Original article

Treatment of advanced pancreatic carcinoma with a combination of protracted infusional 5-fluorouracil and weekly carboplatin: A Mid-Atlantic Oncology Program study


Summary

Background: Advanced pancreatic cancer is a rapidly fatal disease whose course has been little influenced by chemotherapy. Earlier studies have shown some modest promise for the combination of protracted infusional 5-fluorouracil (PIF) and cisplatin. We sought to evaluate a regimen of possibly lesser toxicity, PIF plus weekly carboplatin.

Patients and methods: Fifty-four patients with advanced adenocarcinoma of the pancreas were treated with a regimen of protracted infusional fluorouracil 300 mg/m²/day for 70 days and carboplatin 100 mg/m²/weekly on weeks 1 through 10 of a 12-week cycle. After a two-week rest, cycles were repeated until progression.

Results: Median duration on treatment was 82 days (range 4-490 days). Toxicity was mild. Grade 3-4 toxicities were anemia 11%, leukopenia 6%, thrombocytopenia 2%, nausea/vomiting 7%, diarrhea 9%, mucositis 9%, and renal 2%. Response was evaluable in 47 patients. There were two complete and seven partial responses (17% overall objective response rate among all patients). Stable disease for greater than 12 weeks was seen in 19 patients (40%) and progression in 19 (40%). The median overall survival was 22 weeks (1-99), with 61 weeks median survival in responders (22-99). One-year survival was 13%.

Conclusions: Response and survival results with this regimen are at least equal to the best combination regimens reported, and were obtained with a low overall rate of serious toxicity.

Key words: carboplatin, fluorouracil, pancreatic carcinoma, response, survival, toxicity

Introduction

Adenocarcinoma of the pancreas is currently the fourth most common cause of cancer related death in the United States, with 28,100 deaths expected in 1997 [1]. Worldwide new cases in 1985 were estimated at 185,100 [2]. At presentation only 10%-15% of patients have lesions suitable for potentially curative resections, and the five-year survival even for this selected group is only of the order of 10% [3]. Overall five-year survival is less than 2%. Once metastatic, the median survival with pancreatic cancer is only 3-4 months [4], a figure which is not significantly influenced by therapy.

Combination chemotherapy in pancreatic carcinoma has produced mixed results in small trials, but larger cooperative group trials have generally produced dismal results [5]. Two of the most widely used chemotherapy combinations, FAM and SMF, produced 30%-40% response rates in small single-institution trials [6-9], but a larger CALGB trial of FAM produced only a 9% response rate among 56 patients [10], and in two large randomized comparisons performed by the Gastrointestinal Tumor Study Group (GITSG) and the Cancer and Acute Leukemia Group B (CALGB), neither regimen produced a response rate as high as 15% [11, 12].

In all of the combination treatments described above, responses were of relatively short duration, with median response durations in the 6-10 month range. Median survival in patients with metastatic disease has been rather uniformly about 3-4 months, with only about 10% of patients surviving as long as one year. The body of evidence suggests that combination chemotherapy results in some improvement in response rate over single agents in pancreatic cancer, just as in other more responsive tumors. However, combination therapy results have thus far had essentially no impact on the natural course of the disease.

The use of protracted infusional 5-fluorouracil (5-FU) has been demonstrated to be well tolerated and to significantly enhance the therapeutic efficacy of this drug in colorectal cancer [13]. Synergy of 5-FU and cisplatin has been suggested by the efficacy of this combination in head and neck cancer [14, 15] and may be related to a cisplatin-induced increase in the intracellular level of methylenetetrahydrofolate [16]. Even in colorectal cancer, where cisplatin is not recognized to have significant
single agent activity, in vitro assays have shown synergy under some conditions [17], suggesting a pharmacomodulatory effect. Although single-agent data on cisplatin in pancreatic cancer are not available, it has been used in combination therapy [18, 19] and appears to have some activity.

