A Phase II Trial of Gemcitabine for Metastatic Neuroendocrine Tumors

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Supported by the Eli Lilly Corporation (Indianapolis, IN).

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Received January 26, 2004; revision received June 1, 2004; accepted June 1, 2004.

BACKGROUND. Treatment with traditional cytotoxic chemotherapy regimens containing streptozocin or dacarbazine has resulted in only marginal benefit for patients with metastatic neuroendocrine tumors. The use of these regimens has been further limited by their potential toxicity. Gemcitabine is generally well tolerated and possesses demonstrated activity against a wide range of malignancies. The authors assessed the efficacy of gemcitabine in the treatment of patients with metastatic neuroendocrine tumors.

METHODS. Eighteen patients with metastatic neuroendocrine tumors were treated with gemcitabine administered on a standard weekly schedule. Patients were followed for evidence of toxicity, response, and survival.

RESULTS. Gemcitabine was well tolerated. However, no radiologic or biochemical responses were observed. Although the majority of patients (65%) experienced disease stabilization as their best response to therapy, the overall median survival duration was only 11.5 months.

CONCLUSIONS. The minimal activity of gemcitabine highlighted the need for novel treatment approaches. ***Cancer* 2004;101:934–9.**

KEYWORDS: neuroendocrine tumors, carcinoid, pancreatic islet cell, gemcitabine.

Neuroendocrine tumors often pursue an indolent clinical course. As they progress, however, patients may become symptomatic as a result of either hormonal hypersecretion or tumor bulk. Somatostatin analogs and, to a lesser extent, interferon alpha have proven successful in treating symptoms of the carcinoid syndrome and other symptoms related to hormonal hypersecretion.[1,2] These agents only rarely, however, result in tumor regression.[3] Furthermore, over time, many tumors may become refractory to such therapy, requiring patients to pursue other forms of treatment.

The role of cytotoxic chemotherapy in the treatment of patients with metastatic neuroendocrine tumors remains controversial. Combinations including streptozocin, 5-fluorouracil (5-FU), or doxorubicin have yielded only modest response rates, and have been associated with significant toxicity in patients with carcinoid and pancreatic islet cell tumors.[4–6] Similarly, whereas dacarbazine (DTIC) also possesses some degree of activity in such tumors, toxicity concerns have precluded its widespread use.[7,8] Patients with pheochromocytoma, a less common neuroendocrine tumor, have been treated with streptozocin and DTIC-based chemotherapy regimens, also with only limited success.[9,10] Recent attempts to develop novel treatment regimens with less associated toxicity have been relatively unsuccessful. Phase II studies of paclitaxel and docetaxel, for example, have shown little activity against neuroendocrine tumors.[11,12]

DOI 10.1002/cncr.20466

Gemcitabine is a nucleoside analog with structural similarities to cytarabine. Currently, on the basis of data from a randomized Phase III study, it is widely used in the treatment of patients with advanced pancreatic adenocarcinoma. That Phase III study reported improvements in survival and clinical benefits such as reduced pain intensity, decreased analgesic use, and improved performance status (PS).[13] The mild toxicity profile of gemcitabine, in addition to its antitumor activity in other malignancies, led us to evaluate its worth as a potential therapeutic agent for patients with metastatic neuroendocrine tumors. To our knowledge, the current clinical trial is the first to evaluate gemcitabine in this setting.

In the current multicenter Phase II study, 18 patients with metastatic neuroendocrine tumors were treated with systemic gemcitabine administered on a standard weekly schedule. Patients were followed for response, toxicity, and survival.

