Octreotide as an Antineoplastic Agent in the Treatment of Functional and Nonfunctional Neuroendocrine Tumors

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Background. **Although patients with neuroendocrine tumors typically exhibit an indolent clinical course, the pace of disease accelerates and the prognosis deteriorates once objective progression of disease begins. Thirty-four patients with advanced neuroendocrine tumors were treated with octreotide as antineoplastic therapy. This treatment was begun only after documentation of clear objective progression of disease.**

Methods. **A Phase II trial was performed at a tertiary comprehensive cancer center.**

Results. **The median survival for this patient population from the start of octreotide therapy has not been reached, with a median follow-up of 29 months (range, 1–47 months). No major objective tumor regressions were seen. Seventeen patients (50%) experienced a computed tomography-documented stabilization of disease that was maintainable for a minimum of 2 months (median, 5 months; range, 0–27 months). Of the 34 patients, 20 patients received octreotide as their first antineoplastic therapy. The median survival for these 20 patients has not been reached, with a median follow-up also of 29 months (range, 12–41 months).**

Conclusions. **Octreotide may influence the natural history of neuroendocrine tumors. The survival in patients treated with octreotide, as measured from the time of progression of disease, compares favorably with that of historical controls. Proof of a survival advantage for patients treated with octreotide would require a multicenter, randomized trial. *Cancer* 1993; 72:244–8.**

Key words: octreotide, antineoplastic agent, neuroendocrine, survival.

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Neuroendocrine tumors are a rare group of neoplasms derived from cells that share the cytochemical capability of amine precursor uptake and decarboxylation (APUD); as such, these neoplasms often referred are to as APUD tumors or "apudomas." Histologically, these tumors, which include carcinoid tumors and islet cell carcinomas, are characterized by the presence of neurosecretory granules. The natural history of these diseases is one of slow, indolent growth. Initial management is characterized by aggressive surgical resection when possible, pharmacologic control of hormone-induced symptoms, and then, in stable patients, expectant observation. Eventually, however, these tumors reach a phase of more accelerated progression and pursue a more aggressive clinical course. Once these tumors enter this progressive phase, their natural history is one of continued growth, with median survivals of approximately 1 to 2 years. At the time of progression of disease, chemotherapy is a standard treatment for palliation of symptoms that result either from hormone production or from increasing tumor bulk. In patients with carcinoid tumor, response rates to chemotherapy have been modest and no clear impact on survival has been demonstrated. Response rates are higher in patients with islet cell carcinomas, and a survival advantage has been suggested for patients receiving certain regimens.[1] With both histologic subtypes, chemotherapy toxicity can be substantial, with treatment-related mortality occasionally reported.[1–3]

Octreotide (Sandostatin, Sandoz Pharmaceuticals, East Hanover, NJ) is a synthetic octapeptide with structure and activities similar to those of the native hormone somatostatin, but with a significantly longer half-life (90 minutes) and duration of action (8 hours) than the native substance.[4,5] Octreotide has been reported to be equally effective in controlling the hormone-induced symptoms of patients with functional (hormone-pro-

Table 1. Patient Characteristics

Median age in years (range)	60 (25–76)
Male:female	19:15
Prior therapy	
None	21
Chemotherapy	13
Radiation therapy	0
Histologic diagnoses	
Carcinoid	20
Islet cell	13
Neuroendocrine, unknown primary	1
Functional:nonfunctional	21:13

ducing) islet cell[6–9] and carcinoid[10,11] tumors. It also has been shown to be useful in the management of carcinoid crisis.[12] Although scattered reports of tumor regression to octreotide have been published,[10,13] the antineoplastic activity of this drug has not been widely studied, either in terms of its effect on tumor growth or in terms of its effect on patient survival. Furthermore, the drug has not been studied previously in substantial numbers of patients with nonfunctional neuroendocrine tumors.

We evaluated the antineoplastic activity of octreotide in 34 patients with advanced functional and nonfunctional neuroendocrine tumors. We studied both islet cell and carcinoid tumors because octreotide has shown similar effectiveness as a biologic agent, in terms of control of symptoms, in both tumor types. Furthermore, the incidence of somatostatin receptors on islet cell and carcinoid tumors has been shown to be similar.[14,15]

Patients and Methods

All patients were evaluated before initiation of octreotide at Memorial Sloan-Kettering Cancer Center (New York, NY). All had advanced, incurable, neuroendocrine tumors with pathologic status confirmed at our institution. Patients with active hormone production, demonstrated either by blood or urine measurement, were classified as having a functional carcinoid or islet cell tumor. Patients with a known primary tumor site but no demonstrable hormone production were considered to have nonfunctional carcinoid or islet cell tumors. Patients with nonfunctional tumors in whom pathologic review of a metastasis, usually from the liver, was consistent with a neuroendocrine tumor but in whom a primary site could not be identified, were classified as having a neuroendocrine tumor of unknown primary site. Histologic data for patients in this study are shown in Table 1.

