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Phase I trial of 5-fluorouracil, leucovorin, and cisplatin in combination

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Summary. The ongoing evaluation of combination chemotherapy with 5-fluorouracil (5-FU) and cisplatin in several tumors prompted a phase I clinical trial of cisplatin with 5-FU modulated by leucovorin. A total of 26 patients were treated with varying doses of 5-FU by continuous i.v. infusion for 5 days; 200 mg/m^2 leucovorin was given by daily bolus injection for 5 days; and 20 mg/m^2 cisplatin was infused over 2 h on each day of treatment. Courses were repeated every 21–28 days. The starting dose of 5-FU was 300 mg/m^2. Poor-risk patients (extensive prior radiation, performance status of 2 or worse) did not tolerate the initial dose; the maximum tolerated dose of 5-FU in this group was 200 mg/m^2 daily. Good-risk patients tolerated 300 mg/m^2, but a majority had excessive toxicity at higher doses. The dose-limiting toxicity was gastrointestinal (mucositis/diarrhea) and/or myelosuppression; additional side effects included were nausea and vomiting ($\leq$grade 2) and ataxia (one patient). Among 13 patients with colorectal cancer, 4 partial responses were observed. The marked reduction in the tolerable dose of 5-FU occasioned by the addition of modulating doses of leucovorin is noteworthy. The responses observed support further investigation of this regimen in phase II trials.

Introduction

Cisplatin and 5-fluorouracil (5-FU) are frequently combined in the treatment of several tumors [9–13], although their interaction at a cellular level is incompletely understood. Scanlon et al. [22] have studied the interaction of cisplatin and 5-FU in vitro. Exposure of cells to clinically achievable concentrations of cisplatin (10 μM) results in elevated levels of reduced folates and enhanced binding of 5-fluoroudeoxyuridine monophosphate (FdUMP) to its target enzyme, thymidylate synthase [22]. These authors demonstrated that the inhibition of methionine transport obtained by incubation of cells with cisplatin [21, 23] leads to a state of methionine deprivation, which results in enhanced intracellular synthesis of reduced folates [22]. Thus, the effect of cisplatin on 5-FU cytotoxicity appears to be indirect.

Cisplatin and 5-FU may have supra-additive activity when combined in the treatment of head and neck, esophageal, and gastric cancers. In these diseases, phase II results of combination treatment appear to be superior to those obtained for each single agent alone [9–11, 13]. Although the optimal schedules have not been clearly defined, the use of continuous-infusion 5-FU seems to be important for the maximization of the interaction [12]. The preclinical in vitro data cited above demonstrate that the interaction of cisplatin and 5-FU may occur at cisplatin concentrations that have been obtained using doses ranging from 30 to 100 mg/m^2 [6, 24].

Numerous preclinical and clinical studies indicate that the cytotoxicity of 5-FU (to both normal and tumor tissues) may be enhanced by the addition of an exogenous supply of reduced folate [15, 25]. The optimal in vitro folate concentration may be as high as 10 μM; such levels may be sustained in humans with the use of 200 mg/m^2 leucovorin [15]. Randomized trials in colorectal cancer have demonstrated higher response rates for the combination of leucovorin and 5-FU than for 5-FU alone [3, 5, 17, 19, 20].

Clinical studies are in progress to evaluate low doses of cisplatin in combination with 5-FU and leucovorin. In the present study, we also opted to maximize the dose intensity of cisplatin. We report the clinical results of a phase I trial in which full doses of cisplatin in combination with high-dose leucovorin were used. The results show that toxicity was surprisingly severe with this combination.

Patients and methods

Patient population. Patients were accrued to this study between April 1987 and January 1988. Those eligible for this study had a histologic diagnosis of cancer and had exhausted the standard therapeutic options for their disease. All were required to have a performance status of 0–3

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(ECOG), to be >18 years of age, and to have adequate bone-marrow (WBC, >3,000/ml^3; platelet count, >100,000/ml^3), liver (bilirubin, ≤2 mg/dl), and renal (creatinine, ≤1.5 mg/dl) function. Exclusion criteria included prior treatment with either 5-FU or cisplatin, and all patients gave written informed consent in accordance with federal, state, and institutional guidelines.

