

Phase I trial of weekly cisplatin, irinotecan and paclitaxel in patients with advanced gastrointestinal cancer

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Summary Objectives: To determine the maximum tolerated dose (MTD), toxicities, and suitable dose for weekly 1-h paclitaxel combined with weekly cisplatin and irinotecan to treat advanced gastrointestinal malignancies. **Methods:** Thirty patients with metastatic or locally advanced (unresectable or recurrent) gastrointestinal solid tumors were enrolled on this single-center, phase I study. Patients were treated with paclitaxel given over 1h at 1 of 4 dose levels (40, 50, 65, or 80 mg/m²). Paclitaxel was followed by fixed doses of cisplatin (30 mg/m²) and irinotecan (50 mg/m²). All treatment was administered sequentially, once a week, in 6-week cycles (4 weeks on, 2 weeks off). Dose-limiting toxicity (DLT) was defined as a 2-week delay in treatment for grade 3 or 4 non-hematologic toxicity, neutropenic fever, a 1-week delay for grade 4 hematologic toxicity, or a 2-week delay for grade 3 hematologic toxicity. **Results:** Thirty patients were recruited; 28 patients were assessable for safety. Most of the patients (70%) had no prior chemotherapy. The primary first-cycle DLTs were neutropenia, diarrhea, and nausea. Paclitaxel at 65 mg/m² was defined as the MTD. The most

common grade 3–4 toxicities observed during all cycles were neutropenia (57%), febrile neutropenia (11%), diarrhea (29%), fatigue (29%), and nausea (18%). No patients had G-CSF (Neupogen, Amgen Inc., Thousand Oaks, CA) support. Responses were observed in gastric, esophageal, and pancreatic cancers. **Conclusion:** Paclitaxel at 65 mg/m², cisplatin (30 mg/m²), and irinotecan (50 mg/m²) given weekly can be safely administered to patients with solid tumor malignancies. To improve cumulative toxicities, a schedule modification was required (3-week cycle; 2-on, 1-off) Neutropenia was the most common DLT. This combination showed substantial activity, particularly in patients with gastric and esophageal adenocarcinoma, and phase II evaluation could be considered.

Keywords Cisplatin · Irinotecan · Paclitaxel · Phase I · Gastrointestinal cancer

Introduction

In 2008, more than 35,000 Americans will be diagnosed with esophageal or gastric cancer and nearly 70% will die of their disease [1]. Despite advances in surgical technique and treatment, 5-year overall survival remains low for both esophageal (14%) and gastric (40%) cancers since metastatic or unresectable disease is found at presentation in more than half of patients [2, 3]. Single-agent or platinum-based combination chemotherapy is a palliative treatment option. Older combination regimens with cisplatin and fluorouracil tend to produce higher response rates, but with excessive toxicities [3–5]. Over the past decade, clinical research has focused on combining cisplatin with newer agents, including paclitaxel (Taxol; Bristol-Meyers Squibb, Princeton, NJ) and irinotecan (CPT-11, Camptosar; Phar-

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macia Corp., Peapack, NJ). Recent trials in upper gastric cancer support the addition of docetaxel to infusional fluorouracil and cisplatin, although increased response rates and survival come at the cost of significant toxicity [6].

Irinotecan, an inhibitor of topoisomerase-1, has emerged as a significant cytotoxic agent in gastrointestinal and lung cancer. Preclinical studies suggest synergy between irinotecan and cisplatin by interrupting the repair of the platinum-DNA adducts and hence further cancer cell death [7–9]. In a randomized trial in Japanese patients with small cell lung cancer, a survival advantage was observed with this combination [10]. However, these results were not replicated in a similar trial in the United States [11]. In gastric cancer, monthly cisplatin and irinotecan every 2 weeks provided response rates exceeding 40%, but with excessive grade 4 neutropenia [12, 13]. At Memorial Sloan-Kettering Cancer Center, a phase I study evaluated this combination on a weekly, more tolerable schedule, with dose-limiting neutropenia [14]. In the subsequent phase II gastroesophageal cancer trials, response rates were substantial in the first-(57%) and second-line (31%) settings, with minimal toxicities [15–17]. These promising results led to further investigation with concurrent radiation in locally advanced cancer [18–20] and suggested that incorporation of a third agent in metastatic cancer may be feasible.

