Treatment of advanced pancreatic cancer with opioid growth factor: phase I

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Opioid growth factor (OGF) is an endogenous pentapeptide that inhibits growth of human pancreatic cancer cells in culture, as well as xenografts in nude mice. To establish the maximum tolerated dose (MTD), and determine safety and toxicity of OGF, a phase I trial was performed in patients with advanced unresectable pancreatic cancer. Patients with unresectable pancreatic adenocarcinoma were treated with escalating doses of OGF for 30 min i.v. to determine the MTD. The s.c. route of administration also was evaluated. Once the MTD was established, a group of patients was treated chronically, and monitored for safety and toxicity. Hypotension was the dose-limiting toxicity, resulting in a MTD of 250 μg/kg i.v. Due to limited solubility of OGF in small volumes, a maximum dose of 50 μg/kg twice daily was determined by the s.c. route of administration. No adverse events were reported for oxygen saturation, cardiac rhythm, laboratory values or neurological status in either the acute or chronic parts of the study with the i.v. or s.c. routes. During the chronic i.v. phase, two subjects had resolution of liver metastases and one showed regression of the pancreatic tumor. Mean survival from the time of diagnosis was 8.7 months (range 2–23 months) in the i.v. group and 9.5 months (range 1–18 months) in the s.c. group. We conclude that OGF can be safely administered to patients with advanced pancreatic cancer. Further studies are needed to determine the efficacy of OGF alone or in combination with present modes of therapy for the treatment of pancreatic cancer. *Anti-Cancer Drugs* 15:203–209 © 2004 Lippincott Williams & Wilkins.

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Introduction

Pancreatic cancer is a fatal malignancy that occurs in approximately 170 000 people annually. With a mortality to incidence ratio of 98% [1], survival from pancreatic cancer remains the lowest of all malignancies [2]. Since pancreatic cancer is rarely detected in the early stages when surgical resection is a treatment option [3], chemotherapy remains the major therapeutic modality for this disease. Among the chemotherapeutic agents tested, gemcitabine has been used most frequently either alone or in combination with other agents [4–7], but a clear survival benefit has not yet been demonstrated.

Modulation of growth factors and receptors is a promising approach in the treatment of pancreatic cancer [8–11]. One group of peptides, the endogenous opioids, has been shown to have an important role in pancreatic cancer [12–15]. The native opioid, [Met^5]-enkephalin [termed opioid growth factor (OGF)], is a constitutively expressed pentapeptide that interacts with the OGF receptor (OGFr) to inhibit pancreatic cancer growth both *in vitro* [13,14] and *in vivo* [15]. The action of OGF is stereospecific, reversible, non-cytotoxic, independent of serum and occurs at physiologically relevant concentrations [13]. OGF is targeted to DNA synthesis [14] and is directed toward the G_0/G_1 interface of the cell cycle [16]. Interruption of the peptide–receptor interaction by sustained opioid antagonism (e.g. the potent and long-acting opioid antagonist, naltrexone) results in a substantial increase in cancer cell number compared with control levels [13], suggesting the tonic and constitutive nature of OGF–OGFr interfacing. OGF and OGFr have been identified in human pancreatic cancer cells by immunohistochemistry, radioimmunoassay and receptor-binding analysis [13,14,17].

Given the inhibitory properties of OGF in human pancreatic cancer, both *in vitro* and *in vivo*, we have

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initiated an examination of the effects of OGF in patients with pancreatic cancer. The present study was designed as a phase I clinical trial to test the safety and toxicity, and determine the maximum tolerated dose (MTD), of OGF when administered to human subjects with unresectable pancreatic cancer.

Methods

Study design

This phase I clinical trial was divided into two separate parts: acute drug administration where the MTD and the routes of administration were tested, and chronic drug administration where the safety and toxicity, as well as the routes of administration were evaluated. The protocol and patient consent form were approved by the Human Subjects Protection Committee at the Pennsylvania State University College of Medicine, and by the Oncology Section of the Food and Drug Administration (FDA). The studies were performed under a FDA approved IND number (#50,987), and conducted in the General Clinical Research Center at Pennsylvania State College of Medicine. Safety monitoring was performed by a committee from Pennsylvania State University and under the approval of the FDA.

