A Phase II Study of High-Dose Paclitaxel in Patients with Advanced Neuroendocrine Tumors

Stephen M. Ansell, M.D., Ph.D.[1]
Henry C. Pitot, M.D.[1]
Patrick A. Burch, M.D.[1]
Larry K. Kvols, M.D.[2]
Michelle R. Mahoney, M.S.[3]
Joseph Rubin, M.D.[1]

[1] Division of Medical Oncology, Mayo Clinic, Rochester, Minnesota.

[2] GI Tumor Program, H. Lee Moffitt Cancer Center, Tampa, Florida.

[3] Division of Statistics, Mayo Clinic, Rochester, Minnesota.

BACKGROUND. New agents with antitumor activity in patients with neuroendocrine tumors are sorely needed. A Phase II study of high-dose paclitaxel in patients with metastatic carcinoid and islet cell tumors was performed at the Mayo Clinic. Granulocyte–colony-stimulating factor (GCSF) also was administered to ameliorate neutropenia.

METHODS. Twenty-four patients (14 with carcinoid tumors, 9 with islet cell tumors, and 1 with an anaplastic tumor) were enrolled on this Phase II study of paclitaxel given as a 24-hour continuous infusion at a dose of 250 mg/m^2 every 3 weeks plus GCSF at a dose of 5 μg/kg/day subcutaneously, beginning 24 hours after the completion of the paclitaxel dose and continuing until the absolute neutrophil count was $> 10,000/\mu$L.

RESULTS. All 24 patients were evaluable for analysis. The overall response rate was 8% (95% confidence interval [95% CI], 0–0.11). At last follow-up all patients except 1 had developed disease progression, with an estimated median time to disease progression of 3.2 months (95% CI, 1.6–6.0 months). The estimated median survival was 1.5 years (95% CI, 1.0–1.8 years). Hematologic toxicity was significant with 12 of 24 patients developing Grade 4 (according to the National Cancer Institute Common Toxicity Criteria scale) neutropenia; however, there were no septic deaths reported. There were 17 episodes of Grade 4 neutropenia in these 12 patients and the duration of these events ranged from 2–5 days. More common nonhematologic toxicities included arthralgia (21 patients), anorexia (15 patients), nausea (15 patients), diarrhea (12 patients), and allergic reactions (2 patients).

CONCLUSIONS. Given the lack of antitumor activity of paclitaxel and the significant hematologic toxicity observed despite the use of GCSF support in the current study cohort of patients with neuroendocrine tumors, further studies of this combination in this particular patient population are not recommended. *Cancer* **2001;91: 1543–8.** © *2001 American Cancer Society.*

KEYWORDS: paclitaxel, neuroendocrine tumors, carcinoid tumor, islet cell tumor.

Gastrointestinal neuroendocrine tumors are rare human malignancies and may present as a constellation of nonspecific symptoms mimicking more common diseases. These tumors can be divided between the gastrointestinal submucosal carcinoid tumors and the endocrine islet cell tumors of the pancreas. A smaller subset of tumors with anaplastic histology are classified as anaplastic carcinomas. They are derived from the enterochromaffin or Kulchitsky cells[1] and are classified histologically as APUDomas (amine precursor uptake and decarboxylation) but are indistinguishable from one another by light microscopy. They may be found anywhere in the human body but traditionally are described as originating from the foregut, midgut, or hindgut.[2] Neuroendocrine tumors commonly present with disseminated disease. Although the disease may have an indolent course in

many patients, the overall survival of patients correlates significantly with the stage of disease. Patients with unresectable abdominal metastases and hepatic metastases fare poorly, with median survivals of 5 years and 3 years, respectively.

Paclitaxel is derived from the bark of the Pacific yew, *Taxus Brevifolia*, and is one of a group of compounds with a unique mechanism of cytotoxicity as a promoter of microtubular assembly and stabilization.[3,4] Paclitaxel binds to microtubules and causes cells to form abundant arrays of disorganized and dysfunctional microtubules. Treated cells have a replication block in the G_2- and M-phases of the cell course. Paclitaxel has shown activity against ovarian carcinoma and breast carcinoma[3,5] and also has demonstrated effective single agent activity against non-small cell lung carcinoma.[6,7] In human trials, the primary dose-limiting toxicity associated with paclitaxel has been neutropenia. The administration of granulocyte–colony-stimulating factor (GCSF) after intensive chemotherapy has been shown to reduce the duration of neutropenia and was administered in the current trial in an effort to minimize the need for dose reductions secondary to myelosuppression.

