Phase III, Double-Blind Study of Depot Octreotide Versus Placebo in the Prevention of Acute Diarrhea in Patients Receiving Pelvic Radiation Therapy: Results of North Central Cancer Treatment Group N00CA

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ABSTRACT

Purpose

To assess the effectiveness of depot octreotide for the prevention of diarrhea during pelvic radiation therapy.

Patients and Methods

Patients receiving pelvic radiation therapy (planned minimum dose, 45 Gy; 1.7 to 2.1 Gy daily) were eligible for the study. From May 10, 2002, through October 14, 2005, 125 patients were randomly allocated in a double-blind fashion to receive octreotide (100 μ g, administered subcutaneously on day 1, followed by depot octreotide, 20 mg, administered intramuscularly on days 2 and 29; n = 62) or to receive a placebo (n = 63).

Results

Grade 0, 1, 2, and 3 diarrhea were observed in 18%, 31%, 31%, and 21% of patients in the octreotide arm, respectively, and in 25%, 32%, 22%, and 21% of patients in the placebo arm, respectively ($P = .64$). Grade 0, 1, 2, and 3 abdominal cramps were observed in 32%, 45%, 21%, and 2% of patients receiving octreotide, respectively, and in 51%, 24%, 21%, and 5% of patients receiving the placebo, respectively ($P = .053$). Some patient-reported symptoms were worse in the octreotide group, including nocturnal bowel movements (70% v 45%; $P = .004$), clustering of bowel movements (90% v 69%; $P = .004$), and bleeding with bowel movements (57% v 35%; $P = .01$).

Conclusion

As administered in this study, octreotide did not decrease diarrhea during pelvic radiation therapy. Some gastrointestinal symptoms were worse in patients treated with octreotide. Octreotide is not indicated for prevention of diarrhea during pelvic radiation therapy.

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INTRODUCTION

Pelvic radiation therapy is used in various clinical settings as an adjuvant or primary treatment for patients with gastrointestinal, gynecologic, genitourinary, or other pelvic cancers. Diarrhea is the major form of acute toxicity for these patients.¹⁻⁵ In a North Central Cancer Treatment Group (NCCTG) trial involving adjuvant radiation therapy for rectal cancer, 53% of patients treated with concurrent pelvic radiation therapy and fluorouracil had diarrhea.⁵ Placebo-treated (control) patients in a study of sucralfate for diarrhea prevention during pelvic radiation therapy had a 28%, 34%, 24%, and 14% incidence rate of grade 0, 1, 2, and 3 diarrhea, respectively.³ A similar incidence rate and distribution of severity of diarrhea were observed in a clinical trial

that evaluated glutamine for prevention of bowel toxicity during radiation therapy.¹

Treatment with octreotide results in the relief of diarrhea for patients with various pathologic conditions. Octreotide reduces the secretion of many pancreatic and gastrointestinal hormones. It also prolongs intestinal transit time, thereby promoting absorption of electrolytes.⁶⁻¹¹ Octreotide markedly relieves diarrhea in patients with carcinoid syndrome,¹² and it is approved by the US Food and Drug Administration for long-term treatment of diarrhea associated with metastatic carcinoid tumors and diarrhea associated with vasoactive peptide-secreting tumors. Phase III clinical trials have shown that octreotide effectively controls diarrhea caused by fluorouracil.¹³⁻¹⁵ A phase III clinical trial has also shown octreotide to be effective in the secondary

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prevention of diarrhea in patients receiving cisplatin.¹⁶ A phase III, placebo-controlled trial showed a pronounced reduction in stool frequency and volume in patients with large-volume, refractory, AIDS-associated diarrhea.¹⁷ Suggestive evidence also indicates that octreotide provides relief from diarrhea in patients with short bowel syndrome¹⁸ and dumping syndrome.¹⁹ Octreotide was recommended for the control of chemotherapy-induced diarrhea in guidelines from the American Society of Clinical Oncology²⁰ and by a second group that published updated recommendations in 2004.²¹

Yavuz and colleagues²² reported the results of a randomized clinical trial that assessed the effectiveness of octreotide in patients with diarrhea caused by pelvic radiation therapy. Patients with grade 2 or 3 diarrhea were allocated randomly to receive either octreotide or a combination of diphenoxylate and atropine. Octreotide was associated with improved control of diarrhea. Twenty of 33 patients treated with octreotide had resolution of diarrhea within 3 days of starting the medication, but only four of 28 patients treated with diphenoxylate and atropine had resolution ($P = .002$). However, use of octreotide for diarrhea prevention during pelvic radiation therapy is limited by the need to administer injections 3 times daily. Administration of depot octreotide, which requires an injection every 4 weeks, is considerably more convenient.