Paclitaxel, an antimetabolic agent, has broad-spectrum antitumor activity, especially in platinum combinations, in several malignancies including ovarian and lung cancer. In upper gastrointestinal cancer, Ajani and colleagues reported the single activity (32%) of paclitaxel given in a 24-h infusion [21]. When 24-h paclitaxel was combined with cisplatin every 3 weeks, response rates were substantial (44%); however, unacceptable neutropenia and hospitalizations limited its use [22]. Paclitaxel has also been studied with the use of a shorter infusion rate (3 h every 3 weeks or 1 h every week), which appears to reduce the myelosuppressive toxicity. In patients with esophageal cancer, weekly 1-h paclitaxel has been shown to be active and well tolerated [23].

Based on our experience with phase I/II trials with cisplatin–irinotecan combinations in gastrointestinal cancers and the non-overlapping mechanisms of paclitaxel, we undertook this phase I trial to see if this three-drug combination is feasible. The primary objectives were: (1) to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) for the combination of weekly paclitaxel given over 1h, with weekly cisplatin (30 mg/m²) and irinotecan (50 mg/m²) each given over 30 min; (2) to determine the qualitative and quantitative toxicities of this combination; and (3) to seek preliminary evidence of therapeutic activity with this combination regimen in several different gastrointestinal malignancies.

Patients and methods

Patient selection

To be eligible for this trial, all patients had to meet the following criteria: (1) histologic proof of a locally advanced (unresectable or recurrent) or metastatic solid tumor malignancy; (2) bi-dimensionally measurable or evaluable disease was preferable but not required; (3) one prior chemotherapy regimen was allowed in the first cohort (the protocol was amended after cohort 2 to exclude any patients with prior chemotherapy); (4) prior radiation was allowed, provided at least 4 weeks had elapsed and the radiation portal did not include the pelvis; (5) ≥ 18 years of age; (6) Karnofsky performance status [KPS] of $\geq 70\%$; (7) signed consent; and (8) adequate organ function as documented by laboratory studies (white blood count $\geq 3,000/\mu\text{L}$, neutrophils $\geq 1,500/\mu\text{L}$, platelets $\geq 100,000/\mu\text{L}$, serum bilirubin ≤ 1.5 mg/dL, serum creatinine ≤ 1.5 mg/dL, and AST (SGOT) $\leq 3\times$ upper reference value, except when abnormal value was due to liver metastases, in which case $\leq 5\times$ upper reference value was acceptable).

Patients were excluded from this trial for the following criteria: (1) active or uncontrolled infection; (2) brain metastases or carcinomatous meningitis; (3) interstitial pulmonary fibrosis; (4) unstable angina or grade III/IV NYHA cardiac disease; (5) uncontrolled diabetes mellitus (blood glucose ≥ 250 mg/dL); (6) hypercalcemia (serum Ca ≥ 12.0 mg/dL); (7) pregnant or lactating women; (8) history of Gilbert's disease; (9) history of a seizure disorder and on antiepileptic medications; or (9) unable to comply with the protocol or to undergo the specified follow-up for safety or effectiveness. All patients were required to read, agree to, and sign a statement of informed consent prior to enrollment, as approved by the Institutional Review Board at our institution.

