with insulinomas, glucagonomas, carcinoid syndrome, and Vipomas. Despite these benefits, the clinical usefulness of SMS is limited by the fact that its very short half-life requires the use of continuous intravenous infusion.

Octreotide is a somatostatin analogue (SMS 201.995) that is more specific and longer acting than somatostatin itself. Moreover, it can be administered subcutaneously three times daily in a conformationally stabilized form, and it retains that part of somatostatin that is presumed to be essential to its biological activity.¹⁴ A comparison of the intravenous and subcutaneous administrations has already been made by other authors.¹⁵ This compound may act at various levels to relieve the symptoms caused by the excessive secretion of tumor products by impairing the release of these hormones and/or by interacting with a released peptide blockade.¹⁶ Preclinical evidence also suggests that the drug has inhibitory effects on the growth factors involved in cell proliferation, such as insulin-like growth factor, somatomedines (IGF I and IGF II), epidermal growth factor, fibroblast growth factor, and transforming growth factor (TGF alpha). Although a number of mechanisms have been suggested to explain the antitumor activity of octreotide, its precise action is not yet

clear; moreover, the inhibition of peptide and amine release achieved with the analogues suggests that tumoral cells retain some functional somatostatin receptors. Oberg has recently reported evidence that high doses of somatostatin may induce programmed cell death or apoptosis.¹⁷ Octreotide has been administered to patients with carcinoid syndrome by means of subcutaneous injections every 8 hours at doses ranging from 50 to 500 $\mu\text{g}/\text{die}$, with symptomatic improvement and a significant reduction in the levels of urinary 5-hydroxyindoloacetic acid (5-HIAA); a number of studies have reported that doses of more than 500 μg three times a day induce tumor shrinkage in 16% of carcinoid patients.^{18,19}

In an attempt to identify the role of somatostatin analogues in the treatment of this heterogeneous series of neoplasms, it was decided to test the efficacy of octreotide in inducing tumor regression.

PATIENTS AND METHODS

This study was conducted as an open multicenter trial, with the patients enrolled at 13 different Italian Trials in Medical Oncology (ITMO) Centers coordinated by the Division of Medical Oncology B, Istituto Nazionale per lo Studio e la Cura dei Tumori, in Milan, Italy.

All patients were required to have a histologic diagnosis of carcinoid or other neuroendocrine tumor, disease progression, and at least one clearly measurable lesion, visible either by computerized tomography or ultrasound. The histologic diagnosis was based on an examination of tissue routinely fixed on hematoxylin and eosin-stained slides and, in some cases, on immunocytochemical phenotyping. In cases of histological uncertainty, the Division of Pathology of the Istituto Nazionale Tumori reviewed the diagnosis.

Pretreatment with surgery and/or limited radiation therapy fields was allowed, as was any previous chemotherapy that had been discontinued because of disease progression; previous treatment with biological response modifiers was also allowed. Patients with disease progression and those with symptomatic carcinoids without tumor progression were included. All of the patients had to be aged 75 years or younger and have a performance status ≤ 2 (Eastern Cooperative Oncology Group [ECOG] scale).

Adequate renal (serum creatinine < 1.5 mg/dl), hepatic (bilirubin < 3 $\mu\text{g}/\text{dl}$), and hematologic (leukocyte count $\geq 4000/\text{mm}^3$ and a platelet count $> 12,000/\text{mm}^3$) functions were also necessary. The exclusion criteria were the presence of severe concomitant illness, active heart disease, cholelithiasis, and a life expectancy of less than two months with rapidly progressing, life-threatening metastases.

The nature of the program was explained to each patient and their informed consent was obtained according to European Economic Community Good Clinical Practices.

The staging procedures performed before starting therapy included physical examination, a biochemical profile, thyroid function test, chest X-ray, electrocardiography, and an abdominal ultrasound/computerized tomography scan; additional procedures (percutaneous liver biopsy or laparoscopy) were used according to each clinical presentation.

The protocol was approved by the Human Investigation Committee of the Istituto Nazionale per lo Studio e la Cura dei Tumori of Milan.

Tumor Marker Analysis

Hormone markers indicating the functional status of the tumors were obtained at the start of therapy. 5-HIAA levels were measured by taking 24-hour urine samples from all of the patients; the serum levels of carcinoembryonic antigen, calcitonin, and neuron-specific enolase also were measured. In patients with elevated levels, these measurements were repeated every eight weeks during the treatment.

