Octreotide Improves Biochemical, Radiologic, and Symptomatic Indices of Gastroenteropancreatic Neoplasia in Patients with Multiple Endocrine Neoplasia Type 1 (MEN-1)

Implications for an Integrated Model of MEN-1 Tumorigenesis

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Supported by a research grant from the Cancer Council of Tasmania.

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Received February 18, 1999; revision received June 16, 1999; accepted July 9, 1999.

BACKGROUND. Multiple endocrine neoplasia type 1 (MEN-1) is an autosomal dominant tumor syndrome associated with parathyroid, gastroenteropancreatic (GEP), and pituitary neoplasia. Gastrinoma and GEP malignancy are common life-threatening endocrine complications of MEN-1. An effective management strategy for these disorders remains to be determined. The authors attempted to determine the role of the somatostatin analogue, octreotide, in ameliorating features of hypergastrinemic GEP neoplasia associated with MEN-1.

METHODS. Five MEN-1 patients with hypergastrinemia and either symptoms of GEP neoplasia or hepatic metastases received a trial of octreotide, 100 μg subcutaneously, three times daily for 3 months.

RESULTS. Treatment with octreotide was associated with a rapid symptomatic and biochemical response. In all patients serum gastrin fell to $<$ 25% of the pretreatment value. The serum glycoprotein-αsubunit (a marker of enterochromaffin-like [ECL] cell hyperplasia, gastric carcinoidosis, and disseminated enteropancreatic malignancy) was elevated at baseline in three patients. In each case the serum glycoprotein-αsubunit normalized after treatment with octreotide. Hepatic metastases were present in two patients at baseline. The size of the metastases diminished by up to 15% during the period of octreotide treatment. Four patients reported symptoms prior to treatment: lethargy, easy fatigability, and generalized musculoskeletal discomfort. A marked symptomatic improvement occurred in each case. No patient experienced side effects related to octreotide therapy and all elected to remain on treatment after completion of the trial.

CONCLUSIONS. Octreotide is a safe and effective adjunct to surgical strategies for the management of GEP neoplasia in hypergastrinemic MEN-1 patients. ***Cancer* 1999;86:2154–9.** © *1999 American Cancer Society.*

KEYWORDS: multiple endocrine neoplasia type 1 (MEN-1), gastrinoma, malignancy, carcinoid, octreotide.

Multiple endocrine neoplasia type 1 (MEN-1) is an autosomal dominant tumor syndrome.[1-3] The MEN-1 gene behaves as a tumor suppressor gene and is expressed in a broad range of endocrine and nonendocrine tissues.[1,4] Greater than 90% of patients inheriting MEN-1 develop at least 1 manifestation of the syndrome by age 30 years.[3]

Hyperparathyroidism develops in $>$ 95% of patients, with onset usually occurring during the second decade of life.[3,5] Gastroentero-

pancreatic (GEP) neoplasia is detected in up to 75% of patients with MEN-1.[1,3,5] Hypergastrinemia diagnostic of gastrinoma usually develops after age 30 years whereas GEP malignancy generally manifests after the fourth decade of life.[1,3,5]

Neuroendocrine tumors of the upper gastrointestinal tract are a major source of MEN-1 related morbidity and mortality.[1,2,6] Gastrinomas are reported to occur in approximately 50% of gene carriers, half of whom ultimately develop metastases.[3,7,8] Hypergastrinemic MEN-1 patients who have a first-degree relative with enteropancreatic malignancy have a 6.7-fold increased risk of developing GEP malignancy.[7] The anatomic source of gastrin hypersecretion usually is occult, arising from multicentric duodenal and/or pancreatic neuroendocrine lesions, many of which are microscopic.[5,8]

We previously described a correlation between hypergastrinemia, neuroendocrine cell hyperplasia, enteropancreatic malignancy, and elevated serum glycoprotein-α subunit.[7] The α subunit is expressed in, and secreted by, the hyperplastic enterochromaffin-like (ECL) cells that arise in response to hypergastrinemia in MEN-1.[7,9,10] Elevated levels of serum glycoprotein-α subunit in hypergastrinemic MEN-1 patients suggest premalignant or malignant gastric ECL cell transformation.[7]