The primary objective of this study was to determine the effectiveness of depot octreotide in reducing acute treatment-related diarrhea in patients receiving pelvic radiation therapy. We also determined the incidence of rectal bleeding, abdominal cramps, tenesmus, and constipation during radiation therapy. Our secondary objective was to assess the effect of depot octreotide on patient-reported symptoms. Because long-term use of octreotide has been associated with development of gallstones,²³⁻³¹ the study included a specific provision for prompt reporting of any symptomatic, biliary toxicity resulting from gallstone formation.

PATIENTS AND METHODS

Patient Selection Criteria

Candidates for this study were patients with histologic proof of cancer in the pelvis (without distant metastases) who were scheduled to receive a continuous course of radiation therapy, either as definitive treatment or in an adjuvant setting. Patients had to enter the study before the third radiation therapy fraction was administered. Patients were required to have a planned daily radiation therapy dosage of 1.7 to 2.1 Gy and a planned total dosage of 45.0 to 53.5 Gy. The protocol required specification of the radiation dosage at the isocenter for plans using a posterior and two lateral fields and for plans using posterior, anterior, and lateral fields. Specification of the dosage at the midplane was required for plans using opposed anterior-posterior fields. The entire pelvis had to be included in the radiation therapy field. Patients treated concurrently with pelvic and para-aortic radiation therapy were eligible for the study. Planned boost therapy was allowed after completion of pelvic radiation therapy. The Mayo Clinic institutional review board approved this study. Written, informed consent was required for entry of any patient into this study.

Criteria for ineligibility included allergy to octreotide, inflammatory bowel disease, renal failure, grade 3 or higher diarrhea before study entry, Eastern Cooperative Oncology Group performance status of 3 or 4, planned concurrent radiation therapy and cytotoxic chemotherapy (other than with fluorouracil or cisplatin), planned brachytherapy before completion of external radiation therapy, lack of a functional rectum, and fecal incontinence. Women with childbearing potential were required to use effective contraception, and pregnant or nursing women were excluded from the study. Patients

with a history of cholecystitis were ineligible unless a cholecystectomy had been performed previously.

Randomization

The operations office of the NCCTG, in Rochester, MN, was the randomization center for this study. Prerandomization stratification factors included history of anterior resection of the rectum, total irradiation dosage, use of chemotherapy during radiation therapy, primary cancer site, the superior border of the radiation field, inclusion of the perineum in the radiation field, and whether intracavitary radiotherapy was planned (Table 1). Patients were randomly assigned in a double-blind fashion to receive octreotide or the placebo.

Treatment

On day 1 of therapy, patients received octreotide acetate (100 µg, administered subcutaneously) or a placebo injection. Patients were assessed on day 2. If patients had no signs of toxicity after the initial injection, they received depot octreotide (20 mg, administered intramuscularly) or a placebo injection. A second intramuscular injection of octreotide (20 mg) or placebo was administered on day 29; it was not administered if grade 3 or higher diarrhea, rectal bleeding, biliary toxicity, or abdominal cramps were observed because these findings were considered evidence of octreotide toxicity or failure of octreotide to prevent treatment-related toxicity. Measurement of study end points (described below) continued for patients who discontinued study medication.

Table 1. Baseline Characteristics

Characteristic	Octreotide (n = 62)		Placebo (n = 63)		P*
	No.	%	No.	%	
History of rectal surgery	1	2	11	17	.003
Primary cancer site					.02
Rectum	16	26	29	46	
Prostate	20	32	18	29	
Gynecologic	20	32	16	25	
Other	6	10	0	0	
Extent of cancer					.31
None	13	21	20	32	
Microscopic	12	19	8	13	
Gross	37	60	35	56	
Medication					
Cisplatin	10	16	7	11	.41
Leucovorin	4	6	6	10	.53
Fluorouracil					.15
None	43	69	33	52	
Bolus	2	3	4	6	
Continuous infusion†	17	27	26	41	
Superior border of the radiation field at or inferior to L4-5‡	58	94	61	97	.39
Cumulative radiation dosage, Gy					.90
45-53.5	40	65	43	68	
53.51-60	4	6	4	6	
> 60	18	29	16	25	
Brachytherapy planned after completion of radiotherapy§	12	19	13	21	.86

Abbreviation: L4-5, interspace between the fourth and fifth lumbar vertebrae.

*Exact Wilcoxon test.

†The number of patients treated with continuous infusion of fluorouracil was not significantly different in the 2 arms of the study ($P = .17$).

‡Para-aortic radiation was defined as a superior border for the radiation field above the L4-5 interspace.

§Information about the planned use of brachytherapy was not collected from 10 patients in each group because it initially was not a protocol-specified stratification factor.