The Mid-Atlantic Oncology Program (MAOP) has recently conducted studies of 5-FU by protracted infusion in combination with low-dose weekly cisplatin (20 mg/m²/week) in colorectal cancer [20] and pancreatic cancer [21]. In the pancreatic trial, 56 patients with metastatic disease were treated. The response rate was 18 percent; median survival was 5.6 months with a 25% one-year survival. Grade 3 or higher toxicity occurred in 44% (4% life threatening) and included diarrhea (13%), anemia (11%), nausea/vomiting (9%), mucositis (7%), leucopenia (2%), and other (13%). We were encouraged by the relatively high one-year survival, but wished to further reduce toxicity, considering the purely palliative nature of chemotherapy in advanced pancreatic cancer. MAOP therefore undertook a study of protracted infusional 5-FU combined with carboplatin in this disease.

Patients and methods

Patients

Fifty-four patients were treated on this trial. All had biopsy proven adenocarcinoma of the pancreas without prior chemotherapy. All were either metastatic (89%) or had disease too extensive for palliative radiation therapy (greater than a 400 cm² radiation port). Disease had to be measurable in two dimensions. The most frequent metastatic site was the liver (76%), and hepatic lesions required quantitation by abdominal scanning; physical measurement of hepatomegaly was not allowed. Patients were required to have a Zubrod (ECOG) perfor-

Treatment

After implantation of either a permanent venous access device or tunneled subclavian catheter, 5-FU was administered as a continuous intravenous infusion at a rate of 300 mg/m²/week by means of a battery operated ambulatory infusion pump. Although anticoagulants were not required, they were allowed in those patients deemed to be at high risk for thrombosis and generally consisted of a low-dose coumadin regimen or low-dose heparin admixed with the 5-FU. Toxicities were graded according to the standard intergroup criteria [22]. For grade 3 or greater toxicity, the infusion was interrupted until resolution of the toxicity and then restarted at 250 mg/m²/week. If further toxicity occurred, the same procedure was followed with re-initiation of the infusion with a 50 mg/m²/week reduction of the rate following each such interruption. There were 10 weeks of therapy per cycle, and cycles were repeated every 12 weeks. Weeks lost due to treatment interruptions were not made up.

Carboplatin was administered by rapid intravenous infusion (15 minutes) on the first day of weeks 1–10 at a dose of 100 mg/m². If on the day of scheduled carboplatin the WBC count was less than 3500/µl or the platelet count less than 125,000/µl, the carboplatin dose was reduced by 50%. For a WBC of less than 2500/µl or platelet count of less than 75,000/µl, carboplatin (but not 5-FU) was interrupted for one week or until the hematologic abnormalities resolved. Carboplatin was to be held for a creatinine greater than 25% above the baseline value unless the creatinine clearance was greater than 60 ml/min. Carboplatin was to be discontinued if symptomatic peripheral neuropathy or unacceptable hearing loss occurred. If the development of late nausea or vomiting (greater than 12 hours after carboplatin administration) or of severe and extended anorexia interfering with the ability to tolerate protocol therapy, the dose of carboplatin was to be reduced by 25%.

Chlorhexadane mouthwash three times per day was given as prophylaxis for mucositis and pyridoxine 150 mg three times daily was used as prophylaxis for the hand-foot syndrome [23-25]. Antiemetic regimens were at the discretion of the individual investigators.

Evaluation

Before entry into the study, all patients underwent an evaluation consisting of a history and physical examination, tumor measure-
ments, performance status assessment, chest radiograph, abdominal imaging (CT or MRI), complete blood count (CBC), and blood chemistries. A 24-hour urine collection was obtained for creatinine clearance if the serum creatinine level was greater than 1.5 mg/dl.

Patients were observed during physician visits on each of the 10 weeks on treatment with history and physical examination; particular attention was paid to toxicity. Imaging as required for indicator lesion measurement was performed at weeks 6 and 11 of the first cycle and then at 12-week intervals thereafter, during each two-week treatment interruption. Before each dose of carboplatin, a CBC and serum creatinine level were obtained. Treatment continued until disease pro-
gression was documented; all patients were observed until death.