Pretreatment evaluation included a complete medical history and physical examination, complete blood count, biochemical screening profile, serum creatinine, chest radiograph, and a computed tomography (CT) scan of pertinent indicator lesions. Hormone markers indicating the functional status of the tumors were obtained at the start of octreotide therapy. 5-Hydroxyindoleacetic acid (5-HIAA) levels were measured by 24-hour urine collection in carcinoid patients, and serum measurements of the appropriate hormone (gastrin, glucagon, insulin, or vasoactive intestinal peptide) were performed in islet cell patients. In patients with an elevated hormone level, measurements were repeated every 4 to 6 weeks. A decline in the hormone level was considered to be a biologic response. This was reported as a complete biologic response if the hormone level returned to normal, or a partial biologic response if there was a reduction in the hormone level of 50% or more. An increase of greater than 25% in the hormone level was considered to be biologic progression.

All patients had bidimensionally measurable tumor masses that were imaged at the beginning of octreotide therapy and again after 6 to 8 weeks of treatment. Further measurements were obtained at approximately 8- to 10-week intervals thereafter. Responses were evaluated using the criteria of Miller et al.[16] Most patients had measurable disease in the liver. Other sites of measurable disease included lung, lymph nodes, and skin nodules.

Octreotide therapy was given by subcutaneous injection. Treatment was begun at an initial test dose of 50 μg twice daily on day 1 and then escalated. The maximum daily dose ranged from 150 to 250 μg three times daily, with a median dose of 250 μg three times daily.

As stated earlier, patients initially were followed expectantly, and octreotide therapy was begun only after clear objective progression of disease had been documented. Progression of disease was defined as greater than 25% tumor growth on serial CT scans over a 2- to 4-month interval, or unequivocal development of new lesions. Strict evidence of objective tumor growth was the basis for study entry. Increased hormonal activity alone was not accepted as adequate evidence of disease progression. For this reason, patients receiving octreotide solely for the control of refractory hormone-induced symptoms were not included in this study. All patients were informed of the investigational nature of this trial, and all patients consented to participation before beginning octreotide therapy.

Results

Thirty-four patients with documented progression of disease were enrolled in this study. Patient characteris-

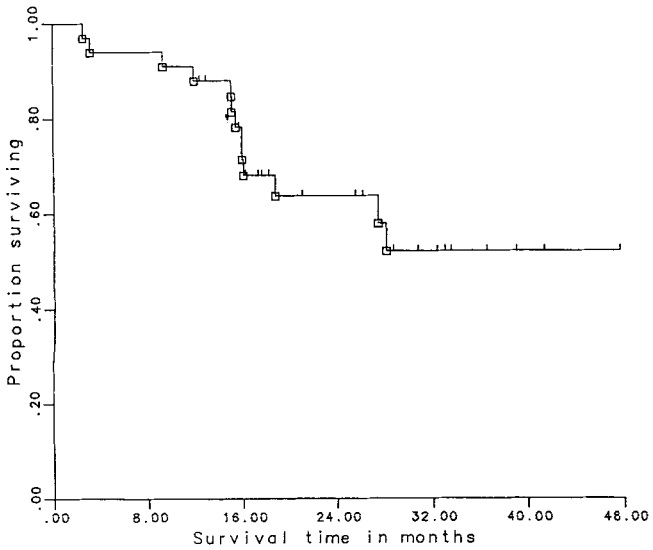

Figure 1. Survival from start of octreotide in patients receiving octreotide as antineoplastic therapy for neuroendocrine tumors. Tick mark indicates last follow-up.

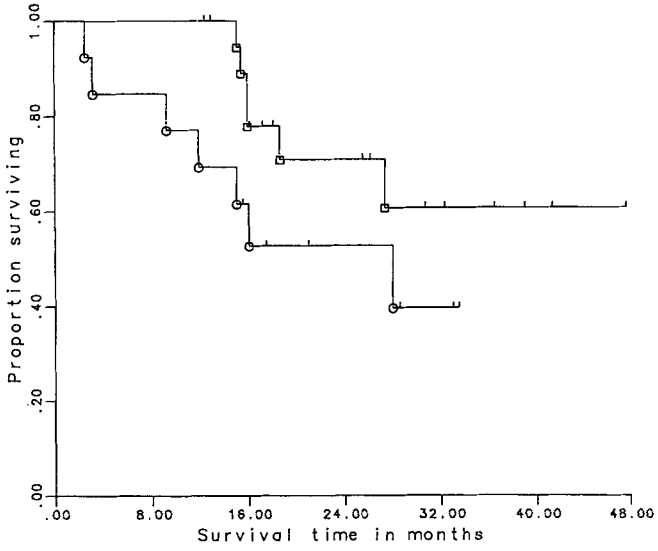

Figure 2. Survival from start of octreotide in patients receiving octreotide for treatment of neuroendocrine tumors; comparison of patients with carcinoid versus islet cell tumors (open squares: carcinoid; open circles: islet). Tick mark indicates last follow-up.

