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Research paper

Oxaliplatin combined to 5-fluorouracil and folinic acid: an effective therapy in patients with advanced colorectal cancer

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Patients with colorectal carcinoma progressing after a 5-fluorouracil (5-FU)-containing regimen were eligible. One treatment cycle consisted of repeated administrations of 5-FU combined to folinic acid for six times and to oxaliplatin for three times over 50 days. 5-FU was given at the dose of 2.6 g/m^2 as a continuous infusion over 24 h on days 1, 8, 22, 29 and 43 preceded by i.v. folinic acid (FA) at a dose of 500 mg/m^2 over 1 h. Oxaliplatin was given 1 h after 5-FU at the dose of 130 mg/m^2 over a 2 h infusion on days 1, 22 and 43. A total of 37 patients were treated according to this schedule. The rates of objective responses after the first and second treatment cycles were 28 and 17%, respectively, with rates of tumor growth control, i.e. including the stabilizations, of 55 and 28%. The median duration of response was 10 months and the median duration of stabilizations was 6 months. The median survival time from initiation of oxaliplatin-containing therapy is 10 months (2–28+). The median survival time from the diagnosis of metastatic disease is 24 months (2–40+). The main toxicities were leucopenia, diarrhea, fatigue and paresthesias. The combination of 5-FU/FA/oxaliplatin was well tolerated and appears as a meaningful therapy after failure of a previous 5-FU-containing treatment. [© 1998 Lippincott-Raven Publishers.]

Key words: 5-Fluorouracil, colorectal cancer, oxaliplatin.

Introduction

Oxaliplatin (*trans*-l-diaminocyclohexane oxalatoplatinum) is a new platinum derivative with an oxalato ligand and a 1,2-diaminocyclohexane 'dach' carrier. The mechanism of action of oxaliplatin is probably close to that of cisplatin, the main site of action of DNA being the intrastrand cross-link between two adjacent guanines d(GpG) or two adjacent guanine adenine d(GpA) base pairs. However, preclinical data suggest several unique attributes related to the cytotoxic antitumoral activity of oxaliplatin compared to cisplatin. DACH-Pt adducts are bulkier and more hydrophobic than *cis*-diamine-Pt adducts and may be more effective in DNA synthesis inhibition.[1] DNA mismatch repair complexes do not recognize DACH-Pt,[2] and experimental data on naked and intracellular DNA[3] suggest a higher cytotoxic efficacy of oxaliplatin DNA-Pt adducts than cisplatin DNA-Pt adducts. These adducts block both replication and transcription.

Oxaliplatin causes minimal hematological toxicity, no renal toxicity, no clinical ototoxicity and no hairloss. The dose-limiting toxicity is neurological. Unlike cisplatin, the neurotoxicity of oxaliplatin has both an acute and a chronic component. The neurotoxicity associated with oxaliplatin is sensitive and affects most of the patients. It occurs within hours after the treatment, sometimes starting at the first cycle. During the first cycles, it usually regresses before the next administration. Typical symptoms include paresthesias (usually without pain), cold-related dysesthesias and cramps.

An uncommon syndrome is a laryngopharyngeal dysesthesia exacerbated by the cold that causes a feeling of difficulty in breathing or swallowing. It resolves rapidly and could be prevented by prolonging the duration of infusion.

Neurotoxicity is cumulative and dose limiting. As patients receive more cycles of oxaliplatin, the symptoms tend to last longer, no longer vanishing between cycles. Neurotoxicity associated with oxaliplatin has not been reported to worsen after stopping treatment and most patients showed an improvement within 3–6 months after stopping treatment.[4]

The development of oxaliplatin was temporarily interrupted after the second phase I study performed

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in 1986, probably due to the atypical toxicity disclosed by that agent.[5] Phase II investigations in first and second line for colorectal cancer using oxaliplatin as single agent by short i.v. infusion were performed only recently. Objective response rates of 27 and 10% were observed in first and second line, respectively.[6,7] Based on the known synergism between 5-fluorouracil (5-FU) and folinic acid (FA) and the synergism observed between 5-FU and oxaliplatin in preclinical studies;[8] most of the phase II studies were performed with the combination of 5-FU, FA and oxaliplatin. Response rates of 28–50% were reported.[9,10]

These results prompted us to combine oxaliplatin to a high-dose continuous infusion of 5-FU over 24 h[11] on a compassionate-need basis in patients progressing after one or more previous 5-FU-based chemotherapy.

