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Combination chemotherapy of cisplatin and 5-fluorouracil for advanced colorectal adenocarcinoma

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Summary. A total of 24 patients with advanced colorectal adenocarcinoma were entered into a phase I–II study of 5-fluorouracil (5-FU) and cisplatin, 21 of whom had previously received 5-FU. The starting dose of cisplatin was 20 mg/m^2 diluted in 1000 cc normal saline, given over 20 h daily for 5 days, together with 600 mg/m^2 5-FU diluted in 1000cc fluid, given simultaneously over 20 h daily for 5 days. This regiment was given every 4 weeks. The dose-limiting toxicity was renal and cumulative. All 24 patients were evaluable for toxicity. Of 12 patients on the above-mentioned starting dose, 8 underwent a cisplatin dose reduction to 15 mg/m^2 due to a progressive decrease in creatinine clearance following the second or third course of treatment. Of 12 patients who started cisplatin at 15 mg/m^2 and 5-FU at 600 mg/m^2, 11 were maintained at this dose. A WBC nadir count of $<2000/mm^3$ was seen in four patients. Thrombocytopenia occurred in three patients who received 15 mg/m^2 cisplatin and 600 mg/m^2 5-FU. In all, 21 of the 24 patients had objectively measurable disease and were also evaluable for response as follows: 1 complete response, 2 partial responses, 1 case of stable disease, and 17 patients with progressive disease.

Introduction

The treatment of advanced colorectal adenocarcinoma with 5-fluorouracil (5-FU) is of limited therapeutic value [6]. 5-FU is considered the standard chemotherapy for colorectal carcinoma, but response rates have only been in the 15%–20% range. Moreover, these responses are usually partial and of short duration.

The rationale for the cisplatin and 5-FU regiment described in this report is based on the results of animal data indicating that cisplatin host toxicity can be minimized when the drug is given by a 24 h infusion of toxic doses equal to 30 mg/m^2 in man. At a higher dose equivalent to 60 mg/m^2 in man, the drug produced >99% cell kill but the mice died of toxicity. Therefore, cisplatin has its greatest selectivity at low doses under conditions with no observed host toxicity [10].

Recent animal data (Fig. 1) indicate that the therapeutic selectivity of cisplatin in combination with 5-FU against mice bearing transplantable tumors can best be achieved when cisplatin is given at a dose equivalent to 7.5 mg/m^2 in man and 5-FU, at the maximally tolerated dose equivalent to 300–600 mg/m^2 in man. The administration of cisplatin by a single i.v. push yielded results similar to those obtained when the drug was injected i.p., suggesting that the therapeutic selectivity of cisplatin can best be achieved when the drug is given either by continuous i.v. infusion or at low doses by a single i.p. or i.v. push.

The animal data of Schabel et al. [8] has also indicated a rather marked therapeutic synergism for the combination of cisplatin and 5-FU whereas cisplatin has been ineffective as a single agent in human colorectal carcinoma [4, 5, 7]. The phase II study by Einhorn et al. [1], based on the Schabel et al. data, used 60 mg/m^2 cisplatin every 3 weeks for six doses and 15 mg/kg 5-FU weekly by i.v. push during the courses of cisplatin. In 38 patients with metastatic colorectal carcinoma, there were 11 partial responses and

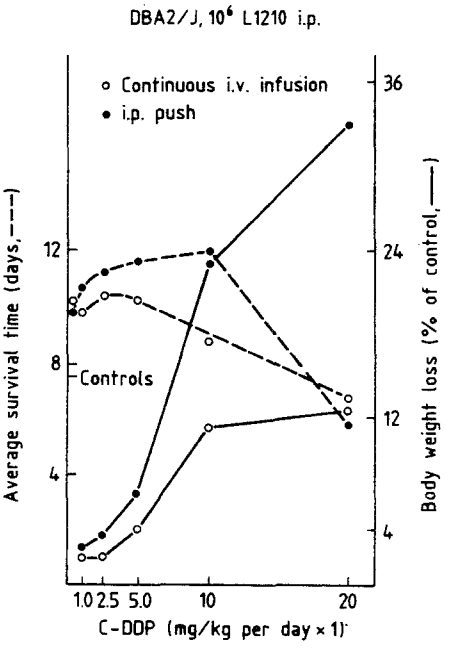

Fig. 1. Antitumor activity and toxicity of cisplatin given i.p. or by a 24 h continuous i.v. infusion to mice bearing leukemia L1210 cells. Treatments were initiated 24 h after the transplantation of 10^6 tumor cells

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1 complete response, for a response rate of 32%. None of these patients had previously received 5-FU or cisplatin.

