Annals of Oncology 9: 105–108, 1998.

Short report

Oxaliplatin as single agent in previously untreated colorectal carcinoma patients: A phase II multicentric study

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Summary

Background: Oxaliplatin is a new cytotoxic agent from the diaminocyclohexane family with proven antitumor activity against colon cancer cell lines. Activity in patients with colorectal carcinoma previously treated with 5-fluorouracil has been studied in three single-agent phase II trials, showing a reproducible response rate of 10%. Here we report a phase II trial with oxaliplatin as a first-line chemotherapy for metastatic colorectal cancer.

Patients and methods: Twenty-five patients were entered in the study. All of them had metastatic disease without previous chemotherapy, and at least one lesion had to be measurable by computed tomography (CT). Therapy consisted of a two-hour infusion of oxaliplatin at a dose of 130 mg/m^2 every 21 days.

Results: The overall response rate determined by investigators was 20% (95% CI, 6.8%–40.7%). Eight patients (32%) had stable disease. The median time to disease progression in responders was six months (range four to nine). The median progression-free survival was four months and median overall survival 14.5 months (95% CI, 10–20 months). The main toxic effects were peripheral neuropathy (92%) and laryngopharyngeal dysesthesia (75%). No severe grade 3–4 neurotoxicities (NCI–CTC) were found. Gastrointestinal and hematological toxicities were mild.

Conclusions: Oxaliplatin is an active agent in first-line chemotherapy for advanced colorectal cancer. It was well tolerated, caused no toxic deaths, had low hematotoxicity, well controlled gastrointestinal toxicity, and frequent but mild peripheral neurological symptoms. Therefore, it is of interest to associate oxaliplatin with other active compounds.

Key words: advanced colorectal carcinoma, oxaliplatin, phase II study

Introduction

Colorectal cancer is the second most frequent cause of cancer-related mortality in the Western world [1]. Early detection and radical surgery will be curative for 50% of those patients diagnosed in a non-metastatic stage of the disease. Furthermore, adjuvant chemotherapy has proved to reduce disease recurrence and to improve survival for this group of patients [2–4].

Nevertheless, an important number of patients still needs palliative chemotherapy treatment for metastatic disease.

The most widely used chemotherapy agent for patients with colorectal cancer during the past 30 years has been 5-fluorouracil (5-FU). Recent studies have demonstrated that the addition of leucovorin enhances 5-FU cytotoxicity with higher response rates, but without improvement of overall survival [5]. Other combination chemotherapies such as cisplatin have failed to demonstrate an advantage in response rate or survival, while having a considerable increase of toxicity [6].

Oxaliplatin is a new platinum complex, diaminocyclohexane (DACH) compound, with proven antitumor activity against colon cancer cell lines [7]. Toxic effects of oxaliplatin include sensitive neuropathy, vomiting, diarrhea and mild myelosuppression. There is no renal toxicity [8]. The activity of oxaliplatin single agent in metastatic colorectal patients who have progressed on 5-FU has been recently studied in three different phase II trials, with a 10% response rate in all three of them [9, 10].

The data of this phase II study which aimed to determine the activity of single-agent oxaliplatin as first-line treatment in metastatic colorectal cancer are presented and discussed.

Patients and methods

Patients

From June 1994 to November 1995, 25 patients diagnosed with metastatic colorectal adenocarcinoma, were included in a multicenter phase II study. Patient characteristics are listed in Table 1. The eligibility criteria were: all patients were required to have histologic evidence of metastatic colorectal cancer; no previous chemotherapy for advanced disease, except prior adjuvant chemotherapy if it had been completed

Table 1. Patients characteristics.

Total number of patients	25
Age	
Median	60
Range	38–70
Sex	
Male	17
Female	8
Performance Status (ECOG)	
0	12
1	13
Grade of differentiation	
Highly differentiated	4
Moderately differentiated	13
Undifferentiated	2
Unknown	6
Sites of tumor involvement	
Liver only	8
Liver and other sites	10
Lung only	2
Lymph nodes only	1
Other multiple sites	4
Number of sites of metastatic tumor involvement	
1	11
2	6
3	6
> 3	2
CEA tumor marker blood level	
< 10 ng/ml	9
> 10 ng/ml	13
Unknown	3
CA 19.9 tumor marker level	
< 60 IU/l	6
> 60 IU/l	10
Unknown	9
Previous treatment	
Adjuvant radiotherapy	1
Adjuvant chemotherapy	6
Adjuvant chemotherapy + radiotherapy	1

at least 12 months before study entry; at least one lesion had to be measurable in two dimensions by computed tomography (CT); age between 18 and 70 years; ECOG performance status 0–1; absence of peripheral neuropathy; medullar, hepatic and renal function in normal range; written informed consent was required prior to start of treatment. Patient with the following conditions were not eligible: severe organ dysfunction, uncontrolled hypercalcemia, other prior primary cancers except basal cell epithelioma, *in situ* cervix uteri carcinoma, complete or partial intestinal obstruction, severe neurologic or psychiatric disease, and women of childbearing age, with potential for fertilization (using no contraceptive method) or who were lactating.