Prior to therapy a medical history, physical examination, complete blood count, biochemical profile, urinalysis, electrocardiogram, and chest X-ray were performed. Patients were monitored with regular blood counts, renal function tests, and clinical examinations during each course. Dose reductions were based on the toxicity of the previous course. Results are reported using the Common Toxicity Criteria (Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, Maryland, 1988). Patients with measurable disease were evaluated (usually by computerized tomographic scan or X-ray) during every other course; those with stable disease or better were continued on therapy. Standard response criteria were used [16].

Treatment plan. 5-FU was given at escalating doses by 5-day continuous infusion; the starting dose was 300 mg/m^2 daily. Leucovorin (200 mg/m^2) was given i.v. daily, beginning immediately before initiation of the 5-FU infusion. Cisplatin (20 mg/m^2) was given i.v. daily for 5 days. Cisplatin administration was preceded by hydration with 1 l 5% dextrose/0.45% sodium chloride and by 20 mg i.v. furosemide. Dose escalations of 30% were planned, and a minimum of three patients was to be entered at each dose level. Drug administration was performed in the Mary S. Schinagl Clinical Pharmacology Unit at Fox Chase Cancer Center. The recommended phase II dose was defined as being that at which <50% of patients had developed either grade 3–4 myelosuppression or grade 2–4 extramedullary toxicity. Courses were repeated every 3–4 weeks.

Results

A total of 26 patients were treated with 94 courses. Their demographic characteristics are summarized in Table 1, which indicates that most patients had a good performance status (median PS, 1) and had not received extensive prior treatment. Over half of the patients had colorectal cancer.

Toxicity

The starting dose of 5-FU was 300 mg/m^2 daily given for 5 days by continuous infusion, which is only some 30% of that conventionally tolerated in combination with cisplatin on this schedule [10]. Despite this low dose, four of the eight patients treated on the first two dose levels (5-FU, 300 and 400 mg/m^2 experienced grade 3 or 4 toxicity (one episode of ataxia, one episode of mucositis, and two patients with both mucositis and neutropenic sepsis). Analysis of these patients for pretreatment characteristics that were associated with the occurrence of toxicity revealed that all four had a history of prior radiation therapy. Also, whereas two of five patients with a PS of 0 or 1 developed toxicity, two of three subjects with a PS of ≥2 were so affected.

On the basis of these observations, we stratified accrual to this study into "good-risk" (PS, 0 or 1; no prior radiation) and "poor-risk" (PS, ≥2; history of prior radiation) groups. In good-risk patients we set out to define the MTD by increasing accrual to the 400-mg/m^2 level; we subsequently expanded it at the 300-mg/m^2 level. In poor-risk patients we reduced the dose to 200 mg/m^2. The toxicity in these patients is summarized separately in Tables 2 and 3.

In good-risk patients, 400 mg/m^2 5-FU produced dose-limiting leukopenia and mucositis, with three of nine patients developing grade 3 or 4 toxicity; one additional subject had grade 4 thrombocytopenia. Diarrhea was not dose-limiting in these patients. Other than the individual who developed grade 3 ataxia after a single course of therapy at 300 mg/m^2, neurologic toxicity was characteristic of cisplatin: four patients developed peripheral neuropathy (three cases, grade 2; one case, grade 3) following a median of seven cycles of treatment. Based on these findings, 300 mg/m^2 5-FU was recommended as a phase II dose for good-risk patients.

In poor-risk patients, mucositis was dose-limiting at 300 mg/m^2. At 200 mg/m^2 no patient had mucositis worse than grade 2, although grade 3 leukopenia occurred in two of six patients at this dose. In poor-risk patients diarrhea was reported, but it was not severe. Among all of the patients, nausea and vomiting were common: in 14 of 26 cases these toxicities were grade 2 and in 2 patients, grade 3.