Response criteria

Patients were evaluated during the 6th and 12th weeks of cycle one and at 12-week intervals thereafter. Standard response criteria were used. To qualify as a response, lesion cross-sectional area had to be quanti-

Statistical methods

Objective response and survival were the primary endpoints of this study. Standard statistical measures and procedures were used. De-
scriptive statistics were used to test results including patient char-
acteristics, demographic and background characteristics, treatment characteristics, tumor response, survival experience, and treatment-related toxicities. Nominal variables (sex, metastatic site or ordinal variables [PS or tumor response]) were presented as the number and percent of patients in each category. Continuous variables (age and leucocyte count) were summarized in terms of standard measures of location (mean, median) and scale (standard error, range). Tumor response was summarized by presenting the number and percent in each category. Confidence intervals for the tumor response
rate were constructed based on the exact binomial distribution. Duration of tumor response was calculated for the number of days between the initial PR or CR and the date progression occurred or the last available tumor measurement. Time to tumor response was the number of days between registration and initial PR or CR. Overall survival was calculated as the number of days from the date treatment first started until death or until the patient was last known to be alive. In the latter case, the survival time was censored and all that was known was that the patients survived for at least that amount of time. Survival curves for evaluating median survival were generated by product limit methods and a confidence interval for the median was constructed based on Greenwood's formula using the estimated standard error. These same methods were used to describe the time to disease progression. Time to progression was taken as the number of days from the start of treatment until disease progression was noted; if no progression was noted, then the time to progression was censored. Treatment related toxicities were defined as the most deleterious toxicity grade observed for each patient while they were on treatment for each of the hematologic, mucositis, and other toxicity categories. Toxicity grades were quantified as none, mild (grade 1), moderate (grade 2), severe (grade 3), life threatening (grade 4), and lethal (grade 5). Toxicity was summarized by presenting the number and percent of patients in each category.

Results

Fifty-four patients were treated under this protocol during the period June 1989 to April 1992. Sixteen centers participated. Patient characteristics are summarized in Table 1. Forty-eight percent of the patients were men, with racial distribution (76% white) roughly paralleling the US population. The ages of the patients ranged from 35–83 years with a median age of 62 years. Most patients had an excellent PS: 86% had a PS of 0 (asymptomatic) or 1 (fully functional) and 14% had a PS of 2 (bedridden less than 50% of the time). Eighty-nine percent of patients had distant metastatic disease. At the time of analysis, 91% of the patients were dead, 7% alive, and one patient was lost to follow-up.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>54</th>
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<tbody>
<tr>
<td>Age</td>
<td>62</td>
</tr>
<tr>
<td>Range</td>
<td>35/83</td>
</tr>
<tr>
<td>Sex</td>
<td>26 (48%)</td>
</tr>
<tr>
<td>Male</td>
<td>28 (52%)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (22%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Sites of metastatic disease</td>
<td>41 (76%)</td>
</tr>
<tr>
<td>Liver</td>
<td>13 (24%)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>7 (13%)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Adrenal</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Distribution by number of sites</td>
<td>27 (50%)</td>
</tr>
<tr>
<td>One site</td>
<td>15 (28%)</td>
</tr>
<tr>
<td>Three or more sites</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>No metastatic disease</td>
<td>6 (11%)</td>
</tr>
</tbody>
</table>

Response

Forty-seven patients were evaluable for response. Seven patients were not evaluable for the following reasons: patient decision to discontinue treatment before week 6 with no on-treatment tumor measurements (5), early death unrelated to malignancy or treatment (2). Two patients (4%) achieved a CR (one documented as a complete pathologic response at incidental second look surgery). Seven patients (15%) achieved a PR. Considering the full cohort of 54 enrolled patients (intent to treat analysis) the overall objective response rate was 17% (9/54, 95% confidence interval (95% CI), 8%–29%). If the inevaluable patients were excluded, the overall response would be 19% (9/47, 95% CI, 9%–35%). Nineteen patients (40%) progressed in 12 weeks or less. The remaining 19 patients (40%) remained stable for a period of 12 weeks or more.

Survival and time to disease progression

The median survival for all 54 patients was 22 weeks (61 weeks in responders, 21 weeks in non-responders, Figure 1). One of the CR's had a survival of 99 weeks. The other was still surviving at 53 weeks. The median time to progression in all patients was 12 weeks. Thirteen percent of patients survived one year or longer.

