Phase III Evaluation of Octreotide versus Chemotherapy with 5-Fluorouracil or 5-Fluorouracil Plus Leucovorin in Advanced Exocrine Pancreatic Cancer: A North Central Cancer Treatment Group Study

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ABSTRACT

There continues to be a need for new systemic approaches for the treatment of advanced pancreatic cancer. The purpose of this study was to compare the antitumor activity of the somatostatin analogue octreotide to 5-fluorouracil chemotherapy in a Phase III setting. Eighty-four patients with an Eastern Cooperative Oncology Group performance status of 0 or 1 and limited tumor volume were randomized to receive octreotide 200 µg three times daily or 5-fluorouracil with or without leucovorin. After the first 12 patients had been randomized to octreotide, we increased the dose in the remaining patients to 500 µg three times daily. This change was based on early reports in other studies, suggesting that our original dose may not have been effective and that higher doses of octreotide were well tolerated. A planned interim analysis performed after 84 patients were enrolled demonstrated inferior time to progression and survival for the patients randomized to octreotide. Further accrual to the octreotide arm of this protocol was therefore terminated. Octreotide in doses of 200–500 µg three times daily does not delay progression or extend survival in patients with advanced pancreatic cancer compared with treatment with 5-fluorouracil with or without leucovorin.

INTRODUCTION

Adenocarcinoma of the pancreas is the second most common gastrointestinal malignancy, with 28,600 new cases predicted to occur in the United States in 1999 (1). Nearly all patients develop metastatic disease and may become candidates for systemic treatment.

Unfortunately, the efficacy of chemotherapy have been poor. Most Phase II studies have not produced response rates reliably above 20%. Median survival typically is in the 3- to 5-month range (2, 3). Combination chemotherapy has not been proven to be superior to FU alone (4, 5). More recently, clinical response and survival have been improved modestly with the introduction of gemcitabine (3). Clearly, there is a continued need for more effective treatment in this disease.

Somatostatin is a naturally occurring tetradecapeptide originally isolated from the hypothalamus (6). Its name is derived from its ability to inhibit the release of pituitary growth hormone, but it is known to inhibit the secretion of many hormones and neurotransmitters (6). The somatostatin analogue octreotide is a synthetic octapeptide that exhibits a pharmacological effect similar to that of native somatostatin but possesses a much longer duration of action (7).

Octreotide, RC-160, and somatuline are the primary somatostatin analogues that have undergone testing for oncological applications. There is evidence that these analogues suppress the growth of both endocrine and nonendocrine tumors. In 1983, Redding and Schally (8) demonstrated growth inhibition of the SWARM chondrosarcoma in Sprague Dawley rats after injection of somatostatin analogues. Reubi (9) independently re-
ported similar findings in his studies with the same tumor using octreotide. Subsequently, a number of investigators reported that somatostatin analogues inhibit cell growth of a number of tumor models including small cell lung (NCI-H69), breast (MCF-7, MTX), colon (HA/K121), and glioblastoma (U-87, U-373) (10–14). Finally, a variety of pancreatic cancer cell lines have exhibited sensitivity to these agents (15–22).

Somatostatin analogues may suppress tumor growth in carcinoma of the exocrine pancreas through a variety of actions. In vitro studies have suggested that various gastrointestinal hormones that are suppressed by somatostatin such as cholecystokinin, secretin, and gastrin may stimulate growth of pancreatic adenocarcinoma cancer cells (23). A direct inhibitory effect on pancreatic cell growth is likely to be mediated through cellular SSTRs. Five such receptors have been characterized (SSTR-1 to SSTR-5) (23, 24). Native somatostatin binds to all five subtypes similarly, but different somatostatin analogues vary in their affinity for these receptors (24). The somatostatin analogues RC-160 and octreotide inhibit the proliferation of cells expressing SSTR-2 through stimulation of tyrosine phosphatase (25). Somatostatin analogues may also work indirectly in tumors that do not possess somatostatin receptors by suppression of growth factors such as epidermal growth factor and insulin-like growth factor 9, 23, 24). Finally, inhibition of angiogenesis has been reported with these agents (26).