With the exception of parathyroidectomy to ameliorate the trophic effect of calcium on gastrin secretion, surgical interventions for hypergastrinemia in MEN-1 patients largely are ineffective.[11,12] Additional efforts to reduce serum gastrin in patients with either a high risk of GEP malignancy or evidence of progressive gastric ECL cell dysplasia therefore are appropriate, although the optimal strategy is unclear.[7]

Octreotide is an analogue of the cyclic polypeptide somatostatin.[13] Somatostatin receptors are expressed widely in GEP neuroendocrine tumors that mediate the antiproliferative and antisecretory action of somatostatin.[13] Octreotide has an established role in the treatment and palliation of GEP tumor species associated with carcinoid syndrome and vasoactive intestinal peptide hypersecretion.[13,14] Octreotide also lowers serum gastrin levels and ameliorates ECL cell hyperplasia in the setting of gastrinoma.[10,13] The role of octreotide in the management of hypergastrinemia associated with MEN-1 remains to be established.

In this study the efficacy and role of octreotide in the management of hypergastrinemic MEN-1 patients were examined.

MATERIALS AND METHODS

The investigational and clinical characteristics of the Tasmanian MEN-1 families have been described in detail previously.[3,15] Between 1997 and 1998, five hypergastrinemic patients with either symptoms attributable to GEP neoplasia or radiologic evidence of hepatic metastases were offered and consented to a therapeutic trial of octreotide (Sandostatin®; Sandoz Australia Pty Ltd.). All candidates received treatment for 3 months at a dose of 100 μg subcutaneously three times daily. All patients completed the trial. Biochemical parameters of MEN-1-related endocrinopathy were assessed prior to and after commencement of octreotide.

Hormone Assays

Gastrin

Fasting serum gastrin was measured by DPC (USA) radioimmunoassay. A range $<$ 45 pg/mL was considered normal. Hypergastrinemia diagnostic of gastrinoma was defined as persistent fasting gastrin levels $>$ four times the upper limit of normal recorded on at least two occasions.[3,7]

Serum glycoprotein-α subunit

Serum glycoprotein-α subunit was measured by the Bioclone (AUST) immunoradiometric assay. The normal range was considered to be 0.05–0.50 IU/L for males and premenopausal females and 0.05–1.5 IU/L for postmenopausal females. Values greater than twice the upper limit of normal were considered to be elevated significantly.[3,7]

RESULTS

Of the five patients studied, radiologic evidence of hepatic metastases was present in two patients and local lymph node metastases were detected in one patient (Table 1). Four patients had a high risk immediate family history of malignancy. All patients achieved a rapid biochemical response to octreotide treatment (Table 2) (Fig. 1). In all cases serum gastrin fell to a level $<$ 25% of the baseline value by the third month of treatment (Fig. 1). The size of the hepatic metastases diminished by 15% in 1 patient and remained stable in the second patient, although the basal rate of tumor growth prior to octreotide treatment was unknown (Table 1). Serum ionized calcium, which was elevated in two of the five patients, appeared to be unaffected by octreotide treatment.

Serum glycoprotein-α subunit was elevated significantly in two patients and was of borderline elevation in one patient. Only the two patients with significantly elevated serum glycoprotein-α subunit levels had evidence of gastric carcinoidosis. The patient with the borderline elevation of serum glycoprotein-αsubunit levels had extensive hepatic metastases and a large pancreatic mass but no evidence of gastric mucosal

