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Phase II Study of Paclitaxel plus the Protein Kinase C Inhibitor Bryostatin-1 in Advanced Pancreatic Carcinoma

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Abstract

Purpose—To determine the efficacy and toxicity of the protein kinase C inhibitor bryostatin-1 plus paclitaxel in patients with advanced pancreatic carcinoma.

Methods—Each treatment cycle consisted of paclitaxel 90 mg/m² by intravenous (IV) infusion over 1 hour on days 1, 8, and 15, plus bryostatin 25 mcg/m² as a 1 hour IV infusion on days 2, 9, and 16, given every 28 days. Patients were evaluated for response after every 2 treatment cycles, and continued therapy until disease progression or prohibitive toxicity. The primary objective was to determine whether the combination produced a response rate of at least 30%.

Results—Nineteen patients with locally advanced or metastatic pancreatic adenocarcinoma received a total of 52 cycles of therapy (range 1–10). Patients received the combination as first-line therapy for advanced disease (N=5) or after prior chemotherapy used alone or in combination with local therapy. No patients had a confirmed objective response. The median time to treatment failure was 1.9 months (95% confidence intervals 1.2, 2.6 months). Reasons for discontinuing therapy included progressive disease or death in 14 patients (74%) or because of adverse events or patient choice in 5 patients (26%). The most common grade 3 to 4 toxicities included leukopenia in 26%, anemia in 11%, myalgias in 11%, gastrointestinal bleeding in 11%, infection in 10%, and thrombosis in 10%.

Conclusion—The combination of weekly paclitaxel and bryostatin-1 is not an effective therapy for patients with advanced pancreatic carcinoma.

Introduction

Carcinoma of the pancreas is the fourth leading cause of overall cancer death in the United States, accounting for an estimated 35,000 deaths projected for 2008.¹ Surgery and radiation

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therapy are curative in less than 5% of patients with potentially operable or locally advanced disease.²⁻⁴ Gemcitabine and erlotinib are the approved systemic therapies for treating advanced disease, but median survival remains less than 6 months.^{5,6} Multiple studies have found no benefit for combining gemcitabine with a variety of other cytotoxic agents.⁷ New treatment approaches are needed.

Phosphoinositide protein kinase C (PKC) is an 80 kDa enzyme that play a key role in regulating apoptosis.⁸ Many chemotherapeutic agents induce their antineoplastic effects by promoting apoptosis, which is modulated by pro- and anti-apoptotic proteins that are reciprocally regulated through the sphingomyelin signal transduction pathway mediated by PKC. Several PKC inhibitors have been shown to promote chemotherapy-induced apoptosis, including bryostatin-1, which is a natural product isolated from the marine invertebrate *Bugula neritina*, a member of the phylum Ectoprocta. Byrostatin-1 inhibits proliferation, induces differentiation, and promotes apoptosis in a variety of hematologic and solid tumor cells lines⁹, and also inhibits the mitogen-activated protein kinase pathway.¹⁰ Bryostatin-1 has also been shown to enhance the cytotoxic and antiangiogenic effects of paclitaxel in a sequence specific manner.¹¹ In a phase I trial of sequential paclitaxel followed by bryostatin-1 in 17 patients with advanced cancer, 1 of 5 patients with pancreatic cancer demonstrated stable disease for 14 months, and another had partial regression of liver metastases. Based upon the preclinical data demonstrating that byrostatin-1 enhanced the antineoplastic effects of paclitaxel *in vitro*, and clinical data suggesting activity for the combination in pancreatic carcinoma, we therefore initiated a phase II trial to evaluate the efficacy and toxicity of sequential weekly paclitaxel, followed by bryostatin-1 in patients with advanced pancreatic cancer. The primary objective was to determine whether the combination produced a response rate of at least 30%.

Methods

Eligibility Criteria

Eligibility criteria included histologically confirmed pancreatic adenocarcinoma that was metastatic or not considered surgically respectable with bidimensionally measurable disease, age 18 or older, an Eastern Cooperative Oncology Group performance status of 0 to 1, and adequate bone marrow (neutrophils $1500/\text{mm}^3$ and platelets $150,000/\text{mm}^3$), liver (total bilirubin 1.5 mg/dL), and renal function (serum creatinine 1.5 mg/dL). Exclusion criteria include brain metastases, a history of active angina or myocardial infarction within 6 months, a history of significant ventricular arrhythmia requiring therapy, serious uncontrolled medical illnesses, or psychiatric disorders rendering patients incapable of complying with the requirements of the protocol. One prior course of adjuvant chemotherapy (excluding a taxane) with irradiation: patients may have also received up to 1 prior palliative non-taxane chemotherapy regimen for advanced disease. Patients who received prior radiotherapy were only included whether the lesions within the field of radiation showed evidence of disease progression because the completion of treatment (defined by a 50% increase in the longest diameter or 100% increase in the product of 2-dimensional radiographic evaluation). The trial was approved by the institutional review board at each participating institution, and all patients provided written informed consent. The trial reviewed, approved, and sponsored by the National Cancer Institute Cancer Therapy Evaluation Program ([Clinical Trials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00031694) Identifier NCT00031694).

