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Weekly fluorouracil and high-dose leucovorin: efficacy and treatment of cutaneous toxicity

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Summary. Intensive therapy with 5-fluorouracil (FU) and leucovorin (LV) has proved to be effective in the treatment of advanced colorectal cancer. The toxicity of this regimen has not been systematically evaluated. In the present study, 52 patients with advanced colorectal and refractory cancers received sequential 2-month cycles of weekly FU and high-dose LV and were monitored for toxicity as well as response in 103 cycles. Of 24 evaluable patients with colorectal cancer, 1 complete and 9 partial responses were seen (42%); 4 of 10 patients who had been refractory to conventional FU treatment responded to the FU/LV regimen. One partial response was observed among six patients with gastric carcinoma, and three minor responses were seen in five women with refractory breast cancer. A total of 24 patients (46%) completed the first cycle on schedule, although 7 subjects required a reduction in the dose of FU. The majority of patients required treatment breaks because of toxicity. Gastrointestinal toxicity proved to be dose-limiting on this schedule, necessitating FU dose modification and treatment of both diarrhea in 15 subjects and acute abdominal pain in 7 cases. No patient required a further treatment delay of FU dose adjustment. Myelosuppression was an uncommon complication on this regimen. Cutaneous toxicity was also prominent in this series of patients, with the hand-foot syndrome developing in 14 cases (27%); 11 subjects who developed this complication were treated with pyridoxine (150 mg daily), and all experienced improvement in their symptoms within 1 week. Partial and complete responses were observed in 41% of evaluable patients with colorectal cancer and in one of six evaluable patients with gastric carcinoma. We conclude that FU and high-dose LV can safely be given on a weekly basis, although acute gastrointestinal and cutaneous toxicity are common.

Introduction

The addition of high-dose leucovorin (LV) to 5-fluorouracil (FU) appears to have increased the efficacy of FU in advanced colorectal cancer. Two schedules have been used: the weekly schedule of Roswell Park Memorial Institute and the 5-consecutive-day regimen piloted at the Princess Margaret Hospital. The former consists of an injection of FU (600 mg/m^2) midway through a 2-h infusion of LV (500 mg/m^2). Patients are treated weekly for 6 consecutive weeks of an 8-week cycle. The dose-limiting toxicity of this regimen is diarrhea, occurring in 40% of patients with stomatitis, or myelosuppression, occurring in only 10% of subjects.

The Princess Margaret Hospital regimen uses a lower dose of LV (200 mg/m^2) given prior to FU (370 mg/m^2) on 5 consecutive days every 28 days. Stomatitis developed in 43% of cases and diarrhea, in 42% of patients treated in this manner. Less frequent toxicities reported by other investigators for this regimen include dermatitis, conjunctivitis, and alopecia. Both schedules have been subjected to phase III trials comparing FU and LV with FU alone in advanced colorectal cancer. Response rates were consistently higher for patients treated with LV [1–4, 13, 14].

At the University of Washington, a consecutive series of patients with advanced colorectal cancer and other refractory malignancies were treated with FU and high-dose LV according to the Roswell Park Memorial Institute's weekly regimen. In an attempt at careful identification of the toxicity, we followed patients with diaries and weekly visits and developed a dose modification schema to manage these complications. The results of this study are reported herein.

Materials and methods

Patients with newly diagnosed advanced colorectal cancer and malignancies refractory to conventional chemotherapy were considered to be candidates for therapy. Patients who had received prior FU were eligible,