Responses

Among the 26 patients entered in this study, 15 had measurable disease and were evaluable for response. There

Table 1. Demographic characteristics of patients entered on study

Number of patients	26
Median age (range)	60 (46–72) years
Sex (M/F)	14/12
Performance status (ECOG):	
0	6
1	14
2	5
3	1
Primary tumor site:	
Colorectal	13
Lung	4
Head and neck	4
Other	5
Prior treatment:	
None	3
Chemotherapy	9
Radiotherapy	9
Both	5

Table 2. Toxicity of 5-FU/leucovorin/cisplatin in good-risk patients

5-FU dose	Patients (*n*)	Grade				
		0	1	2	3	4
Leukopenia:						
300 mg/m^2	4	1	1	2	0	0
400 mg/m^2	9	1	2	3	2	1
Thrombocytopenia:						
300 mg/m^2	4	2	1	1	0	0
400 mg/m^2	9	6	1	1	0	1
Mucositis:						
300 mg/m^2	4	3	0	0	1	0
400 mg/m^2	9	2	2	2	3	0
Diarrhea:						
300 mg/m^2	4	4	0	0	0	0
400 mg/m^2	9	6	2	1	0	0

Table 3. Toxicity of 5-FU/leucovorin/cisplatin in poor-risk patients

5-FU dose	Patients (*n*)	Grade				
		0	1	2	3	4
Leukopenia:						
200 mg/m^2	6	2	0	2	2	0
300 mg/m^2	4	1	0	2	1	0
400 mg/m^2	3	0	0	1	1	1
Thrombocytopenia:						
200 mg/m^2	6	4	1	0	0	1
300 mg/m^2	4	4	0	0	0	0
400 mg/m^2	3	2	0	0	1	0
Mucositis:						
200 mg/m^2	6	4	1	1	0	0
300 mg/m^2	4	2	0	1	1	0
400 mg/m^2	3	0	0	1	2	0
Diarrhea:						
200 mg/m^2	6	4	1	0	1	0
300 mg/m^2	4	2	1	1	0	0
400 mg/m^2	3	2	1	0	0	0

were 4 partial remissions among a total of 13 patients with colorectal cancer; 1 patient with head and neck cancer achieved a partial remission; and 1 subject with non-small-cell lung cancer showed a minor response.

Only one of the colon cancer patients who responded to treatment had received prior chemotherapy. This was a 61-year-old man with a cecal primary who had received adjuvant 5-FU for 18 months after surgery; his chemotherapy ended 3.5 years before his entry in this study. He relapsed with peripancreatic adenopathy and a hepatic metastasis; the former cleared completely after five cycles of treatment. Cisplatin was withheld after three cycles because of peripheral neuropathy. This patient went on to receive 27 cycles of treatment in 28 months and remains free of progressive disease. The other partial remissions were observed in three women who had not undergone prior chemotherapy. All had disease confined to the liver and achieved substantial partial remissions that lasted 2, 10, and 11 months; their duration of survival was 11, 20, and 25 months, respectively.

Discussion

Randomized trials in colorectal cancer have shown that leucovorin increases both the toxicity of and the response rate to 5-FU. The extent to which leucovorin modifies toxicity may be a function of the schedule of 5-FU administration. In the North Central Cancer Treatment Group trial, 5-FU given at 500 mg/m^2 daily $\times 5$ by i.v. bolus produced toxicity approximately equal to that caused by 5-FU given at 375 mg/m^2 daily $\times 5$ plus leucovorin at 200 mg/m^2 daily $\times 5$ [17]; that is, the use of 200 mg/m^2 leucovorin required a reduction of 25% of the 5-FU dose. The use of continuous-infusion 5-FU with leucovorin is less well characterized. The Southwest Oncology Group evaluated 5-FU given by continuous infusion at 1,000 mg/m^2 daily $\times 4$ with leucovorin given at 200 mg/m^2 daily $\times 4$ [1]. At these doses, 25 of 62 patients (40%) developed grade 3 mucositis. These data imply that on the 5-day infusion schedule, the addition of leucovorin should not require substantial reduction of the 5-FU dose. However, the present study shows that the addition of leucovorin to the combination of 5-FU and cisplatin requires a reduction of >60% of the 5-FU dose in good-risk patients; these patients (defined as those with a performance status of 0 or 1 and no history of radiation therapy) are comparable to those entered in phase II studies on colorectal cancer. Not unexpectedly, the poor-risk patients required an even greater reduction of the 5-FU dose in this combination.