Patient selection

Eligibility criteria for the study included histologically confirmed advanced pancreatic cancer that was unresectable and measurable by radiologic techniques, and a Karnofsky performance score of 50% or greater [18]. Patients also were eligible for this study if they had failed prior chemotherapy or radiation therapy. A minimum of 4 weeks after surgical procedures or administration of i.v. antibiotics was required for inclusion in the study.

Patients with other significant medical conditions such as active coronary artery disease, chronic obstructive pulmonary disease, poorly controlled diabetes mellitus, uncontrolled hypertension, seizure disorders, brain metastases or pregnancy were not allowed in the study. Criteria for exclusion also included fever greater than 37.8°C, pulse < 60 or > 110/min and systolic blood pressure > 170 or < 90 mmHg. Patients with abnormal laboratory tests including white blood count $< 3.5 \times 10^3$/μl, absolute neutrophil count $< 1.5 \times 10^3$/μl, hemoglobin < 8.5 g/dl, BUN > 30 mg/dl, creatinine > 2.0 mg/dl, total bilirubin > 4.0 mg/dl, platelets $< 100\,000$/μl, prothrombin time > 2 s over control, sodium < 130 mmol/l, potassium < 3.2 mmol/l or serum glucose > 300 or < 60 mg/dl were not eligible in this clinical trial. Subjects admitted for the trial were not allowed to take other antitumor medications or oral steroids and other immunosuppressive drugs.

Drug synthesis and preparation

OGF was manufactured under cGMP conditions by Peninsula Laboratories (San Carlos, CA). The composition of the lyophilized powder was analyzed by the manufacturer after two passages through HPLC and its purity was determined to be 97.7%. Composition analysis and stability testing was performed under FDA regulations. The purified OGF was dispensed (10 mg/vial) into non-sterile 5-ml type 1 borosilicate glass vials, capped and crimp sealed using a 13-mm gray butyl rubber stopper by Peninsula Laboratories. OGF vials were stored at 4°C in the Investigational Pharmacy at Pennsylvania State College of Medicine.

At least 24 h prior to each administration, OGF concentration and patient's weight were provided to the Investigational Pharmacist. Using aseptic technique, OGF was reconstituted by an approved study pharmacist under a laminar flow hood with 10 ml of sterile saline (0.15 M NaCl, USP). Using a sterile needle and syringe, the appropriate dose was drawn from each vial and passed through a 22-μm filter. The solution was tested and certified by Celsis Laboratory Group (St Louis, MO) for pyrogens, bacterial endotoxin and fungus, and deemed sterile prior to patient use. All drugs were prepared on the day of i.v. administration and a 1-week supply of sterile syringes with drug were provided to patients receiving the s.c. route of therapy.

Acute drug administration

To determine the MTD, patients with pancreatic cancer were infused i.v. for 30 min with OGF prepared in 60 ml of sterile saline. The initial dose was determined based upon calculations from prior animal studies [15]. Three subjects were tested per dose and seven doses were evaluated in an escalating manner: 25, 50, 75, 100, 150, 200 and 250 μg/kg. Prior to each infusion, baseline laboratory values (CBC, glucose and electrolytes) and basal OGF levels were obtained. During the infusion, subjects were monitored for vital signs (pulse, respirations and blood pressure), cardiac arrhythmias and oxygen saturation. Neurological and mental status was checked prior to and at completion of the infusion, and 3 h after drug administration. Vital signs and laboratory values were recorded 3 h after the infusion. OGF plasma levels were measured just prior to and at completion (i.e. 30 min) of infusion and 3 h following drug administration (i.e. 210 min). Toxicity was assessed by the WHO criteria [19] and if a grade 4 toxicity or two grade 3 toxicities occurred at a particular dose, a higher dose was not administered. Prior to and 1 week after infusion, all patients completed a questionnaire about their well-being and side-effects. Questions included symptoms regarding constipation, nausea, vomiting, depression, fever, chills, difficulty urinating, headache, ill-feeling or other symptoms.