TABLE 1
Characteristics of Five Patients Treated with Octreotide

Patient characteristic	Patient A	Patient B	Patient C	Patient D	Patient E
Gender	Female	Female	Female	Male	Female
Age at initiation of octreotide (yrs)	47	59	72	57	47
Hyperparathyroidism	Yes	Yes	Yes	Yes	Yes
Prior parathyroidectomy	Yes	Yes	Yes	Yes	Yes
Baseline ionized calcium[a]	1.19	1.20	1.27	1.45	1.34
GEP neoplasia	Yes	Yes	Yes	Yes	Yes
Baseline gastrin[b]	321	256	326	562	7025
Baseline α subunit[c]	0.4	1.2	0.7	4.0	3.4
Gastric carcinoidosis[d]	No	No	No	Yes	Yes
Pancreatic adenoma[e]	Yes	Yes	No	Yes	Yes
Metastases	No	Liver + lymph nodes	No	Liver	Lymph nodes
Octreotide scintigraphy	Not done	Abnormal	Normal	Not done	Abnormal
Pituitary neoplasia	No	No	Yes	No	Yes
Baseline prolactin[f]	22.0	4.4	9.5	7.1	35.8
Adenoma on MRI scan	No	No	Yes	No	No
Indication for octreotide	Single	Single	Single	Multiple	Multiple
Symptoms	Yes	No	Yes	Yes	Yes
Metastases	No	Yes	No	Yes	Yes

GEP: gastroenteropancreatic; MRI: magnetic resonance imaging.
[a] Reference range, 1.14–1.29 mmol/L.
[b] Reference range, < 45 pg/mL.
[c] Serum glycoprotein-alpha subunit expressed as a ratio to upper limit of the assay reference range.
[d] Determined by gastroscopic biopsy and histopathology.
[e] Pancreatic adenoma and hepatic metastases determined by computed tomography scan and ultrasonographic imaging.
[f] Reference range, < 20 μg/L.

TABLE 2
Indication for Octreotide and Treatment Outcome

Patient	Indication for octreotide	Treatment outcome: Beneficial	Treatment outcome: Adverse
A	Lethargy	Symptomatic improvement	Nil
	Musculoskeletal pain	Symptomatic improvement	
		Reduced gastrin	
B	Hepatic metastases	10–15% size reduction in metastases	Nil
	Elevated ASU	Reduced gastrin and ASU	
C	Musculoskeletal pain	Symptomatic improvement	
	Abdominal pain	Able to cease narcotic analgesia	Nil
		Reduced gastrin	
D	Lethargy	Symptomatic improvement	
	Hepatic metastases	Metastasis size stable	Nil
	Elevated ASU	Reduced gastrin, ASU	
E	Lethargy	Symptomatic improvement	
	Diarrhea	Diarrhea resolved	Nil
	Elevated ASU	Reduced gastrin and ASU	

Serum ASU: serum glycoprotein-α subunit.

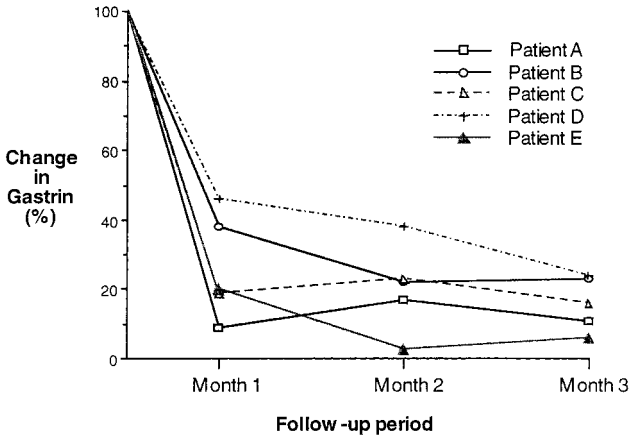

FIGURE 1. Serum gastrin concentration relative to baseline after the initiation of treatment with octreotide.

ECL cell disease. The glycoprotein-α subunit levels normalized in all three patients after treatment with octreotide (Fig. 2). Of the two patients with an initially normal serum glycoprotein-α subunit, levels fell further in one patient and increased slightly in a patient who was perimenopausal at the outset of the trial and postmenopausal at its conclusion.