There has been extensive experience with octreotide therapy in gastrointestinal neuroendocrine carcinomas (27, 28). Not only have the endocrine symptoms associated with these neoplasms been well palliated with this therapy but also objective tumor responses have been seen (27, 28). Toxicity has been remarkably low at therapeutically effective doses. These reactions consist primarily of mild and transient discomfort at the site of injection, infrequent nausea and vomiting, transient elevations of blood sugar levels, steatorrhea which is seldom significantly symptomatic, and rare development of cholelithiasis (29). Given the above laboratory and clinical data coupled with the need for new agents in advanced pancreatic cancer, we designed a study to test the value of a somatostatin analogue in advanced pancreatic cancer.

We believed the best way to evaluate a potentially cytostatic-like somatostatin analogue for this disease was in a controlled study with a primary end point of overall survival. We therefore designed a randomized Phase III clinical trial comparing octreotide to chemotherapy with FU with or without leucovorin in a select group of patients with small volume metastatic disease and good performance status. We purposely did not collect data on tumor response in this study given the inability of tumor response to predict enhanced survival in Phase III trials of advanced pancreatic carcinoma. For pancreatic carcinoma, we believed that survival was a more appropriate end point than tumor response. A secondary goal was to determine the survival benefit of biochemical modulation of FU with leucovorin compared with FU alone. This report addresses the primary goal of this study.

**PATIENTS AND METHODS**

**Eligibility and Stratification.** Patients were required to have histological or cytological proof of locally unresectable, residual, recurrent, or metastatic ductal adenocarcinoma of the pancreas, with no hope of surgical cure. All patients were required to have an Eastern Cooperative Oncology Group performance status of 0–1 and to be maintaining an oral intake of at least 1200 calories daily before randomization. Radiotherapy to the primary pancreatic lesion >4 weeks before to study entry was allowed provided there had been convincing evidence of progressive disease. Hematological parameters included a leukocyte count >3600 cells/mm$^3$ and platelet count >100,000/mm$^3$.

Before randomization, all patients underwent a history and physical examination, an evaluation of tumor status, and chest radiograph. Baseline chemistries (bilirubin, aspartate aminotransferase, alkaline phosphatase, calcium, creatinine, glucose) and total thyroxine were obtained. Women of childbearing age were required to have a negative pregnancy test. After signing informed consent, patients were randomized using an imbalanced design with one-half of the patients assigned to octreotide, one-fourth to FU alone, and one-fourth to FU plus leucovorin. Randomization was stratified by site of metastatic disease (abdominal only, abdominal with liver involvement, or extraabdominal) and by the presence or absence of measurable disease.

**Treatment Protocol.** The first 12 patients on the octreotide arm were treated at a dose of 200 μg by s.c. injection three times daily. We then became aware of the results of a small trial where patients with advanced pancreatic cancer had shown no discernible benefit with the use of octreotide at this dose (30). Data also became available that octreotide could be given in doses as high as 2000 μg three times daily with acceptable toxicity and evidence of tumor regressions in patients with carcinoid tumors (28). We therefore escalated the dose of octreotide in the remaining patients to 500 μg three times daily. Higher doses than 500 μg would have required multiple injections per dose or s.c. infusions. Patients on the chemotherapy arms received either FU 500 mg/m$^2$ by i.v. bolus injection for 5 consecutive days or FU 425 mg/m$^2$ plus leucovorin 20 mg/m$^2$ daily for 5 consecutive days. Chemotherapy cycles were repeated every 5 weeks.

**Evaluation of Progression.** Patients were evaluated every 5 weeks. Patients were cored at each evaluation as either "stable" or "progression." For patients with nonmeasurable disease, progression was declared if any of the following occurred: appearance of new areas of disease; a decrease of >1 level on the Eastern Cooperative Oncology Group performance scale; the development of new jaundice or ascites; or definite increase in areas of previously existing disease. For patients with measurable disease, progression was declared according to the criteria above or when there was a >25% increase in measurements of indicator lesions.

**Statistical Methods.** The primary efficacy analysis consisted of a comparison of octreotide to the combination of the two chemotherapy arms. The trial was designed to enroll 160 patients to provide 95% power to detect a 50% reduction in the hazard rate of death for patients randomized to the octreotide arm using a 2-sided logrank test at significance level 0.05. An interim analysis was specified after 30 deaths had occurred in 1 of the 2 treatment groups. If at the time of the interim analysis the $P$ from a one-sided logrank test for overall survival for the
superiority of the octreotide regimen exceeded 0.50, accrual to the octreotide arm would be discontinued (31).