Treatment Plan

Octreotide (Sandostatina[®], Sandoz Pharmaceuticals, Basle) was given by subcutaneous injection in two doses.

The first 23 patients were treated with octreotide, 500 μg three times daily. Following the published data suggesting that higher doses may control tumor growth,^{18,19} we decided to increase the dosage. The remaining 35 patients were given 1000 μg of octreotide three times daily specifically in order to investigate the possible antitumor effect of the drug. Therapy was continued until tumor progression. The drug was self-administered on an outpatient basis. The patients were seen weekly during the first month and then followed at four-week intervals to assess tolerability. In the case of severe toxicity, according to the World Health Organization (WHO) classification, dose reduction and the interruption of treatment was planned.²⁰ Treatment compliance was assessed in terms of the number of days off treatment for refusal and, at each visit, special care was taken to investigate the injection sites.

The patients with progressive disease during octreotide therapy were eligible for polychemotherapy with dacarbazine, (DITC) 200 mg/m^2 ; fluorouracil (FU), 250 mg/m^2 ; and epi-doxorubicin (EpiADM), 25 mg/m^2 administered intravenously on Days 1, 2, and 3. The cycles were repeated every three weeks. A total of 25 patients received this schedule.²¹

Evaluation of Response

A case history, physical examination, hemogram, blood biochemistry, and tumor measurement by ultrasound/computerized tomography and radiography were performed every two months. Flushing and diarrhea were checked monthly. Three response categories were assessed: tumor growth control, symptomatic response, and biochemical response. Tumor growth control was defined according to the International Union Against Cancer: complete remission (CR) occurs with the complete disappearance of all known disease for a minimum of 1 month, confirmed at 2 examinations; partial remission (PR) which occurs with at least a 50% decrease in the sum of the products of the 2 largest perpendicular diameters of all tumor masses for at least 1 month; and stable disease, which occurs with a less than 50% decrease or a less than 25% increase in the size of measurable lesions or the appearance of new sites after at least 6 months of treatment. Patients with stable disease for less than six months were arbitrarily considered as treatment failures. Progressive disease was defined as an increase of at least 25% in the size of any tumor lesion or the appearance of new lesions.

For the symptomatic response of the syndrome, CR was defined as the complete relief of all symptoms and PR as a reduction of at least 50% in both the frequency and intensity of flushing and/or diarrhea attacks. For the biochemical response of the marker, CR was defined as the return of values to within the normal range for at least 1 month and PR as a decrease of 50% or more for at least 1 month.

Statistical Considerations and Analytical Plan

The main tumor response efficacy variable in this study was the proportion of patients with PR or CR. All patients who completed at least six months of therapy were considered adequately treated, as were those whose treatments were discontinued early due to tumor progression. According to the Simon optimal 2-stage design, the study was planned to compare a response probability of 10% under the null hypothesis with a response probability of 25% under the alternative hypothesis, with a 0.05 α level and a power of 80%.²² Patients with carcinoids and those with neuroendocrine tumors (islet cell carcinoma, Merkel cell carcinoma, and medullary thyroid carcinoma), were considered separately in the analysis. The treatment had to be rejected if no more than 2 and 7 responses were observed at the end of the first (18 patients) and second stages (43 patients) of the trial, respectively. All of the enrolled patients were considered evaluable. Response duration was calculated from the time the tumor became evident to the time of progression. The time to treatment failure and time to death were assessed from the beginning of the treatment to the event (progression or death),

TABLE 1
Main Patient Characteristics

	No. of patients		
	Overall	500 µg × 3/die	1000 µg × 3/die
Total entered	58	23	35
Sex: Male/Female	29/29	13/10	16/19
PS (ECOG): 0–1/2	54/4	22/1	32/3
Carcinoid syndrome	15	3	12
Flushing	5	1	4
Diarrhea	1	–	1
Flushing and diarrhea	9	2	7
Abnormal urinary 5-HIAA excretion	15	3	12
Abnormal serum calcitonin level	12	5	7
Abnormal serum NSE level	6	5	1
Abnormal serum CEA level	6	2	4
Histological type			
Carcinoid	31	11	20
Merkel cell carcinoma	3	3	–
Medullary thyroid carcinoma	12	5	7
Islet cell carcinoma	12	4	8

