Phase II Trial of Irinotecan in Combination with Amifostine in Patients with Advanced Colorectal Carcinoma

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BACKGROUND. Irinotecan is effective in patients with advanced colorectal carcinoma in both first-line and salvage settings but its use can be limited by serious side effects. Amifostine has been shown to reduce the incidence of cisplatin-induced cumulative renal toxicity in patients with advanced ovarian carcinoma and nonsmall cell lung carcinoma. In the current pilot Phase II trial, the authors examined the potential role of amifostine as a protective agent against irinotecan-induced diarrhea and myelosuppression and evaluated an every-2-weeks regimen as an alternative schedule for the administration of irinotecan in patients with previously treated metastatic colorectal carcinoma.

METHODS. All patients received amifostine, 740 mg/m^2, followed by irinotecan, 250 mg/m^2, every 2 weeks. A 6-week cycle of chemotherapy (every 2 weeks for 3 treatments) was chosen to assess toxicity and response. The main objective of the current study was to evaluate the impact of amifostine on gastrointestinal and hematologic toxicity.

RESULTS. A total of 22 patients entered the current study. Six of these 22 patients (27%) had WHO Common Toxicity Criteria Grade 3 or 4 diarrhea, including 2 patients (9%) with Grade 4 diarrhea. Eight of 22 patients (36.3%) developed Grade 3 or 4 neutropenia (Grade 4 in 4 of the 22 patients [18%]). Dose reduction was required in 25% of the treatment cycles. Five of the 22 patients (23%) withdrew from the trial due to amifostine toxicity. Of the 15 patients who were evaluable for response, 4 patients (26.6%) had achieved a partial response and 9 (60%) had stable disease as their best response.

CONCLUSIONS. The combination of irinotecan with amifostine in patients with previously treated metastatic colorectal carcinoma did not appear to reduce irinotecan toxicity. Amifostine did not appear to interfere with the cytotoxic effect of irinotecan. The results of the current study did demonstrate efficacy and safety of the every-2-weeks irinotecan schedule that was comparable to other established regimens and these results support its feasibility as a reasonable alternative in this disease setting. ***Cancer* 2002;94:2174–9.** *© 2002 American Cancer Society.*
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As a member of the camptothecin family, irinotecan (Camptosar®; Pharmacia, Peapack, NJ), a topoisomerase I inhibitor, blocks a nuclear enzyme that plays a critical role in DNA replication and transcription and thus interferes with DNA repair.[1,2] Irinotecan has been widely accepted as a second-line treatment for patients with advanced colorectal carcinoma who have failed treatment with 5-fluorouracil (5-FU).[3–6] More recently, irinotecan has been assessed as

first-line therapy for patients with metastatic colorectal carcinoma. The results of randomized Phase III trials conducted in the U.S. and Europe were remarkably similar, demonstrating a statistically significant improvement in the response rate, progression free survival, and overall survival in patients receiving irinotecan, 5-FU, and leucovorin (LV) compared with patients treated with 5-FU and LV alone.[7,8] Because of these results, the irinotecan/5-FU/LV regimen is considered by some to be the standard of care in the initial management of patients with advanced colorectal carcinoma. However, because of increased toxicity due to irinotecan, some physicians still prefer to use the 5-FU/LV combination.

Irinotecan is associated with significant toxicity, particularly diarrhea and neutropenia. The majority of studies published to date have reported Grade 3 or 4 diarrhea occurring in up to 34% of patients.[9] Although the severity of diarrhea can be reduced by treatment with loperamide,[10,11] it still represents a cause of significant morbidity. The incidence of Grade 3 or 4 neutropenia ranges between 23–44%.[9] Amelioration of gastrointestinal toxicity and myelosuppression might improve the therapeutic index for irinotecan.

Amifostine (Ethyol®; ALZA Corporation, Mountain View, CA) is an organic thiophosphate that was developed to protect normal tissues against the toxicities of chemotherapy and radiation therapy.[12] The drug has been shown to provide protection against cisplatin-induced renal toxicity.[13] Some clinical data suggest it protects against hematologic toxicities associated with cyclophosphamide.[14]

Preclinical data also demonstrated protection of the intestinal crypt cells in xenografts from chemotherapy and radiation injury.[15,16] These protective effects have been achieved without any evidence of diminished antitumor activity. Such data suggest a potential clinical role for amifostine in preventing irinotecan-induced hematologic and gastrointestinal toxicities.

