Annals of Oncology **10**: 1311–1316, 1999.

Original article

Oxaliplatin added to 5-fluorouracil-based therapy (5-FU ± FA) in the treatment of 5-FU-pretreated patients with advanced colorectal carcinoma (ACRC): Results from the European compassionate-use program

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Summary

Purpose: To provide evidence for the therapeutic efficacy of oxaliplatin (Eloxatin®) when given as a 2–6-hour i.v. infusion, alone or in combination with 5-fluorouracil/folinic acid (5-FU ± FA) in patients with advanced colorectal carcinoma (ACRC) who have failed 5-FU-based therapy. To confirm the safety of the drug and its combination in an extended-access context.

Patients and methods: Prescribing physicians were supplied oxaliplatin on a nominative compassionate-use basis, after obtaining informed consent. Europe-wide, 206 ACRC patients in 44 centers received 1168 cycles of chemotherapy with oxaliplatin (80–100 mg/m^2 q 2 weeks or 100–135 mg/m^2 q 3 weeks) delivered as a short (2–6 hours) i.v. infusion, 177 of them (1026 cycles) receiving oxaliplatin + 5-FU ± FA.

Results: Oxaliplatin added to the 5-FU ± FA regimens of 111 verified 5-FU-refractory patients (imaging and/or clinical proof of progression under prior 5-FU-based regimen), elicited objective responses in 25 of 98 evaluable patients, (ORR: 25.5%, 95% confidence interval (95% CI: 17–35). The median time to progression was 4.1 months (95% CI: 3.3–5.0) and the median overall survival was 9.6 months (95% CI: 8.2–10.9). Differences in the toxicity profile of the oxaliplatin + 5-FU ± FA combination appear related to administration modality, dose and schedule of the 5-FU-based regimen.

Conclusions: The addition of oxaliplatin (2–6-hour i.v. infusion) to 5-FU ± FA regimens is active in ACRC patients with clinical resistance to fluoropyrimidines. The therapeutic index of oxaliplatin + 5-FU ± FA combinations administered as salvage therapy compares favorably with those reported in recent phase II–III trials involving other new agents or combinations active in 5-FU-refractory ACRC patients.

Key words: 5-fluorouracil, efficacy, oxaliplatin, platinum compounds, salvage chemotherapy

Introduction

Despite the investigation of a variety of 5-FU-based regimens, the superiority of any particular one has not yet been established. In first-line treatment for ACRC, both high-dose and continuous-infusion chemotherapy are more active than lower dose or bolus 5-FU regimens but have marginal impact on patient survival [1–3]. Recent 'hybrid' regimens seem to be more active than the standard regimens in terms of response and time to progression (TTP) [4–7]. The likelihood of response to a new 5-FU-based treatment has been linked to the clinical resistance status observed during prior 5-FU chemotherapy; only patients with primary objective response or disease stabilization are likely to benefit from second-line 5-FU regimens [8–10].

Oxaliplatin (Eloxatin®, Sanofi-Synthelabo, France) is a diaminocyclohexane (DACH) platinum compound with a spectrum of activity and toxicity different from cisplatin and carboplatin [11]. Preclinical experiments have shown that oxaliplatin has synergistic cytotoxic effects when combined with 5-FU [12, 13]. In the past decade, the oxaliplatin + 5-FU ± FA combination has been explored extensively in the treatment of 5-FU-pretreated ACRC patients. In all such studies, significant antitumor activity has been observed, with objective response rates (ORRs) consistently higher than 20% [14–17]. In these studies, median TTP has been between 6 and 10 months and median overall survival (OS) between 10 and 17 months, with a significant number of patients (20%) living more than 2 years.

Following these reports, treating physicians submitted many individual requests for oxaliplatin as early as 1993. At that time, most available published data concerning the treatment of ACRC patients with oxaliplatin were based on its continuous 4–5-day administration, either chronomodulated or given as a flat infusion [14]. Simultaneously, the French Agence du médicament requested supplementary evidence of safety and efficacy for oxaliplatin at the recommended administration modality and

schedule (2–6-hour i.v. infusion every 3 weeks). Due to the perception of potential benefit for the ACRC patient population, a nominative, compassionate-use program had been implemented for the treatment of ACRC patients failing 5-FU-based therapy. This analysis describes results from the European-wide ACRC compassionate-use patient cohort treated with short i.v. infusion oxaliplatin + 5-FU ± FA, focusing in particular on the antitumor activity of the combination in patients with third-party-reviewed disease progression under a 5-FU-based therapy (5-FU-refractory).