Treatment

Therapy consisted of a two-hour. infusion of oxaliplatin (Debiopharm S.A., Lausanne, Switzerland) at a dose of 130 mg/m^2, repeated every 21 days. The drug was dissolved in 250–500 ml of a 5% glucose solution. All patients received a minimum of three treatment courses and a maximum of six courses when stable or responding after the third course; progression of the disease or severe toxicity led to patient withdrawal. The dose of oxaliplatin was reduced by 25% in instances of NCI grade 3 neutropenia, thrombocytopenia, or peripheral neurotoxicity, or grade 2 renal toxicity. In case of grade 4 neutropenia, thrombocytopenia or grade 3 renal toxicity, the dose was reduced by 50%. Any grade 4 non-hematological toxicity led to discontinuation of the treatment. Patients were given prophylactic and curative antiemetic treatment if required.

Patient evaluation

Before each treatment course, all patients gave a complete medical history and underwent a physical examination. Laboratory tests including hemogram, biochemistry, CEA and CA 19.9 were performed and toxicity monitored before each cycle, using NCI–CTC criteria. The antitumor response was evaluated every three cycles by CT scan, according to the WHO criteria. The response was validated by an expert committee of radiologists independent of the study. The time to disease progression was calculated from the date of initiation of therapy to the date of progression of disease. Overall survival was calculated from the date of initiation of therapy to that of patient's death. Survival analysis was performed by the Kaplan–Meier method.

Results

The 25 patients included in the study were evaluated for response and toxicity. They received 123 cycles, 119 (96.7%) of them were given at the full dose of 130 mg/m^2 and only four at reduced doses. The median number of cycles per patient was five (range one to nine). Twelve patients received at least six cycles, although one patient received the sixth cycle incompletely because of a hypersensitivity reaction during the treatment. The other 13 patients could not receive six cycles of chemotherapy because of progression of the disease. The median dose intensity of oxaliplatin was 43.3 mg/m^2/week (range 30.7–44.0), and the median cumulative dose per patient was 650 mg/m^2 (range 130–1170).

Efficacy

The overall response rate found by investigators was 20% (95% CI, 6.8%–40.7%) (one CR + four PR). Eight patients (32%) had disease stabilization and 12 (48%) had progressed. For the expert committee of radiologists independent of the study, the response rate was 12% (three PR, 12 SD, eight PD). The median time to disease progression in responders was six months (range four to nine). The median progression-free survival (PFS) was four months (range two to seven), and median overall survival was 14.5 months (95% CI, 10–20 months).

Toxicity

The 25 included patients received at least one cycle of oxaliplatin, and all of them were therefore evaluated for toxicity. Only one patient (4%) had to discontinue the treatment prematurely because of toxicity, when in the sixth cycle he showed a generalized erythema 15 minutes after the infusion had started. The same symptomatology occurred again when one week later the treatment was reinitiated. In both occurrences corticosteroid treatment controlled the symptoms.

The main toxic effects are shown in Table 2. Peripheral neuropathy (92%) and laryngopharyngeal dysesthesia (75%) were the side effects most often observed. However, no severe grade 3–4 neurotoxicity (NCI–CTC) was observed except in one patient who presented with laryngopharyngeal dysesthesia, and severe dyspnea after

Table 2. Toxic effects by patient.

Toxic effect	NCI-CTC			
	1	2	3	4
Neutropenia	2 (8%)	3 (12%)	0	0
Thrombocytopenia	4 (16%)	2 (8%)	0	0
Anemia	19 (76%)	1 (4%)	0	0
Peripheral neuropathy	16 (67%)	6 (25%)	0	0
Vomiting	1 (4%)	2 (8%)	2 (8%)	1 (4%)
Diarrhea	7 (29%)	0	1 (4%)	0

oxaliplatin administration, and had to be admitted to hospital. This patient did not withdraw from the study and was administered full-dose oxaliplatin in the succeeding cycle in a 360-minute infusion without recurrence of the symptoms. The median time preceding the appearance of symptoms was one cycle. The median time of recovery from sensitive neuropathy was nine weeks after chemotherapy treatment was discontinued. Other mild neurologic side effects were cramps, Lhermitte's sign (momentary, electrical shock-line paresthesias from the neck to the extremities, precipited by neck flexion) and abolition of osteotendinous reflexes. Nausea and vomiting were frequent (56% and 24%, respectively) but of only mild-moderate severity, although 92% of patients received prophylactic anti 5-HT3 treatment. Moderate diarrhea occurred in eight patients (33%). No grade 4 diarrhea was observed. Hematological toxicity was mild, with no grade 3–4 anemia, neutropenia or thrombocytopenia.

