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Short report

5-Fluorouracil, folinic acid and cisplatin in advanced colorectal cancer: a pilot study

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The combination of 5-fluorouracil (5-FU) and folinic acid (FA) has demonstrated activity in colorectal cancer (CC). Cisplatin is reported to have synergistic activity with 5-FU. We examined the combination FA + 5-FU + cisplatin in patients who had previously received chemotherapy with FA + 5-FU and relapsed. Two months after the last dose of FA + 5-FU and documentation of relapse, patients continued with the regimen consisting of cisplatin 20 mg/m² in 15 min i.v. infusion followed by FA 500 mg/m² in 1 h i.v. infusion, in the middle of which 5-FU 500 mg/m² i.v. bolus was administered, with adequate post-hydration. This was repeated weekly for 4 weeks followed by a 2 week rest, for a maximum of six cycles. A total of 30 patients with CC that had relapsed to the combination of FA + 5-FU were treated; 23 had previous surgery and none had radiotherapy. Local recurrence was found in eight patients, metastases in the liver in 21, in lymph nodes in six, lung six and peritoneal metastases in seven. Seven patients responded partially. Toxicity requiring dose reduction or discontinuation of treatment included neutropenia 42% (grade 3:7%), mucositis 28% (grade 1:2), diarrhea 63% (Grade 3:10%), nausea–vomiting 55% (Grade 3:10%), increased creatinine value in three patients and peripheral neuropathy in two patients. We conclude that evaluation of this regimen shows substantial toxicity, with satisfactory response as a second line chemotherapy in these heavily pretreated patients.

Key words: Advanced colorectal cancer, cisplatin, 5-fluorouracil, folinic acid.

Introduction

The combination of 5-fluorouracil (5-FU) and folinic acid (FA) has demonstrated activity in most gastrointestinal tumors. Cisplatin is reported to have synergistic activity with the combination of 5-FU + FA only *in vitro*. Some phase II studies using the combination of 5-FU + FA + cisplatin reported increased toxicity and a response rate of 30%.[1,2] We examined the role of the combination in this trial.

Early trials of FA + 5-FU in patients with metastatic colon cancer were reported in 1982 by Machover and Bruckner,[3,4] both observing responses in patients with cancers refractory to 5-FU and improved responsiveness over that expected with 5-FU alone in previous untreated patients.[5–10] Toxicity was substantial, consisting of neutropenia, diarrhea, stomatitis and neurological symptoms. Following these initial reports, many institutions have tested FA + 5-FU combinations[5,6] and experienced similar results, although doses and schedules have varied widely.[11–13]

The combination of 5-FU and cisplatin has given controversial results in different studies.[7,8] On the other hand, the addition of cisplatin to the FA + 5-FU combination has given encouraging results,[1,2,9,10] which were not confirmed in a recent randomized study.[14] For this purpose patients with no response or with progressive disease after therapy with FA + 5-FU were continued with the combination of cisplatin + FA + 5-FU in order to examine the potentiation of response and toxicity.

Materials and methods

Patients

Thirty patients with advanced colorectal cancer and prior therapy with FA + 5-FU, 17 men and 13 women, mean age 58 (47–66), were entered into this study. Performance status (Karnofsky) was 100: 6, 90: 6, 80: 10, 70: 8. With respect to the primary site there were 13 colon and 17 orthosigmoid cancers, with the following histologic grading; II: 26, III: 4. Metastatic sites were liver (21), lymph

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nodes (six), peritoneal (seven), lung (six) and eight patients had local recurrence.

All our patients had radiological, serological and/or clinical evidence of progressive disease under FA + 5-FU. None of our patients had previous radiotherapy and 23 were operated for colorectal cancer. All patients had previous chemotherapy with the combination of FA + 5-FU and relapsed; FA 500 mg/m^2/day in 1 h i.v. infusion and 5-FU 400 mg/m^2/day was administered as a mid-infusion i.v. bolus.

Patients started therapy with cisplatin + FA + 5-FU at least 2 months after the diagnosis of relapse in previous therapy with FA and 5-FU. All patients on FA + 5-FU had clinical, radiological and serological (tumor markers: CEA, CA 199) evidence of progressive disease. It was felt that initiation of cisplatin + FA + 5-FU should begin after recovery from toxicity of previous therapy or avoid possible excessive toxicity by instituting treatment after a short interval. Their response rate to initial FA + 5-FU therapy was six partial responders, 16 with stable disease and eight with progressive disease (Table 1).