Historically, clinical trials with irinotecan generally have employed two schedules of administration. In trials in the U.S., the drug has been given once weekly at a dose of 125 mg/m^2 for 4 of 6 weeks[4,5] whereas in Europe, the dose has been 350 mg/m^2 once every 3 weeks.[3,6] Indirect comparisons of the schedules suggest similar safety and effectiveness. An intermediate dosing schedule of 250 mg/m^2 every other week attempted to maximize dose frequency and intensity without increasing toxicity.[17,18] In designing the current trial, we chose the every-2-weeks regimen as described by Rothenberg et al.[19] and studied in our clinic as part of a multicenter trial.

The observation of the higher dose intensity achieved with the biweekly schedule along with a suggestion of enhanced myelosuppression led to this Phase II trial of amifostine and irinotecan to examine whether amifostine could reduce the anticipated incidence of irinotecan-induced Grade 3 or 4 neutropenia and diarrhea. Other endpoints included evaluation of amifostine toxicity, overall irinotecan dose intensity, and antitumor response.

MATERIALS AND METHODS

Entry Criteria

The current study was approved by the Human Subjects Protection Committee (HSPC) of the University of California, Los Angeles (UCLA) Medical Center. Informed consent was obtained according to federal and institutional guidelines. Eligible patients had a histologically confirmed diagnosis of metastatic colorectal carcinoma, a predicted life expectancy of at least 12 weeks, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and had recovered from the toxicities of previous treatment before entering onto the study. No prior therapy with irinotecan was allowed, but more than one prior regimen for advanced disease was acceptable. All patients were required to have adequate organ function prior to treatment, including a granulocyte count of $> 1500/mm^3$, hemoglobin of > 9.0 g/dL, platelet count of $> 100{,}000/mm^3$, serum creatinine of < 2.0 mg/dL, total serum bilirubin of < 2.0 mg/dL, and an aspartate transaminase level below 3 times the upper limit of normal. Patients were excluded from the study if they had active or uncontrolled infection, clinically apparent central nervous system metastasis, or severe concurrent illness. Patients who were unable to stop taking antihypertensive medications 24 hours prior to the administration of amifostine also were excluded from participation.

Study Design

This was a single-institution, pilot Phase II study supported by the ALZA Corporation.

Each patient received hydration with 1000 mL of normal saline over 2 hours prior to the administration of amifostine. Premedication then was comprised of dexamethasone, 20 mg intravenously (i.v.); granisetron, 1 mg i.v.; diphenhydramine, 50 mg i.v.; and famotidine, 20 mg i.v.[20] All patients received 740 mg/m^2 of amifostine administered i.v. over 10 minutes. At 15 minutes after the completion of the amifostine infusion, irinotecan, 250 mg/m^2, was given i.v. over the course of 90 minutes. Amifostine was provided by the ALZA Corporation. Irinotecan was given every 2 weeks as described by Rothenberg et al.[19] A 6-week cycle of chemotherapy (every 2 weeks for 3

treatments) was chosen to assess the toxicities of each agent, the cumulative total dose of irinotecan, and response to therapy.

Atropine, 0.25–1.0 mg i.v., was administered to any patient experiencing the cholinergic side effects of irinotecan. Patients received loperamide at the earliest signs of diarrhea as described by Abigerges et al.[10]

Therapy was continued until tumor progression, unacceptable toxicity, or the patient requested to stop treatment. Primary endpoints of the study included assessment of the toxicity of the combination regimen (including amifostine) and the total dose of irinotecan given during the 6-week cycle; secondary endpoints were response rate and median response duration. In the current analysis, all patients who received at least 1 treatment dose were assessed for toxicity, but response analysis was performed only for those patients who completed at least 6 weeks of combined treatment. Toxicity assessments were based on the worst toxicity observed at any point during any cycle of therapy. To determine whether the incidence of diarrhea was at least 50% less in those patients receiving amifostine prior to irinotecan infusion, we estimated the need to enroll 20 patients (power = 0.85 and $P = 0.05$).

Dose Modification

Amifostine

The amifostine dose was calculated on the basis of actual weight. Dose modification was not allowed. Amifostine was discontinued only in those patients experiencing a severe adverse event (usually intolerable Grade 3 or 4 nausea and emesis) believed to be related to amifostine treatment.

