Phase II Trials of 5-Fluorouracil and Leucovorin in Patients with Metastatic Gastric or Pancreatic Carcinoma

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BACKGROUND. Previous trials in patients with colorectal carcinoma have indicated that enhancement of 5-fluorouracil (5-FU) by leucovorin (LV) can result in an improved response rate and increased survival.

METHODS. Phase II trials were performed with patients who had either gastric or pancreatic adenocarcinoma with metastases. Forty-one gastric carcinoma patients and 31 pancreatic carcinoma patients with measurable disease were treated with 5-FU, 425 mg/m^2 intravenously (i.v.), on Days 1–5 plus LV, 20 mg/m^2 i.v., on Days 1–5, repeated at 4 and 8 weeks, and then every 5 weeks thereafter.

RESULTS. The patients with metastatic gastric carcinoma had a median survival of 4.8 months. There was a 22% objective response rate, including a 4.9% complete response rate and a 17.1% partial response rate. Among the 31 patients with pancreatic carcinoma, there was a median survival of 5.7 months. No patients in this group showed a response.

CONCLUSIONS. The response rate for patients with metastatic gastric adenocarcinoma was modest and this regimen may provide temporary palliation for some patients. However, 5-FU and LV treatment is ineffective against metastatic pancreatic carcinoma. ***Cancer* 1996; 78:1888–91.** © *1996 American Cancer Society.*

KEYWORDS: 5-fluorouracil, leucovorin, gastric carcinoma, pancreatic carcinoma.

It is anticipated that more than 25,000 new cases of gastric carcinoma will be diagnosed in the U.S. annually and that fewer than 15% of these patients can be cured surgically. Most patients with gastric carcinoma become potential candidates for systemic chemotherapy for the treatment of recurrent or metastatic malignant disease. Chemotherapeutic agents such as 5-fluorouracil (5-FU), doxorubicin, the nitrosoureas (carmustine, semustine), mitomycin C, cisplatin, and folic acid antagonists have all demonstrated some antitumor activity against gastric carcinoma. Combination chemotherapy with a variety of regimens has yielded tumor regressions in 25–50% of patients in some series.[1–9] The Gastrointestinal Tumor Study Group (GITSG) has demonstrated a small but statistically significant survival advantage for patients with advanced gastric cancer treated with 5-FU, doxorubicin, and semustine (FAME) in a series of controlled clinical trials.[3–5]

However, the most favorable patient median survival in these trials has been in the range of 6–9 months, with only approximately 10% of patients surviving beyond 2 years. Thus, there is clearly a need for innovative chemotherapeutic strategies to provide higher tumor regression rates and more substantive prolongation of patient survival.

Adenocarcinoma of the pancreas ranks fifth in this country as a cause of cancer death. Treatment results to this date by any single modality or combination modalities have been dismal. National end results statistics show that 98% of patients afflicted with this disease will die. Only rarely will patients with pancreatic carcinoma be eligible for resection with curative intent and even under these rare circumstances fewer than 10% of patients will be cured. Chemotherapy to date has been an exercise in futility. The most active single agents have not produced response rates reliably above 15% and the duration of response is generally in the range of 3 to 4 months. Combination chemotherapy has occasionally led to claims for high response rates, but these have not been confirmed in more extensive follow-up studies. An example of this phenomenon is the early report of a favorable response rate with the combination of 5-FU, doxorubicin, and mitomycin C (FAM).[10] Results of both GITSG and cancer and leukemia group B (CALGB) FAM trials showed disappointing response rates of only 14%.[11,12] The Mayo North Central Cancer Treatment Group study had only 1 response in 13 patients.[13] Clearly, there is a need for more effective treatment in this disease.

There are extensive preclinical data and evidence from clinical trials indicating enhancement of 5-FU antitumor activity by the addition of leucovorin (folinic acid, citrovorum factor) (LV). An excess of intracellular reduced folates appears to be necessary for optimal inhibition of thymidylate synthase by fluorinated pyrimidines. Multiple controlled clinical trials from Roswell Park Institute,[14] City of Hope,[15] and Princess Margaret Hospital[16] have confirmed statistically significant increases in objective tumor response rates in patients with metastatic colorectal carcinoma with 5-FU and LV compared with 5-FU alone. In addition, analysis of a Mayo/NCCTG advanced colorectal carcinoma protocol of 420 eligible patients randomized into 1 of 6 treatment arms indicated that the 2 regimens that were comprised of 5-FU and folinic acid produced statistically significant improvement in patient survival and quality of life compared with intensive-course, single agent 5-FU.[17] However, not all studies have shown superiority of this combination over 5-FU alone.[18]

5-FU has demonstrated some single agent activity against metastatic gastric and pancreatic adenocarcinomas. Because of an enhanced effect of 5-FU and folinic acid in colorectal carcinoma, it appeared reasonable to study this combination in the treatment of advanced gastric and pancreatic adenocarcinomas because Phase II studies had not been reported for these diseases. If substantial therapeutic activity were observed with this regimen, then a controlled comparative trial would be performed in the future in each tumor type.

The goal of this study was to determine the Phase II activity of 5-FU and leucovorin given in a 5-day schedule every 4 to 5 weeks for patients with advanced gastric or pancreatic carcinomas who have not had prior chemotherapy exposure.