Patients and treatment

Patients with a histologically proven colorectal carcinoma progressing after any adequate 5-FU regimen were eligible for the present study.

One treatment cycle consisted of 5-FU given at the dose of 2.6 g/m^2 as a continuous infusion with a Pharmacia pump over 24 h, on days 1, 8, 22, 29, 43 and 50 (day 64 = day 1 of next cycle), FA i.v. at a dose of 500 mg/m^2 in 5% glucose over 1 h before 5-FU, and oxaliplatin i.v. at the dose of 130 mg/m^2 over 2 h in 5% glucose on days 1, 22 and 43.

Patients who had already been treated by infusional 5-FU did not receive the 5-FU/FA infusion on days 8, 29 and 50. In case of hematological toxicity or diarrhea WHO grade 2 on the day of retreatment, the administration was withheld until complete normalization and then the dose of 5-FU reduced by 10%. In the case of grade 3 or 4 toxicity, the dose of 5-FU was reduced by 20%. In case a dose reduction had been required more than twice, the treatment was stopped.

Peripheral neuropathy was graded as follows according to an adapted scale:[12] grade 1 when the duration of symptoms was less than 7 days, grade 2 when the duration of symptoms was less than 21 days, grade 3 when the symptoms were permanent and grade 4 when functional impairment was reported. In case of grade 3 neurotoxicity, the dose of oxaliplatin was reduced by 20% and stopped in the case of grade 4.

All patients received prophylactic antiemetic treatment with a 5-HT$_3$ receptor antagonist.

Tumor measurements were performed according to the WHO criteria. For practical reasons in a compassionate-need program, the assessments were performed every 8 weeks corresponding to one complete cycle of treatment with a minimum of three oxaliplatin/5-FU/FA administrations on days 1, 22 and 43. The confirmation of a response was not obtained after 4 weeks but after another 8 week period of time corresponding to a second complete treatment cycle.

Results

From October 1994 to August 1996, a total of 37 patients were treated according to this schedule. One patient with a history of colon cancer was not eligible because she was found to have hepatic metastases from a previous breast cancer.

The characteristics of all 36 eligible patients are detailed in Table 1. There were 18 males and 18 females with a median age of 61 years (34–75) and a median ECOG performance status of 1 (0–3).

As adjuvant treatment, eight patients had received a 5-FU-based therapy. As treatment of their advanced disease, all patients were pretreated with 5-FU containing regimens. A total of 21 patients received one prior treatment, 12 received two and three received three. Fourteen had received high-dose 5-FU/FA ± methotrexate, as first-line therapy in eight or when progressing after bolus 5-FU in six. Moreover, nine patients had received other drugs as first- or second-line treatment among which irinotecan, mitomycin C, carboplatin, cyclophosphamide, paclitaxel (for a wrongly diagnosed ovarian cancer) and batimastat.

The primary site of tumour was colon in 23 patients and rectum in 13. The metastatic sites were liver in 28 patients (of whom 18 had metastases at the time of the initial diagnosis), lung in 13, abdomino-peritoneal in 12 and other sites in eight.