The s.c. route of OGF administration also was evaluated in a population of pancreatic cancer patients. Subcuta-

neous injections of OGF were given in the upper ventral surface of the thigh. The procedures for patient monitoring and laboratory testing were similar to that for the i.v. method. Pharmacokinetics of OGF in the plasma was measured at baseline (just prior to the s.c. injection), and at 30 and 210 min after drug administration. Groups of three subjects with pancreatic cancer were treated with OGF at a dosage of 50 μg/kg at various intervals. Because of limitation in the solubility of OGF in the small volume of vehicle required for injection (1.0 ml), the concentration of drug could not exceed 50 μg/kg. The frequency of the s.c. injections, and the effects on safety and toxicity were evaluated. OGF was given either once weekly, daily for 7 days or twice daily for 7 days.

Chronic drug administration

In the chronic portion of the study, subjects with pancreatic cancer were treated with OGF either by a weekly i.v. infusion (250 μg/kg) or a s.c. injection (50 μg/kg twice daily). Tumor size was assessed by radiographic evaluation scanning techniques [computed tomography (CT)] prior to enrollment and every 12 weeks thereafter. Pancreatic tumor size was defined as product of the two greatest perpendicular diameters. Tumor markers (CEA and CA19-9) and routine laboratory tests were measured prior to therapy and at 4-week intervals.

Three quality of life surveys, the Sickness Impact Profile (SIP) [20], the Beck Depression Inventory [21] and the McGill Pain Questionnaire [22], as well as a diary of pain medication, were administered to patients prior to administration of OGF and monthly thereafter. Patients continued therapy if they exhibited either stable disease or regression of the radiographic tumor marker. Progressive disease was defined as the development of any new lesion not previously identified or an increase in the radiologic tumor marker of greater than 50% from the prior assessment. If patients developed progressive disease they were discontinued from the study and followed for the length of survival.

Radioimmunoassay

Plasma OGF levels were evaluated by radioimmunoassay using radiolabeled [Met^5]-enkephalin (Peninsula) and followed earlier procedures [23]. Samples were assayed in duplicate. The results of each treatment group were averaged and changes in OGF levels were compared to baseline values.

Biostatistics

The mean values from patient's systolic blood pressure, pulse, respiratory rate and oxygen saturation were analyzed for changes from baseline at each point recorded. Differences between doses (in the i.v. part) and between dosing schedules (in the s.c. part) were evaluated. Laboratory blood values were determined and analyzed by analysis of variance for statistical differences between baseline and post-OGF administration as well as between various doses or dosing schedules.

Data collected using the SIP, McGill Pain Questionnaire, Beck Depression Inventory and Karnofsky performance status (KPS) instruments were summarized for each patient. The SIP is comprised of 12 categories describing behaviors related to sleep and rest, eating, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness behavior, emotional behavior, work, and communication. Percentage scores were calculated for each category separately where a score of 0 indicated no dysfunction and 100 indicated complete dysfunction. In addition, a composite score was calculated by averaging the category specific scores. The McGill Pain Questionnaire included four classes of pain: sensory, affective, evaluative and miscellaneous. Pain Rating Index (PRI) scores were assessed by summing the rank value of all pain-related words selected in a given class. PRI scores were calculated for each class separately and a composite score was obtained by averaging the class-specific PRI scores. Scores for the number of words chosen (NWC) were computed by counting the number of pain-related words selected in a given class. NWC scores were evaluated for each class separately and a composite score was obtained by averaging the class specific NWC scores. For both the PRI and NWC scores, higher values indicated an increase in pain. The McGill Pain Questionnaire also included a five-point scale that ranged from mild to excruciating; this score was considered the Present Pain Intensity (PPI). The Beck Depression Inventory reflected the sum total of responses to 21 questions and values ranged from 0 to 63. The total score is interpreted according to the following scale: 1–10 'These ups and downs are considered normal', 11–16 'Mild mood disturbance', 17–20 'Borderline clinical depression', 21–30 'Moderate depression', 31–40 'Severe depression' or over 40 'Extreme depression'.