MATERIALS AND METHODS

Study Population

The study population consisted of patients with histologically confirmed, locally unresectable or metastatic neuroendocrine tumors (excluding small cell carcinoma). Previous treatment with chemotherapy was allowed. Patients may also have received previous treatment with chemoembolization or cryotherapy, provided that the areas of disease used for tumor measurements were not affected by these treatments. Further inclusion criteria included Eastern Cooperative Oncology Group (ECOG) PS ≤ 2, life expectancy ≥ 12 weeks, absolute neutrophil count (ANC) $> 1500/mm^3$, and platelet count $> 100{,}000/mm^3$. Adequate renal (serum creatinine level < 2.0 mg/dL and hepatic functioning (bilirubin level < 2.0 mg/dL and aspartate aminotransferase level < 5 times the upper limit of normal) were also required. Patients with either clinically apparent central nervous system metastases or carcinomatous meningitis who had experienced a myocardial infarction in the past 6 months or who were pregnant or lactating were excluded from receiving protocol treatment. Patients at the Dana-Farber Cancer Institute (Boston, MA), Massachusetts General Hospital (Boston, MA), and the Brigham and Women's Hospital (Boston, MA) were eligible for enrollment. Informed consent was obtained from all patients as required by the institutional review boards of the participating institutions.

Treatment Program

Pretreatment evaluation included acquisition of a medical history, physical examination, hematologic and biochemical analysis, and confirmation of the histologic diagnosis by a pathologist at one of the treating institutions. Baseline radiologic tumor measurements were obtained by chest X-ray and by abdominal computed tomographic (CT) scanning.

Each treatment cycle consisted of gemcitabine administered weekly for 3 weeks followed by a 1-week rest period. Gemcitabine was delivered as a 30-minute intravenous infusion, with a starting dose of 1000 mg/m^2. Dose adjustments were made on the basis of platelet counts, leukocyte counts, and ANC as measured before the administration of each dose of gemcitabine. Patients with an ANC of 500–999/mm^3 or a platelet count of 50,000–99,999/mm^3 received a 25% dose reduction. Treatment doses remained the same for patients who had an ANC $< 500/mm^3$ or a platelet count $< 50{,}000/mm^3$. Doses that were withheld due to toxicity or that were missed were not administered at a later time. Patients who did not recover after a 3-week delay were withdrawn from the study. All adverse events were documented and graded according to the National Cancer Institute Common Toxicity Criteria, Version 2.0.

Radiologic tumor assessments were performed after every two cycles of treatment. Patients with evidence of response (i.e., a complete response [CR] or a partial response [PR]) to treatment or stable disease (SD) remained in the study until there was evidence of disease progression or unacceptable toxicity, or until the patient chose to have therapy discontinued. Radiologic response was classified according to the World Health Organization (WHO) criteria. A CR required total resolution of all detectable disease for ≥ 4 weeks. A PR was defined as a decrease of $> 50\%$ in the sum of the products of the largest perpendicular diameters of all measurable lesions persisting for ≥ 4 weeks without progression at any unmeasurable site and without the appearance of new sites of disease. SD was defined as a decrease of $< 50\%$ or an increase of $\leq 25\%$ in the sum of the products of the largest perpendicular diameters of all measurable lesions. Progressive disease (PD) was defined as an increase of $\geq 25\%$ in the product of the largest perpendicular diameters of 1 or more measurable lesions, the development of new lesions, or progression at an unmeasurable but evaluable site of disease.

Statistical Considerations

The current Phase II study was originally designed with the primary endpoint of response rate for the 30 patients with advanced carcinoid tumors. A Simon two-stage design was used to test the null hypothesis that the true objective response rate was $< 20\%$.[14] As predefined by the protocol, the study was terminated

TABLE 1
Baseline Patient Characteristics

Characteristic	No. of patients (%)
Median age (range)	59 yrs (range, 22–76 yrs)
Median time from original diagnosis (yrs)	1.8 (range, 1 mo–8 yrs)
Gender	
Male	9 (50)
Female	9 (50)
ECOG PS	
0	8 (44)
1	9 (50)
2	1 (6)
Tumor type	
Carcinoid (total)	9 (50)
Ileal primary	6 (33)
Unknown primary	3 (17)
Pancreatic endocrine	7 (39)
Pheochromocytoma	2 (11)
Tumor grade	
Well differentiated	16 (89)
Poorly differentiated (atypical)	2 (11)
Previous treatment	
No	9 (50)
Yes treatment[a]	9 (50)
Median time from previous treatment (mos)	3.5 (range, 1–7)
Liver function	
Total bilirubin (mg/dL)	0.7 (range, 0.2–1.2)
Alkaline phosphatase (U/L)	158 (range, 61–578)
Aspartate aminotransferase (U/L)	34 (range, 19–162)