The renal toxicity of cisplatin appears to be lessened by long-term infusion without an apparent decrease in effectiveness [3]. Vermorken et al. [11] have reported that higher peak levels of free drug are achieved with a rapid infusion (8.62 μg/ml) than with a 3 h (1.96 μg/ml) or 24 h infusion (0.27 μg/ml). Nevertheless, the area under the curve (AUC) of free platin concentration vs time (an index of free platin availability) was similar for all three infusion rates. If the efficacy of cisplatin is related to the AUC, it should not be compromised by a slow drug infusion. Additionally, if toxicity is related to high peak plasma levels, the use of prolonged infusions might be a means of limiting drug toxicity.

Based on these concepts, a study to evaluate the therapeutic efficacy and toxicity of continuous infusion cisplatin and 5-FU was carried out in previously treated patients with metastatic colorectal adenocarcinoma.

Materials and methods

A total of 24 patients with histologic documentation of colorectal carcinoma were included in this retrospective review; 21 patients had previously been treated with 5-FU and 3 had received no prior chemotherapy. All patients had normal hematologic, renal, hepatic, and cardiac function parameters except when abnormalities resulted from direct tumor invasion. There were 15 males and 9 females; the median age was 56 years, with a range of 54–83 years. The monitoring lesions were as follows: lung, 12 patients; liver, 5 patients; inguinal mass, 2 patients; pelvic mass, 3 patients; abdominal wall mass, 1 patient; and soft tissue metastases to the upper extremity, 1 patient.

Treatment plan and dose. Cisplatin (20 mg/m^2) was diluted in 1000 cc normal saline, and 600 mg/m^2 5-FU was diluted in 1000cc dextrose and water. The drugs were simultaneously infused i.v. during 20 h daily for 5 days every 4 weeks. Following each 20 h infusion, 500 cc dextrose and 0.45 normal saline with 20 mEq potassium chloride were given i.v. for 4 h. A 5-day infusion of cisplatin and 5-FU was considered to be one course.

Study parameters. Prior to each course of treatment, every patient underwent a complete blood count, serum electrolyte determination, liver function tests, serum creatinine, blood urea nitrogen, chest X-ray, liver scan, and abdominal and pelvic computerized axial tomographic (CAT) scan where appropriate.

Prior to each course of chemotherapy, a 24 h urine specimen was collected for the determination of creatinine clearance. If the creatinine clearance was <50 cc/min at the time of the next course of treatment but the serum creatinine was <1.5 mg%, the dose of cisplatin was decreased by 5 mg/m^2. If the serum creatinine was >1.5 mg%, chemotherapy was delayed until it reached <1.5 mg%, whereupon the cisplatin dose was decreased by 5 mg/m^2.

Patients were considered evaluable for toxicity if they received at least one course of therapy and were evaluable for response after two courses of treatment. Standard response criteria were used to evaluate the antitumor effect: (1) complete response, defined as the complete disappearance of all recognizable tumor masses; (2) partial response, a 50% reduction in the product of the largest perpendicular diameters of the most clearly measurable area of known metastatic disease, in addition to no increase in the size of other measurable disease and no appearance of new lesions; (3) stable disease, a decrease in tumor size of less than that representing a partial response, without the appearance of new lesions; (4) progressive disease, an increase in a measurable lesion of $>25\%$ and/or the appearance of new lesions.

Results

Clinical responses

In all 21 of 24 patients were evaluable for response. The other three patients were evaluable only for toxicity; two of the latter had only one course of 5-FU and cisplatin before refusing further therapy. The third patient developed a serum creatinine of 2.4 mg% midway through the second course of chemotherapy, which was subsequently stopped; this patient also refused further treatment.

The remaining 21 patients had objectively measurable disease and received at least two courses of 5-FU and cisplatin. The median number of courses was 4 (range, 2–7); a total of 73 courses of 5-FU and cisplatin were given to these 21 patients. Twelve of them began treatment with 20 mg/m^2 cisplatin and 600 mg/m^2 5-FU; the remaining nine began with 15 mg/m^2 cisplatin and 600 mg/m^2 5-FU. Partial responses were seen in two patients and a complete response was seen in one for a response rate of 15%. The responding patients all began cisplatin at 20 mg/m^2. Another patient with pulmonary metastases had stable disease for 4 months and subsequently refused further chemotherapy. These three responders and the one case of stable disease had all previously received 5-FU. The other 17 patients had progressive disease.