At baseline and at weekly intervals while receiving radiation therapy, patients were evaluated by a radiation oncologist, a nurse, or a midlevel provider, at which time toxicity was assessed according to National Cancer Institute Common Toxicity Criteria, version 2.0.³² Any symptoms of biliary toxicity were reported as adverse events. Use of antidiarrheal medication and laxatives was documented. Patients also completed a bowel function questionnaire (online-only Appendix) at baseline and on a weekly basis throughout the course of radiation therapy and for 4 weeks after completion of radiation therapy. The bowel function questionnaire also was administered at 12 and 24 months after completion of radiation therapy. The questionnaire was derived from prior studies of the effect of radiation therapy on bowel function.^{1,2,33} This method of assessing patient-reported outcomes focused on determining whether symptoms were perceived as problematic by the patient. Included in the bowel function questionnaire was a Uniscale quality-of-life measure.³⁴ This single-item, linear, analog, self-assessment measure allowed patients to indicate their overall quality of life on an 11-point scale, with 10 being "as good as it can be" and 0 being "as bad as it can be." This measure was used successfully in other clinical trials,^{1,2} and normative data have been reported.³⁵

The primary end point of treatment efficacy was the highest grade of diarrhea incurred during radiation therapy. The incidence of rectal bleeding, abdominal cramps, tenesmus, and constipation measured during radiation therapy also was evaluated. Long-term bowel function (12 and 24 months after radiation therapy) will be the subject of a separate report. The number of bowel problems experienced by patients was assessed by summing the number of "yes" responses (indicating problems) for questions 1 through 9 on the bowel function questionnaire.

Statistical Analysis

Summary statistics were used to compare treatment arms. The Kruskal-Wallis and Fisher's exact tests were used, as appropriate, to compare baseline characteristics. The distribution of diarrhea severity between study arms, the average grade of long-term diarrhea and other toxicities, the average bowel function questionnaire score, and average Uniscale score during radiation therapy were compared using two-sided Wilcoxon rank sum tests. Incidence rates of toxicity, responses to the bowel function questionnaire, and use of antidiarrheal medications were analyzed using the Fisher's exact test. Correlation coefficients were calculated to compare the

Fig 1. Study flow diagram.

Uniscale score with the total bowel function questionnaire score and with scores for individual questions.

The study was designed for a Wilcoxon rank sum test and required 112 fully analyzable patients for 85% power to detect a 1-grade decrease in diarrhea severity between patient groups. The estimate for the expected incidence and severity of diarrhea was made on the basis of our experience with previous diarrhea prevention trials.¹⁻³ The accrual goal for the study was 125 patients, which allowed 10% of enrolled patients to ultimately be ineligible or not analyzable.

RESULTS

From May 10, 2002, through October 14, 2005, 130 patients were enrolled in the study (NCCTG policy allows actual patient accrual to slightly exceed the target accrual) and were randomly assigned in a double-blind fashion to receive treatment with a placebo or with depot octreotide. After assignment to treatment arms, five patients decided to not receive any protocol treatment with placebo or octreotide. These five were not included in the analysis. The remaining 125 patients constitute the subject of this report (Fig 1).

Baseline treatment characteristics are presented in Table 1. A significantly higher number of patients with a history of rectal surgery or primary rectal cancer were included in the placebo arm of the study. These imbalances potentially could cause more bowel problems for patients in the placebo group.^{5,36-39} Data regarding administration of the final dose of study medication (day 29) was available for all patients in the octreotide arm of the study and for all but one of the

Table 2. Effect of Octreotide on Gastrointestinal Symptoms

Symptom*	Octreotide (n = 62)		Placebo (n = 63)		P†
	No.	%	No.	%	
Diarrhea					.64
None	11	18	16	25	
Mild	19	31	20	32	
Moderate	19	31	14	22	
Severe	13	21	13	21	
Abdominal cramps					.053
None	20	32	32	51	
Mild	28	45	15	24	
Moderate	13	21	13	21	
Severe	1	2	3	5	
Rectal bleeding					.30
None	36	58	41	65	
Mild	24	39	22	35	
Moderate	2	3	0	0	
Tenesmus					.32
None	38	61	47	75	
Mild	15	24	12	19	
Moderate	6	10	2	3	
Severe	3	5	2	3	
Constipation					.16
None	41	66	52	83	
Mild	16	26	8	13	
Moderate	4	6	3	5	
Severe	1	2	0	0	

*Maximum grade of symptom is indicated. The terms "None," "Mild," "Moderate," and "Severe" correspond to grades 0, 1, 2, and 3 toxicity, respectively.

†Exact Wilcoxon test.