Treatment plan

All chemotherapy was administered in the outpatient setting, and all agents were obtained commercially. Paclitaxel (Bristol-Myers Squibb, Inc., Princeton, NJ) was administered as an intravenous (IV) infusion over 60 min, followed by IV cisplatin over 30 min, and then IV irinotecan (Pharmacia Corp., Peapack, NJ) over 30 min. Paclitaxel was dose escalated (40–50–65–80 mg/m²) with fixed doses of cisplatin (30 mg/m²) and irinotecan (50 mg/m²). All chemotherapy was given once weekly for 4 weeks, followed by a 2-week break. Each treatment cycle lasted 6 weeks.

To prevent hypersensitivity reaction, patients were pre-treated with dexamethasone (20 mg IV once), diphenhydramine (50 mg IV once), and cimetidine (300 mg IV once) just prior to paclitaxel. For antiemetic control, granisetron (2 mg

oral) was given prior to paclitaxel. Recognition and management of treatment-related diarrhea was outlined for each patient. All patients were instructed to begin loperamide at the earliest sign of diarrhea that occurred more than 12 h after receiving irinotecan. Loperamide dosing was as follows: 4 mg at the onset of diarrhea, then 2 mg every 2 h as needed until resolution of diarrhea ≥ 12 h. Loperamide was not taken prophylactically. Atropine (0.5–1 mg IV bolus) was given for diarrhea or abdominal cramping that occurred within 1 h of receiving irinotecan. If a patient required atropine, all subsequent irinotecan doses were preceded by atropine. To prevent renal dysfunction, patients were advised to maintain an oral intake $\geq 1\text{L}/\text{m}^2$ on the day of treatment and were hydrated with 5% dextrose in normal saline at a minimum of 250 mL/h for 2 h prior to cisplatin.

Erythropoietin (Procrit, Amgen Inc., Thousand Oaks, CA) was permitted per institutional guidelines. Filgrastim (G-CSF, [Neupogen, Amgen Inc., Thousand Oaks, CA]) use was not permitted during cycle 1, as hematologic toxicity or treatment delays due to hematologic toxicity defined DLT. After cycle 1, filgrastim could be used at the discretion of the treating physician.

Dose escalation and definition of MTD and DLT

Three to six patients were accrued at each dose level until DLT was reached. DLT was defined based on toxicities in the first cycle of treatment. If a DLT was experienced in one out of three patients, then another cohort of three patients were evaluated prior to dose escalation. A maximum of six patients were enrolled in each cohort. If fewer than one out of the three or two out of the six patients experienced a DLT, then the next cohort of patients were treated at the next higher dose level of paclitaxel (25% dose escalation). However, prior to any dose escalation, all patients in the cohort had to have completed one full cycle (6 weeks) of therapy. If more than one out of the three, or two out of the six, patients experienced a DLT, then no further dose escalation was made and that level was considered to have exceeded the MTD. The level immediately preceding that level was designated as the MTD. Up to a total of ten patients were treated at the MTD to further define any toxicities that may have subsequently occurred with this regimen. Of these ten patients, at least three with stable disease or response were to receive at least three cycles (18 weeks) of therapy to detect any long-term toxicity associated with this drug combination.

Toxicities were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria, version 1.0. Fatigue and asthenia were graded by the Cancer and Leukemia Group B (CALGB) criteria. Hematologic DLT was any grade 4 toxicity (absolute neutrophil count [ANC] $< 500/\mu\text{L}$, platelets $< 25,000/\mu\text{L}$) lasting longer than 7 days,

neutropenic fever ($\geq 38.1^\circ\text{C}$ with ANC $< 1,000/\mu\text{L}$), or dose delay lasting greater than 2 weeks. Renal DLT was defined as serum creatinine > 1.8 mg/dl lasting longer than 2 weeks. Gastrointestinal DLT was defined as grade 3 diarrhea lasting longer than 2 days (despite intensive loperamide therapy), grade 4 diarrhea, grade 3 stomatitis lasting longer than 7 days (despite intensive viscous lidocaine therapy), or grade 4 stomatitis. Grade 3 or 4 peripheral neuropathy lasting longer than 2 weeks or grade 4 fatigue lasting longer than 1 week was defined as a DLT. Other non-hematologic DLTs (except nausea and vomiting) must have been grade 3/4 and determined treatment related by the principal investigator.