Irinotecan

The irinotecan dose was reduced in those patients who experienced significant drug toxicity and was based on worst toxicity observed after the preceding treatment. The dose was reduced by 10% in a case of a Grade 3 gastrointestinal or hematologic toxicity and by 20% in the case of a Grade 4 gastrointestinal or hematologic toxicity or neutropenic fever. A new course of treatment began when the granulocyte count was $> 1500/mm^3$, the platelet count was $> 100{,}000/mm^3$, and treatment-related diarrhea had resolved to $\leq$ Grade 1.

Pretreatment and Follow-Up Evaluation

Before the initiation of therapy, all patients provided a medical history and underwent a physical examination, assessment of ECOG performance status, determination of tumor measurements (including radiologic studies such as computed tomography or magnetic resonance imaging scans), urinalysis, and routine laboratory studies. Blood counts and assessment of adverse events were performed weekly during the first cycle and every other week thereafter. A chemistry panel, carcinoembryonic antigen level, physical examination, and evaluation of ECOG performance status were performed every 6 weeks at the beginning of the next cycle. Disease assessment was performed at the end of Cycle 1 and Cycle 2 and every 12 weeks thereafter. A complete response was defined as the complete disappearance of all measurable and assessable disease. A partial response was defined as at least a 50% decrease from baseline in the sum of the products of the perpendicular greatest dimensions of all measurable lesions. Disease progression was defined as a $\geq$ 25% increase in the overall area of the tumor or the appearance of new lesions.

RESULTS

Patient Characteristics

A total of 22 patients with metastatic colorectal carcinoma were enrolled in the current study between January 1998 and January 2000. Patient characteristics are shown in Table 1. All patients had metastatic disease and 36% of the patients had advanced disease at the time of the original diagnosis. Approximately 50% of the patients had $>$ 1 organ involved, with the most common site of metastases being the liver (77% of the patients). Of the 22 patients, 17 (77%) had received 5-FU for the treatment of metastatic disease and 9 patients (41%) had received it as adjuvant chemotherapy. Three patients (14%) had received $>$ 1 prior chemotherapy regimen for metastatic disease. Approximately one-third of the patients (32%) had received prior local abdominal or pelvic radiation.

Fifteen patients completed at least 1 cycle of treatment and were evaluated for response. Reasons for discontinuation of the study drugs during the first cycle were withdrawal of consent in five patients because of intolerable nausea and emesis related to amifostine, rapid progression of the disease in one patient, and insurance reasons in one patient. Four of these seven patients continued to receive irinotecan alone off study, three of whom achieved objective responses.

Toxicity

All 22 patients who received at least 1 treatment were included in the toxicity assessment. The toxicity profile is shown in Table 2.

Six of the 22 patients (27%) developed Grade 3 or 4 diarrhea; 2 of those patients (9%) had Grade 4 diarrhea and required hospitalization. Diarrhea was managed with loperamide. All six patients with severe di-

TABLE 1
Baseline Characteristics of the Patients

Demographics	No.	Percent
Gender		
Male	15	68%
Female	7	32%
Median age (yrs) (range)	59 (29–80)	
ECOG performance status		
0	5	23%
1	14	64%
2	3	13%
Primary tumor location		
Colon	16	73%
Rectal	6	27%
Sites of metastasis		
Liver	17	77%
Lung	7	32%
Peritoneum	2	9%
Local recurrence	4	18%
Other	4	18%
No. of organs involved		
1	11	50%
2	5	23%
≥ 3	6	27%
Previous RT (abdominal or pelvic)	7	32%
Previous chemotherapy regimens		
5-FU adjuvant	9	41%
5-FU metastatic	17	77%
5-FU adjuvant + 5-FU metastatic	6	27%
> 1 prior chemotherapy regimen for advanced disease	3	14%
Time from diagnosis to advanced disease		
Median time (mos) (range)	34 (7–108)	
Metastatic disease at diagnosis	8	36%

ECOG: Eastern Cooperative Oncology Group; RT: radiation therapy; 5-FU: 5-fluorouracil.

arrhea required a dose reduction of irinotecan, which resulted in improved tolerance. One patient required three sequential dose reductions secondary to recurrent episodes of Grade 4 diarrhea.