Table 1. Details of 30 patients with advanced colorectal cancer

No. of patients	30
Age	58 (47–66)
Sex	
men	17
women	13
Performance status (Karnofsky)	
100	6
90	6
80	10
70	8
Degree of differentiation	
II	26
III	4
Primary site	
orthosigmoid	17
rest	13
Metastates	
liver	21
lymph nodes	6
local recurrence	8
peritoneal	7
lung	6
Prior surgery	23
Prior radiotherapy	0
Prior chemotherapy with FA + 5-FU	30
Response to prior chemotherapy	
complete	0
partial	6
stable disease	16
progressive disease	8

Eligibility criteria included (i) biopsy-proven adenocarcinoma of the colon or rectum, (ii) measurable metastatic disease, (iii) Karnofsky performance status of 60 or better, with life expectancy of at least 2 months, and (iv) without brain metastases.

Therapy

The treatment schedule was as follows: cisplatin 20 mg/m^2, 5-FU 500 mg/m^2 mid-infusion bolus during FA 400 mg/m^2 i.v. 1 h infusion. This was repeated every week, for 4 weeks, followed by a 2 week rest. Post-hydration after cisplatin included administration of 2350 ml 0.9% NaCl in 150 min with 60 ml Manitol 20% at the beginning of the infusion.

The dose of cisplatin was modified according to toxicity, with a 10% increase in the case of no toxicity. A 10% dose decrease of cisplatin or 5-FU was administered on the first cycle and in the event of grade 2–3 myelosuppression or grade 3 mucositis, in subsequent cycles.

The administration of drugs was as follows:

250 ml N/S + 8 mg Odansentron in 15 min i.v. infusion (1 tablet Odansentron 4 mg in the afternoon and another before sleeping).

500 ml N/S–60 ml N/S + 60 ml Manitol 20% + 2 g KCl in 30 min i.v. infusion.

100 ml N/S + cisplatin in 15 min infusion.

500 ml N/S + 2 g KCl in 30 min i.v. infusion.

1000 ml N/S + FA in 60 min i.v. infusion (in the middle of infusion 5-FU was administered by i.v. push).

This was repeated weekly for 4 weeks followed by 2 weeks rest.

Evaluation

Patients had weekly complete blood cell counts (CBCs), physical examination and serum chemistries. Ultrasonography or computed tomographic (CT) scans were repeated at 6 and 12 week intervals in order to observe bidimensionally measurable lesions. Lesions visible on chest X-ray were evaluated every 6 weeks. A 50% or more shrinkage in the sum of the products of two perpendicular diameters of measurable lesions for at least 1 month was defined as a partial response (PR), with the complete disappearance of all laboratory parameters and clinically evaluable disease of at least 1 month duration constituting a complete response (CR) to therapy. A 0–50% decrease in the sum of measured diameters was defined as stable disease (SD) on physical examination and radiologic studies.

Toxicity parameters were estimated according to WHO,[15] except nausea and vomiting.[16] For nausea, we used metoclopramide and only in three cases with severe neutropenia (neotrophils < 500) we administered granulocyte stimulating factor (G-CSF).

Statistical evaluation was based on the χ^2 test and Student's *t*-test.

Results

Thirty patients with advanced colorectal cancer received 87 courses (mean number 2.9 courses/patients; three patients: six courses, 1: 5, 5: 4, 7: 3, 9: 2, 5: 1; each course consisted of four doses of cisplatin + FA + 5-FU) of chemotherapy with cisplatin + FA + 5-FU.

The response rate is shown in Table 2. The percentage of responders (only PR) was 23%, for progressive disease (PD) 40% and for SD 37% (Table 2). Responders were four patients with liver and lung metastases, two with liver and peritoneal metastases, and one with liver and lymph nodes metastases.

A correlation between response to previous therapy with 5-FU + FA and subsequently to cisplatin + 5-FU + FA was observed. In the present study PRs (seven patients) were patients achieving PR (four) and SD (three) on previous chemotherapy with FA + 5-FU; patients with SD (11) were patients with PR (one), SD (eight) and PD (two) on previous therapy with FA + 5-FU; patients with progressive disease (12) were patients with PR (one), SD (five) and PD (six) on previous chemotherapy with FA + 5-FU.

The median duration of response was 13 (4–22) weeks, the survival time 34 (3–73) weeks and the time to progression 20 (0–64) weeks. Seven patients remained alive until the last evaluation (Table 2).

Toxicity was estimated according to the number of therapy courses. The incidence of neutropenia (< 2000) [1–3] was 32%, anemia [1–2] 61%, thrombocytopenia [1] 15%, nausea and vomiting [1–3] 90%, diarrhea [1–3] 63%, anorexia [1–3] 84% and fatigue [1–3] 74%). Five patients presented with neurotoxicity (25%), which was manifested as persistent headache, vertigo, fine tremor of the extremities, and in elderly patients restlessness and isomnia. Alopecia was uncommon. Hyperpigmentation of the skin, particularly in areas exposed to the sun, was observed in three patients, 15% (Table 3). All symptoms reported were evident after the start of the second line therapy with cisplatin + FA + 5-FU.