A phase I–II study of cisplatin, 5-FU, and leucovorin in patients with head and neck cancer was reported by Vokes et al. [26]. 5-FU (800 mg/m^2) given by 5-day continuous infusion was well tolerated. In that study, leucovorin was given p.o. at 50 mg/m^2 every 6 h for 4 doses, and cisplatin at 100 mg/m^2. Oral administration of leucovorin results in lower plasma leucovorin levels than the high-dose i.v. schedules [26], but these levels appear to be sufficient to modulate 5-FU toxicity [17]. Based on responses reported by Vokes et al. [26] and on those observed in a study of 5-FU/oral leucovorin in colorectal cancer by Hines et al. [7], some enhancement of 5-FU activity may result from the use of oral leucovorin. However, the use of high-dose i.v. leucovorin markedly reduces the MTD of 5-FU.

These data appear to conflict with the results of Dreyfuss and colleagues [4], who recently reported that previously untreated patients with head and neck cancer tolerated 125 mg/m^2 cisplatin, 5-FU given at 800 mg/m^2 daily $\times 5$, and leucovorin given at 500 mg/m^2 daily $\times 5$. This cisplatin dose is marginally higher than that in the present study, whereas the leucovorin dose results in comparable plasma reduced-folate levels, which are sustained throughout the infusion period. In all, 94% of patients had $\geq$ grade 2 mucositis, and 31% of subjects developed grade 3 or 4 mucositis, requiring dose reduction. This degree of toxicity is similar to that experienced at 400 mg/m^2 5-FU in the present trial. The major difference between the groups would appear to relate to the more extensive prior treatment experienced by our patients. Our results suggest that this combination be used with caution in previously treated patients. Further study of the pharmacology of 5-FU in this regimen may improve the therapeutic index of treatment.

The pharmacologic basis for this increased susceptibility to 5-FU is not immediately apparent. Leucovorin (5-formyl-tetrahydrofolate) is metabolized intracellularly to expand pools of 5,10-methylene-tetrahydrofolate, the cofactor involved in formation of the ternary complex of 5-fluoro-deoxyuridylate and thymidylate synthase, which leads to the arrest of DNA synthesis. Scanlon et al. [21, 22] and Shionoya et al. [23] have shown that cisplatin inhibits methionine transport, which presumably stimulates endogenous methionine synthesis, and thereby expands reduced-folate pools [21–23]. It is possible that the effects of leucovorin and cisplatin may be additive in assuring more complete inhibition of DNA synthesis through inhibition of thymidylate synthase. Alternatively, the interaction of

these agents at more than one biochemical level may be envisioned.

Despite the low dose of 5-FU tolerated in this regimen, the combination is clearly active as evidenced by a high rate of response for a phase I study. It should be noted that three of the five responders who had colorectal cancer had not previously been treated with 5-FU. These results support further evaluation of this regimen in gastrointestinal malignancies. However, in colorectal cancer specifically, the role of cisplatin remains equivocal. Phase II results obtained using infusional 5-FU and cisplatin are quite variable in the response rates reported; partial remissions in 5%–70% of patients have been observed [2, 8, 18]. One randomized study on bolus 5-FU administration has shown no benefit to the cisplatin/5-FU combination [14]. A randomized phase III study is currently under way in the Eastern Cooperative Oncology Group to clarify the role of cisplatin in this disease.

The regimen outlined in this phase I study modulates the toxicity of 5-FU and shows preliminary evidence of efficacy. Phase II studies of this regimen are planned in colorectal and gastric cancers.

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