Toxicity

Treatment-related toxicities are summarized in Table 2. Toxicity was generally mild, with only three patients (6%) experiencing grade 4 toxicity, and no treatment-related deaths. Anemia was the most common side effect, occurring to some degree in 76% of those treated. However, the majority of those affected had only mild to moderate anemia without symptoms and did not require therapy. Grade 3 anemia was seen in 4 patients (7%) and grade 4 anemia in 2 (4%). Leukopenia was the second most common toxic effect and occurred in 50% of those
treated. However, only 6% had grade 3 leukopenia and none had grade 4. Thrombocytopenia occurred in 46% of those treated and reached grade 4 in one patient (2%). The well-recognized toxicities associated with protracted infusion of 5-FU – mucositis, diarrhea and hand-foot syndrome – were seen in 48%, 31% and 15% respectively, and reached grade 3 or higher in 9%, 9% and 0%. Renal insufficiency and neurotoxicity were rare, with only one instance (2%) of grade 3 renal toxicity and none of grade 3 neurotoxicity.

Discussion

Although many chemotherapeutic maneuvers have been investigated in carcinoma of the pancreas, most trials have failed to demonstrate any significant impact of chemotherapy on survival in this disease. In one possible exception, Glimelius et al. randomized 90 patients with pancreatic or biliary cancer to receive either supportive care alone or supportive care plus chemotherapy. A significant survival advantage (6 vs. 2.5 months, \( P < 0.01 \)) was seen in the chemotherapy arm [26]. Quality of life was also better in the chemotherapy group. However, analysis was based upon intention to treat; patients randomized to supportive care were allowed to receive chemotherapy (on request or for symptoms) and 8 of the 43 patients in the supportive care group actually received chemotherapy. Also, radiotherapy was allowed in both arms and was given earlier in the supportive care group. The only other trial showing impact of chemotherapy on survival is the recent phase III trial of gemcitabine vs. bolus 5-FU, where the gemcitabine arm showed a survival advantage (5.7 vs. 4.2 months) [27]. However, until confirmatory results are available, the primary objective of chemotherapy in pancreatic cancer must be considered to be palliation of symptoms [5].

In four publications of the GITSG, testing 14 different regimens in more than 450 patients, response rates of 0%–15% were seen, with median survival ranging from 6 to 18 weeks [11, 28–30]. In two large scale studies of the Mayo Clinic and the North Central Cancer Treatment Group (NCCTG), testing 5 chemotherapy regimens and involving 333 patients, survival was the primary endpoint, with median survival times ranging from 14 to 22 weeks [19, 31]. One speculation is that the longer survival in these trials versus those of the GITSG may have reflected the inclusion of a substantial percentage (> 75%) of patients with unmeasurable disease. In one of these trials results were broken out for measurable vs. unmeasurable patients, and survival was 64% longer in the unmeasurable patients (23 vs. 14 weeks) [31]. However, even with this possibly more favorable patient mix, among the total of 333 patients treated in the two large Mayo/NCCTG trials, only 13% of patients survived as long as one year. All of the patients in the MAOP trial had measurable disease.

The recent study among 126 patients with advanced pancreatic cancer (71% metastatic) randomized between gemcitabine and bolus 5-FU suggests that gemcitabine may have a significant clinical benefit (CB) in metastatic pancreatic cancer. When CB was defined in terms of pain reduction (or reduction in analgesic use) or performance status improvement, 14/63 patients treated with gemcitabine (22%) realized a CB, versus 5% treated with bolus 5-FU [27]. Objective response rates were 5% in the gemcitabine arm and 0% in the bolus 5-FU arm. Median survival in the gemcitabine arm was 24 weeks (vs. 18 weeks for bolus 5-FU).

Another widely used regimen in gastrointestinal cancer is 5-FU with leucovorin. Three studies of 5-FU/leucovorin in advanced pancreatic cancer have been published [32–34], totaling 95 patients and including both the NCCTG low-dose leucovorin and GITSG high-dose leucovorin regimens. A total of 3 responses (3%, all partial) were reported among these three studies.

