A Phase III Evaluation of a Somatostatin Analogue (Octreotide) in the Treatment of Patients with Asymptomatic Advanced Colon Carcinoma

Richard M. Goldberg, M.D., Charles G. Moertel, M.D.,† Harry S. Wieand, Ph.D.,* James E. Krook, M.D.,‡ Allan J. Schutt, M.D.,* Michael H. Veeder, M.D.,§ James A. Mailliard, M.D.,‖ and Robert J. Dalton, M.D.,‡ for the North Central Cancer Treatment Group and the Mayo Clinic*

Background. **The purpose of this study was to determine by randomized, controlled, double-blind evaluation whether therapy with the somatostatin analogue, octreotide, would delay tumor progression and improve survival of patients with metastatic colorectal carcinomas who were ambulatory with no significant symptoms.**

Methods. **Two hundred sixty patients with an Eastern Cooperative Oncology Group performance status of 0 or 1 and without symptoms related to colon cancer were randomized to receive 150 μg of octreotide subcutaneously three times daily or, initially, no treatment. After 91 patients were entered in the double-blind study, saline placebo injections were used for patients in the control arm.**

Results. **The randomization culminated in balanced assignment of patients with respect to disease site(s), presence or absence of measurable or evaluable disease, and interval from diagnosis of metastasis to protocol entry. Steatorrhea and diarrhea, usually mildly severe, resulted more often from treatment than from the placebo. The major end points were time to progression and survival. Curves for both parameters overlapped in the blind and open trial segments.**

Conclusion. **Octreotide at a dose of 150 μg given three times daily is not effective therapy for patients with advanced asymptomatic colon carcinoma. *Cancer* 1995;76: 961–6.**

Key words: advanced colon carcinoma, octreotide.

From the *Mayo Clinic and Mayo Foundation, Rochester, Minnesota; ‡Duluth Community Clinical Oncology Program, Duluth, Minnesota; §Illinois Oncology Research Association community Clinical Oncology Program, Peoria, Illinois; and the ‖Nebraska Oncology Group, Creighton University, University of Nebraska Medical Center and Associates, Omaha, North Dakota.

Additional participating institutions include: Cedar Rapids Oncology Project CCOP, Cedar Rapids, Iowa (Martin Wiesenfeld, M.D.); Saskatchewan Cancer Foundation, Allan Blair Memorial Clinic, Regina, Saskatchewan, Canada (Michael A. Poon, M.D.); Siouxland Hematology-Oncology Associates, Sioux City, Iowa (John C. Michalak, M.D.); Carle Cancer Center Community Clinical Oncology Program, Urbana, Illinois (Alan K. Hatfield, M.D.); Sioux Community Cancer Consortium, Sioux Falls, South Dakota (Loren K. Tschetter, M.D.); The St. Cloud Clinic of Internal Medicine, Ltd., St. Cloud, Minnesota (Harold E. Windschitl, M.D.); Ochsner Community Clinical Oncology Program, New Orleans, Louisiana (Carl G. Kardinal, M.D.); St. Luke's Hospitals CCOP, Fargo, North Dakota (Ralph Levitt, M.D.); Quain and Ramstad Clinic, Bismarck, North Dakota (Delano M. Pfeifle, M.D.); Grand Forks Clinic, Ltd., Grand Forks, North Dakota (John A. Laurie, M.D.); Billings Clinic, Billings, Montana (Donald I. Twito, M.D.); Rapid City Regional Oncology Group, Rapid City, South Dakota (Larry P. Ebbert, M.D.); Toledo Community Clinical Oncology Program, Toledo, Ohio (Paul L. Schaefer, M.D.).

Supported in part by Grants CA 25224, CA 37404, CA 35448, CA 35269, CA 35113, CA 52352, CA 35195, CA 35103, CA 35272, CA 37417, and CA 35415 from the National Cancer Institute, National Institutes of Health.

† Deceased.

Address for reprints: Richard M. Goldberg, M.D., E-12 Mayo Clinic, 200 First Street, SW, Rochester, MN 55905.

Received April 26, 1995, accepted May 16, 1995.