The goal of the current study was to determine the therapeutic activity and toxicity of paclitaxel given with GCSF support in patients with advanced neuroendocrine carcinoma.

MATERIALS AND METHODS
Eligibility/Evaluation

Patients with histologic or cytologic proof of a neuroendocrine tumor who were seen at the Mayo Clinic were eligible for the current study. All patients had radiologically documented evidence of extensive stage disease. All patients had measurable or evaluable disease and had an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 1, or 2. Preenrollment staging tests included a history and physical examination; complete blood count; standard blood chemistries; serum levels of either insulin, gastrin, glucagon, or adrenocorticotropic hormone (ACTH), or vasoactive intestinal peptide or 24-hour urine 5-hydroxyindoleacetic acid (5-HIAA) levels; chest radiograph; computed tomography (CT) scan or magnetic resonance imaging of the abdomen; and an electrocardiogram.

Contraindications to protocol entry included a leukocyte count $< 4000/\mu L$, a platelet count $< 130,000/\mu L$, a hemoglobin level < 10 g/dL, liver function tests > 3 times the institutional upper limit of normal, or a total bilirubin greater than the institutional upper limit of normal. Other contraindications to protocol entry included more than two prior chemotherapy regimens, radiation therapy to the axial skeleton or pelvis, pregnant or nursing women, and patients with significant cardiac disease. The cardiac exclusions included a history of angina or congestive heart failure, cardiac arrhythmias, myocardial infarction occurring within the previous 6 months, or electrocardiographic evidence of a right or left bundle branch block. Patients with a prior history of cancer other than skin cancer, superficial bladder carcinoma, American Joint Committee on Cancer (AJCC) Stage I colon or rectal carcinoma, or in situ cervical carcinoma were excluded unless they had a 5-year disease-free interval without treatment. Patients with a history of allergic reactions to cremophor-containing or *Escherichia coli*-derived drugs were excluded. Informed consent was obtained from all patients.

Tumor responses were classified as a complete response (CR) or a partial response (PR). A measurable lesion was defined as a lesion apparent on physical examination, CT scan, or radiography with clearly measurable perpendicular dimensions. CR was defined as the total disappearance of all tumor. PR was defined as a reduction of $\geq 50\%$ in the sum of the products of the longest perpendicular dimensions of the indicator lesion(s). All patients were required to have measurable tumor or definite hormonal abnormalities that would serve as indicators of response to therapy. Elevated serum levels of either insulin, gastrin, glucagon, ACTH, or vasoactive intestinal peptide or elevated 24-hour urine 5-HIAA levels were required for entry onto the study if no other measurable lesions were found.

Treatment

All patients received pretreatment with dexamethasone, 20 mg orally, at 12 hours and 6 hours before the initiation of paclitaxel. In addition, patients received diphenhydramine, 50 mg intravenously, and cimetidine, 300 mg intravenously, 30 minutes before the administration of paclitaxel. The administration of paclitaxel took place over 24 hours by intravenous infusion at a dose of 250 mg/m^2 in normal saline or 5% dextrose. Treatment was administered in the hospital setting or General Clinical Research Center and repeated every 21 days. GCSF was given subcutaneously at a dose of 5 μg/kg/day until the absolute neutrophil count (ANC) was $> 10,000/$L after the nadir. GCSF was initiated 24 hours after the completion treatment with paclitaxel. Patients who achieved a PR or stable disease continued treatment until disease progression, unless they experienced undue toxicity. The dose of paclitaxel was decreased by 30% in patients with an ANC $< 500/\mu L$ for 5 days or an ANC $< 500/\mu L$ with fever/sepsis or a platelet count $< 25,000$ with associ-

TABLE 1
Design Considerations

Parameter	Subgroup	
	Carcinoid	Islet cell and anaplastic[a]
Null hypothesis	0.20	0.20
Alternative hypothesis	0.40	0.50
Power, significance level	(0.90, 0.09)	(0.89, 0.10)
Stage I accrual	17	9
Responses needed in Stage I to proceed to Stage II	4	3
Stage II accrual	20	9
Responses needed in Stage I and Stage II combined to declare activity	11	6

[a] Identical designs were used for these two subgroups.

ated bleeding. Treatment was discontinued in any patients experiencing ≥ Grade 3 cardiac arrhythmia, allergic reaction, and/or neuropathy (grades of toxicity based on the National Cancer Institute Common Toxicity Criteria scale). If the leukocyte count was < 4000/μL or the platelet count was < 100,000/μL at the time of retreatment, treatment then was delayed until the counts recovered. Similarly, any patient with Grade 3/4 mucositis/stomatitis at the time of retreatment had their treatment delayed until this toxicity resolved and the dose was decreased by 30% for subsequent courses.