Table 1. Patient characteristics

Eligible patients	36
Male/female	18/18
Median age (years) (range)	61 (34–76)
Median ECOG PS	1 (0–3)
Adjuvant chemotherapy	8
No. of prior chemotherapy regimens for metastatic disease	
1	21
2	12
3	3
Primary site	
rectum	13
colon	23
Metastatic sites	
liver	28
lung	13
abdominal	12
other	8

A total of one or less cycles (one to three oxaliplatin administrations) were given in eight patients, two or less cycles (four to six oxaliplatin administrations) in 18 patients, three or less cycles (seven to nine oxaliplatin administrations) in six patients and more than three cycles in four patients. Fourteen patients previously treated with an infusional schedule of 5-FU were treated on a 3-weekly basis with the combination.

At the time of the first assessment, i.e. 8 weeks after treatment initiation, we observed 10 partial responses and 10 stabilizations including two minor responses. At the time of the next tumor assessment, i.e. at week 16, the response was confirmed in six patients, not measured in two and unstained in two. The stabilization was confirmed in four patients, unstained in four and not measured in two. The rates of objective responses after the first and second treatment cycles were 28 and 17%, respectively, with rates of tumor growth control, including the stabilizations, of 55 and 28%.

The sites of responses were liver in eight patients, lung in four, lymph nodes in two and other viscera in one. The majority of patients were heavily pretreated. The pretreatments given in the responders, not including the adjuvant treatment, are detailed in Table 2.

The median duration of response was 10 months and the median duration of stabilizations was 6 months. The median survival time from initiation of oxaliplatin-containing therapy was 10 months (2-28+). It was 15 months in the responding or stabilized patients and 7 months in the progressing patients. The median survival time from the diagnosis of metastatic disease was 24 months (2-40+). It was 28 months in the subgroup of 18 patients without hepatic metastases at the time of initial diagnosis and 17 months in those 18 patients with synchronous hepatic metastases. In April 1997, five patients were alive and one was still on therapy.

The main toxicities were leucopenia, nausea/vomiting, diarrhea, fatigue and paresthesias. The worst WHO gradings are presented in Table 3, with a specific scale for neurotoxicity as defined in the section 'Patients and treatment' and UICC scale for fatigue.

Grade 3-4 leucopenia was observed in three patients, febrile neutropenia in two and documented septicemia in one. Nausea was severe in four patients (11%) and vomiting in two patients (6%) with no grade 4 (11%).

Diarrhea occurred in 12 patients but was severe (grade 3) in four (11%). It was probably due to the combined toxicity of 5-FU/FA and oxaliplatin. Fatigue was moderate in 14 patients and never severe. The peripheral neuropathy was grade 3 in one patient. It was grade 4 in one, requiring to stop the treatment after nine oxaliplatin administrations for a total dose of 2160 mg. Shortly after the oxaliplatin infusion, one patient had a laryngo-pharyngeal dysesthesia with wheezing and cyanosis occurring a few seconds following the breathing of cold air. The symptoms vanished as soon as the patient was brought back in a warm surrounding.

Table 2. Characteristics of responders

Patient no.	Sites of responses	Response duration (months)	Pretreatment
1	liver, lung	4	1. HD 5-FU+LD MTX 2. 5-FU/FA bolus 3. HD 5-FU 24 h
2	liver, lung	3	1. HD 5-FU+LD MTX 2. 5-FU/FA bolus
4	lung	6	1. HD 5-FU/FA (de Gramont) 2. batimastat
6	liver, lung	10	1. 5-FU continuous infusion over 2 years
9	liver, lymph nodes	2	1. 5-FU/FA bolus
16	liver	7	1. 5-FU bolus (+radiotherapy)
23	liver	9	1. 5-FU/FA bolus
24	liver	12	1. 5-FU bolus+MMC by hepatic artery
28	lymph nodes, other viscera	12	1. carboplatin+endoxan 2. taxol 3. 5-FU/FA+MTX
29	liver	11	1. 5-FU/FA bolus

HD, high dose; LD, low dose.

Table 3.