MATERIALS AND METHODS

Patient eligibility required all patients to have known primary gastric (or originating in columnar esophageal mucosa) adenocarcinoma or pancreatic adenocarcinoma beyond the hope of cure. There must have been histologic proof of residual primary, recurrent, or metastatic disease. Patients had measurable disease to serve as an objective indicator of response to therapy. Lesions for which size could only be estimated would not be considered measurable. Hepatomegaly could be employed as a measurable lesion if the liver had been proven to contain metastasis and if the liver edge was clearly palpable at least 5 cm below the xiphoid process or costal margins at quiet respiration. A positive liver scan or a computed tomography scan in the absence of hepatomegaly could be used if there was a clearly defined defect of 5 cm or greater in dimension. Patients had to have recovered from prior surgery. Contraindications to admission were Eastern Cooperative Oncology Group (ECOG) performance status of 3 or 4, any prior chemotherapy, prior radiation therapy involving greater than one-third of the bone marrow, severe malnutrition, leukopenia or thrombocytopenia, and any coexistent malignant disease.

All patients had a history, physical examination, and tumor measurements. A complete blood count, 12-channel chemistry group and chest X-ray were performed prior to admission on study.

TREATMENT

LV was given at 20 mg/m^2 intravenous (i.v.) bolus on Days 1 through 5. 5-FU was given at 425 mg/m^2 i.v. bolus on Days 1 through 5 immediately after the dose of LV. Courses were repeated at 4 weeks, 8 weeks, and then every 5 weeks until progression.

RESULTS

There were 41 patients with gastric adenocarcinoma and 31 patients with pancreatic adenocarcinoma. Pa-

TABLE 1
Patient Characteristics

	Gastric adenocarcinoma	Pancreatic adenocarcinoma
Total patients	41	31
Male/female	38/3	13/18
Age median (range) (yrs)	63 (48–82)	64 (50–80)
ECOG PS		
0	8	5
1	26	19
2	7	7

ECOG: Eastern Cooperative Oncology Group; PS: performance status.

TABLE 2
Toxicity N = 72

	% overall	% grade 4
Stomatitis	85	22
Diarrhea	60	8
Vomiting	46	10
Myelosuppression		
Leukopenia[a]	83	19
Thrombocytopenia[b]	10	4

[a] Overall leukocyte count < 4000.
[b] Overall platelet count < 100,000.
National Cancer Institute criteria. Note 3 patients died secondary to toxicity.

tients characteristics are shown in Table 1. The majority of patients had an ECOG performance score of 0 or 1 and were good chemotherapy candidates.

Toxicity is listed in Table 2. There were three possible drug-related deaths. One patient with leukopenia died of septicemia. A second patient who had a history of congestive heart failure was admitted to the hospital with severe diarrhea and dehydration. The patient died in cardiogenic shock. A third patient who was borderline diabetic had severe diarrhea and was admitted to the hospital with a glucose of 1200 mg/dL. This could not be reversed, and the patient died. There was no correlation in the three deaths as to tumor primary, initial performance status, or known premorbid condition that could explain the severity of the toxicity. Five additional patients had to receive i.v. fluids for severe stomatitis or vomiting. One additional patient was admitted to the hospital with an exfoliative dermatitis. Although stomatitis, diarrhea, and vomiting were frequently seen, they were not generally severe. Grade 4 (National Cancer Institute criteria) myelosuppression occurred in only a small percentage of patients.

RESPONSES

There was a total response rate of 22% in patients with gastric carcinoma (4.9% complete responses and 17.1% partial responses). Median survival was 4.8 months (range, 0.43 to 25.2 months). No responses were observed in patients with pancreatic carcinoma. Median survival was 5.7 months (range, 0.5 to 19.3 months).

DISCUSSION

5-FU has been used as a single agent for both gastric and pancreatic carcinomas. It also has been the basis for combination chemotherapy for both of these diseases. There have been numerous clinical trials utilizing 5-FU and combinations that have translated into little overall improvement in survival for the patient. The combination of 5-FU and LV has proven beneficial to patients with metastatic adenocarcinoma of the colon. The addition of LV to 5-FU increases the binding of fluorodeoxyuridylate to thymidylate synthase. This has translated into both increased response rates and length in these patients with metastatic colon carcinoma. Because of the benefit of 5-FU with LV in patients with metastatic colon carcinoma and 5-FU being the basis for combination therapy for patients with both gastric and pancreatic carcinoma, it is hoped that the combination 5-FU plus LV would translate into benefit for patients with these tumor types. Unfortunately, although the treatment was tolerated, the combination has only modest activity for patients with gastric carcinoma and is ineffective for patients with pancreatic carcinoma. This study confirms the negative studies by Crown et al. and DeCaprio et al. in patients with pancreatic carcinoma utilizing 5-FU plus LV, although on a different schedule.[19,20]

The combination of 5-FU and LV given by this dosage schedule is ineffective for patients with measurable metastatic pancreatic carcinoma. The response rates and median survival for 5-FU and LV in measurable metastatic gastric adenocarcinoma are modest. It is still to be determined if this regimen has a role in these diseases for patients with less tumor burden who are at an earlier stage of disease progression. Further innovative and novel approaches to these diseases will be necessary before significant advancement will be made for these patients.

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