PS: performance status; ECOG: Eastern Cooperative Oncology Group; 5-HIAA: 5-hydroxyindoloacetic acid; NSE: neuron-specific enolase; CEA: carcinoembryonic antigen.

with the regular follow-up of patients no longer receiving treatment but still alive. The survival function for time to treatment failure and time to death was estimated using the Kaplan–Meier method.²³

RESULTS

Fifty-eight patients were sequentially enrolled in this multicenter study between January 1992 and May 1994. The main characteristics of the enrolled patients are listed in Table 1 according to the dosage used. Their ages ranged from 27 to 75 years, with a median of 55 years. Carcinoids were the predominant histological type (31 patients); there were 11 patients with foregut carcinoids, 10 patients with midgut carcinoids, 2 patients with hindgut carcinoids, and 9 patients in whom the primary site was unknown. In addition, there were 12 islet cell tumors, 12 medullary thyroid carcinomas, and 3 neuroendocrine (Merkel cell) carcinomas of the skin. The liver was the most frequent site of metastatic disease, being involved in 38 out of 58 patients; other sites of measurable lesions included the lung, lymph nodes, and skin nodules. Thirty-five patients had multiple lesions and 23 had a single lesion. All were outpatients and most were capable of full- or part-time work.

Carcinoid syndrome was documented in 15 patients and abnormal baseline urinary 5-HIAA excretion in 15 patients (median, 33 mg/24 hours; range, 11–745; normal laboratory range, 0–10 mg/24 hours); 7 cases presented

TABLE 2
Results of Octreotide Treatment

Response	No. of patients				
	Observed	CR	PR	SD	PD
• Symptomatic	15	6 (40%)	5 (33%)	2 (13%)	2 (13%)
Flushing	14	3 (21%)	4 (29%)	5 (36%)	2 (14%)
Diarrhea	10	3 (30%)	1 (10%)	4 (40%)	2 (20%)
• Biochemical					
5-HIAA	13	4 (31%)	6 (46%)	3 (23%)	–
• Tumor	58	–	2 (3%)	27 (47%)	29 (50%)

CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; 5-HIAA: 5-hydroxyindoloacetic acid.

both manifestations. The calcitonin level was altered in the 12 patients affected by medullary thyroid carcinoma (median, 8,000 $\rho\text{g/ml}$; range, 120–94,191; normal laboratory range, < 30 $\rho\text{g/ml}$); carcinoembryonic antigen in 6 patients (median, 277 $\mu\text{g/ml}$; range, 52–1018; normal laboratory range, < 5 $\mu\text{g/ml}$); and neuron-specific enolase in 6 patients (median, 25 $\mu\text{g/ml}$; range, 13.3–102; normal laboratory range, < 12 $\mu\text{g/ml}$).

Twenty-three patients had undergone radical surgery of the primary tumor and 12 had undergone palliative resection; only 15 had undergone explorative surgery. Chemotherapy, including streptozocin, had been previously used for nine patients, and radiotherapy had been given to seven. Seventeen patients had received more than 1 treatment. Octreotide was administered as first-line treatment to 46 patients.

Tumor Response

After a median treatment duration of 5 months (range 2–32+), 2 carcinoid patients (3%) showed an objective response (Table 2). These individuals had liver metastases with an unknown primary site, and partial regressions were documented by ultrasound after four months of treatment. The duration of response was 14 and 10 months, respectively. One of these patients was in the first group treated with 500 μg , the other in the second group. Stable disease of at least 6 months' duration was observed in 27 cases (47%), and it is worth noting that the disease was stable for 1 year or more in 13 patients (22%) (Table 3). Progressive disease was observed in 29 patients after a median time of 6 months. The time to treatment failure is shown in Figure 1.

The median survival of the patients as a whole was 22 months (range 1–32+) (Fig. 2). After a median follow-up of 12 months, the median survival for the carcinoid patients has not yet been reached, and the median survival for the patients with other neuroendocrine tumors was 12 months (Fig. 3). No correlation between disease

TABLE 3
Characteristics of 13 Patients with Stable Disease Lasting Longer Than 1 Year

Characteristic	No. of patients	
	Observed	Stabilized (%)
Median age	55	49
Histology		
Carcinoid	31	9 (29)
MTC	12	4 (33)
Octreotide dose		
500 µg	11	6 (54)
1000 µg	20	7 (35)
Disease sites		
Liver	38	7 (18)
Lung	11	3 (27)
Nodes	30	3 (10)

MTC: medullary thyroid carcinoma.

