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A Phase II Trial of Irinotecan in Patients with Previously Untreated Advanced Esophageal and Gastric Adenocarcinoma

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Chemotherapy options for esophagogastric adenocarcinoma remain limited. Irinotecan has demonstrated broad activity in a variety of epithelial malignancies. Forty-six patients with previously untreated, measurable, unresectable, or metastatic esophagogastric adenocarcinoma were enrolled. Patients received irinotecan (125 mg/m^2 intravenously over 90 min weekly) for 4 consecutive weeks followed by a 2-week rest. Forty-three patients received at least one treatment and were evaluable for response and toxicity. One complete and five partial responses were observed, for an overall response rate of 14% (95% CI, 4–24%). Median survival for all 43 patients was 6.4 months (95% CI, 4.6–8.2 months). Grade 3 to 4 toxicity included 10 patients (23%) with neutropenia, 13 patients (30%) with late diarrhea, 6 patients (14%) with vomiting, and 6 patients (14%) with fatigue. We conclude that although single-agent irinotecan is an active agent for esophagogastric adenocarcinoma, the schedule utilized in this trial is associated with moderate toxicity. When used as a single-agent, a triweekly schedule may be preferable for this patient population.

KEY WORDS: esophageal adenocarcinoma; gastric adenocarcinoma; irinotecan; chemotherapy; phase II trial.

In 2005, an estimated 36,380 new cases of esophageal and gastric cancer will be diagnosed in the United States (1). Unfortunately, most patients with esophageal or gastric cancer will present with either unresectable or metastatic disease, leading to an expected 25,080 deaths from these malignancies (2). As a result, 5-year survival rates for both diseases remain quite low, in the range of 10 to 15%.

Historically, 5-fluorouracil (5-FU) has been the most extensively studied chemotherapeutic agent for esophageal or gastric cancers, associated with a response rate of approximately 20% (3, 4). Other drugs with reported activity include cisplatin, the taxanes, the anthracyclines, and mitomycin. Complete responses with single agents are rare and partial regressions have been relatively brief. The histopathology and natural history of esophageal adenocarcinoma and gastric adenocarcinoma appear to be quite similar (3, 4), and the two cancers appear to respond similarly to systemic chemotherapy (5–8).

The camptothecin derivative, irinotecan (CPT-11), is a topoisomerase I inhibitor with single-agent activity against several human tumors including esophageal, gastric, and colorectal carcinomas (9–12). SN-38, the active metabolite of irinotecan, binds to and stabilizes the topoisomerase I–DNA complex, preventing the religation of DNA during replication and transcription (13, 14). Subsequent collision between this stable complex and an advancing replication fork results in double-stranded DNA breaks and apoptosis.

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Matsuoka and colleagues examined the in vitro activity of irinotecan and its metabolite SN-38 in primary gastrointestinal carcinomas (15, 16). In gastric carcinoma tumor cells, the growth inhibitory effect of SN-38 was similar to that of such other anticancer agents as doxorubicin, cisplatin, and 5-FU.

Investigators in Japan conducted a phase II study of irinotecan in patients with advanced gastric cancer (17). Fifty-six of the seventy-six evaluable patients had received prior chemotherapy. Irinotecan was administered intravenously at doses of 100 mg/m^2 weekly or 150 mg/m^2 every 2 weeks. Fourteen patients (23%) achieved a partial response. The median duration of partial response was 2.2 months and the median survival was 5.7 months. Major toxicities ($\geq$Grade 2) included leukopenia (76%), anemia (57%), and diarrhea (38%).

Given the encouraging preliminary preclinical and clinical studies, we conducted a multicenter study to examine the efficacy and tolerability of single-agent irinotecan in a Western population of patients with advanced esophageal and gastric adenocarcinoma. Moreover, to optimally assess the activity of irinotecan in these diseases, we restricted enrollment to patients who had received no prior chemotherapy. We selected a weekly $\times$4 schedule based on the successful North American registration trials of irinotecan in 5-FU-refractory colorectal cancer (18–20).