Somatostatin is a peptide hormone synthesized in a wide variety of human tissues that has been characterized as the universal endocrine inhibitor.[1] Although its functions are varied and incompletely understood, somatostatin's principal roles, which are of interest with regard to cancer treatment, are at the cellular level. There it inhibits endogenous growth and DNA synthesis through interference with centrosome separation.[2] It also may have a direct antiproliferative effect mediated by cell surface somatostatin receptors. In addition, somatostatin inhibits secretion of a number of gastrointestinal hormones thought to affect tumor growth including growth hormone, gastrin, secritin, and other growth factors.[3] The outcome of a variety of exocrine,

endocrine, paracrine, and autocrine activities is a regulatory-inhibitory function.

The therapeutic effect of native somatostatin proved impractical because of the evanescence of its antisecretory effects and short circulating half-life of approximately 3 minutes. Systematic design and synthesis of somatostatin analogues resulted in the development of octreotide acetate (Sandostatin, Sandoz Pharmaceutical Corp., East Hanover, NJ), which has a half-life of 113 minutes and is 19 times more potent than native somatostatin in inhibiting growth hormone secretion.[4]

Octreotide has been demonstrated to have its most notable activity in human trials against gastrointestinal neuroendocrine carcinomas.[5] Clinically meaningful control of hormonal excesses was possible in the majority of patients with the carcinoid syndrome and the variety of endocrine syndromes associated with islet cell carcinomas. Actual tumor regression was noted in a minority of patients treated with octreotide.

Octreotide has demonstrated substantive in vitro and in vivo activity in animal and human tumors. When added to cultured cells known to express somatostatin, receptors originating from a rat chondrosarcoma and a hamster insulinoma somatostatin analogue inhibited cell growth.[6,7] A human small cell lung carcinoma cell line in culture and in murine xenograft and a human breast carcinoma cell line in culture all showed growth inhibition when a somatostatin analogue was added to the systems.[8,9] In murine colon cancer models and in human tumor xenografts to nude mice, significant growth inhibition has been documented in response to long-acting somatostatin analogues.[10,11]

These preclinical data indicating a general effect on growth inhibition and specific activity in colon cancer led us to investigate the activity of octreotide in humans with proven metastatic colon cancer. We believe that a justifiable standard practice of treating patients with metastatic and surgically unresectable but asymptomatic colon cancer is close observation until symptoms or substantive progression become manifest. This hiatus between diagnosis and initiation of chemotherapy seemed an ideal interlude during which to test the efficacy of a somatostatin analogue in retarding tumor growth.

Patients and Methods

Eligibility and Stratification

Patients were required to have histologic or cytologic confirmation of unresectable or metastatic adenocarcinoma with the site of organ confirmed to be in the large bowel. An exception was made to histologic confirmation if there were two or more pulmonary nodules observed to be enlarging on serial chest X-rays.

Patients were not accessioned if they were candidates for potentially curative surgery or radiotherapy. Patients were not required to have measurable disease. Patients could have only no or minimal symptoms related to their malignancy. For example, cancer-related pain had to be well controlled with nonnarcotic analgesics. Performance status of Eastern Cooperative Oncology Group (ECOG) 0 or 1 was required. Potential entrants were required to be emotionally, physically, and intellectually capable of self-injection.

Individuals could have received prior chemotherapy, immunotherapy, or radiation therapy for colon cancer as an adjuvant to surgery performed with curative intent. No patient who received prior chemotherapy for unresectable or recurrent carcinoma was enrolled. Liver function impairment defined as an alkaline phosphatase level greater than twice an institution's upper normal limit or any elevation of direct reacting or total serum bilirubin levels excluded individuals from entry. Pregnant or lactating women could not participate. No eligible patient could have a history of another active malignancy within 5 years of entry.

Before randomization, patient history, results from physical examination, body weight, and measurement or evaluation of indicator lesion(s), if present, were recorded. An automated blood chemistry evaluation to include alkaline phosphatase, total bilirubin, and fasting blood glucose levels and a thyroxine level was collected. A chest X-ray was required. Women of childbearing potential were required to have a negative pregnancy test.

After signing informed consent documents, patients were stratified for sites of metastases into pulmonary, hepatic, abdominal, and other categories. Whether a patient had measurable disease and interval from diagnosis of advanced malignancy to study entry (<4 weeks, 4–8 weeks, or >8 weeks) were additional stratifiers.