Dose modifications

Prior to each weekly treatment, complete blood count and serum creatinine were performed. For cycle 1, treatment could proceed on Day 1 if: ANC $\geq 1,500/\mu\text{L}$, platelets $\geq 100,000/\mu\text{L}$, and creatinine ≤ 1.5 mg/dL. After week 1 in

Table 1 Patient characteristics ($n=30$)

Characteristics	No of patients	
Age, years		
Median (range)	54 (31–74)	
Baseline performance status (KPS)		
Median	80% (70–90%)	
Sex		
Male	26	87%
Female	4	13%
Diagnosis		
Esophageal squamous cell carcinoma	2	7%
Esophageal/GE junction adenocarcinoma	8	27%
Gastric adenocarcinoma	8	27%
Pancreatic adenocarcinoma	7	23%
Adenocarcinoma of unknown primary	4	13%
Hepatocellular carcinoma	1	3%
Stage		
IV	30	100%
Common sites of measurable disease		
Liver	20	67%
Lymph nodes	18	60%
Peritoneum/carcinomatosis	7	23%
Lung	6	20%
Bone	2	7%
Prior treatment		
Radiation	1	3%
Surgical resection	2	7%
Chemotherapy regimens		
0	21	70%
1	6	20%
2	3	10%

KPS Karnofsky performance status, GE gastroesophageal

cycle 1, treatment could proceed if: ANC $\geq 1,000/\mu\text{L}$, platelets $\geq 75,000/\mu\text{L}$, and creatinine $\leq 1.8 \text{ mg/dL}$. If these parameters were not met, all treatment was delayed for 1 week, up to 2 weeks in total. If renal function or blood counts did not improve after a 2-week delay, DLT was defined and the patient was removed from the study.

Dose reductions were not permitted during cycle 1, as toxicity defined DLT. Dose reductions during cycle 2 or thereafter were permitted for hematologic and non-hematologic toxicity that did not improve after a 2-week treatment delay. Paclitaxel was adjusted for hematologic/neurosensory toxicity and fatigue; irinotecan for hematologic and gastrointestinal toxicity; and cisplatin for renal toxicity and nausea. If a treatment delay was required, all drugs were held until recovery occurred. Dose adjustments were as follows:

Cisplatin If on Day 1 the serum creatinine was >1.5 and $\leq 2.0 \text{ mg/dL}$, then cisplatin was administered at dose level 1 (15 mg/m^2). At any time, if creatinine was $>2.0 \text{ mg/dL}$, all three chemotherapy agents were held. If creatine remained $>2.0 \text{ mg/dL}$ after 2 weeks, then cisplatin and irinotecan were discontinued indefinitely and patients proceeded to single-agent weekly paclitaxel at $80 \text{ mg/m}^2/\text{week}$. For grade 3 or 4 nausea lasting more than 3 days, cisplatin alone was reduced at 5 mg/m^2 intervals.

Paclitaxel For grade 3 neutropenia or thrombocytopenia, paclitaxel was held for 1 week and continued at the same dose if hematologic parameters were met. Dose was reduced by one dose level if: (1) parameters were met only after a 2-week break, (2) grade 4 hematologic toxicity, (3) neutropenic fever, or (4) bleeding due to thrombocytopenia. For grade 3–4 neuropathy, paclitaxel was held for 1–2 weeks. If improved to grade 2, paclitaxel was restarted and reduced one dose level. If persistent, the patient was removed from the study. For grade 4 fatigue, paclitaxel was reduced by one dose level.

Irinotecan Dose attenuations for irinotecan were made for grade 3–4 hematologic toxicity and grade 4 fatigue only

after maximal dose reductions for paclitaxel (40 mg/m^2) occurred. Dose reductions for grade 3–4 diarrhea or mucositis were made from 50 to 40 mg/m^2 , and if toxicity persisted, patients were removed from study.