Prior to the initiation of octreotide four patients reported nonspecific symptoms: lethargy, easy fatigability, and generalized musculoskeletal discomfort. Marked symptomatic improvement occurred in each case. Octreotide scintigraphy (Indium111-labeled) was performed in three patients and failed to identify

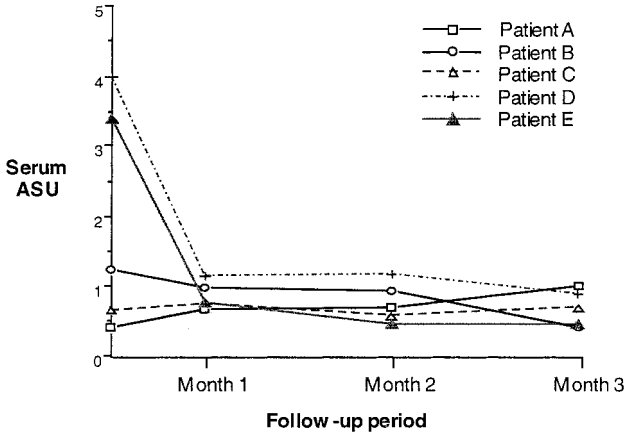

FIGURE 2. Change in serum glycoprotein-α subunit (ASU) after the initiation of octreotide. Serum ASU was expressed as a ratio to the upper limit of the assay reference range.

skeletal metastases. Abnormal octreotide uptake was demonstrated in two patients, occurring at sites of radiologically apparent GEP disease. No adverse effects of octreotide therapy were encountered. In particular, no patient developed diabetes mellitus (one patient with preexisting diabetes remained stable), biliary colic, or exacerbation of diarrhea and abdominal pain. All patients elected to continue treatment with octreotide beyond the initial 3-month trial period.

DISCUSSION

Hypergastrinemic MEN-1 patients commonly experience a range of debilitating symptoms, including lethargy, diarrhea, and musculoskeletal discomfort.[13,14] These symptoms are attributable to either manifestations of hypergastrinemia or indirect complications of GEP neoplasia. We previously described a beneficial effect of octreotide in the setting of bone pain arising from skeletal metastases associated with MEN-1.[14] None of the patients described in the current study had evidence of skeletal metastases. Although the neuroendocrine basis for symptoms of lethargy and musculoskeletal discomfort is unclear, the antisecretory effect of octreotide may mediate this beneficial response.[13]

GEP tumors occurring in MEN-1 patients frequently exhibit plurihormonal immunohistochemical positivity.[5,16] Overtly "nonsecretory" lesions may exhibit positivity for multiple hormone species whereas hypersecretory syndromes can occur in the absence of demonstrable GEP tumors.[5,16] It is likely that in addition to gastrin, other peptide species are elevated in hypergastrinemic MEN-1 patients. Some of these species may contribute to both symptomatology and tumorigenesis in MEN-1. Although the results of the current study are encouraging, an important flaw in its methodology is the lack of a placebo control group to validate the symptomatic improvement noted in the patients treated with octreotide. Nonetheless, we consider a therapeutic trial of octreotide worthwhile for hypergastrinemic MEN-1 patients with debilitating, albeit nonspecific, symptoms that appear to be unresponsive to other therapies.

The reduction in serum gastrin and glycoprotein-α subunit levels noted in the current study indicate both an antisecretory and antiproliferative effect of octreotide.[13,10] Although posttreatment gastric mucosal biopsy was not undertaken in this study, the decrease in levels of serum glycoprotein-α subunit is consistent with a reduction in the degree of gastric ECL cell hyperplasia and dysplasia.[7,17]

Tumorigenesis is a multistep process.[1,18] An inherited germline mutation of the MEN-1 gene is central to the conventional model of MEN-1 tumor pathogenesis. However, the occurrence of acquired somatic mutations in the wild-type MEN-1 allele is potentially a late step in the evolution of some MEN-1 tumor species.[1,19,20,21] This appears to be the case especially in adrenocortical, and gastric neuroendocrine tumors. In these tumors, a phase of diffuse hyperplasia may precede somatic mutations of the MEN-1 gene.[1,19,21,22] In the adrenal gland, for example, loss of heterozygosity and/or mutations of the wild-type MEN-1 allele are uncommon in hyperplastic tissue yet frequently are detected in malignant areas.[1,5,21]

Therefore it may be possible to divide MEN-1 tumors into two categories: primary tumors and induced tumors. This dichotomy provides a framework for approaching the investigation and treatment of MEN-1 phenotypic disease. Although primary tumors (such as those in the pancreas and pituitary gland) develop as discrete monoclonal lesions in the absence of diffuse background hyperplasia, induced tumors may be defined as those that develop in the context of preexisting hyperplasia. This morphologic dichotomy may reflect the differing underlying susceptibility of various endocrine tissues to such growth factors as may be active in MEN-1, as well as a divergence in tissue susceptibilities to the mutational events critical for MEN-1 tumorigenesis.