Evaluation
Patients were evaluated at study entry and after every course of therapy by physical examination, chest radiography, complete blood count, and a chemistry profile. If the indicator lesion was measurable or assessable by CT scan only, the scan then was repeated with every other course of therapy. The incidence of toxicity was monitored at each evaluation and toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria scale. In particular, patients were monitored for any signs or symptoms of cardiac toxicity.

Study Design
Patients were classified as having carcinoid, islet cell, or anaplastic carcinoma. Due to the anticipated difference in the responses of these patient populations to the chemotherapy regimens, we designed the current study as three sub-Phase II studies with the same primary endpoint of therapeutic activity (i.e., response rate). The study was not designed nor powered for direct comparisons between the three subgroups of patients. Table 1 provides a summary of the two-stage

Simon[8] designs and power considerations for the three substudies. A patient was classified as having a confirmed tumor response if a CR or PR was sustained for at least 2 consecutive evaluations that were at least 3 weeks apart.

All patients were followed for disease progression, duration of response, and survival. Patients who died (or were lost to follow-up) without disease progression were considered to have disease progression at the date of death (or last contact) unless documentation proved otherwise, in which case they would be considered as having no disease progression at the date of last tumor evaluation. The duration of response was calculated from the earliest date of tumor response (i.e., CR or PR) to the date of disease progression. Time to progression was calculated from the date of study entry to the date of disease progression. Time to death (i.e., survival) was calculated from the date of study entry to the date of death or last follow-up contact.

Statistical Analysis
Summary statistics (e.g., mean, median, quartiles) and Wilcoxon tests were used to describe and compare the distributions of continuous variables (e.g., age, leukocyte count nadirs). Hematologic toxicity was summarized as a lowest value (i.e., nadir) per patient and course. Nonhematologic toxicity was reported as the maximum grade (i.e., severity) for a given type of event. The chi-square and Fisher exact tests were used to compare the frequency distributions of categoric data. Exact binomial confidence intervals were used for estimating the confirmed response rate. Kaplan–Meier[9] methodology was used to estimate the distributions of duration of response, time to progression, and survival.

RESULTS
This study accrued a total of 24 patients, all of whom were evaluable for response and toxicity. A tabulation of patient characteristics at study entry is shown in Table 2. Only one patient with an anaplastic tumor was accrued and this patient's data were combined with those of the group of patients with islet cell carcinoma. All patients had advanced disease with 88%(21 of 24 patients) presenting with liver metastases and 29% (7 of 24 patients) presenting with lung metastases. The median age of the patients was 55 years; however, the patients in the carcinoid tumor group were significantly older than those in the islet cell/anaplastic tumor group ($P = 0.0025$).

Patients received a total of 83 courses of paclitaxel plus GCSF (median, 3 courses; range, 1–7 courses). One patient did not receive the third course of GCSF because of a skin rash. The primary hematologic tox-

TABLE 2
Patient Characteristics

Factor	Carcinoid	Islet cell and anaplastic	Overall
		Subgroup	
No. of patients	14	10	24
Age (yrs)			
Median	60.5	47.5	55
Range	41–71	26–60	26–71
Gender (M/F)	8/6	3/7	11/13
ECOG PS			
0	1	2	3
1	12	7	19
2	1	1	2
Prior doxorubicin-containing therapy	2	6	8
Metastatic disease site			
Bone	1	0	1
Liver	8	5	13
Lung	1	0	1
Two sites	3	4	7
Three sites	1	1	2
Previous treatment	5	7	12

M: male; F: female; ECOG PS: Eastern Cooperative Oncology Group performance score.

TABLE 3
Toxicity[a]: Maximum Severity per Patient (N = 24)

Type	1/2	3	4
	Grade (%)		
Allergy	0	1 (4)	1 (4)
Alopecia	22 (92)	NA	NA
Anorexia	13 (54)	2 (8)	0
Diarrhea	11 (46)	0	2 (8)
Infection	0	1 (4)	0
Myalgia	13 (54)	2 (8)	0
Nausea	12 (50)	3 (13)	0
Neurosensory	13 (54)	1 (4)	0
Stomatitis	7 (29)	1 (4)	1 (4)
Emesis	9 (38)	0	1 (4)
Skin	5 (21)	1 (4)	0
Neuromotor	5 (21)	0	0
Arthralgia	17 (71)	4 (17)	0
Leukopenia	7 (29)	8 (33)	3 (13)
Neutropenia[b]	—	—	12 (50)
Thrombocytopenia	15 (63)	1 (4)	0

NA: not applicable.