ECOG PS: Eastern Cooperative Oncology Group performance status; U: units.
[a] Previous agents: streptozocin (5 patients); doxorubicin (5 patients); docetaxel (3 patients); carboplatin (2 patients); etoposide (2 patients); cisplatin (1 patient); interferon (1 patient); irinotecan (1 patient); vincristine (1 patient); cyclophosphamide (1 patient).

early, after the accrual of 18 patients, due to the absence of a radiologic response in any of these patients. Progression-free survival (PFS) was calculated from the start of therapy to the time of disease progression or death due to any cause (whichever occurred first). Overall survival (OS) was calculated from the start of therapy to the date of death. For survival calculations, patients were censored at the date of last patient contact. The distributions of duration of PFS and survival were estimated using the Kaplan–Meier method.[15]

RESULTS

Patient Population

Eighteen patients were enrolled between June 1999 and September 2000. The baseline characteristics of the study cohort are summarized in Table 1. The median age of the study population was 59 years, with equal numbers of men and women. Seventeen patients had an ECOG PS of 0 or 1, and 1 patient had a PS of 2. Nine patients had carcinoid tumors (six ileal tumors and three tumors of unknown origin), six had pancreatic endocrine tumors, and two had pheochromocytomas. No patient had a family history or clinical presentation suggestive of multiple endocrine neoplasic type 1 (MEN-1) or type 2 (MEN-2). Tumors were well differentiated in 16 patients, whereas 2 patients had poorly differentiated (*atypical*) neuroendocrine tumors. The median time from original diagnosis was 1.8 years (range, 1 month–8 years).

Of the 18 patients in the study cohort, 9 had previously received chemotherapy, which most commonly consisted of streptozocin and/or doxorubicin. Of these nine patients, only one had previously experienced a response to chemotherapy; of the remaining patients, six had SD as their best response, and two had PD. The median time from completion of prior chemotherapy was 3.5 months. Nine patients in the current study had evidence of active tumor growth on the baseline CT scan performed before the initiation of study treatment. The rate of prior tumor progression in the remaining nine patients could not be determined. Because the length of time since the preceding reference CT scan may have been greater than the 2-month restaging interval used in the current study, it was not possible to formally assess disease progression before therapy according to the study criteria.

Duration of Treatment

Eighty-one 4-week treatment cycles of gemcitabine (3 weekly infusions, followed by a 1-week break) were administered. A median of 3 treatment cycles were administered (range, 1–17 cycles), and the median time on study was 2.8 months. The majority of patients (12 [75%]) had treatment discontinued due to disease progression, and 3 patients withdrew consent. Two patients had treatment discontinued for other reasons—one patient underwent elective surgery, and another developed progressive symptoms due to carcinoid heart disease. One patient died during the study due to hepatic failure, which was likely to have been attributable to the progression of extensive hepatic metastases.

Toxicity

All 18 patients were assessable for toxicity. Gemcitabine was well tolerated in the current patient population. The most common toxicity was myelosuppression: Grade 3 or 4 neutropenia occurred in 5 (28%) patients (Table 2). In addition, two patients developed febrile neutropenia. Other toxicities included Grade 3 thrombocytopenia in one patient and Grade 3 dyspnea in two patients.

TABLE 2
Treatment-Related Toxicity

Toxicity	Maximum toxicity grade (%)			
	1	2	3	4
Anemia	4 (22)	4 (22)	0	0
Thrombocytopenia	4 (22)	3 (18)	1 (6)	0
Neutropenia	2 (11)	0	4 (22)	1 (6)
Febrile neutropenia	—	—	2 (12)	0
Fever w/o neutropenia	5 (28)	1 (6)	0	0
Fatigue	7 (39)	1 (6)	0	0
Anorexia	5 (28)	5 (28)	0	0
Nausea	9 (44)	2 (11)	0	0
Dyspnea	0	1 (6)	2 (11)	0

TABLE 3
Best Response to Therapy

Response	No. of patients (%)
Stable disease	11 (65)
Progressive disease	7 (35)