Treatment

Treatment consisted of weekly sequential administrations of paclitaxel followed by bryostatin-1. A 1-hour infusion of paclitaxel was given at a dose of 90 mg/m^2 on days 1, 8, and 15 every 28 days. Twenty-four hours after the paclitaxel infusion, a 1-hour infusion of

bryostatin-1 was given at a dose of 25 mcg/m² on days 2, 9, and 16. Each treatment cycle consisted of 3 consecutive weekly treatments followed by a 1-week break. Cycles were repeated every 28 days until progression of disease. For patients who required omission of drug dosing due to toxicity or other reasons, the missed dose was considered the 1-week break between cycles. Therapy was resumed at a reduced dose once the toxicity had resolved. All patients received dexamethasone 20 mg intravenously prior to the initiation of the paclitaxel infusion and cimetidine 300 mg and diphenhydramine hydrochloride 50 mg 30 to 60 minutes before the infusion. Filgrastim was used for episodes of neutropenic fever or prolonged neutropenia.

Adverse effects were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0. Because myalgias had been the dose-limiting toxicity in phase I trials of bryostatin-1, the bryostatin-1 dose alone was decreased if patients experienced grade 3 or 4 myalgias (not controlled with analgesics) in the absence of grade 3 or 4 hematologic toxicities. For the first occurrence of grade 3 or 4 myalgias, the bryostatin-1 dose was decreased to 20 mcg/m². If the toxicity recurred for the second time, the dose was further decreased to 15 mcg/m²; if this dose was not tolerated, the patient was removed from study. If consecutive bryostatin-1 doses were well tolerated after a dose reduction (grade: 0-2), attempts at re-escalation were made at the discretion of the treating physician. The dose of paclitaxel was reduced, if there were grade 4 hematologic or grade 3 to 4 non-myalgia toxicities, to 80 mg/m² for the first dose reduction, and 70 mg/m² for the second dose reduction.

Study Evaluations

Patients had computerized tomography of the chest, abdomen, and pelvis performed within 28 days of registration, and after every 2 cycles of therapy. Response was categorized according to RECIST criteria.¹²

Statistical Considerations

The primary endpoint was to determine if the objective response rate for the combination was at least 30%. A Simon 2-stage design was used, with a minimum number of 18 patients in the first stage. If only 2 or fewer had an objective response, the study would be closed early and deemed negative. If 3 or more complete or partial responses were achieved during the first-stage, enrollment would be extended to another 17 patients. In this second stage, if the total number responding was less than or equal to 6, the regimen would then be declared ineffective. This 2-stage design yielded a study power of 90% whether the true response rate was at least 30%. It yielded a 0.95 probability of a negative result if the true response rate was 10% or less, with a 0.71 probability of early study termination. Treatment-failure-free survival was analyzed using the Kaplan-Meier method and 95% confidence intervals were constructed using Greenwood's formula; treatment failure was defined as progressive disease, or discontinuation of therapy due to toxicity or other reasons. All P-values are 2-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in SAS version 9.1 (SAS Institute, Inc., Cary, NC) and Stata version 8.0 (Stata Corporation, College Station, TX).

Results

Patient Characteristics

Nineteen patients were enrolled from 5 centers between March 2002 and October 2003, and their characteristics are shown in Table 1. The median age was 56 years (range: 21-81 years), median Eastern Cooperative Oncology Group performance status was 1 (range: 0-1).

Ten patients (53%) had received chemo therapy, 4 (21%) received prior irradiation, and 4 (21%) had prior surgery.

Treatment Administration

A total of 52 cycles of therapy were administered. The median number of courses given was 2 (range: 1-10 cycles). Reasons for discontinuing therapy included progressive disease or death in 14 patients (74%), or adverse events or patient choice in 5 patients (26%).

Response Rate

No patients had a confirmed objective response; 1 patient had an unconfirmed partial response (5%). Nine patients (47%) had stable disease as their best response, and 9 patients (47%) had progression as their best response to therapy. The median time to treatment failure was 1.9 months (95% confidence intervals: 1.2, 2.6 months). After a median follow-up of 3 months (1-11+ months), 9 of the 19 patients enrolled had died because of disease progression (N=7) or within 30 days of receiving therapy (N=2), as described below (Figure 1).