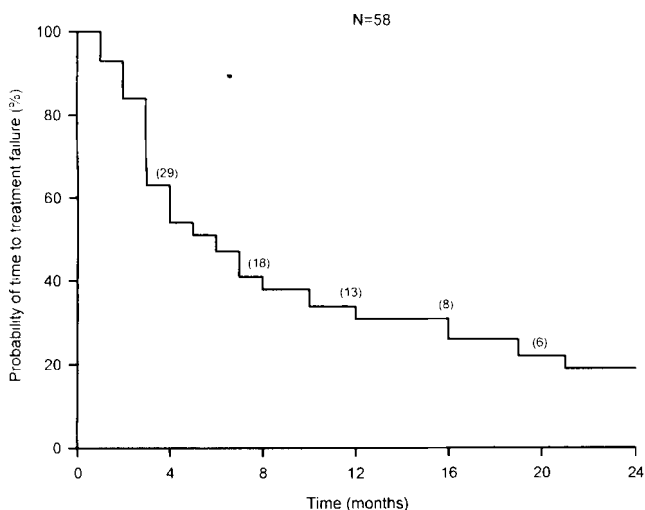


FIGURE 1. Treatment failure free survival. Patients who remain at risk of treatment are shown in parenthesis.

status and survival can be made because of the heterogeneity of the studied population.

Symptomatic Response

Of the 15 patients presenting with carcinoid syndrome, 6 (40%) experienced a complete reduction in their symptoms and signs, and 5 (33%) a partial reduction. In particular, control of diarrhea was obtained in 40% of 10 patients (30% CR, 10% PR), and control of flushing in 50% of 14 patients (21% CR, 29% PR). In these instances, the median treatment duration was 4 months (range 2–24 months). The responses occurred after one month and lasted throughout the treatment period (Table 2).

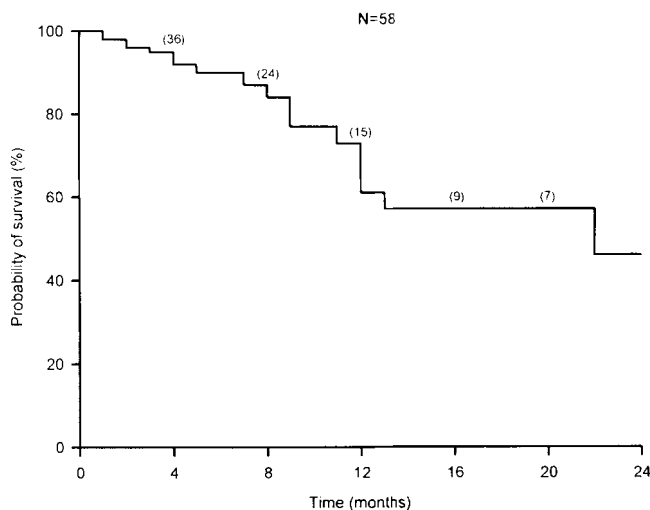


FIGURE 2. Overall survival from start of octreotide treatment in 58 patients. Patients who remain at risk of survival are shown in parenthesis.

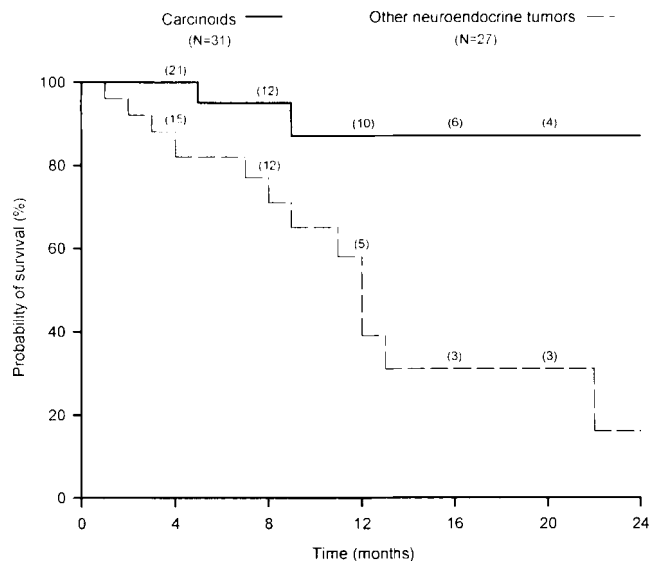


FIGURE 3. Survival according to histological subtypes. Patients who remain at risk of survival are shown in parenthesis. solid line: carcinoids; dotted line: other neuroendocrine tumors.