Grade 3 or 4 neutropenia was observed in 8 of the 22 patients (36%); 4 of these patients (18%) had Grade 4 neutropenia. Two patients (9%) required hospitalization for febrile neutropenia. Six of the eight patients developed Grade 3 or 4 neutropenia during the first cycle of treatment. One of the patients requiring hospitalization developed febrile neutropenia as well as severe diarrhea. This patient had received prior local pelvic radiation treatment, a known risk factor for gastrointestinal and bone marrow toxicity. The overall frequency of side effects was similar in those patients who had and those who had not received prior abdominopelvic radiation therapy.

Five patients (23%) developed Grade 3 or 4 nausea and emesis, mostly during or immediately after the infusion of amifostine. No significant hypotension or other frequently described amifostine-related toxicities (such as hypocalcemia and allergic reaction) were observed during or immediately after the administration of amifostine.

Dose Reduction and Dose Intensity

Dose reduction and dose intensity were assessed only for those patients who received at least one full cycle of irinotecan with amifostine.

Fifteen patients completed 1 cycle of treatment and 12 of the 15 patients received ≥ 2 cycles. The median number of cycles per patient was 3.9 (range, 1–12 cycles). These 15 patients received a total of 49 cycles and the dose was modified in 25% of the cycles. Two patients required more than one dose reduction (one of them required three subsequent dose reductions). The reasons for dose reduction were either Grade 3 or 4 diarrhea or Grade 3 or 4 neutropenia. Repeated dose reductions were performed because of severe recurrent Grade 3 neutropenia in one patient and recurrent Grade 4 diarrhea in the second patient.

The median irinotecan dose intensity of 118.5 mg/m^2/week was 95% of the planned dose intensity of 125 mg/m^2/week. The overall median dose for the 6-week cycle was 711 mg/m^2 of a possible 750 mg/m^2.

Antitumor Activity

Of the 15 patients evaluated for efficacy, 4 (26.7%) achieved a partial response with a median response duration of 40 weeks (range, 24–72 weeks). With the addition of those 4 patients who continued to receive irinotecan off the study (3 of whom achieved a partial response), 36% of the patients achieved a partial response. Nine of the 15 patients (60%) had stable disease as their best response, with a median duration of 14.2 weeks (range, 6–24 weeks). Only 2 of the 15 patients developed disease progression during the first treatment cycle.

DISCUSSION

Colon carcinoma remains a leading cause of cancer death in the U.S. The development of irinotecan and oxaliplatin, which act through mechanisms other than the inhibition of thymidylate synthase, provides alternatives to 5-FU for the treatment of this common tumor. Nevertheless, the toxicities associated with these cytotoxic agents remain a major issue.

In this pilot Phase II trial, we examined the role of amifostine as a protectant against irinotecan-associated neutropenia and diarrhea and compared it with previously reported data for different administration schedules including the biweekly regimen.[7,17,19,21] The toxicity data along with historic controls are presented in Table 2.

The safety and efficacy of a biweekly regimen for

TABLE 2
Adverse Events in the Study Population Compared with Alternative Irinotecan Regimens

Adverse events	With amifostine (n = 22) (q 2 wks)	Rothenberg et al.[19] (n = 92) (q 2 wks)	Bleiberg et al.[21] (n = 79) (q 3 wks)	Saltz et al.[7] (n = 223) (q week)
Late diarrhea				
Grade 3 or 4	27%	18.4%	23%	31%
Grade 4	9%	5.4%	2.5%	12.6%
Neutropenia				
Grade 3 or 4	36%	38%	33%	31.4%
Grade 4	18%	25%	18%	12.1%
Nausea/emesis				
Grade 3 or 4	23%		20%	12.1%
Grade 4	4.5%			6.3%

q: every.

the administration of irinotecan recently were evaluated in a Phase II multicenter trial in 92 patients with colorectal carcinoma that was refractory to 5-FU and were shown to be equal to other irinotecan schedules.[19] The response rate with the biweekly schedule (13%) was similar to that of the weekly or every 3-weeks regimen, as was the percentage of patients with stable disease (46%). The spectrum of toxicities with the every-2-weeks schedule also appeared to be similar, with perhaps a somewhat lower incidence of Grade 3 and 4 diarrhea (18% for Grade 3 or 4 and 5.4% for Grade 4) and perhaps a slightly higher incidence of Grade 4 neutropenia (25%). The results of the current study were consistent with this recent report and verified the biweekly schedule as a reasonable alternative to other irinotecan schedules.