Grade	Worst WHO grading of main toxicities				UICC scale	Specific scale
	WBC (%)	Platelets (%)	Nausea/vomiting (%)	Diarrhea (%)	Fatigue (%)	Neurotoxicity (%)
0	19 (53%)	25 (69%)	20/29 (55/81%)	24 (67%)	18 (50%)	6 (17%)
1	4 (11%)	8 (22%)	10/3 (28/8%)	2 (5%)	4 (11%)	21 (58%)
2	10 (28%)	0	2/2 (5/5%)	6 (17%)	14 (39%)	7 (19%)
3	2 (5%)	3 (8%)	4/2 (11/5%)	4 (11%)	0	1 (3%)
4	1 (3%)	0	0/0	0	0	(1) (3%)

Other toxicities were dysgeusia in two patients, stomatitis in one, headache in one and allergic reaction in one during the eighth administration. The patient presented with facial flush, headache and a generalized cutaneous rash. The treatment had to be discontinued because of the recurrence of the reaction with a test dose despite a premedication with corticosteroids.

Discussion

Colorectal cancer has long been considered as a non-chemosensitive disease. Since the late 1980s, modulation of 5-FU with folinic acid increased the response rate as well as survival. The median survival of patients receiving best supportive care alone does not exceed 6 months.[13] The median survival of patients receiving bolus 5-FU-based treatments is around 12 months.[14] Prolonged 5-FU infusion might even be superior to bolus regimen although comparative data between both modalities are scarce[15] and require further confirmation.

Second-line treatments have been poorly investigated. The observation that bolus and infusional 5-FU act as two different drugs led some investigators to administer continuous FU following progression with bolus FU.[16] Response rates of about 9% were reported.[17] No benefit would be expected from 5-FU bolus after failure of continuous infusion. Among our patients who had received two prior 5-FU-containing regimens, no response was observed with the second-line chemotherapy either with bolus 5-FU/FA after high-dose 5-FU/FA ± MTX or with high-dose 5-FU/FA after bolus 5-FU/FA. More recently CPT-11 has been given in second-line treatment in 455 patients progressing after 5-FU. The overall response rate was 13% and another 34% had stabilized disease translating in prolonged progression-free and symptom-free survival,[18] strongly suggesting a real benefit of treatment.

Oxaliplatin as a single agent, in second line, is poorly active with a response rate not exceeding 10%.[6] In combination with 5-FU the response rate reaches levels as high as 30–50%.[9,10]

The present paper underlines the fact that heavily pretreated patients progressing after an adequate 5-FU-based regimen may still be responsive to another treatment and that a true synergism is obtained with oxaliplatin and 5-FU since out of 14 patients not responding to a previous high-dose 5-FU regimen, three responses could be obtained.

Our rate of 28% of tumor growth control at 4 months from treatment initiation is unusual in second- or third-line therapy. If response is generally considered as a criteria of activity in colorectal cancer, stable disease by itself has never been considered as such. In advanced breast cancer, stable disease appears to be a worthwhile category of response if the overall time to progression and survival of this subgroup are not significantly different from those patients with partial remission.[19] The situation could be comparable in colorectal cancer. In a study of 324 patients with advanced colorectal cancer receiving a 5-FU-based chemotherapy, the median survival time of complete response (CR), partial response (PR), no change (NC) and progressive disease (PD) was 21, 15, 12 and 4 months, respectively, suggesting that NC behave more as PR than as PD.[20]

The median survival of our patients after beginning 5-FU/oxaliplatin treatment is 10 months while it is 15 months for the responding or stabilized patients and

only 7 months in those with PD. Despite the fact that our patient population was heavily pretreated and that half of them had synchronous liver metastases, the median survival time from the diagnosis of disseminated disease was 24 months. That period of time is considerably superior to that obtained after first-line 5-FU regimen alone. The definite proof that such a second-line treatment is worth being given should be investigated in a randomized study in comparison to best supportive care.

Conclusion

This combination of infusional 5-FU/FA/oxaliplatin proved to be a safe and promising alternative for patients with colorectal cancer when they have already failed on previous regimens including those containing 5-FU.

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