PATIENTS AND METHODS

Patients with locally unresectable or metastatic esophageal or gastric carcinoma that had been histologically confirmed were eligible for entry into this study. Patients were not permitted to have undergone a prior program of chemotherapy or radiation therapy for esophageal or gastric cancer. Bidimensionally measurable disease was required. Patients were required to be at least 18 years of age, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and have adequate major organ function. Specifically, their bilirubin level had to be $\leq$1.5 mg/dl, aspartate transaminase (AST) $\leq$5 times the institutional upper limit of normal, and serum creatinine $\leq$2.0 mg/dl. Minimum hematologic parameters included an absolute neutrophil count $\geq 1.5 \times 10^9$/L, a platelet count of $\geq 100 \times 10^9$/L, and hemoglobin $\geq$9.0 g/dl. Exclusionary criteria included a concurrent malignancy, clinically apparent central nervous system metastases, a history of seizures while receiving antiepileptic prophylaxis, significant medical comorbidities, serum calcium $\geq$12.0 mg/dl, established Gilbert's disease, or an inability to give written informed consent. Patients from the Dana-Farber Cancer Institute, Massachusetts General Hospital, and North Shore Cancer Center were eligible for enrollment. The study was approved by the Institutional Review Board of the Dana-Farber/Harvard Cancer Center.

Treatment Protocol. Treatment consisted of irinotecan delivered as a 90-min intravenous infusion at a dose of 125 mg/m^2 in an outpatient clinic. One course of treatment comprised four consecutive weekly infusions of irinotecan followed by a 2-week rest. Treatment courses were repeated every 6 weeks unless there was prior evidence of progressive disease (PD). No dose escalation was allowed. The use of antiemetic premedication was left to the discretion of the treating physician.

Prior to study entry, all patients provided a complete history and underwent a physical examination, including an assessment of performance status and concurrent nonmalignant disease and therapy. Laboratory studies included a complete blood count with differential, liver and renal function tests, urinanalysis, and carcinoembyonic antigen titer. A chest radiograph and abdominal-pelvic computed tomographic (CT) scan was required within 21 days of initiation of therapy. For patients with lesions involving the esophagus, a chest CT was also obtained.

Patients were seen by a physician on a weekly basis during treatment for a brief history, physical examination, and toxicity assessment. A complete blood count with differential was measured before each irinotecan treatment. Renal and liver functions were examined every 6 weeks. Measurable disease was assessed radiographically after 6 weeks, after 12 weeks, and then every 12 weeks thereafter. A complete response (CR) was defined as the disappearance of all clinical and radiologic evidence of disease and normalization of tumor markers for a period of at least 4 weeks. A partial response (PR) was defined as a $\geq$50% decrease in the bidimensional tumor measurements, without the appearance of any new lesions or progression of any existing lesions. PD was defined as any of the following: a $\geq$25% increase in the sum of the products of all measurable lesions, the appearance of any new lesion, or the reappearance of any lesion that had disappeared. Stable disease was defined as a tumor response that did not meet the criteria for CR, PR, or PD.

Treatment was continued until one of the following criteria was met: disease progression, unacceptable toxicity, patient refusal, or the need to delay chemotherapy more than 2 weeks. Patients refractory to irinotecan were allowed to receive alternative treatment at their physician's discretion.

Toxicity Evaluation and Dose Modification. Toxicity was evaluated weekly, according to the National Cancer Institute Common Toxicity Criteria, Version 1.0. On Days 1, 8, 15, and 22 of each 28 day treatment cycle, full-dose therapy was given if patients had an absolute neutrophil count (ANC) $\geq$1500/mm^3, platelets $\geq$100,000/mm^3, and no grade 3 or 4 nonhematologic toxicity.

Dose modifications of irinotecan treatment (to 100, 75, or 50 mg/m^2) were based on the worst toxicity observed after the preceding treatment; in the presence of multiple toxicities, the specified greater (greatest) dose reduction was implemented. Patients who experienced grade 2 toxicity continued on therapy but were reduced by one dose level for their next treatment. Patients experiencing grade 3 or 4 toxicity had their treatment interrupted until their toxicity had fully resolved. On resumption of therapy, patients with resolution of grade 3 toxicity were reduced by one dose level, and patients with resolution of grade 4 toxicity were reduced by two dose levels. Patients who experienced toxicity that required dose modification to levels below 50 mg/m^2 were withdrawn from the study due to toxicity.