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Table 1. Patient profile

Patients treated (*n*)	52
Number of cycles	103
Median age (range)	59 (23–86) years
Men: women	30:22
Diagnosis:	
Colorectal cancer	27
Gastric cancer	7
Breast cancer	5
Unknown primary	3
Lung cancer	2
Pancreatic cancer	2
Other	5

provided that they had not received LV with FU. All patients had measurable disease except three subjects with colorectal cancer who were treated in the adjuvant setting. Patients were initially evaluated with a physical examination, complete blood counts, liver function studies, and determination of electrolytes and renal function. Only patients with normal blood counts were eligible for study. In the outpatient setting, 500 mg/m^2 LV (Lederle Laboratories) was infused intravenously over 2 h; after one-half of the dose had been given, FU (600 mg/m^2) was injected. Each 8-week cycle consisted of 6 consecutive weekly injections followed by a treatment break; the cycles were continued until disease progression or toxicity necessitated a dose or schedule modification. Patients were given a diary in which they recorded the number and consistency of bowel movements, as well as any skin, eye, or mouth symptoms that developed. All 52 patients completed the weekly diaries. The patients were evaluated prospectively and a complete blood count was performed prior to each weekly treatment.

Dose modifications due to toxicity. Modifications of the FU dose were made because of mucositis, diarrhea, and myelosuppression. LV doses were not modified due to toxicity.

Response criteria. Standard response criteria were used. A complete response was defined as the disappearance of all measurable disease, with no new disease identified. A 50% reduction in the sum of the products of the biperpendicular diameters of the lesion was considered to be a partial response. A minor response was defined as a decrease of <50% in the sum of the products of measurable lesions. Disease that remained unchanged in size was considered to be stable disease. Lack of disease diminution or stabilization defined progressive disease.

Results

A total of 52 patients received 103 cycles of FU and LV. The median age was 59 years (range, 23–86 years). In all, 27 subjects had colorectal cancer; 7, gastric cancer; 5, refractory breast cancer; 3, carcinoma of unknown primary sites (CUPS); 3, non-small-cell lung cancer; 2, pancreatic cancer; and 1 each, duodenal cancer, Ewing's sarcoma, salivary gland, testis, and ovarian cancers. The initial performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) scale was 0 in 16 cases, 1 in 22 patients, and 2 in 14 subjects. In all, 9 of 27 patients with colorectal cancer and 2 of 3 CUPS cases had received prior FU with or without cisplatin. All women with breast cancer had progressive disease after at least two chemotherapy regimens, one of which contained doxorubicin. All patients whose primary lesions involved Ewing's sarcoma, salivary gland, lung, testis, or ovarian cancers had failed prior chemotherapy. The data is summarized in Table 1.

Table 2. Tumor response

Primary tumor	Evaluable patients	Complete response	Partial response	Minor response	Stable disease
Colorectal	22	1 (5%)	8 (36%)	–	–
Breast	5	–	–	3	–
Gastric	6	–	1 (17%)	–	–
Unknown	3	–	–	1	–
Pancreas	2	–	–	–	2

Table 3. Gastrointestinal toxicity

Patients treated (*n*)	52
Nausea:	
None	49 (94%)
Requiring therapy	3 (6%)
Diarrhea:	
None	16 (31%)
Formed stools (<6/day), no therapy	21 (40%)
Diarrhea (>6/day) responding to therapy	7 (13%)
Diarrhea (>6/day) not responding to therapy	2 (4%)
Dehydration requiring hospitalization	6 (12%)
Abdominal pain:	
None	35 (67%)
No treatment required	10 (19%)
Requiring therapy	3 (6%)
Bedridden	4 (8%)
Mucositis:	
None	44 (85%)
Mild pain	8 (15%)

Response data is summarized in Table 2. A total of 24 patients with metastatic colorectal cancer were evaluable for response; 3 were treated in the adjuvant setting and did not have measurable disease. One complete and nine partial remissions were seen, for an overall response rate of 42%. Among ten patients who had previously received FU, four partial responses were seen. One of six evaluable patients with gastric carcinoma achieved a partial remission. Minor responses were seen in three of five women with disseminated breast cancer and in one of three patients with CUPS. Both patients with pancreatic carcinoma experienced disease stabilization. The median duration of response was 5 months.