Treatment Protocol

The first 91 patients were randomly assigned to receive either no treatment or octreotide. Patients entered thereafter were placed in an amended protocol to receive octreotide or the saline placebo. One hundred fifty micrograms of octreotide were administered twice on Day 1 and three times daily thereafter. The placebo injections were identical in appearance and volume. The first four injections were given in the oncology clinic under supervision. Independent administration by the patients or someone acting on their behalf followed. Treatment was continued until the patient manifested

progressive disease, severe toxicity, or refused further injections. Patients were reevaluated at 1, 2, and 3 months and then every 2 months.

In monitoring patients, we focused particular attention on the development and severity of steatorrhea, nausea, vomiting, or diarrhea. If patients had symptomatically distressing steatorrhea or lost more than 5% of their initial body weight, a 50% dose reduction was prescribed, and if that intervention did not resolve the toxicity, then therapy was discontinued. If nausea and vomiting unresponsive to phenotiazines occurred, identical adjustments were specified. Careful monitoring and appropriate action at the physician's discretion was advised for alteration in therapy for diabetes as a consequence of altered glucose metabolism or for signs or symptoms of cholelithiasis. Any patient withdrawing from the study for toxicity or because of personal preference was followed according to schedule for time to progression and survival.

Evaluation of Response

The subset of patients with measurable disease was characterized as manifesting a partial regression or progression when the product of the perpendicular dimensions of any lesion decreased in the case of regression or increased in the case of progression by 50% or more of the pretreatment measurement. Patients without measurable disease were considered to have disease progression when new areas of malignant disease were documented by physical examination or by investigations prompted by symptoms, laboratory abnormalities, or chest X-rays. If the Eastern Cooperative Oncology Group performance score slipped by one level or more, significant symptoms developed, or weight loss of more than 10% of the patient's weight on entering the study became manifest, progression was declared, and patients were removed from the study. These end points were chosen to ensure that no patient became so sick as to lose the potential opportunity to try chemotherapy for treatment of advancing disease.

Statistical Methods

The study was originally designed to accrue 200 patients to have a power of 0.80 for detecting a 50% increase in median survival. Early results indicated that the time to progression was shorter for untreated patients than for those receiving octreotide. Due to concern that the investigator's knowledge that a patient was receiving treatment might have relevance in his or her determination of time to progression, the study was amended to be double-blind after 91 patients were entered. The plan was to accrue 200 additional patients.

Table 1. Patient Characteristics According to Treatment Arm

Characteristic	Untreated/placebo (n = 129)	Octreotide (n = 131)
Sex		
Male/female	56/44	51/49
Age (yr)		
<50	8	6
50–69	56	52
≥70	36	42
Performance status		
0/1	73/27	76/24
Measurable disease		
Yes/No	43/57	45/55
Grade of anaplasia		
1–2	63	76
3–4	32	22
Unknown	5	2
Site of metastatic disease		
Lung	32	32
Liver	49	50
Abdominal	15	13
Other	5	5
Interval from diagnosis (wk)		
<4	43	37
4–8	23	27
>8	34	36

Values are percent of patients.

The amended design included a formal stopping rule that admitted the possibility of stopping accrual earlier if the observed survival for the patients receiving octreotide was no better than that of untreated patients and those receiving the placebo when half of the anticipated deaths had been observed.[12] This scenario occurred, and accrual was terminated when 260 eligible patients were randomized to receive octreotide and no treatment or the placebo.

Results

Patient Characteristics

This study was activated in May 1988 and completed accrual in March 1992. Three (1.1%) of the 263 patients entered were ineligible and were not considered in the analysis. One patient randomized to receive treatment elected to refuse it, and one patient withdrew from the study by choice and began chemotherapy before there was evidence of disease progression. The latter two patients were included in the primary analysis.