Biochemical Response

Of the 15 patients with normal baseline urinary 5-HIAA excretion levels, 2 could not be evaluated because of the lack of further data during treatment. A biochemical response was observed in 10 patients (77%), with 5-HIAA excretion normalizing in 4. Figure 4 shows 5-HIAA excretion, calcitonin, carcinoembryonic antigen and neuron-specific enolase levels at baseline and at the discontinuation of treatment due to progressive disease.

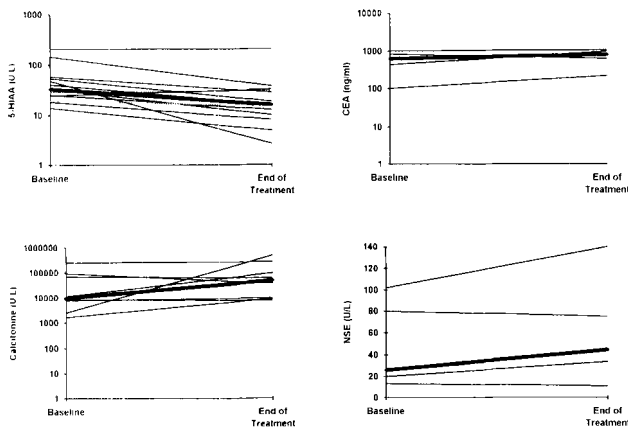


FIGURE 4. Behavior of tumor markers during octreotide treatment. dark line: average; thin line: individual data.

Toxicity and Compliance

Treatment was refused by only 1 patient who, after 12 months, did so for psychological reasons. Two patients experienced steatorrhea (WHO Grade 3), which was partially resolved after the oral administration of pancreatic enzymes. Cholelithiasis was observed in 2 cases after 5 and 7 months of treatment, respectively, with 1000 μ g of octreotide and was resolved by discontinuing octreotide for 3 weeks and administering biliary salts. There was no evidence of hematologic, renal, or hepatic toxicity. No case of hypothyroidism was documented and no local reaction was seen at the rotating subcutaneous injection sites.

DISCUSSION

Although neuroendocrine tumors and carcinoids present many different and challenging clinical problems, they share a number of common characteristics. The natural history of these tumors is usually one of slow growth, and may be marked by dramatic clinical syndromes such as hormone overproduction. When a tumor cannot be resected, its treatment has two objectives: the first is to control the symptoms produced by the possibly life-threatening hormone secretion and the second is to attempt to extend survival by limiting the growth or ablating metastatic tumor tissue.²⁴ The remarkable success of octreotide in controlling the symptoms of endocrine pancreatic tumors has led some authors to investigate whether higher doses may lead to tumor growth control. The results of these studies are conflicting and we consequently investigated the possible role of octreotide as a cytoreductive agent.¹⁸⁻¹⁹

This study tested a large number of patients and, although the patient population was heterogeneous, we did not find that octreotide was efficacious in inducing tumor regression. Only two carcinoid patients (RR: 3%) obtained the partial response of their hepatic metastases,

and no responses were observed in the other histologic groups. In our experience, long term treatment with relatively high doses of octreotide leads to disease stabilization for a median duration of 12 months (range 6-32+). Table 3 shows the characteristics of the 13 patients whose disease was stable for at least 1 year. These results were obtained only in carcinoids and medullary thyroid carcinomas and were not dose related.

In addition, we can assume some changes take place within the tumor, with the reduction in the number of tumor cells being balanced by an increase in fibroblasts in such a way that the size of the tumor appears unchanged at ultrasound or computerized tomography scan. However, there are no data in the literature confirming that octreotide causes the fibrosis of a tumor mass.¹⁷

A number of recent studies have also investigated the antineoplastic activity of octreotide administered subcutaneously to patients with endocrine pancreatic tumors. The German study documented no tumor regression in 21 patients treated with 200 μ g 3 times per day,²⁵ and the same results were obtained in another study involving 34 patients conducted in the United States.²⁶ It is worth noting that, in both studies, disease stabilization was obtained after a median duration of 14 months.