Gastrointestinal toxicities for all treated patients are summarized in Table 3. Nausea was uncommon, requiring antiemetic therapy with perchloperazine in only three (6%) patients. Much more common was diarrhea, which developed in 36 (69%) cases; its incidence was equal in cancers of gastrointestinal or nongastrointestinal origin. Typically, the diarrhea began 4–6 days after the 3rd or 4th weekly injection. In all, 21 patients experienced <6 diarrheal stools/day, which worsened when FU was continued at the same dose. Subsequently, these patients required a 25% reduction in the FU dose, with treatment continuation at the lower dose resulting in resolution of their symptoms. Nine patients (17%) received diphenoxylate hydrochloride (Lomotil) for more severe diarrhea; seven subjects responded to therapy and two did not.

Table 4. Cutaneous toxicity

Hand-foot syndrome	14/52 (27%)
Presenting complaint:	
Erythema	7
Pain only	1
Pain and erythema	6
Location:	
Hands only	10
Feet only	1
Face	1
Hands and feet	2
Timing:	
First cycle	8/52
Second cycle	5/27
Third cycle	1/15

Patients whose diarrhea responded to therapy continued treatment on schedule with a 25% reduction in the FU dose, as did those with less severe diarrhea. In all, 6 patients had to be hospitalized for dehydration resulting from diarrhea: 1 after the 3rd week, 2 after the 4th week, and 3 after the 5th week of FU/LV treatment; their age ranged from 44 to 71 years and was not skewed to elderly patients. In all instances, stool frequency had begun to increase with the previous 2 weeks' therapy but did not seem severe enough to warrant intervention. FU and LV were withheld until all symptoms resolved; thereafter, FU was restarted at 50% of the starting dose, which was slowly escalated until stool frequency increased.

The most severe gastrointestinal toxicity developed after the 3rd weekly treatment in a 44-year-old women with colorectal cancer. She developed profuse watery diarrhea, abdominal pain, and diffuse hemorrhagic gastritis. No etiology was identified other than acute FU toxicity, and reinstitution of FU at 50% of the starting dose was accompanied by recurrent symptoms. Chemotherapy was discontinued. Abdominal pain in the absence of diarrhea occurred in onyl one patient.

Stomatitis was infrequent, occurring in eight patients (16%), of whom subsequently developed diarrhea within 1 week. One of these patients noted a bloody stoma 1 week prior to the development of stomatitis. Although stomatitis did not limit therapy directly, its development heralded further gastrointestinal toxicity.

Cutaneous toxicity developed in the hands, feet, or face in 14 cases (27%) (Table 4). It appeared as a slightly raised, erythematous lesion on the dorsum of the hand or plantar surface of the foot and occurred either bilaterally or unilaterally; often it was pruritic and tender to the touch, although not warm. The involved hand was unrelated to the site of chemotherapeutic injection. Two of the patients developing cutaneous lesions received all chemotherapy through a central venous port. Ten patients showed involvement of the hands only, and the hands and feet were affected in two cases; one patient each showed involvement of the feet and face only. Of the 14 affected patients, 9 developed skin changes with the first 8-week cycle of chemotherapy, and the other 5 became symptomatic during subsequent cycles.

In all, 11 of these patients were treated with pyridoxine (150 mg p.o. qd) [12]; 8 experienced complete resolution of pain and erythema and the other 3 obtained pain relief in the face of persistent erythema. Symptoms improved in all of the patients within 1 week of instituting the vitamin and they were continued on pyridoxine throughout their chemotherapy. Two patients discontinued the vitamin while still receiving FU and LV, and their lesions recurred within 2–3 weeks. Because of symptomatic improvement in all of the treated patients, FU dose modifications due to cutaneous toxicity were unnecessary. Patients who demonstrated objective tumor regression prior to the institution of pyridoxine continued to show tumor response while receiving the vitamin.

Five patients (10%) complained of hyperlacrimation with crusting of the eyes upon waking. At an ophthalmologist's suggestion, artificial lubricating tears were used q.i.d. in one patient, with improvement of symptoms. Interestingly, all patients who developed hyperlacrimation also experienced some degree of diarrhea.

