Annals of Oncology 7: 95–98, 1996.

Short report

Two consecutive phase II studies of oxaliplatin (L-OHP) for treatment of patients with advanced colorectal carcinoma who were resistant to previous treatment with fluoropyrimidines

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Summary

Background: Oxaliplatin (L-OHP) is a platinum complex that possesses activity against human and murine cells in vitro and in vivo, including colorectal carcinoma-derived cell lines, and cells that have been selected for resistance to cisplatin. We report two consecutive phase II trials of L-OHP for treatment of patients with advanced colorectal carcinoma.

Patients and methods: Fifty-eight patients were entered in study I, and 51 patients in study II. All of the patients had tumor progression when they were treated, prior to their enrolment, with a fluoropyrimidine-containing regimen. In both trials treatment consisted of L-OHP, 130 mg/m^2, by i.v. infusion for two hours; the treatment was repeated every 21 days.

Results: Response to therapy: *Study I*: Fifty-five patients were assessed for response. The response rate was 11% (95% CI, 0.03–0.19). *Study II:* All 51 patients were assessed for response. The response rate was 10% (95% CI, 0.017–0.18). The overall response rate for the 106 evaluated patients was 10% (95% CI, 0.046–0.16). Times to disease progression in responders were 4, 4, 4.5+, 5, 5, 6, 6, 6, 6+, 9, and 13 months. The dose-limiting toxic effect was sensory peripheral neuropathy. The incidence of severe peripheral neuropathy grades was: *Study I:* grade 3, 23% of patients, and grade 4, 8% of patients. *Study II:* grade 3, 14% of patients, and grade 4, 4% of patients. Severe neuropathy had a favorable course in all of the patients who had long-term neurologic follow-up. Diarrhea and myeloid impairment were minor.

Conclusion: L-OHP produced modest, but definite antitumor activity in patients with advanced colorectal carcinoma who were previously resistant to chemotherapy including fluoropyrimidines. Toxicity is within acceptable limits of tolerance at the dose and schedule of oxaliplatin used in this trial.

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

Introduction

Oxaliplatin [trans-L-1,2-diaminocyclohexane] oxalatoplatinum (II), (L-OHP) is a platinum complex with an oxalato ligand as leaving group and a 1,2-diaminocyclohexane (dach) carrier [1, 2]. The drug exerts antitumor activity against a number of human and murine tumor cells in vitro and in vivo, including colorectal cancer-derived cell lines [1–4]. It possesses a higher cytotoxic potency on a molar basis than do cisplatin and paraplatin [3], and it is active on various cell lines that have been selected for resistance to cisplatin [3, 4], Preliminary studies have suggested that combination therapy with 5-fluorouracil (5-FU) and L-OHP is synergistic against L1210 leukemia transplanted into mice [2].

Toxic effects of oxaliplatin include peripheral neuropathy, vomiting, diarrhea, and mild myelosuppression. The drug has no renal toxicity [2, 5]. L-OHP given at a circadian rhythm-modulated i.v. infusion rate to patients with advanced colorectal carcinoma yielded response rates of 58% when given in combination with 5-FU and folinic acid irrespective of the patients' previous treatment status [6].

Patients and methods

Patients (Table 1)

Each patient was required to have a previously diagnosed colorectal carcinoma with metastases that could be measured by CT scan. For inclusion, patients had to have confirmed tumor progression when they had been treated with a fluoropyrimidine-containing regimen. Patients with any of the following conditions were not eligible for

Table 1. Patient characteristics.

Characteristic	No. of patients (%)	
	Study I	Study II
No. of patients entered	58	51
Age range, years		
39–50	6 (10)	9 (18)
51–60	19 (33)	15 (29)
61–75	33 (57)	27 (53)
Sex		
Male	36 (62)	32 (63)
Female	22 (38)	19 (37)
Site of primary tumor		
Colon	38 (66)	28 (55)
Rectum	20 (34)	23 (45)
ECOG performance status		
0–1	50 (86)	46 (90)
2	7 (12)	5 (10)
3	1 (2)	–
Sites of metastatic tumor involvement		
Liver only	30 (52)	20 (39)
Liver and other sites[a]	18 (31)	20 (39)
Other sites[b]	10 (17)	11 (22)
Number of sites of tumor involvement		
1	40 (69)	31 (61)
2	17 (29)	17 (33)
3	1 (2)	3 (6)
Previous dose of 5-FU in g/m^2 [c]		
≤30	21 (36)	34 (67)
31–60	19 (33)	15 (29)
>60	18 (31)	2 (4)
No. of prior regimens of chemotherapy[d]		
1	24 (41)	39 (76)
2	33 (57)	9 (18)
3	1 (2)	3 (6)

[a] Including lung, adrenals, lymph nodes, bone, ovaries, peritoneum, pelvis, and spleen.