Descriptive statistics (mean, standard deviation, minimum and maximum) were calculated for each of the outcome measures described above at the screening visit, and at weeks 4, 8, 12, 16, 20, 24, 28 and 32. The paired *t*-test was used to assess differences in outcome measures between week 4 and baseline, and between week 8 and baseline. Differences in outcome measures between baseline and later visits were not formally assessed due to insufficient numbers of subjects. All analyses were carried out using the SAS statistical software package version 8.0.

Results

Patient demographics

The patient demographics at enrollment for both the acute and chronic parts of the study are shown in Table 1.

Table 1 Demographics of patients in OGF phase I trial

	Acute	Chronic
Age (years)	64 ± 14	59 ± 11
Gender (M/F) (%)	50/50	62/38
Prior therapy (%)		
none	50	56
chemotherapy	37	25
chemotherapy and radiation	13	19
Stage of disease (%)		
I	0	0
II	25	6
III	12	19
IV	63	75
Histology grade (%)		
moderately differentiated	38	25
poorly differentiated	38	38
cytology	24	37
Karnofsky score (mean ± SEM)	79 ± 7	77 ± 13

Approximately one-half of the subjects were naive to chemotherapy and the remainder referred to the study had previously failed standard treatment. All study subjects had unresectable pancreatic cancer; approximately two-thirds presented with metastases. The histologic grade of the tumors was determined in 76% of the patients who underwent biopsy, with the remainder of patients undergoing cytologic evaluation.

Acute drug administration

OGF was administered i.v. up to a dose of 250 μg/kg. At this dose, two grade III toxicities were recorded, thereby establishing 250 μg/kg as the MTD according to protocol guidelines. The side-effects and toxicity recorded at each i.v. dose of OGF using the WHO criteria grading scale is shown in Table 2. Several subjects noted perinasal paresthesia during the onset of OGF infusion at dosages of 100 μg/kg or greater. The most serious side-effect in patients receiving OGF was hypotension, but this complication was not associated with any changes in cardiac rhythm or neurological status. One patient receiving a dose of 250 μg/kg of OGF was recorded to have a decline in systolic blood pressure to 60 mmHg. No adverse effects on oxygen saturation or mental status were observed during the OGF infusion or in the following 3 h.

With respect to the s.c. route of administration, one subject developed a fever (grade II) and another patient experienced cutaneous mottling (grade II). Pulse, blood pressure, respiratory rate and neurological status remained stable in those patients receiving s.c. administration of OGF. Moreover, none of those subjects receiving OGF by the acute s.c. route reported gastrointestinal symptoms or paresthesias.

The results of various laboratory tests from patients with pancreatic cancer evaluated prior to and 3 h after i.v. infusion of OGF are shown in Table 3. Five of the seven

Table 2 Toxicity of OGF during the 30-min acute i.v. administration by the WHO grade toxicity scale

OGF (μg/kg)	Side-effects	WHO grade toxicity	Total score
25	emesis	II	2
50	bradycardia	II	4
	hypotension	II	
75	bradycardia	II, II, II	8
	hypotension	II	
100	paresthesia	I	5
	hypopnea	I	
	bradycardia	II	
	hypotension	I	
150	paresthesia	I, I	13
	hypotension	II, III	
	emesis	II	
	bradycardia	II, II	
200	paresthesia	I, I, I	6
	hypotension	I, II	
250	paresthesia	I, I, I	9
	hypotension	III, III	

$N = 3$ patients/dose.