Fig 2. Mean diarrhea grade during pelvic radiation therapy. No significant differences were observed between patients treated with octreotide and patients treated with the placebo.

patients in the placebo arm. The day 29 dose of study medication was administered to 49 (79%) of 62 of patients in the placebo arm and 43 (69%) of 62 of patients in the octreotide arm ($P = .22$). The primary efficacy end points are summarized in Table 2. Octreotide did not appear to reduce the severity or incidence of diarrhea during pelvic radiation therapy. The average grade of diarrhea during pelvic radiation therapy was not reduced substantially at any point in time for patients treated with octreotide (Fig 2). Abdominal cramps were worse in patients on the octreotide arm of the study, but the difference did not achieve statistical significance ($P = .053$). Other measures of toxicity were similar for patients in the two arms of the study. No cases of biliary toxicity or development of gallstones were reported. Patient-reported measures of bowel function are presented in Table 3. Octreotide-treated patients reported significantly more problems with nocturnal bowel movements, clustering, and blood with bowel movements ($P < .05$ for all). Patients treated with octreotide reported an average of 5.2 problems with bowel function compared with an average of 4.2 problems for those treated with the placebo ($P = .03$). The median patient-reported quality of life (scale, 0 to 10) during the study was 7.8 for patients treated with octreotide and 7.7 for patients receiving the placebo ($P = .29$).

DISCUSSION

For this patient population, depot octreotide (dosage, 20 mg on day 1 and day 29 of pelvic radiation therapy) did not reduce the incidence or severity of diarrhea. Indeed, these findings suggest that some gastrointestinal symptoms may worsen with octreotide. This conclusion was not compromised by the higher number of patients with a history of rectal surgery in the placebo arm of the study. Such patients have greater risk for compromised bowel function and lower quality of life;^{37,39} this imbalance, if it had any effect, would tend to make patients in the octreotide study arm appear to have better bowel function. The imbalance does not, therefore, detract from the central message of a negative outcome. In this heterogeneous group of patients receiving pelvic radiation therapy, it is certainly possible that imbalances in other factors such as variation in the radiation fields or volume of small bowel irradiated could affect a patient's chance of having diarrhea. Although this study did not control for all possible factors, an imbalance in parameters that might have resulted in false conclusions about octreotide's effectiveness is unlikely in view of the double-blind, phase III study design.

The NCCTG now has evaluated four agents for the prevention of diarrhea during pelvic radiation therapy: olsalazine,³ sucralfate,² glutamine,¹ and octreotide (this study). In each case, no benefit was observed for patients receiving the agent under investigation. Indeed, for olsalazine, sucralfate, and octreotide, some gastrointestinal symptoms worsened for patients treated with the active medication. These studies show that pharmacologic agents should not be used (outside of a clinical trial) for the prevention of diarrhea during pelvic radiation therapy unless convincing evidence from phase III clinical trials support the intervention.

Several studies suggest that gallstone formation occurs in some patients undergoing long-term treatment with octreotide.²³⁻³¹ In this study, no patients had gallstone formation.

The reason for the negative result in this diarrhea prevention study is unclear. We note that our results do not contradict those of Yavuz and colleagues,²² who showed that octreotide was effective for the treatment of radiation-induced diarrhea. Prevention studies and treatment studies inherently study different patient populations.

Because octreotide is effective for treatment of diarrhea across a broad range of clinical settings,⁶⁻¹⁹ we hypothesized that octreotide

Table 3. Patient-Reported Symptoms

Symptom	Octreotide (n = 61)*		Placebo (n = 62)*		P†
	No.	%	No.	%	
Nocturnal bowel movements	43	70	28	45	.004
Incontinence	29	48	22	35	.17
Multiple bowel movements within 30 min ("clustering" [33])	55	90	43	69	.004
Use of protective clothing or pad	10	16	10	16	.97
Inability to distinguish gas from stool	44	72	38	61	.20
Liquid stools	39	64	39	63	.91
Inability to delay bowel movement	50	82	50	81	.85
Cramping with bowel movements	45	74	37	60	.10
Blood in bowel movements	35	57	22	35	.01

*Data were not received from two patients, one from each arm of the study.

† χ^2 test.

would be effective for prevention of diarrhea during pelvic radiation therapy in an otherwise heterogeneous group of patients. Octreotide did not prevent diarrhea in this population. This study does not exclude the possibility, however, that octreotide might benefit a more homogeneous group of patients. The recently published results of a study by the Radiation Therapy Oncology Group (RTOG) are of interest in this regard. The RTOG study examined use of depot octreotide for diarrhea prevention in patients with rectal and anal cancer receiving pelvic radiation therapy and chemotherapy.⁴⁰ Patients received a somewhat higher dose of depot octreotide (30 mg, administered intramuscularly) 4 to 7 days before the start of radiation therapy and on day 22 of radiation therapy. No significant reduction in diarrhea was observed in octreotide-treated patients. Taken together, findings from the RTOG study and this study provide strong evidence that depot octreotide is not effective for prevention of diarrhea during pelvic radiation therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).