This lack of tumor control can be explained by the increased carcinoembryonic antigen, calcitonin, and neuron-specific enolase levels observed in the patients who discontinued treatment because of progressive disease; in most studies, these increased levels correlated with the extension of the disease.

Although *in vivo* somatostatin-receptor scintigraphy has recently been developed, it was not used in our study, mostly because technical reasons meant that it was feasible only in a few participating centers. However, our results confirm the hypothesis that only somatostatin-receptor-positive tumors might be expected to respond to treatment, and so it might be useful to know whether a tumor contains somatostatin receptors when beginning treatment with somatostatin analogues.²⁷

As far as symptomatic response is concerned, the octreotide doses used by us controlled flushing and diarrhea in 73% of patients and reduced urinary 5-HIAA excretion in 77% of patients. This result agrees with the published data relating to lower doses. No sure control of symptoms correlated with high dose octreotide, but an improvement in hormonal symptoms was obtained with the additional use of interferon. In a previous study, we obtained tumor regression in 10% of carcinoid patients, a symptomatic response in 64%, and biochemical control in 53%,¹² these results are similar to those of the present study, and we therefore believe that octreotide and interferon are equally effective in controlling symptoms. The combination of interferon and octreotide has been shown

to have an additive and synergistic effect, but the number of patients treated in this way is still small.^{28,29} There are at least other two other somatostatin analogues currently being studied in clinical trials (BIM 230146, somatulin, and RC-160 octostatin), and long-acting formulations of all of the analogues have recently been developed containing microcapsules for intramuscular administration.^{30,31}

For such heterogeneous neoplasms, major improvements have been made in terms of diagnosis and the biological definition of the disease, but the therapeutic results are disappointing. On the basis of our experience, we can hypothesize that patients in an advanced stage and with rapid tumor progression might benefit from combinations of chemotherapies, but the largest group (those with stable disease and symptomatic hormone production) can receive octreotide and/or interferon treatment.²²