Table 3 Laboratory values: acute drug i.v. administration

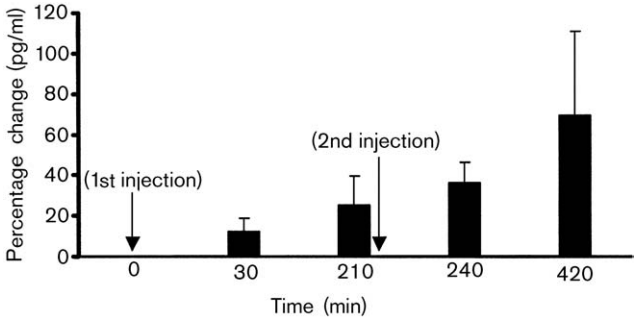
Test	Pre-OGF infusion	Post-OGF infusion
White blood count ($\times 10^3$/μl)	6.5 ± 0.8	6.2 ± 0.7
Hemoglobin (g/dl)	11.8 ± 0.2	11.1 ± 0.4
Absolute neutrophils ($\times 10^3$/μl)	4.9 ± 0.8	4.9 ± 0.9
Platelet count ($\times 10^3$/μl)	204.5 ± 15	188.7 ± 14.2
Glucose (mg/dl)	102.7 ± 2.5	119.7 ± 7.4[a]
Potassium (mmol/l)	4.1 ± 0.01	3.6 ± 0.1[b]
Sodium (mmol/l)	139.8 ± 0.4	140.2 ± 0.6

Laboratory values prior to OGF infusion or 210 min after completion of a 30-min OGF infusion. Data are expressed as means ± SEM. Significantly different from pre-OGF infusion values at [a]$p < 0.05$ and [b]$p < 0.01$.

laboratory tests analyzed showed no statistical difference between the pre- and post-OGF infusion levels. Although plasma glucose and potassium levels increased 16 and 12%, respectively, 3 h after OGF infusion, these values remained in the normal range. Indeed, these changes in glucose and potassium may be attributed to the direct ingestion of food (crackers, juice) rather than a direct effect of OGF since the initial value was drawn in the fasting state. Laboratory values (white blood count, hemoglobin, absolute neutrophil count, platelet count, glucose, potassium and sodium) did not change, and remained normal at 30 min, 3 h, 3 days and 7 days after a s.c. injection of OGF.

Basal levels of OGF were elevated in subjects prior to treatment with the i.v. (225 ± 49 pg/ml) and s.c. routes of delivery (187 ± 54 pg/ml) compared to plasma values of OGF previously measured by radioimmunoassay in normal control subjects (82.5 ± 23 pg/ml) [23]. In spite of the elevated basal OGF plasma levels, OGF plasma values monitored in patients treated with an i.v. infusion increased an average of 60 pg/ml or 28% over basal levels 30 min after each infusion. These plasma OGF levels remained 20% greater than baseline values even 3 h after the infusion. Blood values of OGF in patients with pancreatic cancer receiving a s.c. injection of OGF were

Fig. 1



Percent change in plasma OGF levels after s.c. injection of exogenous OGF. The first and second injections of OGF were administered immediately after the 0 and 210-min sampling points. Percent change in plasma OGF levels compared to baseline values (0) are shown at 30, 210, 240 and 420 min after an OGF injection. Values represent the mean ± SEM of OGF for $N=3$ patients/dose.

12% greater than baseline at the 30-min time point. At the 3-h time interval the blood OGF levels were 25% over baseline in subjects treated s.c. with OGF. In patients who received two s.c. injections of OGF per day, the levels of OGF measured in plasma 3 h after the second injection was 70% over baseline. These opioid peptide levels returned to basal levels the morning after the injection (Fig. 1). Due to the low number of subjects at each dose tested, evaluation of statistical significance was limited.