[a] Toxicity was determined according to National Cancer Institute Common Toxicity Criteria, Version 2.
[b] Data were collected if the absolute neutrophil count was < 500/μL.

icity was neutropenia (Table 3). The ANC values and duration were recorded for analysis purposes if they were < 500/μL. Patients with carcinoid tumors experienced more myelosuppression; however, the difference in the average hematologic nadir between the two groups was not statistically significant. Approximately 61% of patients (14 of 23 patients) experienced either at least Grade 3 leukopenia or Grade 4 neutropenia (ANC < 500/μL). Neutropenia was reported to have occurred 17 times in 12 patients and the duration of these events ranged from 2–5 days. Nine of the 12 events reported in the carcinoid tumor group (75%) involved Grade 3 leukopenia. Leukopenia and neutropenia occurred together in three of five patients in the islet cell/anaplastic group. Four cases of Grade 3/4 leukopenia occurred in the absence of Grade 4 neutropenia. One patient with a carcinoid tumor experienced Grade 4 neutropenia over three treatment courses in conjunction with stomatitis, arthralgia, neurosensory toxicity, and anorexia. This patient developed disease progression within 3 courses and died 3 months later. Another carcinoid tumor patient experienced Grade 4 neutropenia in four of six courses. Severe thrombocytopenia was unremarkable; only 1 patient experienced an overall low platelet count of 48,000/μL.

Nonhematologic toxicity (Table 3) primarily included diarrhea, anorexia, allergic reactions, nausea, and arthralgia. Toxicity patterns were similar between the two groups with the exception of neuropathy and diarrhea. Fifty percent of the patients in the islet cell/anaplastic tumor group (5 of 10 patients) experienced Grade 1/2 neurologic toxicity. Approximately 64% of the patients with carcinoid tumors (9 of 14 patients) experienced neurotoxicity, 1 of which was Grade 3. Seventy percent of patients with islet cell/anaplastic tumors (7 of 10 patients) experienced Grade 1/2 diarrhea versus 36% of patients in the carcinoid tumor group (5 of 14 patients).

All 24 patients were considered to be evaluable for confirmed tumor response. Only two PRs were observed that failed to meet the criteria to proceed to the second stage of accrual for the study design. The overall response rate was 8% (95% confidence interval [95% CI], 0–11%). One patient with a carcinoid tumor experienced a PR, albeit nonsustained (i.e., lasting one course). Similarly, one patient with an islet cell tumor was classified as having a "biochemical" PR (i.e., a > 50% decrease in 5HIAA, but stable CT scans and liver examinations over 2 of 7 treatment courses). A majority of patients (83%) discontinued treatment due to disease progression and 3 patients discontinued treatment due to toxicity or patient refusal to continue.

At last follow-up, 23 patients had developed disease progression. Two patients were alive off-study and 22 patients (92%) had died. The median survival and the median time to disease progression was 1.5 years (95% CI, 1.0–1.8 years) and 3.2 months (95% CI, 1.6–6.0 months), respectively (Figs. 1 and 2). Estimates of the median survival and time to disease
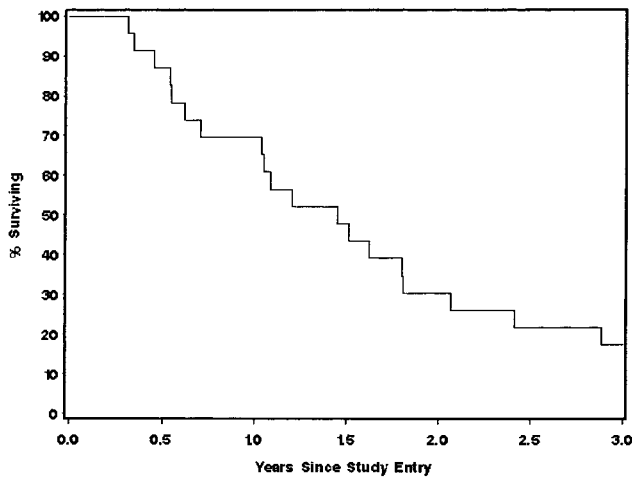
FIGURE 1. Overall survival for patients with metastatic neuroendocrine tumors who were treated with paclitaxel.
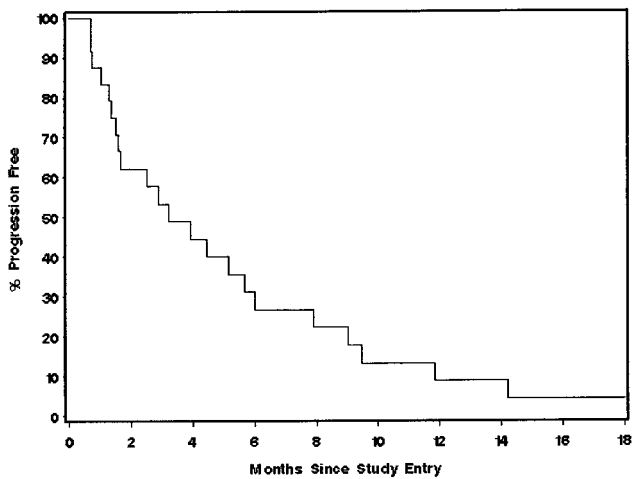