Patient evaluation

Before treatment, patients underwent a full medical history and physical examination. Baseline testing included laboratory data (complete blood cell count, serum chemistry, coagulation profile, and pregnancy test for women of childbearing age), urinalysis, an ECG, and radiographic studies for baseline tumor measurements (chest x-ray, CT or MRI scan, and/or esophagram). For the first two cycles (12 weeks), patients were examined and interviewed by a physician weekly prior to each treatment to assess for interval toxicity. At cycle 3 and thereafter, patients were evaluated by a physician every other week (weeks 1 and 3) and by a registered nurse the remaining weeks (weeks 2 and 4). Clinic visits during the 2-week rest period were made only if the patient required medical attention. A complete blood cell count and serum creatinine was drawn prior to every treatment.

Patients had repeated tumor evaluations, after cycle 1 (week 6), after cycle 2 (week 12), and then after every subsequent two cycles (12 weeks) of treatment. Tumor response was assessed by the same imaging method at baseline, usually a CT scan, according to the modified World Health Organization criteria (i.e., measurable disease, non-measurable disease but assessable disease, non-assessable disease, complete response, partial response, minor response, stable disease, and progressive disease [24]. Time to response, duration of response, time to tumor progression, and survival data were recorded.

Patients were removed from the study if any toxicity endpoints were reached, if there was evidence of disease progression, for a major protocol violation, or if a number of dose attenuations were made (i.e., paclitaxel $<40 \text{ mg/m}^2$, irinotecan $<40 \text{ mg/m}^2$).

Table 2 Treatment administration and first-cycle DLTs (dose levels, given weekly, 4 weeks on, 2 weeks off)

Cisplatin ($\text{mg/m}^2/\text{wk}$)	Irinotecan ($\text{mg/m}^2/\text{wk}$)	Paclitaxel ($\text{mg/m}^2/\text{wk}$)	No. of patients ($n=30$)	Patients with DLTs			
				Emesis (grade 3)	Diarrhea (grade 3)	Prolonged neutropenia (grade 3–4)	Neutropenic fever
30	50	40	8	1	0	0	0
		50	7	0	1	0	1
		65	12	0	1	3	0
		80	3	0	0	2	1

DLT dose-limiting toxicity

Results

Patient characteristics

A total of 30 patients were enrolled between April 1999 and April 2001 (demographics outlined in Table 1). The median age was 54 years, with good baseline performance status; 25 patients (83%) had 80–90% KPS, and five patients (17%) had 70% KPS. The majority of the patients were men (87%), in part due to the gender differences in prevalence of gastroesophageal cancer.

All 30 patients had a stage IV cancer diagnosis, defined as distant nodal or soft tissue metastasis. All patients had either a gastrointestinal or hepatobiliary cancer—16 patients (54%) with adenocarcinoma of the esophagus, GE junction or stomach; two patients (7%) with squamous cell carcinoma of the esophagus; seven patients (23%) with pancreatic cancer; and one patient (3%) with hepatocellular carcinoma. Adenocarcinoma of unknown origin was diagnosed in 4 patients (13%), although all four were suspected to be pancreaticobiliary primaries. The predominant site of measurable disease was the liver (67%) and lymph nodes (60%).

Most of the patients (70%) had never undergone any prior chemotherapy. Six patients (20%) had undergone one chemotherapy regimen. Three patients (10%) had undergone two prior regimens (one patients with gemcitabine alone then gemcitabine plus cisplatin, one patient with gemcitabine alone then gemcitabine plus 5-FU, and one patient with oral Xeloda then oral thalidomide); these three patients were entered into the protocol given excellent performance status and organ function. Two patients (7%) had undergone an attempt at primary surgical resection and one patient (3%) had radiation therapy with gemcitabine for locally advanced unresectable pancreatic cancer.