[b] Including lymph nodes, pelvis, and peritoneum.

[c] Median doses of 5-FU given to patients prior to their enrolment in study I and study II were 40 g/m^2 (range, 6–134 g/m^2) and 23 g/m^2 (range, 5–76 g/m^2), respectively.

[d] Previous fluoropyrimidine-containing regimens comprised 5-FU and folinic acid (FA), and 5-FU with FA combined with hydroxyurea, α-interferon, mitomycin C, lomustine, methotrexate, pyrarubicine, or etoposide, and ftorafur as a single agent.

the studies: CNS metastases, bone metastases, or serosal effusions as the sole indicator of tumor; any prior cisplatin- or paraplatin-containing chemotherapy; performance status (ECOG) >2, a serum alkaline phosphatase or bilirubin level above twice the upper limit of the normal range, or creatinine clearance <60 ml/min. Written informed consent was obtained, and administrative requirements were met.

Two phase II studies were performed consecutively. Fifty-eight patients were included in study I. Of these, three had tumors that could not be measured. After completion of study I, we started a second trial (study II), which accrued 51 patients, all of them evaluable for response to therapy. The 109 patients enrolled in studies I and II were evaluated for toxic effects. Studies I and II were conducted by different groups of investigators.

Treatment protocol

Therapy consisted of a single i.v. infusion of L-OHP at a dose of 130 mg/m^2, repeated every 21 days. The dose of the drug was chosen on the basis of recommendations of the published phase I studies [2, 5]. L-OHP (Debiopharm S.A., Lausanne, Switzerland) was provided as a lyophilised powder. It was reconstituted in a solution of 5% dextrose in water at a final concentration of L-OHP of 2 mg/ml. The solution was infused i.v. over 2 hours. Patients received no prehydration. The dose of L-OHP was reduced by 25% in instances of WHO grade 3 granulocytopenia or thrombocytopenia, or of grade 3 peripheral neuropathy according to the scale in Table 2. A single grade 4 episode of any of these toxic effects led to discontinuation of the treatment. All patients were given antiemetics.

Patient evaluation

Before each treatment course, patients underwent a clinical examination and blood cell counts, liver function tests and determinations of serum creatinine. Patients were monitored for antitumor response after sets of 3 consecutive courses. Plasma CEA and CA 19-9 levels were measured in all patients. Response was determined quantitatively by comparison of the size of all measurable lesions, as evidenced on CT scan. Objective responses were categorized according to the WHO criteria. Response to therapy was determined initially by the radiologist and the patient's clinician, and by a second-party review for final evaluation. The times to disease progression were calculated from the date of initiation of therapy. Survival analysis and plotting of cumulative probability of the incidence of neuropathy according to dose were performed by the method of Kaplan and Meier.

Results

Toxic effects

Study I. The 58 patients received a total of 314 courses of L-OHP (range, 1–16 courses per patient; median, 5 courses) which were evaluated for toxicity (Table 2). The median cumulative dose of L-OHP given to patients during study I was 650 mg/m^2 (range, 130–1990 mg/m^2).

Table 2. Toxic effects.

Toxic effect	Study	Percent of patients with toxicity[c]				
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea[a]	I	55	21	14	10	–
	II	70	11	19	–	–
Nausea/vomiting[a]	I	26	34	23	17	–
	II	40	22	30	6	2
Granulocytopenia[a]	I	89	5	4	2	–
	II	94	6	–	–	–
Anemia[a]	I	65	27	6	2	–
	II	74	19	5	2	–
Thrombocytopenia[a]	I	77	9	14	–	–
	II	88	8	4	–	–
Peripheral neuropathy[b]	I	2	28	39	23	8
	II	4	37	41	14	4
Increase in serum creatinine[a]	I	95	5[d]	–	–	–
	II	100	–	–	–	–

[a] Graded according to WHO.

