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Cisplatin and 5-Fluorouracil Combination Chemotherapy in Advanced and/or Metastatic Colorectal Carcinoma: A Phase II Study

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Abstract—*The possible synergism of cisplatin (P) and 5-fluorouracil was studied in 38 consecutive patients with advanced or metastatic colorectal carcinoma. Cisplatin 60 mg/m² i.v.q. 4 weeks and fluorouracil 600 mg/m² i.v. weekly were administered for at least 2 cycles, on an out-patient basis, to 24 males and 14 females with a median age of 57 years and a median PS of 80 (Karnofsky). Evaluable lesions were: primary unresectable tumor in 2 patients, local recurrence in 11, liver, lung, bone and soft tissue metastases in 21, 7, 2 and 3 patients respectively. With a median number of 3 cycles administered to 35 evaluable patients, 6 partial responses, 16 unchanged and 13 progressions were observed. Responses were observed in the liver (2 patients), lungs (1) and soft tissues (3). Median remission duration was 15 weeks, median duration of 'unchanged' was 12 weeks. The overall median survival was 24 weeks (30.5 weeks for responders and 22.5 weeks for non-responders). Six patients were pretreated with chemotherapy not containing cisplatin (mainly adjuvant 5-FU). None of them responded.*

Toxicity was very tolerable with moderate nausea, vomiting and alopecia in the majority of the patients; bone marrow toxicity was generally mild with no blood transfusions required, no complications of myelosuppression (sepsis or bleeding) and no chemotherapy-related deaths.

In this experience the combination of low dose cisplatin with fluorouracil, does not appear to significantly enhance 5-FU toxicity and the response rate is not superior to that reported with 5-FU alone. However, better designed schedule combinations with optimal doses, sequences and exposure time of the 2-drug regimen, seem necessary to obtain the biochemical events that support the potentiation.

INTRODUCTION

5-FLUOROURACIL (5-FU) remains the treatment of choice in advanced colorectal carcinoma. In spite of the low response rate observed, with a mean value from various reports of approx. 20%, no other drug has been thus far proved superior [1–3]. Schedule modifications, as a prolonged i.v. infusion, or metabolic manipulations (with methotrexate or folinic acid or thymidine) have been reported to improve the response rate to 5-FU [4–11]. In contrast, some early promising data on 5-FU in combination with nitrosoureas, alkylating agents and antimetabolites did not show consistency of results in terms of objective remission and there are no large prospectively randomized studies showing better therapeutic activity than 5-FU alone [3, 12–14]. The heavy metal complex *cis*-dichlorodiammineplatinum II (cisplatin) showed in some studies a significant activity in a variety of human solid tumors but not in colorectal carcinoma [15–18]. However, recent reports with high doses of intra-arterially-administered cisplatin for locally recurrent colon cancer demonstrated a significant activity [19] which was also observed in some *in vitro* studies on human colon carcinoma cell lines [20].

A therapeutic synergism of cisplatin with various drugs in different human tumors has been extensively reported [21–23]. The same synergism has been confirmed also for cisplatin and 5-FU in animal model systems [24] and in humans [25–28]

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and more recently it has been suggested in patients with advanced colorectal carcinoma [29–31].

Based on this rationale, we undertook a phase II study exploring the clinical activity and the toxicity of 5-FU in combination with cisplatin in advanced and/or metastatic colorectal carcinoma.

PATIENTS AND METHODS

Patients with histologically-proven adenocarcinoma of the colon or rectum, with locally advanced unresectable tumor or with recurrent and/or metastatic disease not susceptible to radical surgery were considered eligible for this study. Patient entry was restricted to those with at least 1 bidimensionally-measurable lesion, performance status (Karnofsky score) 40 or greater, serum creatine 1.4 mg/dl or less, no radiotherapy on the evaluable lesions, and in any case completed at least 1 month before, and no previous chemotherapy with cisplatin.

Treatment consisted of cisplatin 60 mg/m^2 i.v. in 250 ml of normal saline on day 1 every 4 weeks and of 5-fluorouracil 600 mg/m^2 i.v. push, every week. Pre-cisplatin hydration consisted of 1 l. of gluco-saline (D5+1/2 NS) infused over 2 hr and 500 ml of mannitol; an oral introduction of about 2 l. of liquids during the previous 24 hr was also recommended to the patients. After cisplatin, patients received additional 500 ml of normal saline. Standard anti-emetic therapy using methoclopramide with or without cortisol was administered to all patients before treatment and continued as needed in cases of excessive nausea and vomiting. Treatment continued until progression or severe (grade IV WHO criteria) toxicity [32]. At least 2 cycles were required for response evaluation. In case of grade II/III toxicity, treatment was delayed until resolution and then resumed with a 25–50% reduction respectively of the responsible agent. Prior to the study, all patients received history and physical examination, routine laboratory tests including BUN, serum creatinine, CBC with platelets, CEA and chest X-rays. Liver and spleen scan, abdominal ultrasound or CT scan were performed if indicated for measurement. In patients with primary unresectable tumor, colon sigmoidoscopy and CT scan were required for evaluation. During the study CBC with platelets was performed weekly and physical examination, BUN, creatinine, and routine tests were performed every 4 weeks. CEA, X-rays and scans, when indicated, were performed every 2 cycles.

Responses to treatment were defined as follows:

complete response—complete disappearance of any evidence of tumor;

partial response—reduction of 50% or more in the sum of products of perpendicular diameters of measurable disease or a 30% or more reduction in the sum of measurements of liver below the costal margin, with no appearance of new lesions;

unchanged—less than 50% reduction or less than 25% increase in the sum of products of perpendicular diameters of measurable lesions or less than 30% reduction or less than 25% increase in the sum of distances below the costal margin;

progression—increase of 25% or more in the sum of products of diameters of measurable lesions or in the sum of liver measurements below the costal margin, or appearance of new lesions;

Partial responses were considered if lasting at least 4 weeks and calculated from the beginning of therapy to the first observation of progression.