Approximately 27% of the patients in the current study developed Grade 3 or 4 diarrhea. The incidence of Grade 4 diarrhea was slightly lower in patients pretreated with amifostine compared with historic controls for the weekly schedule (9% vs. 12.6%), but the incidence of Grade 4 events was at least as high as noted in the every second or every third week schedule. Although abdominal or pelvic radiation is known to be a significant risk factor for gastrointestinal toxicity, only one of the seven patients who received prior abdominal/pelvic radiation therapy in the current study were reported to develop Grade 4 diarrhea. This observation suggests that there might be some benefit to the further evaluation of amifostine in improving the tolerability of irinotecan in these patients.

Grade 3 or 4 neutropenia was observed in 36% of the patients in the current study, with severe Grade 4 neutropenia reported to occur in half of these patients. A majority of the patients experienced adverse events during the first cycle and did not have cumulative toxicity.

Although the reported overall toxicity was not significantly different from previous data, 60% of the patients in the current study were able to tolerate full doses of irinotecan and receive multiple cycles of chemotherapy (up to 12 cycles) with a continuous antitumor response. The response rate of 30% is comparable to that observed in other published reports.

Five of 22 patients (23%) treated with this combination of amifostine and irinotecan withdrew from the study because of intolerable nausea and emesis. Nausea and emesis are an expected complication of treatment with irinotecan. Grade 3 to 4 toxicity is reported to occur in 13–22% of patients receiving irinotecan, but only few of these patients have been reported to develop Grade 4 nausea.[9,17,21] Irinotecan-induced nausea usually is manageable with 5-HT3 antagonists and is not considered to be a dose-limiting toxicity. More striking in this small study was the 23% rate of patient withdrawal due to the nausea and emesis experienced before irinotecan was even administered. Although the incidence of nausea/emesis did not appear to differ dramatically from that in other reports, the current study patients believed the toxicity was intolerable and went on to receive irinotecan alone.[17] Prior results with the every-2-weeks regimen of irinotecan did not suggest the regimen alone is responsible for the increased incidence of nausea and emesis.[19] Amifostine is known to cause acute nausea and emesis akin to that observed in some of the patients in the current study and perhaps, with a different premedication regimen, can be made more tolerable.

None of the other adverse effects previously described with amifostine, such as hypotension, hypocalcemia, or allergic reaction, was observed. Nausea and emesis are the most frequently reported adverse effects of amifostine, and the incidence of these complications in the literature has ranged from 19–

58%.[13,14,20] The principles of adequate antiemetic premedication, hydration, and short infusion time were found to be the most significant factors in the prevention of these amifostine-induced toxicities, although not uniformly effective.[20] The above premedication regimen failed to prevent intolerable nausea and emesis in the current study. The heightened nausea and emesis will continue to limit the potential of amifostine in combination with irinotecan severely unless a better antiemetic scheme can be developed.

The median dose intensity in the recent multicenter Phase II study of a biweekly regimen was 119.3 mg/m^2/week, which was 95.4% of the planned dose intensity of 125 mg/m^2/week.[19,22] The overall dose intensity of irinotecan in the current study also was 95% of the planned dose intensity (118.5 mg/m^2/week of 125 mg/m^2/week [the planned intensity]), which compares favorably with the reported dose intensity with weekly or every 3-week schedules (81 mg/m^2/week and 112 mg/m^2/week, respectively).[23] Whether this increased dose intensity has any clinical relevance remains unclear.

Although it is difficult to draw conclusions from a nonrandomized and quantitatively small Phase II study, the preliminary data from the current study regarding the every-2-weeks schedule support the feasibility of this regimen as a reasonable alternative to other irinotecan schedules. The combination with amifostine did not demonstrate superiority over historic controls in terms of toxicity or response. The results of the current study demonstrated that adding amifostine to cytotoxic chemotherapy (in this case, irinotecan) certainly did not appear to affect the response rate adversely. Although some observations suggest the need for further study to determine the potential benefit for heavily pretreated or radiated patients, we cannot conclude that the regimen studied herein reduces the overall toxicity observed with irinotecan.

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