Dose intensity differences between planned and actual was 20% less for cisplatin and none for 5-FU and FA (Table 4).

Discussion

This study using a second line chemotherapy for advanced colorectal cancer examined if the addition of cisplatin to the combination of FA + 5-FU obtains new responses in patients who had previously received the combination of FA + 5-FU and relapsed. In our patients the only difference between first- and second-line therapy was the addition of cisplatin and, therefore, responses can only be ascribed to additive activity.

This study confirms the findings of other investigators reporting that cisplatin + FA + 5-FU is an active chemotherapeutic regimen in the treatment of advanced colorectal cancer.[1,2]

FA pretreatment enhanced 5-FU efficacy and toxicity by an interesting biochemical mechanism. The FA metabolite, 5,10-methylenetetrahydrofolate, stabilizes the ternary complex between the active 5-FU metabolite fluorodeoxyuridinemonophosphate (FdUMP) and the enzyme thymidylate synthetase (TS), leading to complete inactivation of the enzyme, thus shutting down *de novo* thymidylate synthesis.[1,6]

Table 2. Effect of treatment

	No. of patients	Percent	CI (95%)
Response			
complete	0	0	
partial	7	23	0.35
stable disease	11	37	0.588
progressive disease	12	40	0.705
Duration of response (weeks)	13 (4–22)		
Survival (weeks)	34 (3–73)		
Time to progression (weeks)	20 (0–64)		
Alive patients	7		

Table 3. Toxicity according to WHO[9]

	Grade	Percent
Neuropenia	0	68
	1	17
	2	8
	3	7
Anemia	0	39
	1	26
	2	35
Thrombocytopenia	1	15
Mucositis	0	72
	1	5
	2	23
Diarrhea	0	45
	1	31
	2	14
	3	10
Nausea–vomiting	0	10
	1	35
	2	28
	3	27
Anorexia	0	16
	1	26
	2	47
	3	11
Fatigue	0	26
	1	37
	2	24
	3	13
Increased of creatinine value	3 patients	
Neurotoxicity	5 patients	
Skin hyperpigmentation	3 patients	

Table 4. Dose intensity (mg/m^2/day)

Drug	Planned dose	Administered dose
Cisplatin	1.90	1.52
5-Fu	47.61	45.91
Folinic acid	38.09	38.42

Therapy courses: 87.

The mechanism of synergism between cisplatin and 5-FU has not been completely defined but may be explained in part by the effect of cisplatin on intracellular folate pools.[20] Cisplatin can inhibit the transport of the essential amino acid methionine.[21] Cells deprived of exogneous methionine must then endogeneously synthesize methionine from homocysteine to permit normal growth. This is accomplished by an increase in the conversion of 5-CH_3-FH4. Cisplatin has been reported to increase the pools of FH4 and 5,10-CH_3-FH4 which subsequently can result in an increase in TS ternary complex formation.[22]

Studies on the combination of cisplatin + FA + 5-FU reported that the addition of cisplatin enhances biological effect in response and toxicity, even in previously treated patients who were exposed to fluoropyrimidines. Main toxicities were nausea and vomiting, mucositis, diarrhea, and hematological toxicity.[1,2,23,24] It is interesting that all studies applying cisplatin + FA + 5-FU did not report increased response rates in comparison with those with FA + 5-FU. Based on this experience, and despite the activity of cisplatin + FA + 5-FU, the expense of hospitalization and the cumulative toxicity leads the investigators to conclude that this regimen does not warrant further phase II testing. In a recent randomized study of cisplatin + FA + 5-FU versus FA + 5-FU, the addition of cisplatin produced tolerable toxicity, but the difference in response rates and survival is not significant.[14]

In this study the response rate was 20% and was associated with serious toxicity. We used cisplatin despite the fact that it is known that cisplatin is inactive in colorectal cancer. We believe that its activity is modulatory to the combination of FA + 5-FU and not cytotoxic to colorectal cancer cells. In the present study two points deserve consideration. First, patients pre-treated with FA + 5-FU experienced responses with the combination of cisplatin + FA + 5-FU. In our study initial responders to FA + 5-FU responded again to the combination of FA + 5-FU + cisplatin. Second, many patients undergoing therapy with FA + 5-FU stopped it because of progressive disease, although they have a very good performance status and life expectancy; we believe that, for these patients, the addition of cisplatin in the combination of FA + 5-FU may have a role as an effective second-line therapy. These two points need further investigation. Selected patients with good performance status may benefit from intergrating cisplatin into the FA + 5-FU combination.

We conclude that the addition of cisplatin in the combination of FA + 5-FU is moderately active but toxic and may offer the opportunity to experience a new response to those patients who had previously responded or achieved SD to the FA + 5-FU combination.

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