Dose escalation and determination of first-cycle MTD and DLT

Table 2 lists the number of patients treated at each dose level, the number of patients who progressed during the first cycle, and a description and number of patients with a first-cycle DLT.

At the first dose level (40 mg/m²), three patients were initially enrolled. One patient with pancreatic cancer developed rapid disease progression with a gastric outlet obstruction and was removed from the protocol. One patient developed significant dehydration with a DLT (prolonged grade 3 nausea and grade 3 hyponatremia). The cohort was expanded by five patients. One additional patient with pancreatic cancer had early progression with obstructive jaundice requiring a biliary stent, as well as grade 3 neutropenia. Since only one of the six patients (17%) who completed one full cycle developed a DLT

Table 3 Incidence of cumulative adverse events (all cycles) by paclitaxel starting dose level

Paclitaxel (mg/m ² /wk)	No. of evaluable patients (n=28)	Pts with hospital stay due to toxicity	Neutropenia		Neutropenic fever		Anemia		Diarrhea		Vomit/nausea		Fatigue		Syncope	
			Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
40	6	1 (17%)	3 (50%)	1 (17%)	1 (17%)	1 (17%)	1 (17%)	1 (17%)	1 (17%)	3 (50%)	1 (17%)	1 (17%)	1 (17%)	1 (17%)	1 (17%)	1 (17%)
50	7	4 (57%)	2 (29%)	1 (14%)	1 (14%)	1 (14%)	1 (14%)	1 (14%)	4 (57%)	1 (14%)	1 (14%)	4 (57%)	4 (57%)	4 (57%)	4 (57%)	4 (57%)
65	12	1 (8%)	4 (33%)	2 (17%)	–	–	1 (8%)	–	2 (17%)	–	–	–	2 (17%)	2 (17%)	2 (17%)	2 (17%)
80	3	2 (67%)	2 (67%)	1 (33%)	1 (33%)	–	–	–	1 (33%)	–	–	–	1 (33%)	1 (33%)	1 (33%)	1 (33%)
Total	28	8 (29%)	11 (39%)	5 (18%)	3 (11%)	3 (11%)	3 (11%)	3 (11%)	8 (29%)	5 (18%)	5 (18%)	8 (29%)	8 (29%)	8 (29%)	8 (29%)	8 (29%)

Table 4 Median nadir for each cohort (range)—all cycles

Paclitaxel (mg/m ² /wk)	WBC	ANC	Hb	PLT
40	2.6 (1.3–13.3)	0.95 (0.3–15.7)	9.0 (7.3–14.3)	160 (108–598)
50	2.6 (0.5–39.6)	1.3 (0.3–36.8)	9.7 (7.6–15.7)	165 (131–614)
65	2.3 (1–18.6)	0.95 (0.3–17.1)	10.7 (7.4–15.1)	173 (77–564)
80	1.8 (1.6–5.3)	0.6 (0.4–5.2)	11 (9.6–14.8)	176 (79–351)

WBC white blood cell, ANC absolute neutrophil count, Hb hemoglobin, PLT platelets

(nausea, hyponatremia), it was decided that this dose level was tolerable.

At the second dose level (50 mg/m²), seven patients were enrolled. In the first three patients, two developed a DLT—1 with grade 4 febrile neutropenia and the other with prolonged grade 3 diarrhea requiring hospitalization. Because these patients had prior chemotherapy treatment, the protocol was amended to exclude prior chemotherapy at this point. To clarify the toxicity profile, an additional four patients were treated at this dose level and none of them experienced a DLT. Since only two (29%) out of seven developed a first-cycle DLT, the dose level was escalated as none of five patients without prior chemotherapy had a DLT.

Three patients were treated at the next dose level (65 mg/m²) and none experienced a DLT. The paclitaxel dose was escalated to the next level for three patients (80 mg/m²). One patient required hospitalization for grade 4 febrile neutropenia (DLT). He also developed grade 3 syncope with sinus bradycardia requiring a pacemaker. The second patient had prolonged grade 3 neutropenia (DLT) with grade 3 diarrhea, and the third patient developed grade 3 neutropenia (DLT). Since two (67%) of the three developed a DLT, it was felt that the MTD had been exceeded.