tics are shown in Table 1. Twenty patients (59%) were found to have carcinoid tumors, 14 of which were functional. Thirteen patients (38%) had islet cell tumors, of which seven were found to be functional. Six of the patients with functional islet cell tumors produced gastrin as their primary hormone, and one produced insulin. One patient (3%) had a nonfunctional neuroendocrine tumor of unknown primary site. Consistent with the indolent and variable natural histories of these tumors, the median time from diagnosis of malignancy to start of octreotide in our study population was 22 months, with a range of 1 month to 27 years.

Patient Survival

The median survival of all patients entered on this study, as measured from the start of octreotide therapy, has not yet been reached, with a median follow-up of 29 months (range, 1–47 months). Broken down by histologic subtype, the median survival for the patients with islet cell carcinoma was 23 months, whereas the median survival for patients with carcinoid tumors has not been reached, with a median follow-up of 29 months. Of the total 34 patients entered, 12 have died. Survival data are displayed in Figures 1 and 2.Of the 20 patients in this study who received octreotide as their first antineoplastic therapy, 19 were alive at 1 year from start of their therapy, and the median survival for this group has not been reached, with a median follow-up also of 29 months (range, 12–41 months). Survival data for this group are displayed in Figure 3.

Tumor Response

No patient experienced a major objective response. Of the 34 patients treated with octreotide, 17 (50%, 95% confidence intervals 33%–67%) experienced a CT-documented stabilization of disease that was maintainable for a minimum of 2 months (median, 5 months; range, 0–27 months). One of these patients exhibited some minimal regression in tumor size. Stabilization of dis-

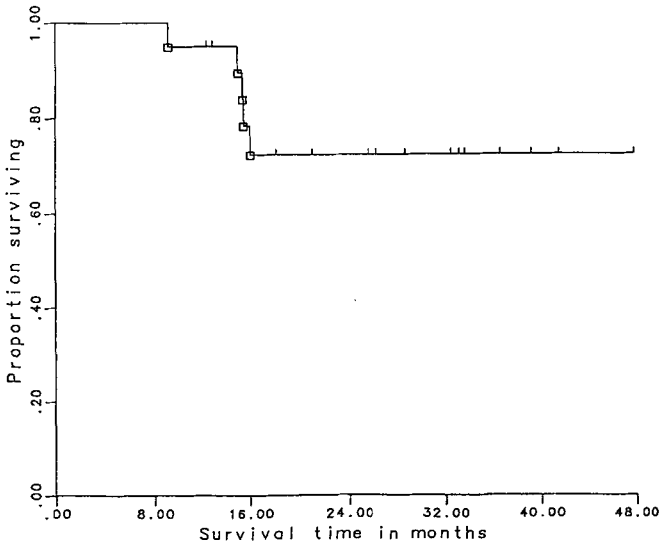

Figure 3. Survival from start of octreotide in patients receiving octreotide as initial antineoplastic therapy. Tick mark indicates last follow-up.

ease occurred in both functional (10 of 21 patients, 47%) and nonfunctional (7 of 13 patients, 54%) tumors.

Of the three patients who had octreotide dose increases after failure to respond, none demonstrated a benefit to the increased dose. Dose increases up to 400 μg three times daily were not associated with toxicity in these patients.

Hormonal Response

Of the 21 patients with functional tumors, 15 (71%) demonstrated either symptomatic improvement or an objective decrease in hormone level (7 documented biologic partial responses). One patient with a gastrin-producing islet cell tumor had a near-normalization of a markedly elevated gastrin level, although her tumor clearly demonstrated objective progression during this period.

Toxicity

Octreotide was well tolerated by most of our patients, and all patients succeeded in learning to self-administer the subcutaneous injections. Two patients experienced toxicities severe enough to require discontinuation of therapy; one patient had a severe, biopsy-documented, allergic dermatitis, and one patient had debilitating abdominal cramps. In both cases the symptoms resolved promptly with cessation of octreotide therapy.