Toxicity was reported according to WHO criteria [32].

Table 1. Characteristics of patients

Number of patients	38
Males/females	24/14
Median age (range)	57 (20/72)
Median Karnofsky PS (range)	80 (50/90)
Prior chemotherapy	6
Primary tumor:	
Colon	13 (34%)
Rectum	25 (66%)
Sites of disease:	
Liver	21
Local recurrence	11
Lung	7
Bone	2
Lymph nodes	2
Primary unresectable tumor	2
Abdominal wall	1

RESULTS

Characteristics of the patients are listed in Table 1. Twenty-four males and 14 females, with a median age of 57 years, a median performance status of 80 and with measurable advanced or metastatic colorectal carcinoma entered the study. Evaluable lesions were: primary unresectable tumor in 2 patients, local recurrence in 11 patients, liver, lung, bone and soft tissue metastases in 21, 7, 2 and 3 patients respectively. Of the 38 entered patients, 3 were considered unevaluable for response because they did not complete at least 2 cycles of therapy. One of these patients refused further treatment after the first cisplatin administration for gastrointestinal toxicity, the 2 remaining patients were lost to follow-up. Six patients were pretreated with chemotherapy not containing cisplatin (mainly adjuvant 5-FU). Among the 35 patients evaluable for response, no complete remissions were observed. Six patients (17%) showed partial response, 16 patients (46%) were unchanged and the remaining 13 patients

Table 2. Objective tumor responses

Response category	No. of patients (%)	Median duration of response (weeks)
Partial	6 (17)	15
Unchanged	16 (46)	12
Progression	13 (37)	—

(37%) showed progression (Table 2). Sites of response were liver metastases in 2 patients, lung in 1 patient, local relapse and abdominal lymph nodes in 1, supraclavicular nodes in 1 and abdominal wall in 1 patient. Median remission duration was 15 weeks. Median duration of 'unchanged' was 12 weeks.

The overall median survival from the onset of therapy was 24 weeks. The median survival for responders was 30.5 weeks and 22.5 weeks for non-responders (unchanged and progressing patients) ($P < 0.1$). The 6 patients who received previous chemotherapy showed progression of disease. All the 38 patients were evaluable for toxicity. The median number of cycles was 3 (range 1–6): almost all patients experienced moderate (grade II–III) nausea, vomiting and alopecia. Bone marrow toxicity was generally mild: leukopenia grade I in 10 patients and grade II in 4 patients; thrombocytopenia grade III in 1 patient and grade I in 6 patients; anemia grade I in 5 patients. There were no blood transfusions required, no complications of myelosuppression (sepsis or bleeding) and no chemotherapy-related deaths. Three patients showed grade III mucositis and 1 patient grade II diarrhoea. A transient rise in serum creatinine grade I in 2 patients and grade II in 1 patient was observed. Two patients complained of tinnitus and hearing loss.

DISCUSSION

In this experience the combination of cisplatin with 5–FU does not appear to excessively enhance 5-FU toxicity but the response rate observed is disappointing and not superior to that reported with 5-FU alone.

Moreover, if only untreated patients are considered, the objective response rate is still 20%. Our study therefore failed to confirm the effectiveness previously reported by others. Loehrer *et al.* for instance, using the same combination of drugs and a similar schedule in 38 untreated evaluable patients with metastatic colorectal carcinoma reported an overall response rate of 29% lasting more than 6 months [33]. Clinical data in colorectal carcinoma are not consistent when a 5-day 5-FU continuous infusion is employed. Madajewicz, employing cisplatin 20 mg/m^2/day and 5-FU 600 mg/m^2/day, both given by continuous infusion over 5 days, observed 3 objective responses out of 8 evaluable pretreated patients, showing the ability of this combination to overcome the tumor resistance to 5-FU [34]. Four objective remissions in 10 evaluable patients were also reported by Dy *et al.* [30] with continuous i.v. infusion of cisplatin (24 hr) and 5-FU (5 days). Shepard *et al.*, however, using the same doses and a similar schedule, did not report any objective remission in 20 patients with metastatic colorectal carcinoma [35]. In this latter study 13 patients were untreated. The synergistic antitumor activity of cisplatin and 5-FU has been recently evaluated in mice bearing leukemia L1210, studying different doses and sequences [36].

In this preclinical setting the antitumor activity was better related to the sequence of the 2-drugs combination than to the dose of cisplatin: the sequence 5-FU followed by cisplatin was significantly superior to other schedules. Also in clinical trials this combination has shown different activity according to the schedule employed.

An impressive synergistic activity of the cisplatin 5-FU combination has been reported in head and neck carcinoma [25], but in this tumor the effectiveness has been also dependent on the form of 5-FU administration. In a randomized study, the high response rate reported using 5-FU in continuous infusion dropped to a very low remission rate when 5-FU was used in i.v. bolus [37]. Moreover, the dose of cisplatin has been shown to be important in some tumors but not in others: in randomized clinical trials a dose-dependent antitumor activity in lung [38] and in breast [39] but not in head and neck cancer [40] has been observed.

All these data, together with the slight activity of cisplatin alone in colorectal cancer, seem to indicate that the synergistic effect could be achieved only with carefully designed schedule combinations. An optimal dose, sequence and exposure time of this 2-drug regimen seems to be necessary to obtain the biochemical events that support the potentiation.

In conclusion, the lack of active drug regimens in colorectal cancer and the mild toxicity of this combination despite the conflicting clinical results, support further trials focusing on a better schedule of cisplatin and 5-FU in the treatment of colorectal carcinoma.

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