Discusssion

Oxaliplatin is a new platinum derivative with proven activity in colon cancer, in *in vitro* [7] and in clinical phase I studies [8]. The recommended dose for phase II studies, was 130 mg/m^2 in short infusion every three weeks. Dose-limiting toxicity is peripheral neuropathy, namely, cumulative and reversible dysesthesia and/or paresthesia.

Up to now, three phase II studies with oxaliplatin as a second-line treatment, in patients who have progressed on fluoropyrimidines, have been carried out, with a 10% response rate in the three of them [9, 10]. In the present study, in patients with no previous chemotherapy the objective response rate determined by investigators was 20% (one CR, four PR), similar to 5-FU plus leucovorin and superior to 5-FU alone, according to Advanced Colorectal Cancer Meta-Analysis Project [5] data. The responses were reviewed by an expert committee of radiologists independent of the study, who found a response rate of 12%. The lack of clinical data about the patients, as well as of the tumor marker blood levels for the committee of radiologists may explain the divergence between the two assessments. The positive clinical and biological evolution could have influenced the investigators in two cases in which radiological shrinkage was close to the limit of 50%; for the expert radiologists, it did not reach the 50% threshold and they therefore considered the response as a stabilization. The patient judged to have a complete response by investigators had residual lesion according to the radiologists. Preliminary results reported recently by Becouarn et al. confirm the activity of oxaliplatin as single agent in untreated colorectal adenocarcinoma (24% PR) [11].

As in the former studies, oxaliplatin was well tolerated. Only one patient showed a serious side effect related to the drug, the major symptoms of which were severe dyspnea and laryngopharyngeal dysesthesia. This toxicity was averted in the succeeding cycles with a longer time of infusion (360 minutes). No grade 3–4 anemia, neutropenia or thrombocytopenia were observed, and neither blood transfusion, patient antibiotic intake due to febrile neutropenia nor dose reduction were required. The most frequently occurring toxicity was neurologic, in terms of paresthesias and laryngopharyngeal dysesthesias (92% and 75%, respectively). No case of grade 3 was observed (functional interference) and there was no requirement for delay of the cycle or dose reduction. The acute gastrointestinal toxicity was moderate. Due to the high emetic potential of platinum compounds, almost all patients received prophylactic treatment by serotonin antagonists. Only three patients (12%) presented grade 3–4 vomiting in four cycles (3%). No alopecia, ototoxicity or nephrotoxicity were seen, which clearly demonstrates a different profile of toxicity from that of cisplatin.

At present, two new drugs have been shown to be active in metastatic colorectal cancer, irinotecan and raltitrexed. Phase II studies with irinotecan have shown 15%–32% response rate for both groups of patients, without previous chemotherapy or pretreated with 5-FU [12]. A recent study with 213 patients with and without previous treatment with 5-FU has shown a 17.7% and a 18.5% response rate, respectively [13]. Even though toxicity in general was moderate, there was 48% grade 3–4 neutropenia and 35% grade 3–4 diarrhea as a main toxicity. Raltitrexed, a specific inhibitor of thymidylate synthase, showed a response rate of 29% [14] in a phase II study involving 177 patients, and in a recent comparative phase III study *versus* 5-FU plus leucovorin the response rate was 19.8%, with a good tolerance, except for grade 3–4 elevation of SGOT and/or SGPT in 10% of patients [15].

In conclusion, oxaliplatin at a dose of 130 mg/m^2 every three weeks as a first-line treatment in metastatic colorectal cancer patients has a moderate activity, similar to that of 5-FU plus leucovorin, irinotecan or raltitrexed, with a good tolerance and a very different profile of toxicity from these other drugs. Therefore, it is of interest to associate oxaliplatin with one or several of these compounds.

Acknowledgements

This work was sponsored, in part, by Debiopharm S.A., 17, rue des Terreaux, Lausanne, Switzerland.

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Received 7 August 1997; accepted 14 October 1997.

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