Adverse Events

Adverse events occurring are shown in Table 2. The most common adverse event was treatment related myalgias, which occurred in 48% of all patients. The most common grade 3 to 4 adverse events occurring in at least 10% of patients included leukopenia in 26%, anemia in 11%, myalgias in 11%, gastrointestinal bleeding in 11%, infection in 10%, and thrombosis in 10%. Two patients discontinued therapy because of adverse events, including 1 patient with grade 3 myalgias after 1 cycle and 1 patient with grade 3 fatigue after 1 cycle. Two patients died within 30 days of receiving therapy for causes that were felt by the treating physician to be unrelated to therapy, including 1 patient with an unconfirmed partial response who had a cardiac arrest after 3 cycles, and 1 patient who died of a liver abscess after 1 cycle.

Discussion

We performed a phase II trial of the PKC inhibitor bryostatin-1 in combination with weekly paclitaxel in patients with locally advanced and metastatic pancreatic cancer. There was considerable preclinical rationale for combining bryostatin-1 with paclitaxel, and the specific sequence of paclitaxel followed by bryostatin-1 was also selected based on preclinical observations *in vitro* and *in vivo*.¹¹ Although paclitaxel was not regarded as a standard agent for advanced pancreatic cancer, several trials had demonstrated activity for docetaxel^{13, 14} and paclitaxel^{15, 16} that were comparable to gemcitabine. The bryostatin-1 dose of 25 mcg/m² given weekly in combination with paclitaxel was chosen based on the results of earlier study of this combination.¹⁷ We observed only no confirmed responses among 19 patients treated, and concluded that the response rate is not likely to exceed 30% for this combination. Although a response rate of 30% may be considered overly optimistic expectation for the combination, the observation of no responses among 19 patients indicates that the true response rate is likely to be less than 20%; in addition, the median time to progression of only 1.9 months was not encouraging.

Other trials have also evaluated the combination of bryostatin-1 and paclitaxel in patients with gastrointestinal cancer. In 1 trial, 24 patients with advanced esophageal cancer received an identical dose and schedule of paclitaxel as used in our trial, followed 24 hours later by bryostatin at a dose of 50 mcg/m².¹⁷ Because of severe myalgias, the paclitaxel dose was reduced to 80 mg/m² and bryostatin-1 dose to 40 mcg/m² then 25 mcg/m². Of 22 evaluable patients, there were 6 responses (27%), and the response rate appeared to be higher with the

higher bryostatin-1 dosing. However, the trial was terminated due to prohibitive myalgias. In a second trial involving 37 patients with advanced gastric and gastroesophageal carcinoma, patients received 80 mg/m² of paclitaxel on days 1, 8, and 15 followed by bryostatin-1 dosage 40 mcg/m² on days 2, 9, and 18. Of 35 evaluable patients, objective response occurred in 10 patients (29%), but severe myalgias likewise occurred in about 55% of patients, proving to be excessively toxic.

Although it appears that the strategy of combining a PKC inhibitor with paclitaxel may be ineffective due to excessive toxicity associated with bryostatin-1, other trials evaluating other agents targeting PKC have also failed to show benefit for this strategy, raising the question as to whether this is a tenable strategy.¹⁸ The results of our trial are consistent with other studies showing no benefit for inhibiting PKC in combination with cytotoxic therapy in patients with advanced cancer.

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Figure 1.
Time to Treatment Failure

Table 1

Patient Characteristics

Characteristic	Number	Percent (%)
Total	19	
Age		
Mean	56	
Range	21 -81	
Sex		
Male (%)	12	63%
Female (%)	7	37%
Ethnicity		
Non-Hispanic Whites	13	68%
Non-Hispanic Blacks	3	16%
Hispanics	3	16%
ECOG performance status		
0	8	42%
1	11	58%
Previous Treatment (n=16)		
None	5	31%
Single agent chemotherapy	2	13%
Multiple agent chemotherapy	2	13%
Surgery	1	6%
Chemotherapy/surgery	2	13%
Chemotherapy/RT	3	19%
Chemotherapy/RT/surgery	1	6%

Table 2

Most Common (>10%) Grade 3 to 4 Adverse Events

Grade	1	2	3	4
<u>Hematologic</u>				
Leukopenia	1 (5%)	0	5 (26%)	0
Anemia	1 (5%)	3 (16%)	0	2 (11%)
<u>Non-Hematologic</u>				
Myalgia	3 (16%)	4 (21%)	2 (11%)	0
Thrombosis/embolism	0	0	1 (5%)	1 (5%)
Abdominal pain	1 (5%)	2 (11%)	2 (11%)	0
Infection - other	0	1 (5%)	1 (5%)	1 (5%)
Alkaline phosphatase	0	0	2 (11%)	0
ALT/SGPT	0	0	2 (11%)	0
AST/SGOT	0	0	2 (11%)	0
Hemorrhage	0	0	2 (11%)	0