The evolution of carcinoid lesions within the gastric mucosa is illustrative. The (ECL) cells of the gastric oxyntic mucosa normally regulate gastric acid secretion.[10] ECL cells secrete histamine in response to gastrin stimulation, which in turn promotes acid secretion by the gastric parietal cells.[10] Gastrin also is an ECL cell growth factor.[10] Chronic hypergastrinemia results in gastric ECL cell hyperplasia, which, in the

setting of MEN-1, can progress to dysplasia and ultimately gastric carcinoid lesions.[9,10]

Hyperplastic and neoplastic ECL cell lesions may themselves promote hypergastrinemia via histamine secretion, resulting in autocrine, paracrine, and endocrine trophism for tumor proliferation by potentiating hypergastrinemia.[10,23] Hypercalcemia also is a potent gastrin secretogogue that may exacerbate this process.[10,24,25] It is interesting to note that basic fibroblast growth factor (bFGF), which has been implicated in the genesis of parathyroid hyperplasia in MEN-1, is expressed by the hyperplastic and neoplastic ECL cells of the gastric oxyntic mucosa.[24,26]

A possible sequence of events in MEN-1 tumorigenesis is the secretion of one or more humoral growth factor(s) (such as bFGF) by "primary" enteropancreatic neoplasms, leading to the induction of "secondary" parathyroid hyperplasia and hyperparathyroidism. Hyperparathyroidism may, in addition to other circulating growth factors, secondarily promote hypergastrinemia and the induction of gastric ECL cell hyperplasia. This process may culminate in ECL cell dysplasia, carcinoid lesions, and malignancy. At each step, the final phenotype can be influenced by mutational events affecting the MEN-1 gene and/or other modifier loci.

Interrupting the hyperplasia-adenoma-malignancy sequence is an attractive goal for early intervention to reduce the prevalence of GEP malignancy. It is possible that a proportion of the malignant complications associated with MEN-1 might be prevented by lifelong maintenance of both normocalcemia and eugastrinemia. It therefore appears appropriate to adopt treatment strategies that will minimize the autocrine, paracrine, and endocrine secretion of growth factors such as gastrin.

Control of hyperparathyroidism temporarily improves hypergastrinemia; however, hypergastrinemia ultimately recurs in the majority of patients.[7,27] This reflects both difficulty in maintaining normocalcemia as well as the natural progression of gastrinoma in MEN-1.[7,11] Nonetheless, we advocate early parathyroidectomy and maintenance of normocalcemia for all MEN-1 patients.[28] It is interesting to note that one of the few centers to report a consistently high level of long term success for the surgical management of gastrinoma also practices concurrent and aggressive treatment of hyperparathyroidism.[29]

Although the current study only describes a 3-month follow-up period, the beneficial response noted with regard to both symptomatic and biochemical parameters of disease activity suggest that long term therapy is worthy of consideration. Long term treatment with octreotide has important economic implications. Although drug costs may fall after the introduction of longer-acting somatostatin analogues, the annual treatment cost using the regimen outlined in this study (100 μg three times daily) is $12,000. The current study suggests a role for octreotide in the treatment of MEN-1 patients with hypergastrinemia; however, further study of this issue is required. Given the relative rarity of MEN-1, this best will be achieved by a prospective, placebo-controlled, multicenter trial.

Conclusions

MEN-1 is a disease in which autocrine, paracrine, and humoral growth stimuli may influence tumor evolution. This model for tumorigenesis provides a rationale for both therapeutic and preventative measures. Early and aggressive surgical control of primary hyperparathyroidism, coupled with the use of a somatostatin analogue to ameliorate hypergastrinemia, is a potential strategy for reducing the risk of ECL cell dysplasia and malignant transformation in MEN-1 patients at high risk for enteropancreatic malignancy.

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