Discussion

The cornerstones of management of patients with neuroendocrine tumors are aggressive surgical resection when possible, pharmacologic control of symptoms due to endocrine hypersecretion, and expectant observation. The natural history of these cancers is one of indolent growth, with patient survival frequently measured in years from the time of diagnosis. Once progression of disease becomes clinically detectable, however, the pace of clinical deterioration appears to increase. In current practice, chemotherapy plays no role in the early management of these diseases, but is widely used for palliation in the later stages when tumor progression leads to pain or uncontrollable hormone-induced symptoms. Before these later stages, it is difficult to justify the risks of chemotherapy-related morbidity and mortality.

At Memorial Sloan-Kettering Cancer Center, chemotherapy in patients with neuroendocrine tumors is initiated only at the time of clear objective progression of disease, or for management of severe, refractory, hormone-induced symptoms. In one study, we noted a median survival of 10.9 months from the start of chemotherapy in patients with neuroendocrine tumors.[17] An Eastern Cooperative Oncology Group trial reported by Moertel et al. noted median survivals from start of therapy of 16 and 26 months in patients with islet cell tumors receiving two different chemotherapy regimens,[2] whereas a Southwest Oncology Group study reported median survivals from start of chemotherapy of 8.1 and 11.7 months in atypical and typical carcinoids, respectively.[18] A more recently completed trial by the Eastern Cooperative Oncology Group reported median survivals of 26.4 months and 16.8 months in patients with islet cell tumors receiving different combination chemotherapies.[1] These studies, taken as a group, provide an indication of the survival ranges reported for neuroendocrine tumor patients undergoing chemotherapy.

Thus, the median survival of patients with advanced neuroendocrine tumors from the time of progression of disease appears to be in the vicinity of 1 to 2 years. Given the long natural history of these tumors, the established practice of delaying chemotherapy until the time of clear tumor progression, and the relatively short survivals observed from the time of initiation of chemotherapy, it is clear that the natural growth pattern of the tumor undergoes a change in its later phases from indolent to more aggressive.

Indications of a survival advantage for patients treated with octreotide during this later, accelerated growth phase have not been reported previously. Although our data are preliminary, the observation that the median survival for our patients has not yet been reached, with a median follow-up of 29 months, compares favorably with historical controls. Also, 19 of 20 patients with documented progression of disease under observation who received octreotide as initial antineoplastic therapy survived for 1 year or more from the start of therapy, and the median survival has not been reached, with a median follow-up of 29 months. Furthermore, these patients received octreotide in a setting in which they would otherwise be receiving cytotoxic chemotherapy; the relatively benign nature of octreotide, as contrasted to the side effects of cytotoxic chemotherapy, would suggest an improved quality of life for these patients receiving octreotide therapy for the advanced stages of neuroendocrine tumors.

Because most previous trials with octreotide in neuroendocrine tumors have concentrated on the biochemical and symptomatic effects of the drug, the treatment of substantial numbers of patients with nonfunctional neuroendocrine tumors has not been reported previously. In patients with hormone-producing islet cell tumors, somatostatin and its analogue octreotide have been shown to decrease endocrine hypersecretion and the resulting symptoms in a large percentage of treated patients.[6,9] Octreotide also has been demonstrated to be

effective in the symptomatic management of patients with carcinoid tumors,[10] and in the management of acute carcinoid crises.[12] Actual reduction in tumor size has been reported only rarely. Our observation of even a modest ability of octreotide to exert a growth-inhibitory effect in functional and nonfunctional neuroendocrine tumors suggests the possibility of an action of the drug other than simple downregulation of hormone production.

It is possible that octreotide, presumably through interaction with the somatostatin receptor, may be exerting a direct antiproliferative effect on tumor cells. Alternatively, octreotide may be suppressing the production of an as yet unidentified autocrine, paracrine, or endocrine substance. Reubi et al. have demonstrated the presence of somatostatin receptors in neuroendocrine tumors by use of autoradiography with a radiolabeled somatostatin analogue, and have demonstrated a strong correlation between the presence of somatostatin receptors in the tumor and the ability of octreotide to produce a biologic response in the patient.[14,15] Similar correlations were noted by Lamberts et al.[19] using a radiolabeled somatostatin analogue to demonstrate somatostatin receptors in vivo. To what degree the presence of somatostatin receptors correlates with clinical antineoplastic or antiproliferative properties, as opposed to antihormonal properties, remains to be determined. Further studies will be required to understand better the complex interactions between octreotide and neuroendocrine tumors.

As in most other studies involving neuroendocrine tumors, the study population in our trial is small, due to the relative scarcity of these tumors. Furthermore, the use of historical controls for survival comparison is not definitive. Nevertheless, the data appear strong enough in our opinion to justify a random assignment trial. Only a prospective, randomized trial can characterize definitively the effects of octreotide on the natural history of neuroendocrine tumors.

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