The randomization process resulted in a well balanced division with respect to patient and disease characteristics (Table 1). There was a slight preponderance

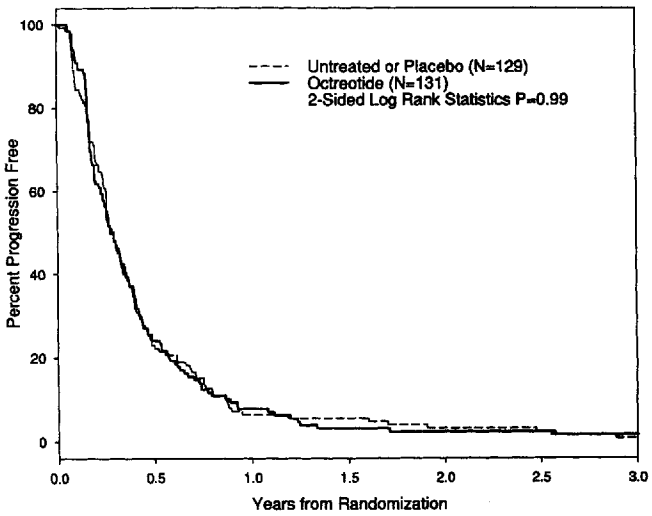

Figure 1. Time to progression according to treatment arm for all patients.

of females, and there were more anaplastic tumors in the patients who were untreated or received the placebo, although neither imbalance was statistically significant. Median patient age was 67 years. All patients were at or near full levels of activity. Most patients had nonmeasurable disease involving the lungs and liver. The median interval from diagnosis of advanced disease to study entry was 6 weeks.

At the time of this writing, the study was mature. Two hundred fifty-five of the 260 eligible patients showed disease progression, and 254 died. All surviving patients (six) were followed for at least 32 months (median, 43 months). The median time to progression for patients receiving the placebo or no treatment was 3.2 months and for those receiving octreotide treatment was 3.4 months. There was no suggestion of a beneficial treatment effect on time to progression ($P = 0.99$) (Fig. 1). The median survival time for the no-treatment/placebo group was 16.8 months and for the octreotide-treated cohort was 17 months, with a two-sided log rank P value of 0.77 (Fig. 2). The overlapping of progression and survival curves occurred in the groups of patients entered before and after the treatment program was double-blind, indicating that physician and patient knowledge of the treatment assigned had no significant influence on end points. In this study, tumor regression was not a primary end point but it is of interest that three partial regressions were recorded, two in the octreotide arm and one in the no-treatment/placebo arm.

The results with respect to the prognostic and stratification factors is shown in Table 2. Sites of metastatic disease, interval from diagnosis of advanced disease to protocol entry, and grade of anaplasia did not significantly influence end points.

Patients with Eastern Cooperative Oncology Group performance score of 0 had a median survival of 17.7 months and lived significantly longer than the cohort with an initial score of 1, who had a median survival of 11.3 months ($P = 0.04$). Survival was poorer for older patients ($P = 0.02$). In a multivariate analysis, age was the only statistically significant variable ($P = 0.03$); performance score was nearly significant ($P = 0.12$). After adjustment for age and performance score, treatment remained a nonsignificant variable ($P > 0.62$).

Because the study was so mature, more than the requisite number of deaths (164 observed, 150 were required) to satisfy the original statistical goals have now occurred in the double-blind cohort. In this subset, as in the entire cohort, octreotide offered no apparent benefit because the relative risk of death was slightly greater (1.02) in the octreotide group than in the placebo group ($P = 0.92$). Progression free and survival curves for this subset of patients are shown in Figures 3 and 4, respectively.

Toxicity

The assigned treatment, whether placebo or octreotide, proved to be well tolerated by the enrolled patients. No life-threatening toxicities of any sort were noted with the exception of a single patient who had grade 4 diarrhea (Table 3). The principal problem was an anticipated one in that 44% of patients who were receiving octreotide had diarrhea and 30% gave a history consistent with steatorrhea. These side effects required dosage reductions in 5% of patients. In the placebo group, diarrhea was reported in 10% and steatorrhea in 3%. A dosage adjustment was required for one patient. Nau-

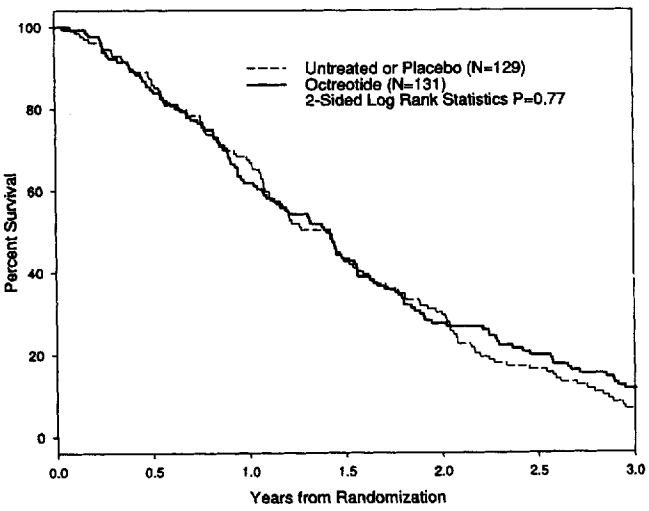

Figure 2. Patient survival according to treatment arm for all patients.