An additional 9 patients were accrued at the prior paclitaxel dose level (65 mg/m²). Four (33%) out of the 12 patients developed a first-cycle DLT—three patients with prolonged grade 3–4 neutropenia without hospitalization and 1 with prolonged grade 3 diarrhea. This dose level (65 mg/m²) was felt to represent the MTD and the recommended phase II dose level for future trials.

Within this last cohort (paclitaxel 65 mg/m²), 7 (58%) out of 12 patients had a 1-week dose delay at the third treatment week for most cycles due to neutropenia. Therefore, the recommended schedule was changed to 2 weeks on, 1 week off, times two, for each 6-week cycle.

Treatment administration and toxicities during all cycles of treatment (cumulative toxicity)

The 28 patients assessable for safety received a total of 74 cycles of therapy (4 treatments per cycle per patient). The median number of cycles was 1.5 (range, 1–9). In total, 14 patients received only one cycle (four progression of

disease [PDs], ten DLTs), five patients had two cycles (three PDs, one toxicity, one went to surgical resection, given near complete response), one patient had three cycles (referred for surgery and taken off study), two patients had four cycles (one PD, one toxicity), two patients had five cycles (one PD, one toxicity), three patients had six cycles (two PDs, one toxicity), and one patient had nine cycles (went to operating room given minimal disease). Eighteen patients (64%) had dose delays longer than 7 days owing to treatment toxicity, primarily myelosuppression.

Table 3 lists the overall incidence of grade 3/4 toxicities for all evaluable patients treated on this trial, and Table 4 lists the median and ranges of hematologic nadirs for each paclitaxel dose level. Grade 3/4 myelosuppression was common with neutropenia (57%) and anemia (11%). Grade 3/4 thrombocytopenia was not observed. Three patients (11%) had neutropenic fever. None of the patients received colony-stimulating factors or erythropoietin during the study. Grade 3 fatigue (29%), diarrhea (29%), and nausea (18%) were consistent with those expected in patients receiving the drugs individually, in particular irinotecan. Eight patients (29%) required hospitalization due to severe toxicity, typically neutropenic fever or diarrhea. One patient developed sinus bradycardia and required a cardiac pacemaker. Increased creatinine and ototoxicity was not observed in any patients. No patient died during or within 30 days of receiving treatment on this study.

Efficacy

Although toxicity is the primary endpoint of this phase I study, radiographic response was determined. Objective tumor response, as a partial radiographic response, was observed in 43% (13/30) of patients; 92% (12/13) had no prior chemotherapy. Complete response was not observed. Eight (27%) patients had stable disease, and nine (30%) had progressive disease. In relation to underlying diagnosis, partial response occurred in patients with gastric adenocarcinoma (63%, 5/8), esophageal or GE junction adenocarcinoma (50%, 4/8), esophageal squamous carcinoma (50%, 1/2), and unknown primary (50%, 2/4). One response was seen in a patient with pancreatic cancer (14%, 1/7).

Discussion

Combination chemotherapy with a platinum agent has become a standard of care in the palliative treatment of upper gastrointestinal malignancies. Metastatic gastric cancer trials have shown a survival benefit with chemotherapy compared to best supportive care alone [3]. In addition, randomized trials have indicated that adding a third agent to the combination of fluorouracil and cisplatin, either epirubicin or docetaxel, may modestly improve response rates, time to progression, and survival with greater therapy-related toxicity [25, 26]. Toxicity for the new proposed standard regimen combining docetaxel with fluorouracil and cisplatin (DCF) can be prohibitive, including high rates of hematologic and gastrointestinal toxicity, and such a regimen may not be feasible to administer in many patients.