Chronic drug administration

Sixteen patients were treated in the chronic part of the study; 10 subjects were treated with an i.v. infusion of OGF at 250 μg/kg weekly and six subjects were treated s.c. with OGF at 50 μg/kg twice daily. When the i.v. infusion was extended 45 min, from 30 min as performed in the acute part, no hypotensive events were reported. Two subjects had complete resolution of hepatic metastases and one of these patients also showed a significant decrease in the size of the primary pancreatic tumor. The decrease in tumor burden in each patient was associated with a decline in serum CA19-9 and CEA levels. However, CEA and CA19-9 plasma levels did increase in all patients with progression of disease. There was no significant change in monthly laboratory values including white blood count, platelets, hemoglobin, glucose, potassium, sodium or plasma OGF levels with either the i.v. infusion or the s.c. route in these chronic studies.

No statistically significant change in KPS, SIP, McGill Pain Questionnaire or Beck's Depression Survey was noted throughout the duration of the study. There was a trend toward improvement in the aspects of the quality of life including social interaction and alertness behavior improved after 4 weeks on chronic OGF. After 8 weeks of chronic OGF therapy there also were trends toward improvement in the categories of sleep and rest, home management, ambulation, mobility, body care management, and communication. Pain medications were increased as needed and patients did not report significant problems with pain. The McGill Pain Questionnaire exhibited a trend toward improvement for both the PRI and NWC scores in only the affective category after 4 weeks of OGF therapy. However, after 8 weeks of therapy all four classes of pain in both categories improved with the exception of evaluative PRI scores. There was no change in the Beck's Depression Scores according to the survey.

Mean survival from the time of diagnosis was 8.7 month (range 2–23 months) in the i.v. group and 9.5 months (range 1–18 months) in the s.c. group. The two subjects who had transient loss of hepatic metastases experienced recurrence of disease while on therapy, but their survivals were 18 and 23 months, respectively.

Discussion

In preclinical experiments involving both tissue culture and animal studies, OGF has been shown to serve as an inhibitory agent to pancreatic cancer [13,15]. Using patients that had advanced unresectable pancreatic cancer, with most subjects having evidence of metastatic disease and more than half of these individuals having failed standard chemotherapeutic modalities, the present study shows that the MTD of OGF was 250 μg/kg using the i.v. route in a 30-min regimen of drug administration. The dose-limiting toxicity was due to the occurrence of hypotension. Most of these episodes of hypotension were detected in the first 5 min of infusion, were of short duration and were conjectured to be the consequence of a rapid rise in plasma OGF levels. This hypotensive response could be due to the sudden increase in OGF levels and interaction with classical opioid receptors (μ, κ) known to mediate such physiological properties [24]. A more gradual infusion process with extension from 30 to 45 min eliminated this hypotensive response. Therefore, given the lack of toxicity with the slower infusion rate, it may even be possible to uses doses of OGF above 250 μg/kg in a safe manner for the treatment of pancreatic cancer.

Well-known dose-limiting toxicities of standard chemotherapeutic agents include bone marrow suppression [25,26], gastrointestinal mucosynovitis [27], emesis with dehydration [28] and renal insufficiency with electrolyte disturbances [29]. Unlike these chemotherapeutic agents, however, OGF did not produce neutropenia, anemia, thrombocytopenia, gastrointestinal disturbances or renal toxicity. Some minor alterations in serum potassium and blood glucose were observed following

acute administration of OGF by infusion. These findings, however, were thought to be due to diet because basal levels of plasma were drawn in the fasting state, whereas the 3-h post-infusion blood levels were obtained after the ingestion of juice and crackers. Thus, these data support the fact that doses of OGF tested in this investigation were safe and non-toxic.