FIGURE 2. Time to progression in patients with metastatic neuroendocrine tumors who were treated with paclitaxel.

progression for patients with carcinoid tumors was 1.8 years (95% CI, 0.7–3.2 years) and 3.4 months (95% CI, 1.3–6.0 months), respectively. Estimates of the median survival and time to disease progression for patients with anaplastic/islet cell tumors was 1.1 years (95% CI, 0.6–1.6 years) and 3.2 months (95% CI, 1.5–9.5 months), respectively. It should be noted that a formal comparison between the two subgroups was not statistically appropriate because the underlying disease process and small sample sizes were believed to account for any significant differences observed.

DISCUSSION
In general, gastrointestinal neuroendocrine tumors are not overly sensitive to cytotoxic chemotherapy. Chemotherapy can be used to reduce tumor burden,

but it generally is reserved for those patients with severe symptomatology or those who develop poor prognostic signs.[10,11] Single cytotoxic agents used in this disease are associated with variable response rates. To our knowledge, doxorubicin, 5-fluorouracil (5-FU), dacarbazine, and interferon-α have produced the best objective response rates reported to date in patients with advanced disease (17–21%).[10–17] Unfortunately, combination chemotherapy has not improved the outlook significantly for patients with advanced carcinoid tumors, although the response rate has been reported to vary between 20–40%.[13,18–19] The combination of streptozocin and 5-FU, used by ECOG[12] and the Mayo Clinic,[10] demonstrated a 33% objective response rate in patients with metastatic carcinoid tumors. Unfortunately, this regimen produced substantial side effects such as nausea, emesis, and anorexia, which limited its prolonged application, and the response duration was reported to be only 7 months. Two other trials[18,19] showed a slightly better response rate (35–40%) when using different combinations (5-FU, doxorubicin, cyclophosphamide, and streptozocin and streptozocin and doxorubicin, respectively) in patients with advanced carcinoid tumors, although no firm conclusions can be drawn because of the extremely small number of patients.

Recent trials investigating new agents have been disappointing. Phase II trials of dacarbazine and mitoxantrone demonstrated minimal activity for these drugs.[17,20,21] Likewise, the Italian Medical Oncology Group studied the combination of dacarbazine, 5-FU, and epirubicin and found it to have no more activity than any one of the single agents used alone.[22] Efforts to biologically modulate 5-FU with the addition of interferon-α are reported to have been met with mixed success in three recent reports. Although the regimens had tolerable toxicity and produced biochemical responses, the objective tumor responses were < 20%.[23–25] Again, because these response rates are similar to the response rates of the agents used individually and because toxicity was increased, we believe the use of combination chemotherapies cannot be recommended routinely and further studies of cytotoxic therapies are needed.

However, patients with aggressive variants of carcinoid tumors as well as those with islet cell tumors appear to have higher response rates to therapy.[26–28] Moertel et al.[27] reported 45 patients with metastatic neuroendocrine tumors who were treated with etoposide and cisplatin. Among 27 patients with well-differentiated carcinoid tumors or islet cell carcinomas, only 2 objective PRs were observed (7%). However, among 18 patients prospectively classified as having anaplastic neuroendocrine carcinomas, there were 9 PRs and 3 CRs, giving an overall regression rate of 67%. The median duration of

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.

fastcase®
Smarter legal research.