Statistical Considerations. This Phase II study was designed to assess the response rate of advanced esophageal or gastric adenocarcinoma to irinotecan among 40 evaluable, previously untreated patients.

Patients with advanced esophageal or gastric adenocarcinoma were admitted in a standard two-stage design (21) to test the null hypothesis that the true objective response rate was less than 10%

TABLE 1A. PATIENT DEMOGRAPHICS

Characteristic	
Total number of patients	43
Males	32 (74%)
Females	11 (26%)
Age	
Median (range)	60 (22–81)
ECOG performance status	
0/1/2	24 (56%)/17 (40%)/2 (5%)
Histology	
Well differentiated	2 (5%)
Moderately/well differentiated	14 (33%)
Poorly differentiated	25 (58%)
Undifferentiated	1 (2%)
Unknown	1 (2%)
Location	
Distal 1/3 of esophagus	14 (33%)
Gastroesophageal junction	4 (9%)
Proximal 1/2 of stomach	11 (26%)
Distal 1/2 stomach	11 (26%)
Diffuse stomach	3 (7%)

against the alternative hypothesis that the true response rate was ≥20%. As predefined by the protocol, at least three responses were required among the first 20 evaluable patients for the study to continue to a total of 40 evaluable patients. At that point, the treatment would be considered promising if a total of 8 or more responses (≥20%) were observed.

The duration of response was measured from the first objective documentation of response to the first objective documentation of disease progression. Progression-free survival was measured from the date of initial treatment to first objective documentation of progressive disease or date of death, whichever occurred first. Survival was calculated from the start of therapy to the date of death. The distributions of time to progression and survival were estimated using Kaplan-Meier methodology (22).

RESULTS

Patient Characteristics. Between December 1997 and August 2000, 46 patients were entered into this trial. Of these, two patients were found to be ineligible and one patient canceled before initiating therapy. Thus, 43 patients received at least one treatment and were eligible for assessment of response and toxicity. Three patients were added to the original goal of 40 patients to compensate for 3 patients who were removed from the study due to disease progression before their third treatment. Baseline patient characteristics are summarized in Tables 1A and 1B. There were 32 men (74%) and 11 women (26%), having a median age of 60 years (range, 22–81 years). Median ECOG performance status for the cohort was 0 (range, 0–2). More than half of the patients (58%) had a poorly differentiated adenocarcinoma and one-third (33%) had a moderately to well-differentiated adenocarcinoma. Primary tumors were evenly distributed among the distal esophagus (33%), proximal stomach (26%), and distal stomach (26%). Nine percent of tumors were located in the gastroesophageal junction, and the stomach was diffusely involved in 7% of cases. All patients had a serum bilirubin of <1.0 mg/dl (median, 0.5 mg/dl), and 20 patients (47%) had an elevated level of carcinoembryonic antigen.

TABLE 1B. BASELINE LABORATORY MEASUREMENTS

Baseline laboratory result	*Median (range)*
Alkaline phosphatase (μ/L)	113 (53–372)
SGOT (μ/L)	24 (10–199)
Total bilirubin (mg/dl)	0.5 (0.2–1.0)
CEA (ng/ml)	4.7 (0.3–1385)

Response and Survival. Among all patients, a total of 292 doses of irinotecan was administered. The median number of doses per patient was 4 (range, 1–43). Twenty-eight patients (65%) were withdrawn from therapy due to disease progression, nine patients (21%) due to physician or patient discretion, and two patients (5%) as a result of treatment-related toxicity; four patients (9%) died while on therapy (see below).

Response was evaluated in all 43 patients, including 8 patients (19%) who were withdrawn from the study before restaging. Of these 43 individuals, 6 patients (14% [95% CI, 4–24%]) achieved a complete or partial response; this included 4 of 18 patients (22% [95% CI, 3–41%]) with esophageal cancer and 2 of 25 patients (8% [95% CI, 0–19%]) with gastric cancer. The median duration of response was 3.4 months. Seventeen patients (40%) had stable disease as their best response and 12 (28%) had progressive disease.