[b] Grade 1: dysesthesia and/or paresthesia, transient, <7 days; grade 2: dysesthesia and/or paresthesia, transient, <14 days; grade 3: dysesthesia and/or paresthesia persisting during the drug-free interval between courses; grade 4: severe dysesthesia and/or hypoesthesia with functional impairment.

[c] Fifty-eight patients were assessed for toxicity in study I, and 51 patients in study II. For patients who had ≥2 episodes of the same toxic effect, only the highest grade of toxicity is reported in the table.

[d] Single episodes of transient increase to ≤1.5× the upper limit of the normal range.

Diarrhea was a toxic effect in 45% of the patients; 10% of them had grade 3 diarrhea, and grade 3 vomiting was observed in 17%. Myelosuppression was mild. Transient increase in the serum creatinine level to $\leq 1.5\times$ the upper limit of the normal range was observed in 5% of the patients.

Sensory peripheral neuropathy was observed in 98% of the patients. Grades were 1 in 28%, 2 in 39%, 3 in 23%, and 4 in 8% of the patients. The incidence and severity of the peripheral neuropathy rose with increasing cumulative doses of L-OHP. A correlation was found between the increasing grades of the neuropathy and the total amounts of the drug given to patients (Spearman Correlation Test, $p < 0.00001$). At cumulative doses of ≤ 780 mg/m^2 of L-OHP, grades 3 and 4 peripheral neuropathy were observed in 14% and 4% of patients, respectively. The projected probability for patients to have neuropathy of grades 3 or 4 after they received cumulative L-OHP doses of 780 mg/m^2 was 22%. A number of patients had long-term neurologic follow-up after discontinuation of L-OHP. Of the 13 patients who had grade 3 neuropathy, 5 had disappearance of all symptoms at between 2 and 4 months, 2 patients had major attenuation after 2–5 months, and 6 patients had no long-term follow-up. Of the 5 patients who had grade 4 neuropathy, 1 had disappearance of symptoms after 2 months, 2 had partial regression at 3 and 5 months, and 2 had no long-term follow-up. During the infusion time of L-OHP, one patient had a transient episode of dyspnea *sine materia* of unknown cause.

Study II. The 51 patients received 203 courses of L-OHP (range, 2–8 courses per patient, median, 3 courses) which were evaluated for toxicity (Table 2). The median cumulative dose of oxaliplatin given to patients during study II was 390 mg/m^2 (range, 260–1010 mg/m^2).

Thirty percent of patients had grades 1 or 2 diarrhea. Grades 3 or 4 vomiting was observed in 8% of patients. Myeloid toxicity was mild.

Sensory peripheral neuropathy was noted in 96% of the patients. Grades were 1 in 37%, 2 in 41%, 3 in 14%, and 4 in 4% of patients. As in study I, the incidence and severity of the peripheral neuropathy rose with increasing cumulative doses of L-OHP. A correlation was found between increasing grades of the neuropathy and the total dose of the drug administered to patients (Spearman Correlation Test, $p = 0.0001$). Of the 9 patients who had grades 3 and 4 neuropathy, 2 had disappearance of all symptoms and 7 had attenuation of symptoms at between 3 and 6 months after discontinuation of L-OHP. However, follow-up was too short for precise evaluation of the regression potential of the neuropathy.

Response to therapy

Study I. The median follow-up time for the 55 evaluable patients was 7 months (range, 1–18.5 months). Six patients attained a PR. The response rate was 11% (95% CI, 0.03–0.19). Times to disease progression in responders were 5, 5, 6, 6, 6+, and 13 months. The time required for achievement of response was 6 weeks in all patients. The median survival time of the 58 patients was 8.2 months. Survival times of the responders were 9, 9+, 12, 14.5, 15, and 18.5 months. Twenty-three patients (42%) had NC, and 26 patients (47%) had PD.