The complete responder was a 69-year-old female who had undergone an abdominoperineal resection for rectal adenocarcinoma, followed 2 years later by a posterior vaginal wall recurrence treated with local excision and 6000 rads to the pelvis, with weekly 5-FU. She developed a second vaginal recurrence and pulmonary metastases, both documented by tissue biopsy, 1 year thereafter. Within 3 months of treatment with 5-FU and cisplatin there was a complete response of the pulmonary mass, documented by chest X-ray, and complete regression of the vaginal recurrence, documented by tissue biopsy. After the seventh course, treatment with 5-FU and cisplatin was stopped due to leukopenia (WBC, 2300/mm^3) and a decrease in creatinine clearance from 70 cc/min to 30 cc/min. This patient is presently alive, has not received any chemotherapy for 14 months, and has remained in complete remission for 24 months.

One patient with lung metastases as the monitoring lesion had a partial response for 6 months. The second partial responder was a patient with soft tissue metastases to the upper extremity; the duration of her response was 5 months. Table 1 describes the patient characteristics of the responders.

Clinical toxicity

The dose-limiting toxicity was renal defined as a decrease in creatinine clearance. Of the 12 patients who started cis-

Table 1. Characteristics of responders on 5-FU + cisplatin

Patient	Sex	Age (years)	Number of courses of cisplatin and 5-FU	Monitoring lesion(s)	Duration and category of response (months)
M.P.	Female	69	7	Pulmonary, Vaginal	24, complete
G.F.	Female	62	6	Upper extremity soft-tissue metastases	5, partial
D.N.	Female	60	6	Lung	6, partial

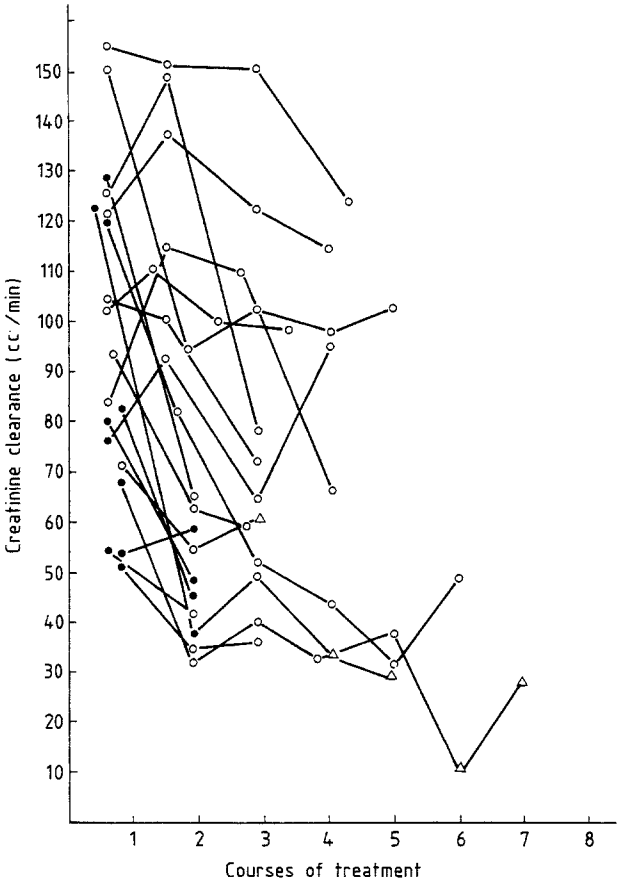

Fig. 2. Renal toxicity as illustrated by the cumulative decrease in creatinine clearance in patients on continuous 5-day infusion of cisplatin and 5-FU. ● = 20 mg/m^2 cisplatin + 600 mg/m^2 5-FU; ○ = 15 mg/m^2 cisplatin + 600 mg/m^2 5-FU; △ = 10 mg/m^2 cisplatin + 600 mg/m^2 5-FU

platin at 20 mg/m^2 and 5-FU at 600 mg/m^2, 4 received two courses of chemotherapy before treatment was stopped due to disease progression. The creatinine clearance in two of these patients remained unchanged, and in the other two it decreased by 50% after the second course of treatment. In the remaining eight patients, the cisplatin dose was reduced from 20 to 15 mg/m^2 due to a decrease in creatinine clearance following the second or third course of treatment; in two of these patients a subsequent reduction to 10 mg/m^2 cisplatin was required.

Initially, 12 patients received 15 mg/m^2 cisplatin and 600 mg/m^2 5-FU, 11 of whom were maintained at this dose. Following the second course of treatment in the remaining patient, the cisplatin dose was reduced to 10 mg/m^2 due to a decrease in creatinine clearance and the 5-FU dose was reduced to 400 mg/m^2 due to leukopenia (WBC, 2500/mm^3). Only 3 of the 24 patients developed an elevation in serum creatinine to 1.6, 1.6, and 1.7 mg% prior to the seventh, fifth, and second courses of chemotherapy, respectively. A fourth patient developed a serum creatinine of 2.4 mg% midway through the second course of treatment; however, this patient had pelvic recurrence with subsequent hydronephrosis. The cumulative renal toxicity that occurred in patients receiving at least two courses of treatment is illustrated in Fig. 2.