Nonetheless, median survival remains less than 1 year, and hence, more active, tolerable regimens are needed. Paclitaxel and irinotecan are highly active single agents in the treatment of metastatic gastroesophageal cancers [21, 26]. Cisplatin-containing regimens with either irinotecan or paclitaxel are showing promising activity in gastroesophageal cancer [12, 15, 17, 22, 27]; however, all three drugs have not been combined in this population. We undertook this phase I trial to see if this three-drug combination is feasible.

We combined weekly, dose-escalation, paclitaxel over 1h with the conventionally used weekly cisplatin and irinotecan [15, 17], and limited our cohort to patients with upper gastrointestinal and hepatobiliary malignancies. In our 28 evaluable patients, first cycle DLTs were expected and consisted primarily of neutropenia with prolonged grade 3–4 neutropenia (five patients, 18%) and febrile neutropenia (two patients, 7%). In addition, grade 4 diarrhea (two patients, 7%) and grade 3 nausea (one patient, 3%) were seen, likely from the irinotecan and to a lesser degree cisplatin, which has been seen at these doses. Two patients were removed from the trial after only two treatments due to rapid disease progression—obstructive jaundice and gastric outlet obstruction. These were not felt to be due to the therapy and were therefore not included as true DLTs.

The recommended phase II dose level for future trials was paclitaxel 65 mg/m²; however, neutropenia requiring dose delays was still significant. In this dose cohort, four (33%) out of the 12 patients developed a first-cycle DLT—three patients with prolonged grade 3–4 neutropenia without hospitalization and one with prolonged grade 3 diarrhea. Most patients (58%) had a 1-week dose delay at the third treatment week for most cycles, which did allow better tolerability. Given this observation, we suggest a modified schedule of this regimen in this cohort (paclitaxel 65 mg/m²) to 2 weeks on, 1 week off, times two, for each 6-week cycle. Only one patient required hospitalization

despite a high incidence of grade 3–4 neutropenia (50%). In addition, no grade 3–4 neuropathy was observed as has been described in other trials with cisplatin–paclitaxel (24- and 3-h infusions) [28, 29]. This however was likely due to the relatively short duration of therapy in most patients.

We also observed substantial activity for this three-drug regimen. The overall response rate of 43% is remarkable, especially since up to a third of patients had prior chemotherapy. As expected, we observed most activity in the patients with upper gastrointestinal cancers—gastric adenocarcinoma (63%), esophageal/GE junction adenocarcinoma (50%), and esophageal squamous carcinoma (50%). Remarkably, activity was seen in a patient with pancreatic cancer (14%).

These results are consistent with previous trials with platinum, taxane, and a topoisomerase inhibitor (irinotecan or topotecan). Another three-drug regimen with weekly docetaxel, cisplatin, and irinotecan in gastroesophageal cancer has also reported preliminary findings of frequent grade 3–4 toxicity (diarrhea [44%] and neutropenia [22%]), which markedly improved with a reduction in the irinotecan to 50 mg/m² (grade 3–4 toxicity: diarrhea [6%], neutropenia [6%]). Antitumor activity was substantial (greater than 50%) and did not appear comprised with irinotecan dose reduction [30]. In non-small cell lung cancer, a regimen of carboplatin (area under the curve [AUC], 5), paclitaxel (175 mg/m²), and irinotecan (100 mg/m²) every 3 weeks has been described in two trials, which had similar neutropenic rates to our trial (50–78%) [31, 32]. Platinum-containing regimens with three agents have been described in various cohorts with similar toxicity profiles and high response rates [33–37].

In summary, this single-center phase I trial has identified a regimen of paclitaxel 65 mg/m², cisplatin 30 mg/m², and irinotecan 50 mg/m² given weekly on a 2-week on, 1-week off schedule. DLT with this regimen was primarily neutropenia, although diarrhea and nausea were observed. The tolerability and activity of this regimen warrants further exploration, especially in upper gastrointestinal malignancies.

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