Granulocytopenia developed in six patients (12%) and was classified as being grade 3 in four cases and grade 4 in two. One patient succumbed to myelosuppressive complications. Two subjects developed grade 1 and grade 4 thrombocytopenia, respectively. In all instances, treatment was withheld until marrow recovery.

In summary, 24 patients (46%) completed the first cycle of chemotherapy within 6 weeks, and 7 of them required a dose reduction because of diarrhea. Treatment was delayed in the remaining patients due to the following complications: diarrhea, 23 cases; abdominal pain, 1; mucositis, 1; myelosuppression, 2; and patient compliance, 1. All but six patients tolerated at least 4 weekly cycles of FU and LV.

Discussion

Using reduced folates in combination with FU, Ullman et al. [17] demonstrated in vitro cytotoxicity 5-fold that obtained with FU alone. Similar "potentiation" has been observed in animal models and in human colorectal cancer xenografts [5, 10, 18]. In three randomized controlled trials in patients with advanced colorectal cancer, the addition of LV resulted in significantly higher response rates, suggesting a therapeutic efficacy as well. However, increased median survival was observed in onyl one series. The optimal dose and schedule for this combination has yet to be defined.

It was shown by Trave et al. [16] that an LV bolus resulted in higher tumor levels than did an infusion. Preliminary clinical trials seem to support the pharmacologic result. With a continuous infusion of LV as salvage therapy for colorectal cancer, no responses were observed [8]. However, bolus LV with FU has resulted in a 30%–50% response rate in some series [9, 11, 15].

The gastrointestinal toxicity observed with FU and LV is more severe than that associated with FU given alone as an infusion or a bolus. Furthermore, the Gastrointestinal Tumor Study Group observed that this toxicity was more common in elderly patients >65 years of age [6]. In the

present study, advanced age did not appear to predict gastrointestinal toxicity. The development of gastrointestinal symptoms was progressive, and mild symptoms preceded more severe symptoms. We recommend that patients developing increasing numbers of formed stools per day during therapy should receive a reduction of 25% in the FU dose beginning with the subsequent week's therapy. In patients experiencing more severe diarrhea, chemotherapy should be withheld until normal bowel function is regained, and the subsequent FU dose should be decreased by 25% throughout the cycle. Anti-diarrheal therapy such as phenoxylate hydrochloride (Lomotil) may be of symptomatic benefit for patients with more severe diarrhea. In dehydrated patients, chemotherapy should be discontinued until the diarrhea completely resolves. Combination therapy may be safely reinstituted at 50% of the FU dose.

Dermatitis has been reported during treatment with FU and LV in 10%–24% of patients [2, 9]. The hand-foot syndrome is the dose-limiting toxicity of continuous FU infusion over 12 weeks; its clinical appearance is similar to that of acrodynia in pyridoxal phosphate-depleted rodents [7]. Based on this observation, patients who developed the hand-foot syndrome with infusional FU were successfully treated with oral pyridoxine [12]. Although phlebitis is a common local side effect of FU, we observed pain and erythema indicative of the hand-foot syndrome in 27% of patients that was unrelated to the site of chemotherapeutic injection. Encouraged by this report, we treated 11 patients with pyridoxine and all subjects showed a dramatic symptomatic response. Patients who discontinued pyridoxine while still receiving chemotherapy developed recurrent symptoms, which further supports the therapeutic efficacy of pyridoxine. In addition, diarrhea and hyperlacrimation were not affected by the vitamin. That several of our patients on pyridoxine continued to show tumor regression suggests that antitumor activity is not altered by the vitamin. This should be confirmed in a larger trial. We recommend that pyridoxine be given daily throughout chemotherapy after patients have developed cutaneous toxicity.

It is curious that the hand-foot syndrome predictably develops when FU is continuously infused or given weekly with high-dose LV. Perhaps an understanding of the pathogenesis of this toxicity and of the role of pyridoxal phosphate in its resolution will enhance our understanding of the cytotoxicity of FU.

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