The hematologic toxicity of this regimen is illustrated in Table 2. A WBC nadir <2000/mm^3 was seen in three patients. Thrombocytopenia occurred in three patients who received 15 mg/m^2 cisplatin and 600 mg/m^2 5-FU; platelet counts of 92000/mm^3, 66000/mm^3, and 55000/mm^3 were recorded following the second, seventh, and second courses of chemotherapy, respectively.

Gastrointestinal toxicity was limited to nausea and/or vomiting controlled with antiemetics. No cisplatin dose reductions were required due to nausea or vomiting. No diarrhea occurred in any of the 24 patients evaluable for toxicity.

Table 2. Toxicity of continuous infusion cisplatin and 5-FU

		WBC nadir (cells/mm^3) (Number of patients)			
Cisplatin (mg/m^2)/5-FU (mg/m^2)	Total[a]	>4000	3000–4000	2000–2999	1000–1999
20/600	12	9	2		1
15/600[b]	22	18	2	1	1
10/600	3	1	1		1

[a] The total number of patients under study was 24; however, several patients were treated on two or three dose levels of cisplatin

[b] Thrombocytopenia in three patients: 92,000/mm^3 (2nd course), 66,000/mm^3 (7th course), 55,000/mm^3 (2nd course), respectively

Discussion

Previous studies have reported varying response rates and toxicity from the combination of cisplatin and 5-FU in colorectal carcinoma [1, 2, 9]. In the Einhorn et al. series [1], toxicity consisted of nausea, vomiting, alopecia, and usually severe granulocytopenia, with many patients having granulocyte nadir count $<1000/mm^3$. In the present series there was one drug death due to sepsis. The dose-limiting toxicity was renal, and myelosuppression was not significant. A total of 3 patients of the 24 evaluable for toxicity had WBC nadir counts $<2000/mm^3$. Thrombocytopenia ($<100000/mm^3$) occurred in three patients, with no sequellae.

Studies of cisplatin in the animal model system are in agreement with the clinical results in that the overall toxicity, particularly the renal toxicity, of cisplatin can be reduced when the drug is given by a continuous i.v. infusion. However, the renal toxicity in the present series was cumulative, as illustrated by a progressive decrease in creatinine clearance with each succeeding course of treatment. Of the 12 patients who started cisplatin at 20 mg/m^2 and 5-FU at 600 mg/m^2, 8 required a dose reduction to 15 mg/m^2 due to a decrease in creatinine clearance following the second or third course of treatment. In all 12 patients who started cisplatin at 15 mg/m^2 and 5-FU at 600 mg/m^2, the creatinine clearance decreased with each succeeding course of treatment. Whether an improvement in creatinine clearance occurred following termination of the cisplatin could not be determined from this group of patients, as progressive disease prevented subsequent urine collections.

The cumulative renal toxicity is best illustrated in the patient who developed a complete response. This patient began cisplatin at 20 mg/m^2 and 5-FU at 600 mg/m^2. Following the seventh course of treatment, the chemotherapy was stopped due to leukopenia and a decrease in creatinine clearance. This patient has remained a complete responder without any additional chemotherapy, illustrating the point that, although induction cisplatin is needed in this combination, maintenance doses may not be necessary. The induction regimen of cisplatin in combination with maintenance 5-FU is currently being evaluated in an Eastern Cooperative Oncology Group trial.

In the present series, 3 of 20 patients (15%) with objectively measurable diesease responded; these responders started cisplatin at 20 mg/m^2. Shepard et al. [9] reported no responses in 20 patients with metastatic colorectal carcinoma who received cisplatin on day 1 at 100 mg/m^2 and 5-FU at 1000 mg/m^2 per day as a 24 h i.v. infusion for 5 days. In the study by Einhorn et al. [1], a response rate of 32% was seen in 38 patients with metastatic colorectal carcinoma. Comparison of these studies is difficult because the dose and drug regimens of 5-FU and cisplatin differ.

The present report also illustrates that creatinine clearance can be used to monitor renal toxicity for the described regimen of cisplatin in combination with 5-FU. The serum creatinine was elevated >1.5 mg% but <2.0 mg% in only three patients. Therefore, using serum creatinine alone would not have reflected the cumulative renal toxicity. The renal toxicity on the present, continuous 5-day regimen again illustrates that induction with cisplatin in combination with 5-FU followed by 5-FU maintenance alone may resolve the cumulative renal toxicity.

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