Study II. The median follow-up time for the 51 patients was 4.5 months (range, 1–13 months). Five patients attained a PR. The response rate was 10% (95% CI, 0.017–0.18). Times to disease progression in responders were 4, 4, 4.5+, 6, and 9 months. The time required for achievement of response was 6 weeks in 4 patients and 12 weeks in 1 patient. Survival times of responders were 4+, 5.5, 6+, 7+, and 12 months. Sixteen patients (31%) had NC, and 30 patients (59%) had PD.

The overall response rate for the 106 evaluable patients treated in the 2 trials was 10% (95% CI, 0.046–0.16). For patients who attained a PR, ratios of initial CEA titer/final CEA titer (in ng/ml) were 2558/19, 77/7, 161/38, 610/153, 453/291, and 25/11 in study I, and 185/7, 230/22, 35/8, 3000/1000, and 23/8 in study II; ratios of initial CA 19-9 titer/final CA 19-9 titer (in units/ml) were 628/32, 2700/380, 106/50, 76/42, 21/15, and 370/380 in study I, and 294/24, 220/24, 900/388, 270/140, and 67/39 in study II.

Discussion

Cisplatin (CDDP) and paraplatin (CBDCA) have failed in the past to demonstrate significant antitumor activity in patients with colorectal carcinoma. When they were administered as single agents, these drugs yielded response rates of 0% to 9% for CDDP [7, 8] and 0% to 5% for CBDCA [9]. In these studies, the mean response rates achieved by patients who had previously received chemotherapy were 3% and 2% for CDDP and CBDCA, respectively. Moreover, combination treatment with 5-FU and cisplatin did not produce a greater response rate than that observed with 5-FU given as a single agent [10].

In the present phase II trials with oxaliplatin, response rates were 11% and 10% in study I and study II, respectively. These apparently modest results compare favorably with those obtained with CDDP and CBDCA [7–9], and they may indicate a significant therapeutic activity of L-OHP because they were obtained in patients with tumors who had demonstrated PD during prior therapy including the use of fluoropyrimidines (Table 1).

The dose-limiting toxic effect of oxaliplatin was sensory peripheral neuropathy, which occurred in almost all of the patients. The major symptom was dysesthesia,

which predominated in the limbs and the mucosae of the upper aerodigestive tract; it was often triggered by exposure to cold temperatures. The incidence and severity of the peripheral neuropathy rose with increasing cumulative amounts of L-OHP. The projected probability for patients to have neuropathy of grades 3 or 4 after receiving a cumulative dose of 780 mg/m^2 (i.e., the amount of drug given in 6 courses of therapy) was 22%. Despite its high incidence, the severe neuropathy had a favorable course after discontinuation of oxaliplatin in patients who underwent a long-term neurologic assessment during their follow-up. Therefore, neuropathy should be considered to be within acceptable limits of tolerance at the dose and schedule of L-OHP used in the present study. However, we recommend cessation of treatment if neuropathy of grades $\geqslant 3$ appears.

Oxaliplatin has major similarities with tetraplatin [tetrachloro(D,L-trans)1,2-diaminocyclohexane platinum (IV)], a platinum complex which, like L-OHP, has a (dach) carrier ligand [3]. However, early clinical studies of tetraplatin have shown that this drug, unlike oxaliplatin, produced severe toxic effects which have prevented its further development. The better toxicity profile of oxaliplatin over that reported for tetraplatin further supports the future development of L-OHP for clinical use.

Preclinical data on L-OHP included a possible potentiation of 5-FU [2]. Therapy with 5-FU, folinic acid, and oxaliplatin given at a circadian rhythm-modulated infusion rate produced high response rates in patients with advanced colorectal carcinoma, which suggests that potentiation may occur in this tumor as well [6].

In the present studies, we have demonstrated that oxaliplatin possesses modest, but definite activity in patients with advanced colorectal carcinoma who were previously resistant to chemotherapy which included fluoropyrimidines. The data reported here will serve as a basis for future studies of L-OHP in various doses and schedules, in combination with 5-FU and folinic acid, for determination of the therapeutic potential of the drug.

Acknowledgments

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

We acknowledge Mélisende Bart and Didier Bert for secretarial work, and Elisabeth Lanzl for editorial assistance.

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Received 14 August 1995; accepted 7 November 1995.

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