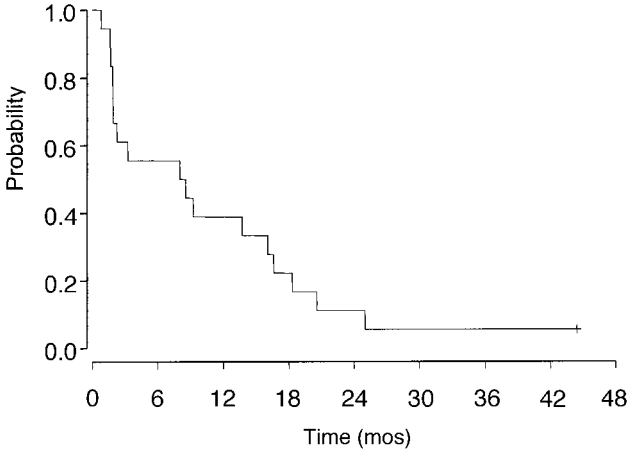

FIGURE 1. Progression-free survival among patients with metastatic neuroendocrine tumors treated with gemcitabine.

Efficacy

Of the 18 patients treated with gemcitabine, none had radiologic evidence of either a PR or CR to therapy. Eleven patients (65%) had SD as their best response to therapy (Table 3[3];0). The median PFS duration was 8.3 months (95% confidence interval [CI], 2.3–6 months; Fig. 1), and the median OS duration was 11.5 months (95% CI, 8.0–16.6 months; Fig. 2). Patients were also followed via serial 24-hour urine collection for the assessment of 5-hydroxyindolacetic acid (5-HIAA) and/or serum chromogranin A (CGA) levels. Six patients had elevated 5-HIAA levels at baseline, and nine patients had elevated CGA levels. Of these patients,

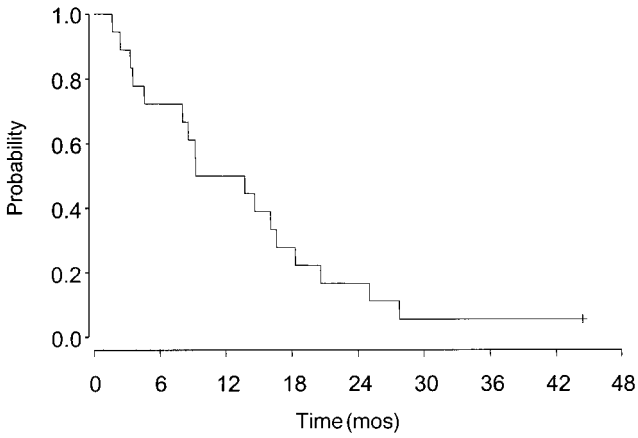

FIGURE 2. Overall survival among patients with metastatic neuroendocrine tumors treated with gemcitabine.

none experienced a decrease of > 50% relative to baseline as a result of therapy. One patient with gastrinoma was followed with serial gastrin levels and also did not exhibit evidence of a response to therapy.

DISCUSSION

Although treatment with gemcitabine was well tolerated in patients with metastatic neuroendocrine tumors, the current study demonstrated little evidence of efficacy. No radiologic or biochemical responses were observed among 18 patients, and the median survival duration was < 1 year. Although the time to tumor progression was 8.5 months and the SD rate was substantial (65%), the relevance of these observations in patients with neuroendocrine tumors is uncertain, given the often indolent course of this disease. In fact, a nearly identical percentage (66%) of patients who had received systemic chemotherapy before enrollment in the current study had experienced disease stabilization in response to their previous chemotherapy regimen.

A number of chemotherapeutic regimens have been used in the treatment of patients with metastatic neuroendocrine tumors. Although several of these regimens appear to have some activity, their widespread use has been limited due to concerns regarding their relative toxicity. In an initial study performed by ECOG, patients with metastatic carcinoid tumors were randomized to receive streptozocin in combination with either 5-FU or cyclophosphamide.[4] Tumor responses, defined as either radiologic regression or decreases in biochemical markers, occurred in 33% of patients treated with streptozocin/5-FU and in 26% of patients treated with streptozocin/cyclophosphamide. Unfortunately, the toxicity associated with streptozocin/5-FU was prohibitive, prompting a second trial in

which the dosing interval between cycles was lengthened. In this second randomized trial, the response rate associated with the streptozocin/5-FU combination decreased to 22%, compared with 21% for patients treated with doxorubicin alone.[5] The median survival durations were 14 and 11 months, respectively, and this difference was not statistically significant.