As of November 2003, 42 patients had died, and 1 was still alive. The median progression-free survival for these 43 patients was 2.6 months (95% CI, 1.4–2.8 months; Figure 1). The median survival for the entire cohort was 6.4 months (95% CI, 4.6–8.2 months; Figure 2), and the probability of survival after 1 and 2 years was 30% and

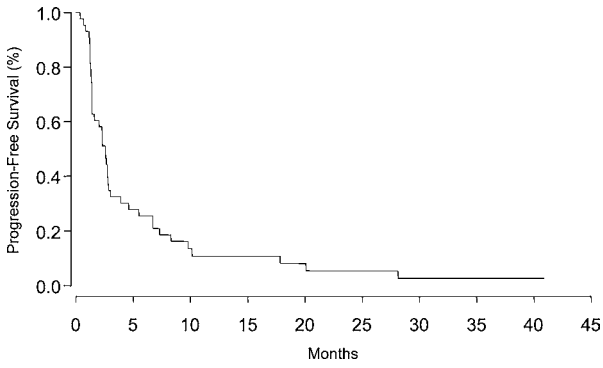

Fig 1. Progression-free survival among all 43 patients.

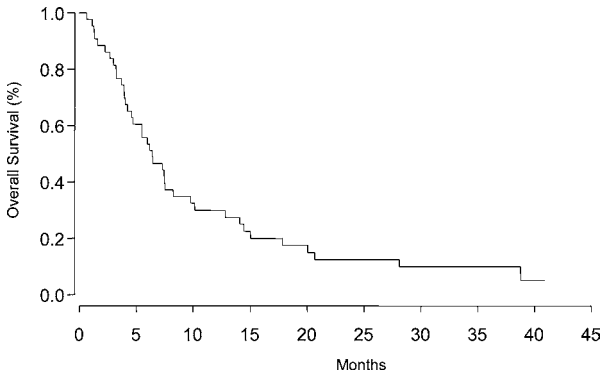

Fig 2. Overall survival among all 43 patients.

12%, respectively. Among the 25 patients with gastric cancer, the median progression-free survival was 2.7 months and the median overall survival was 7.4 months. For the 18 esophageal and gastroesophageal junction cancer patients, median progression-free survival and overall survival were 1.4 and 5.7 months, respectively.

Toxicity. Data on toxicity for all 43 patients are provided in Table 2. The toxicities recorded represent the maximum grade toxicity observed for a given patient for the entire course of therapy. Eighteen patients (42%) required at least one dose reduction of therapy due to treatment-related toxicity. Ten patients (23%) experienced grade 3 to 4 neutropenia, although only two patients (5%) had febrile neutropenia requiring hospitalization. One patient experienced grade 3 thrombocytopenia. Late grade 3 to 4 diarrhea occurred in 13 patients (30%). Grade 3 nausea was recorded in eight patients (19%), and grade 3 to 4 vomiting in six patients (14%). There were four deaths among patients enrolled in the study, of which three were deemed treatment-related: Two patients died from complications arising from severe diarrhea, neutropenia, and dehydration and one patient died of untreated diarrhea and dehydration, not reported to his care team. In addition, one patient who had not developed any prior treatment-related toxicity died unexpectedly in his sleep; an autopsy was not performed.

TABLE 2. MAXIMUM TOXICITY GRADE FOR EACH TOXICITY PER PATIENT

	Number (%)			
Toxicity	*Grade I*	*Grade II*	*Grade III*	*Grade IV*
Hematologic				
Leukopenia	10 (23.3)	6 (14.0)	7 (16.3)	3 (7.0)
Neutropenia	3 (7.0)	10 (23.3)	3 (7.0)	7 (16.3)
Infection	0	1 (2.3)	4 (4.7)	0
Hematocrit	17 (39.5)	16 (37.2)	3 (7.0)	0
Platelets	3 (7.0)	1 (2.3)	1 (2.3)	0
Gastrointestinal				
Nausea	19 (44.2)	11 (25.6)	8 (19.0)	
Vomiting	11 (25.6)	6 (14.0)	3 (7.0)	3 (7.0)
Early diarrhea	3 (7.0)	1 (2.3)	2 (4.7)	2 (4.7)
Late diarrhea	9 (20.9)	7 (16.3)	6 (14.0)	7 (16.3)
Anorexia	15 (34.9)	9 (20.9)	1 (2.3)	1 (2.3)
Fatigue	11 (25.6)	12 (27.9)	5 (11.6)	1 (2.3)
Alopecia	5 (11.6)	3 (7.0)		