The current study reports an objective response rate

<table>
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<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>≥ Grade 3</th>
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<tbody>
<tr>
<td>Anemia</td>
<td>13 (24%)</td>
<td>13 (24%)</td>
<td>22 (41%)</td>
<td>4 (7%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>27 (50%)</td>
<td>15 (28%)</td>
<td>9 (17%)</td>
<td>3 (6%)</td>
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<tr>
<td>Thrombocytopenia</td>
<td>29 (54%)</td>
<td>18 (33%)</td>
<td>6 (11%)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>53 (98%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Infection</td>
<td>52 (96%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>Nausea/vomiting</td>
<td>27 (50%)</td>
<td>9 (17%)</td>
<td>14 (26%)</td>
<td>4 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37 (69%)</td>
<td>10 (19%)</td>
<td>2 (4%)</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
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<tr>
<td>Mucositis</td>
<td>28 (52%)</td>
<td>9 (17%)</td>
<td>12 (22%)</td>
<td>3 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Renal</td>
<td>52 (96%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>1 (2%)</td>
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<tr>
<td>Neurologic</td>
<td>44 (81%)</td>
<td>7 (13%)</td>
<td>3 (6%)</td>
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<tr>
<td>Hand/Foot</td>
<td>46 (85%)</td>
<td>3 (6%)</td>
<td>5 (9%)</td>
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<td>Hypomagnesemia</td>
<td>49 (91%)</td>
<td>5 (9%)</td>
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<tr>
<td>Rhinorrhea</td>
<td>53 (98%)</td>
<td>1 (2%)</td>
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<tr>
<td>Angina</td>
<td>53 (98%)</td>
<td>1 (2%)</td>
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</tr>
<tr>
<td>Alopecia</td>
<td>53 (98%)</td>
<td>1 (2%)</td>
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Distribution of patients according to highest recorded toxicity (any category)

<table>
<thead>
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<th>Grade 3</th>
<th>Grade 4</th>
<th>≥ Grade 3</th>
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<tr>
<td>1 (2%)</td>
<td>9 (17%)</td>
<td>25 (46%)</td>
<td>16 (30%)</td>
<td>3 (6%)</td>
<td>19 (35%)</td>
</tr>
</tbody>
</table>

Table 2. Treatment related toxicities.
of 17% (complete and partial), which is similar to the previous MAOP trial of protracted infusional 5-FU with weekly cisplatin [21] and to another study by Nicolson et al. using protracted infusional 5-FU plus cisplatin administered at a higher dose every three weeks [35]. These three results are all comparable to the best results reported in the GITSG and Mayo trials, but with lower toxicity. Median survival in this trial was 22 weeks, comparable to the earlier MAOP trial and to the best results of historic trials in this disease. All patients in the MAOP trials had measurable disease. The most interesting aspect of this study is that it was conducted largely at community hospitals and consisted of chemotherapy that was substantially less toxic (as were the previous MAOP and Nicolson et al. trials of 5-FU/cisplatin) than many regimens previously reported. The overall incidence of grade 4 toxicity was 6% and no patients required hospitalization. There were no treatment-related deaths. Two complete responses occurred, one of which was documented pathologically at an incidental second operation.

Both this and the previous MAOP trial were based upon protracted infusional 5-FU. It is important to point out that scanty single-agent data for protracted infusional 5-FU alone in pancreatic cancer are available. In a very small series, Hansen et al. reported a 19% partial response rate (95% CI, 4%–46%) and 26-week survival among 16 patients treated with protracted infusional 5-FU alone [36]. Thus, whether the performance of this combination is superior to that of protracted infusional 5-FU alone cannot be determined from this study.

Given the relatively poor results with any chemotherapy in pancreatic cancer, it remains incumbent upon the oncologist to openly discuss the expectations of therapy with the patient before undertaking chemotherapy for advanced disease. Chemotherapy for pancreatic cancer remains palliative in nature. In the absence of a clearly superior treatment, the least toxic regimen, consistent with response and survival, should be chosen. The results of this trial suggest that a regimen of protracted infusion of 5-FU at 300 mg/m²/day plus weekly carboplatin at 100 mg/m²² offers a reasonable treatment consistent with these objectives.

Acknowledgement

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References

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