Pancreatic endocrine tumors are perceived as being more responsive to cytotoxic chemotherapy than are carcinoid tumors. Few randomized trials involving patients with this disease have been performed. In one such trial, 105 patients with pancreatic islet cell tumors were randomized to receive either streptozocin/doxorubicin, streptozocin/5-FU, or chlorozotocin.[6] Compared with the streptozocin/5-FU combination, patients who received streptozocin/doxorubicin had a superior response rate (69% vs. 45%), improved time to tumor progression (20 months vs. 6.9 months), and a longer median OS (2.2 years vs. 1.4 years). A second, smaller study evaluating a combination of streptozocin, doxorubicin, and 5-FU in 11 patients also reported significant activity, with objective responses observed in 6 patients (54%).[16] Retrospective analyses, however, have failed to confirm these encouraging results. In one such study, performed at Memorial-Sloan Kettering Cancer Center (New York, NY), only 1 of 16 patients with pancreatic islet cells treated with streptozocin/doxorubicin experienced a confirmed radiologic response according to standard WHO criteria.[17] A similar series of 16 patients treated at Dana-Farber Cancer Institute also reported only 1 confirmed response.[18]

DTIC has been evaluated as a potential alternative to streptozocin-based therapy for both carcinoid and pancreatic endocrine tumors. In a Southwest Oncology Group study, 56 patients with metastatic carcinoid tumors were treated with DTIC, which was administered at a dose of 650–850 mg/m^2 monthly.[7] Nine patients (16%) had objective radiologic responses. Toxicity was moderate, with 88% of patients experiencing nausea, emesis, or anorexia. The ECOG performed a Phase II study of DTIC administered at a dose of 850 mg/m^2 monthly to 42 patients with advanced pancreatic islet cell carcinoma.[8] DTIC was clearly active in this setting. Objective responses were observed in 33% of patients. However, toxicity was again a concern, with two fatal complications reported. The addition of 5-FU and epirubicin to DTIC does not appear to further enhance antitumor activity beyond what is achieved with DTIC alone; this modification was associated with an objective response rate of 25% in a heterogeneous group of patients with advanced neuroendocrine tumors.[19]

Similar regimens have been used to treat patients with malignant pheochromocytoma, also without overwhelming success. A combination of DTIC, vincristine, and cyclophosphamide resulted in biochemical responses and was associated with anticipated hematologic, neurologic, and gastrointestinal side effects.[10] The role of streptozocin in the treatment of pheochromocytoma is controversial, with only anecdotal responses reported.[9]

Newer chemotherapeutic agents have, to date, proved relatively inactive in neuroendocrine tumors. High-dose paclitaxel, administered with granulocyte–colony-stimulating factor, was evaluated in 24 patients with metastatic carcinoid or islet cell tumors.[12] Significant hematologic toxicity was observed, and responses were noted in only 8% of patients. Docetaxel was associated with biochemical responses but did not result in any radiologic responses in a recent Phase II trial involving 21 patients with carcinoid tumors.[11] It is noteworthy that the median OS periods for patients treated with paclitaxel and patients treated with docetaxel in these trials were 20 months and 24 months, respectively.

The median survival duration of 11.5 months for patients treated with gemcitabine in the current study compares unfavorably with these earlier studies. This finding may be partially attributable to the fact that many patients enrolled in the study already had relatively advanced disease—the median time from diagnosis to study enrollment for patients in the current study was 1.8 years. Even taking this finding into account, however, the short median survival duration observed in the current study lends support to the hypothesis that gemcitabine is relatively inactive against neuroendocrine tumors.

Chemotherapeutic options for patients with metastatic neuroendocrine tumors remain limited. Although regimens containing streptozocin or DTIC have been associated with modest activity, the potential side effects of these regimens, as well as the frequently indolent natural history of these tumors, have prevented their widespread use in this setting. To date, none of the newer and potentially less toxic chemotherapeutic agents have proven to be effective against neuroendocrine tumors. The current study adds gemcitabine to this list of inactive agents and highlights the need for novel approaches in the treatment of such tumors.

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