REFERENCES

- Williams ED, Siebenmann RE, Sobin LH. Histological typing of endocrine tumors. In: International Histological Classification of Tumors. Geneva: World Health Organization, 1980.
- McKinnon JG. Palliative treatment of neuroendocrine tumors. *Semin Surg Oncol* 1993;9:453-8.
- Zilembo N, Buzzoni R, Bajetta E, Di Bartolomeo M, de Braud F, Castellani R, et al. Salvage treatment after r-Interferon alpha 2a in advanced neuroendocrine tumors. *Acta Oncol* 1993;32:245-50.
- Moertel CG, Johnson CM, Mc Kusick MA, Martin JK, Nagorney DM, Kvols LK, et al. The management of patients with advanced carcinoid tumors and islet cell carcinomas. *Ann Intern Med* 1994;120:302-9.
- Ruszniewski P, Rougier P, Roche A, Lagmann P, Sibert A, Hochlaf S, et al. Hepatic arterial chemoembolization in patients with liver metastases of endocrine tumors. *Cancer* 1993;71:2624-30.
- Sharma D, Gurdip F, Grunberg SM. Chemotherapy of metastatic Merkel cell carcinoma: case report and review of literature. *Am J Clin Oncol* 1991;14:166-9.
- Oberg K, Funa K, Alm G. Effects of leukocyte interferon on clinical symptoms and hormone levels in patients with midgut carcinoid tumors and carcinoid syndrome. *N Engl J Med* 1983;309:129-33.
- Moertel CG, Rubin J, Kvols LK. Therapy of metastatic carcinoid tumors and malignant carcinoid syndrome with recombinant leukocyte interferon. *J Clin Oncol* 1989;7:865-8.
- Doberauer C, Mengelkoch B, Kloke O, Wandl U, Niederle N. Treatment of metastatic carcinoid tumors and carcinoid syndrome with recombinant interferon alpha. *Acta Oncol* 1991;30:603-5.
- Oberg K, Norheim I, Lind E, Alm G, Lundqvist G, Wide L, et al. Treatment of malignant carcinoid tumors with human leukocyte interferon: long term results. *Cancer Treat Rep* 1986;70:1297-304.
- Bajetta E, Zilembo N, Di Bartolomeo M, Di Leo A, Pilotti S, Bochicchio AM. Treatment of metastatic carcinoid and other neuroendocrine tumors with recombinant interferon alpha-2A. A study by the Italian Trials in Medical Oncology (I.T.M.O.) group. *Cancer* 1993;72:3099-105.
- Di Bartolomeo M, Bajetta E, Zilembo N, de Braud F, Di Leo A, Verusio C, et al. Treatment of carcinoid syndrome with recombinant interferon alpha-2A. *Acta Oncol* 1993;32:235-8.
- Reichlin S. Somatostatin. *N Engl J Med* 1983;309:1495-501.
- Bauer W, Briner U, Doeppner W. SMS 201-995: a very potent and selective octapeptide analogue of somatostatin with prolonged action. *Life Sci* 1982;31:1133-40.
- Erikson LS, Wahren J. Intravenous and subcutaneous administration of long-activity somatostatin analogues: effects on glucose metabolism and splanchnic haemodynamics in healthy subjects. *Eur J Clin Invest* 1989;12:213-9.
- Raynor K, Murphy WA, Coy DH, Taylor JE, Moreau JP, Yasuda K, et al. Cloned somatostatin receptor identification of subtype-selective peptides and demonstration of high affinity binding of linear peptides. *Mol Pharmacol* 1993;43:838-44.
- Oberg K. Treatment of neuroendocrine tumors. *Cancer Treat Rev* 1994;20:331-55.
- Antony LB, Winn S, Johnson DH, Jones RA, Hande KR, Oates JA. Continuous subcutaneous octreotide infusion for carcinoid tumor/syndrome [ASCO Proceedings Abstract n. 485]. *J Clin Oncol* 1992;11:168.
- Kvols LK, Reubi JC. Treatment of metastatic carcinoid tumors with a somatostatin analogue (octreotide) and correlation of response with the presence of somatostatin receptors (Abstr N.35). In: International Symposium on Somatostatin, XX, Canada, August 1989.
- Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207-14.
- Di Bartolomeo M, Bajetta E, Bochicchio AM, Carnaghi C, Somma L, Mazzaferro V, et al: A Phase II trial of dacarbazine, fluorouracil, and epirubicin in patients with neuroendocrine tumors. A study by the Italian Trials in Medical Oncology (I.T.M.O.) Group. *Ann Oncol* 1995;6:77-9.
- Simon R. Optimal two-stage design of Phase II clinical trials. *Control Clin Trials* 1989;10:1-10.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. *J Am Stat Assoc* 1958;53:457-81.
- Bajetta E, Di Bartolomeo M, Zilembo N, Bochicchio AM. Medical treatment of neuroendocrine tumors. *Tumori* 1994;79:380-8.
- Arnold R, Neuhaus C, Benning R, Schwerk WB, Trautmann ME, Joseph K, et al. Somatostatin analogue sandostatin and inhibition of tumor growth in patients with metastatic endocrine gastroenteropancreatic tumors. *World J Surg* 1993;17:511-9.
- Saltz L, Trochanowski B, Buckley M, Hefferman B, Niedzwiecki D, Tao Y, et al. Octreotide as an antineoplastic agent in the treatment of functional and nonfunctional neuroendocrine tumors. *Cancer* 1993;72:244-8.
- Dy DY, Morris DL. Somatostatin receptors in human gastrointestinal cancer. *Int J Oncol* 1993;3:519-23.
- Evers MB, Hurlbut SC, Tying SK, Townsend CH, Uchida T, Thompson JC. Novel therapy for the treatment of human carcinoids. *Ann Surg* 1991;213:411-6.
- Öberg K. Chemotherapy and biotherapy in neuroendocrine tumors. *Curr Opin Oncol* 1993;5:110-20.
- Antony LB, Krozely MG, Johnson DH, Fang CL, Hande RJ, Oates JA. Phase I trial of somatulin in neuroendocrine neoplasm [ASCO Proceedings Abstract n. 598]. *J Clin Oncol* 1993;12:202.
- Pinski J, Schall AV, Halmos G, Szepeshazi K, Groot K, O'Byrne K, et al. Effects of somatostatin analogue RC-160 and Bombesin/Gastrin-releasing peptide antagonists on the growth of human small-cell and non-small-cell lung carcinomas in nude mice. *Br J Cancer* 1994;70:886-72.