Comparisons of octreotide to FU-based chemotherapy are based on only patients who were randomized while the octreotide arm was open. Comparisons between FU and FU plus leucovorin are based on patients randomized at any time during the study. Toxicity figures include all eligible patients randomized to each arm.

Survival curves were generated using the Kaplan-Meier method (32). Survival and time to progression distributions were compared by the logrank test (33). The Cox proportional hazards model was used to adjust for covariates in multivariate analyses (34). All P values reported are two-sided, and P < 0.05 is used for statistical significance.

RESULTS

Patient Characteristics. During the initial phase of the study, 42 patients were randomized to the octreotide arm, 22 to FU, and 22 to FU plus leucovorin. Patients who progressed after assignment to octreotide were offered a second randomization to one of the two chemotherapy arms. Nineteen (45%) patients were rerandomized, 10 to FU and 9 to FU plus leucovorin. After termination of the octreotide arm, an additional 10 patients were randomized, 5 to FU alone and 5 to FU plus leucovorin.

The patient characteristics are shown in Table 1. Two randomized patients were declared ineligible, one patient on the octreotide arm due to insufficient time from surgery to randomization and one patient on the FU arm due to primary bile duct cancer instead of pancreatic cancer. All 84 eligible patients are evaluable for study endpoints. The patient groups were evenly distributed with respect to sites of metastatic disease and the presence or absence of measurable disease. Of the 84 patients, 81 developed progressive disease and died. Three patients died before disease progression. Two of these deaths were due to treatment-related toxicity and the other from a stroke at day 101 with stable disease.

Survival and Progression. At the time of the first interim analysis the P from the one-sided log-rank test for overall survival in favor of the octreotide arm was >0.50; therefore, accrual to the octreotide arm was terminated. All patients have now died. Based on the complete data, overall survival was not significantly different between the two arms [P = 0.80 (Fig. 1)]. There was a significant difference in time to progression between the two groups. The median time to progression for the octreotide arm was 42 days, compared with 105 days for the combined chemotherapy arms [P = 0.01, Fig. 2]. In a multivariate analysis for time to progression adjusting for age, sex, and the stratification factors, site of metastatic disease (P = 0.003) and age (P = 0.004) were significant prognostic factors in addition to treatment group (P = 0.002), whereas only the site of metastatic disease was an independent predictor of survival. Patients with abdominal only disease had improved time to progression and survival over those with liver involvement or extraabdominal disease.

To justify the primary efficacy analysis, we compared overall survival and time to progression between the two oct-

![Fig. 1 Overall survival:octreotide versus chemotherapy.](image-url)
reotide dose levels. There was no significant difference in the outcome for the two dose levels of octreotide ($P = 0.54$ for time to progression and $P = 0.29$ for survival). In addition, we compared these two outcomes between the two chemotherapy arms. There was no significant difference with respect to time to progression ($P = 0.38$) or survival ($P = 0.08$) between the two chemotherapy arms.

**Toxicity.** Frequently occurring toxicities are shown in Table 2. These toxicities were generally predictable and manageable. The most common adverse events for patients treated with octreotide were nausea, vomiting, and diarrhea; only four $\geq$grade 3 (National Cancer Institute Common Toxicity Criteria) toxicities occurred on this arm. The occurrence of toxicity was greater for patients randomized to the chemotherapy arms and did not differ between FU and FU plus leucovorin. The most common severe toxicities ($\geq$grade 3) included diarrhea (16%), nausea (14%), stomatitis (14%), and leukopenia (25%). Toxicity of patients on chemotherapy after crossover from octreotide was similar to that of those initially assigned to a chemotherapy arm. There were two deaths due to treatment-related toxicity, both on FU plus leucovorin. One patient died of diabetic ketoacidosis and ventricular tachycardia, and the other died due to respiratory arrest.

**DISCUSSION**

In this trial, we studied the antiproliferative potential of the somatostatin analogue octreotide in a cohort of patients with advanced pancreatic cancer who had both a good performance status and small tumor burden. We purposely focused on the end points of time to progression and survival and did not attempt to assess tumor response rates. This was accomplished with the use of a Phase III design with FU chemotherapy as a control. At the time our trial was initiated, FU represented a reasonable standard of care for the treatment of advanced pancreatic cancer.