Using the s.c. route of administration, greater total weekly doses of OGF could be administered (700 μg/kg) compared to the i.v. route (250 μg/kg). The s.c. route of delivery was more convenient for patients and they were able to self-administer their treatment at home. No significant toxicity was reported with the s.c. route and higher doses most likely could have been tolerated. However, due to the lack of solubility of OGF in the small volumes required for safe s.c. injection, the dose administered could not be escalated above 50 μg/kg/injection, thereby limiting the determination of the MTD. Although the amount of OGF given over 24 h was greater by infusion (250 μg/kg) than the maximum daily dose administered s.c. (100 μg/kg), the plasma OGF level 3 h after the second s.c. injection was twice as high as that achieved after the i.v. infusion. The reason for the lower plasma levels with the i.v. route of delivery was thought to be due to the rapid clearance and metabolism of the peptide in contrast to the slower release mechanism known to occur by the s.c. route of administration. OGF is an endogenous peptide, which is detected at basal levels in all subjects; hence, our results indicted that an adequate amount of OGF was administered to the patients to elevate OGF levels above the baseline plasma values and thus impact tumor growth. With a clearer understanding of the pharmacokinetics and the mechanisms of OGF's actions, other delivery systems may also be useful including depot injection with an adjuvant agent or continuous infusion by a pump mechanism. Both of these methods could result in higher plasma levels than by i.v. infusion and carry less risk for hypotensive episodes.

Several quality of life surveys were conducted during the chronic course of this phase I trial even though the purpose of the study was to determine safety and toxicity of the peptide. The results of these surveys showed trends toward improvement but due to the small number of subjects in the chronic part of the study, these were not statistically significant. Although depression is associated with pancreatic cancer [30], there was no change in scores found in study subjects treated with OGF according to the Beck's Depression Survey. Moreover, no additional antidepressants were required during the treatment phase with OGF, suggesting that OGF did not induce depression in these patients, but perhaps this opioid peptide prevented the development of depression in a group of subjects with a terminal condition. Pain is also a common complaint among those with metastatic pancreatic cancer and often these subjects are treated with ganglionic nerve blockade to reduce the neuralgia-like pain from this cancer [31]. Although some of the subjects treated in this phase I OGF clinical trial were taking narcotic analgesic agents upon enrollment, in most situations, the usage of these medications remained stable and was not increased. The McGill Pain Questionnaire confirmed these findings by revealing an apparent diminishment in pain scores at both 4 and 8 weeks of therapy, suggesting that OGF had analgesic properties. Several subjects taking chronic narcotic analgesics for pain management reported no need for pain medication on the day of OGF infusion. The SIP appeared to demonstrate an improvement in several categories of quality of life with OGF administration, including increased scores for in social interaction, body care management, ambulation, mobility, sleep and rest, and communication. Typically, one would expect these categories to show deterioration paralleling the progression of disease. These results with OGF are promising showing a cancer therapy agent that is nontoxic and possibly beneficial by improving the patient's quality of life.

Survival with pancreatic cancer is poor in subjects who are not candidates for surgical resection [1,2] with the mean interval from the time of diagnosis till death being less than 6 months (4.4 months for 5-fluorouracil and 5.6 months for gemcitabine) [32,33]. Although the present study was not intended to examine tumor response or survival, preliminary results from the chronic part of this investigation demonstrated prolonged survival compared to standard treatment. The mean survival for both the i.v. and s.c. routes in this present phase I chronic OGF study was 9.1 months. Albeit, although the number of subjects treated with OGF was small, these patients survived nearly twice as long as those historically treated with 5-FU or gemcitabine. With these encouraging results, a phase II trial would be in order to test the efficacy of OGF in a larger number of previously untreated subjects with pancreatic cancer. Moreover, many chemotherapeutic regimes utilize a 'cocktail' approach when treating malignancy and more than one agent is utilized. Therefore, future studies are needed to determine whether OGF given in conjunction with various other chemotherapeutic agents may be advantageous in treating pancreatic cancer.

Although this pilot trial was conducted in pancreatic cancer, our preclinical studies indicate that OGF also may be useful as an antineoplastic agent in other malignancies that have been shown to be modulated by the OGF–OGFr axis. This would include cancers of the colon [34], head and neck [35], kidney [36], and developing nervous system [37]. Future studies will determine the broad-

spectrum usage of this novel antineoplastic peptide in other malignancies.

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