Table 2. Survival by Patient Characteristic

Factor	Distribution	Median time to progression (mo)	Log rank *P* value (two-sided)	Median survival (mo)	Log rank *P* value (two-sided)
Sex					
Male	139	3.2	0.46	17.4	0.28
Female	121	3.6		14.1	
Age (yr)					
<50	18	3.6	0.73	24.8	0.02
50–69	140	3.2		17.3	
≥70	102	3.4		12.5	
Performance status					
0	193	3.4	0.53	17.7	0.04
1	67	3.4		11.3	
Measurable disease					
Yes	115	2.8	0.003	15.2	0.70
No	145	3.9		17.3	
Grade of anaplasia					
1–2	179	3.4	0.36	17.0	0.46
3–4	71	3.1		13.0	
Site of metastatic disease					
Lung	83	3.1	0.20	17.0	0.62
Liver	129	3.2		17.1	
Abdominal	36	3.9		12.3	
Other	12	4.2		15.8	
Interval from diagnosis (wk)					
<4	104	3.4	0.67	16.7	0.59
4–8	65	3.4		17.1	
>8	91	3.2		15.8	

sea affected 26% of subjects who received octreotide and 12% who received the placebo. Downward dose adjustments were made for two patients receiving octreotide and one patient receiving the placebo as a result. No other significant toxicity was observed, and no patient stopped treatment as a consequence of side effects.

Discussion

The primary objective of this study was to determine if the administration of octreotide in doses known to have

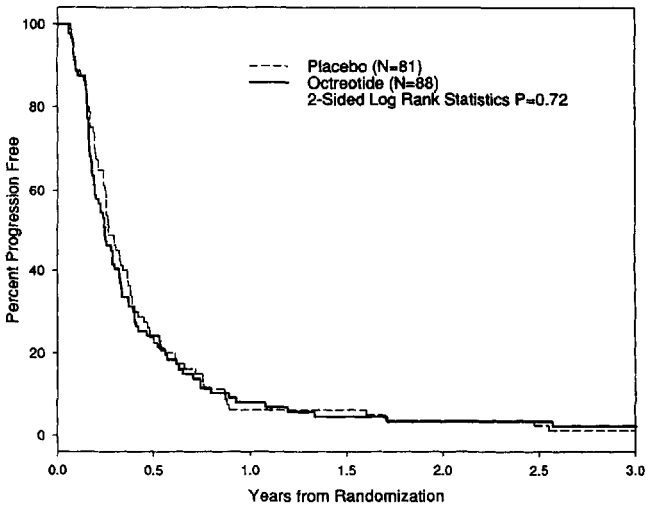

Figure 3. Time to progression according to treatment arm for patients by double-blind evaluation.

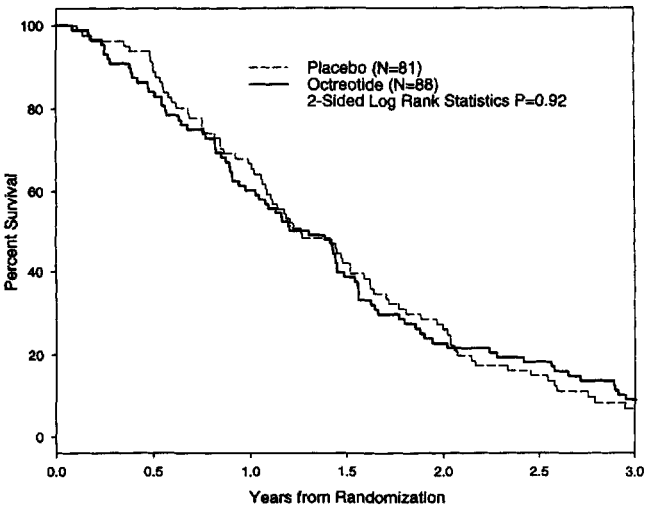

Figure 4. Patient survival according to treatment arm for patients by double-blind evaluation.