Unfortunately, the therapeutic results of our study were disappointing. The patients who were treated with octreotide fared worse with significantly shorter time to progression than those treated with a cytotoxic agent which at best has modest activity in advanced pancreatic cancer. The survival did not differ between the two treatment groups, but this may be due to crossover to FU-based chemotherapy at the time of disease progression on octreotide.

At least seven Phase II trials have been conducted with somatostatin analogues in patients with advanced pancreatic cancer (35–39). Table 3 details the results of these studies. All but 1 have included <25 patients. Rare tumor responses have been recorded, and median survival times are similar (range, 8.6–25.7 weeks) to the current study. The addition of a luteinizing hormone-releasing hormone agonist to octreotide does not appear to improve these results (40–42). However, Rosenberg et al. (42) reported a small study of 12 patients who enjoyed a median survival of 1 year with the use of tamoxifen in combination with octreotide. A historical control group had a median survival of only 3 months. Although the survival of the patients receiving tamoxifen and octreotide is intriguing, the number of patients was small, it was not a prospective randomized trial, and the extent of disease is not stated. As shown by our data, the extent of disease has significant bearing on the outcome of treatment.

Three randomized Phase III studies have been reported comparing somatostatin analogues alone versus an untreated control group (Table 4). In the report by Cascinu et al. (43) there was a suggestion of benefit to the use of octreotide, but larger studies by Pederzoli et al. (44) and a preliminary reporting by
Table 3  Phase II studies of somatostatin analogues in pancreatic cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Response rate (%)</th>
<th>Median survival (wk)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide (100–200 µg tid)</td>
<td>22</td>
<td>0</td>
<td>17.1</td>
<td>Ebert et al. (35)</td>
</tr>
<tr>
<td>Octreotide (200 µg tid)</td>
<td>14</td>
<td>0</td>
<td>8.6</td>
<td>Klijn et al. (36)</td>
</tr>
<tr>
<td>Octreotide (2000 µg tid)</td>
<td>10</td>
<td>0</td>
<td>25.7</td>
<td>Ebert et al. (35)</td>
</tr>
<tr>
<td>Octreotide (6000 µg/day)</td>
<td>49</td>
<td>2</td>
<td>25.3</td>
<td>Buchler et al. (37)</td>
</tr>
<tr>
<td>RC-160 (500 µg tid)</td>
<td>21</td>
<td>0</td>
<td>17.9</td>
<td>Poston (38)</td>
</tr>
<tr>
<td>RC-160 (2000 µg tid)</td>
<td>14</td>
<td>0</td>
<td>25.7</td>
<td>Poston (38)</td>
</tr>
<tr>
<td>BIM 23014 (250–1000 µg/day)</td>
<td>19</td>
<td>6.5</td>
<td>12.9</td>
<td>Canobbio et al. (39)</td>
</tr>
<tr>
<td>Octreotide (150–500 µg tid) + goserelin (3.8 mg/mo)</td>
<td>14</td>
<td>7</td>
<td>25.7</td>
<td>Fazeny et al. (40)</td>
</tr>
<tr>
<td>Octreotide (100 µg tid) + leuprolide (1 mg/day)</td>
<td>21</td>
<td>0</td>
<td>16.4</td>
<td>Suri et al. (41)</td>
</tr>
<tr>
<td>Octreotide (100 µg tid) + tamoxifen (20 mg/day)</td>
<td>12</td>
<td>NS</td>
<td>52</td>
<td>Rosenberg et al. (42)</td>
</tr>
</tbody>
</table>

* tid, three times per day; NS, not significant.