DISCUSSION

In this phase II study of 43 patients with previously untreated, advanced esophageal or gastric adenocarcinoma, irinotecan demonstrated modest activity as a single agent, with an objective response rate of 14% and a median survival of 6.4 months. Consistent with our findings, Köhne and colleagues reported a 17.5% response rate and a median survival of 7.1 months among 40 patients with previously untreated advanced gastric cancer (23). This response rate associated with irinotecan appears comparable to other active single agents in advanced gastric cancer, including 5-FU, cisplatin, and the taxanes.

Among patients treated with irinotecan in our trial, rates of grade 3/4 toxicity were considerable including diarrhea (30%), neutropenia (23%), nausea (19%), vomiting (14%), and fatigue (14%). Moreover, treatment-related mortality occurred in 7% of patients. This toxicity profile in patients with advanced esophageal and gastric cancer is similar to that described when the same weekly $\times 4$ schedule was administered to patients with advanced colorectal cancer (18–20). In fact, an every-3-week schedule was associated with superior toxicity profile compared with the 4-weeks-on/2-weeks-off regimen in a randomized trial of patients with 5-FU-refractory colorectal cancer (24). In their trial of gastric cancer patients, Köhne *et al.* administered irinotecan at 350 mg/m^2 every 3 weeks and noted less grade 3–4 diarrhea (20%), fatigue (10%), nausea (8%), and vomiting (5%) than was observed in our study (23).

Although these data would suggest that the every-3-weeks schedule may have less overall toxicity, other authors have found the every-3-weeks schedule of irinotecan at 320 mg/m^2 to be "excessively toxic" in gastric cancer patients (25). Several investigators have suggested that weekly irinotecan be given on an every 2-out-of-3-weeks schedule. Anecdotally, this modification appears to lessen the degree of toxicity; however, objective studies using the every 2-out-of-3-weeks schedule in advanced esophageal or gastric cancer have not been reported.

An alternative treatment strategy in advanced esophageal and gastric cancers has been to add irinotecan at lower doses to other active agents. In esophageal and gastric cancer, irinotecan has been combined with cisplatin (7, 8, 26), 5-FU (27–29), docetaxel (29–31), oxaliplatin (32), and mitomycin (33, 34). Of these,

irinotecan combinations with cisplatin or 5-FU have been most successful. In North American phase II studies, response rates for chemo-naïve patients with esophagogastric cancer to a weekly combination of irinotecan and cisplatin have been 57% to 59%, with median survival times of 9 to 15 months (7, 8). Grade 3 to 4 toxicity was primarily neutropenia in 27% to 46% and diarrhea in 11% to 22% of patients. The combination of irinotecan and infusional 5-FU has led to documented response rates of 40% to 42% in European multi-institutional, randomized phase II trials, with a median survival of 11.3 months (27, 28). Grade 3 to 4 toxicity was again primarily neutropenia (25–40%) and diarrhea (22–24%). These combinations clearly have higher response rates and longer survival than irinotecan monotherapy, with similar toxicity, and should therefore be used preferentially for patients with esophagogastric cancer.

In summary, irinotecan appears to be an active single agent in the treatment of advanced esophageal and gastric adenocarcinoma. Nonetheless, given the toxicity associated with the 4-weeks-on/2-weeks-off schedule, it would appear that other drug schedules should be utilized to improve patient tolerability. Alternatively, utilizing irinotecan at lower doses in combination with other active agents may offer the best opportunity to improve treatment efficacy while minimizing treatment-related toxicity.

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