Table 3. Toxicities

Toxicity	Placebo (n = 81)	Octreotide (n = 131)
Nausea		
Any	19	26
Severe	1	2
Vomiting		
Any	7	9
Severe	0	0
Diarrhea		
Any	16	44
Severe	2	6
Steatorrhea		
Any	5	30
Severe	0	0

Values are percent of patients.

palliative benefit in patients with neuroendocrine carcinomas would benefit patients who were asymptomatic or mildly symptomatic with advanced, metastatic colon cancer. Protocol compliance and data quality proved to be excellent. Toxicity was tolerable. The cohort of patients with asymptomatic or mildly symptomatic colon cancer proved to be one which could be accrued to a nonchemotherapy trial using an intervention of uncertain utility. These data clearly indicate that octreotide at a dose of 150 μg three times daily is ineffective in extending time to progression or survival in this subset of patients with colorectal cancer. There are currently five known types of somatostatin receptors and a number of somatostatin analogues in preclinical and clinical trials.[13] Despite the failure to discern activity for octreotide in this disease setting and at this dose, activity of analogues that target different receptors should be evaluated in the event that in vitro and in vivo investigations suggest a salutary influence on tumor growth.

References

1. Newman JB, Lluis F, Townsend CM Jr. Somatostatin. In: Thompson JC, Greeley GH Jr., Rayford PL, editors. Gastrointestional endocrinology. New York: McGraw-Hill Book Co, 1987: 286–99.
2. Moscardo RN, Sherline, P. Somatostatin inhibits rapid centrosomal separation and cell proliferation induced by epidermal growth factor. *Endocrinology* 1982;111:1394–6.
3. Evers BM, Parekh D, Townsend CM, et al. Somatostatin analogues in the treatment of cancer. *Ann Surg* 1991;2132:190–8.
4. Schally AV. Oncological applications of somatostatin analogues. *Cancer Res* 1988;48:6977–85.
5. Moertel CG. An odyssey in the land of small tumors. *J Clin Oncol* 1987;10:15023–1522.
6. Redding TW, Schally AV. Inhibition of growth of the transplantable rat chondrosarcoma by analogs of hypothalamic hormones. *Proc Natl Acad Sci U S A* 1983;80:1078–82.
7. Reubi JC. A somatostatin analogue inhibits chondrosarcoma and insulinoma tumor growth. *Acta Endocrinol* 1985;109:108–14.
8. Taylor JE, Bodgen AE, Moreau JP, et al. In vitro and in vivo inhibition of human small cell lung carcinoma (NCI-H69) growth by a somatostatin analogue. *Biochem Biophys Res Commun* 1988;153:81–6.
9. Setyono-Han B, Henkelman MS, Foekens JA, et al. Direct inhibitory effects of somatostatin (analogues) on the growth of human breast cancer cells. *Cancer Res* 1987;47:1566–70.
10. Singh P, Le S, Townsend CM Jr, et al. A long acting somatostatin analogue (SRIF) (201-995) and proglumide (PGL) inhibit the trophic and gastrin receptor (GR) regulatory effects of pentagastrin (PG) on mouse colon cancer (MC-26) cells in vivo [abstract]. *Gastroenterol* 1986;90:1636.
11. Milhoan RA, Milhoan LH, Trudel JL, et al. Somatostatin and Alpha-difluoromethylornithine (DFMO) have additive inhibitory effects on growth of human colon carcinoma (HCC) in vivo [abstract]. *Biomed Res* 1988;9:30.
12. Wieand S, Schroeder G, O'Fallon JR. Stopping when the experimental regimen does not appear to help. *Stat Med* 1994;13: 1453–8.
13. Buscail L, Delesque N, Estève JP, et al. Stimulation of tyrosine phosphatase and inhibition of cell proliferation by somatostatin analogues: mediation by human somatostatin receptor subtypes SSTR1 and SSTR2. *Proc Natl Acad Sci U S A* 1994;91:2315–9.