Table 4  Randomized studies of somatostatin analogues in advanced pancreatic cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Response rate (%)</th>
<th>Median survival (wk)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide (LAR) vs. Placebo</td>
<td>93</td>
<td>0</td>
<td>16.0</td>
<td>Pederzoli et al. (44)</td>
</tr>
<tr>
<td>Placebo</td>
<td>92</td>
<td>0</td>
<td>16.9</td>
<td></td>
</tr>
<tr>
<td>Octreotide (LAR) + FU vs. Placebo + FU</td>
<td>284</td>
<td>1 pt.</td>
<td>22.6</td>
<td>Roy et al. (46)</td>
</tr>
<tr>
<td>Placebo + FU</td>
<td>1</td>
<td>1 pt.</td>
<td>21.6</td>
<td></td>
</tr>
<tr>
<td>Octreotide vs. Control</td>
<td>16</td>
<td>0</td>
<td>15.5*</td>
<td>Cascini et al. (43)</td>
</tr>
<tr>
<td>Control</td>
<td>16</td>
<td>0</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>BIM 23014 vs. Control</td>
<td>43</td>
<td>0</td>
<td>16.3</td>
<td>Huguier et al. (45)</td>
</tr>
<tr>
<td>Decapeptyl R vs. BIM 23014 + Decapeptyl R vs. Control</td>
<td>39</td>
<td>0</td>
<td>23.6</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>43</td>
<td>0</td>
<td>18.4</td>
<td></td>
</tr>
<tr>
<td>Octreotide (200–500 tid) vs. FU ± leucovorin</td>
<td>41</td>
<td>NS</td>
<td>13.4</td>
<td>Current</td>
</tr>
<tr>
<td>FU ± leucovorin</td>
<td>43</td>
<td>NS</td>
<td>27.9</td>
<td></td>
</tr>
</tbody>
</table>

* Estimated from survival curves.

Huguier et al. (45) failed to show any improvement compared with a control group. In our study, octreotide was inferior to chemotherapy. Finally, octreotide plus FU does not offer any improvement compared with FU alone as reported by Roy et al. (46).

There may be several reasons why our clinical results using octreotide were negative. Dose may be a factor in clinical results seen to date. The results in the studies in which 6000 µg/day octreotide or RC-160 were used do tend to show a better median survival than in our study; however, randomized prospective studies of that dose have not been reported (35, 37, 38). In addition, the positive effect of somatostatin in many of the animal studies used doses much higher than those used clinically (47).

Growth factor inhibition has been one proposed mechanism for tumor suppression by somatostatin analogues. Klijn et al. (36) assayed somatomedin C levels in their patients and demonstrated some reduction in serum levels with the initiation of somatostatin treatment, but levels quickly returned to baseline despite continued drug administration. Similarly, Fisher et al. (47) have shown in their animal studies that plasma levels of epidemal growth factor and insulin-like growth factor were not altered by ongoing octreotide treatment.

Recent laboratory investigations provide more insight into the failure of somatostatin analogues to improve results in the treatment of advanced pancreatic cancer. Gillespie et al. (48) reported that the growth of two human pancreatic cancer cell lines was not altered by RC-160 but that a rat pancreatic cancer cell line was. The two human pancreatic lines did not express somatostatin receptors whereas the rat cell line did, suggesting somatostatin receptor expression is important for somatostatin analogues to exert their antitumor effect. Fisher et al. (47) examined the effect of octreotide on five human pancreatic cancer cell lines in nude mice. Growth inhibition was seen in only one of the cell lines, MIA PaCa-2, which was the only one of the five lines that expressed SSTR-2 receptors. Interestingly, the gene for SSTR-2 was detected in all five tumor lines. Reubi et al. (49) were unable to detect somatostatin cellular receptors in the specimens of 12 human pancreatic tumors. Fisher et al. (50) have extended their studies to include more human pancreatic cell lines as well as 11 tumor specimens. mRNA for SSTR-1, -2, and -5 was seen in most of the tumors and cell lines. No mRNA was detected for SSTR-3 or -4. As seen in their earlier studies, only the MIA PaCa-2 cells expressed surface cellular somatostatin receptors. It appears that lack of expression of specific functional somatostatin cell surface receptors may be the best explanation for the lack of therapeutic impact of the somatostatin analogues in advanced pancreatic cancer.

In summary, our study fails to show any advantage to the use of single agent octreotide in advanced pancreatic cancer. In is unclear whether there is a future role for the use of somatostatin analogues in this disease. The study of tamoxifen and octreotide by Rosenberg et al. (42) is intriguing but needs to be confirmed. Cytotoxic analogues of somatostatin containing...
doxorubicin is one other area under current investigation (51). Finally, transfection of cells with SSTR-2 receptors may offer a gene therapeutic approach in the future (52).

REFERENCES

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