Patients and methods

Cohort definition

Between January 1994 and June 1995, a total of 234 ACRC patients were registered to receive oxaliplatin as a 2–6-hour i.v. infusion, excluding chronomodulated and flat continuous i.v. delivery, as salvage therapy in a European compassionate-use program. The patients were enrolled in 44 centers on the basis of individual nominative requests made by their treating physicians.

No restrictions in terms of age, performance status and number or type of previous treatments were applied. All cases were reviewed on-site for consistency and compliance with program guidelines, and all clinical and imaging evidence of resistance to previous 5-FU treatment was reviewed by a team of oncologists and radiologists. Clinical 5-FU refractory status was accorded only when there was third party verified clinical and/or imaging proof of disease progression while on the prior 5-FU-based therapy, or a relapse within six months of completing 5-FU-based adjuvant treatment.

Treatment and patient subgroups

Oxaliplatin was given as a 2–6-hour i.v. infusion in different dose/schedule combinations, either biweekly at 80–100 mg/m^2 or triweekly at 100–135 mg/m^2. Although some patients received oxaliplatin alone (29 patients, categorized as subgroup A and not included in this analysis), the majority of patients received oxaliplatin in combination with a 5-FU ± FA regimen, in which case the oxaliplatin was always administered first.

Patients who received oxaliplatin + 5-FU ± FA but were not verified and/or verifiable for clinical resistance to 5-FU, those with inadequate or inappropriate oxaliplatin dose/schedule, and diagnostically doubtful cases were excluded from the efficacy results but included in the safety analysis (subgroup D).

The subpopulation of confirmed 5-FU-refractory patients receiving oxaliplatin + 5-FU ± FA was divided into two categories for analysis, one consisting of patients receiving oxaliplatin at a dose ≥ 80 mg/m^2 q 2 weeks (subgroup B), and another receiving oxaliplatin at a dose ≥ 100 mg/m^2 q 3 weeks (subgroup C).

The 5-FU-refractory patients were further subdivided according to their 5-FU/FA dose and schedule, with patients receiving an unchanged schedule placed in subgroups B+ and C+ and those receiving a modified regimen with respect to their treatment prior to the introduction of oxaliplatin placed in subgroups B− and C−.

The duration of the treatment was determined by the treating physician, who was responsible for the prescription and for adhesion to the proposed treatment guidelines.

Safety analysis

All patients receiving at least one cycle of oxaliplatin were evaluable for safety. Toxic effects were assessed according to WHO criteria [18], except for neurological toxicity which was graded according to an oxaliplatin-specific scale [19].

Response analysis

To be eligible for the tumor-response assessment, 5-FU-refractory patients had to have adequately documented measurable and /or evaluable disease and had to have received at least two treatment cycles, except in case of early clinical disease progression.

Evidence of clinical objective response, or disease stabilization ≥ 4 months, and proof of disease progression under the prior 5-FU-based regimen reported by the participating physicians for all patients allocated to subgroups B or C were submitted to an external panel of radiologists for review and validation.

As the timing of assessments was at the discretion of the participating physicians, responses were reported according to modified WHO criteria [18] (modifications in italics):

- Complete response (CR): complete disappearance of all evidence of tumor assessed in at least two separate evaluations, one month or more apart.
- Partial response (PR): a $\geq 50\%$ decrease in the sum of products of the two largest perpendicular diameters of all measurable lesions and no increase in size of tumor or appearance of any new lesion.

Patients defined as having CR or PR with only one set of imaging tests were maintained in the same response category in the absence of any clinical or biological signs of progression for at least 8 weeks.

- Disease stabilization (SD): $< 50\%$ decrease of measurable disease and $\leq 25\%$ progression of measurable disease *lasting for at least four months, without clinical, biological or imaging evidence of disease progression, and no evidence of any new lesion.*
- Progressive disease (PD): $\geq 25\%$ increase in the sum of the products of two diameters of one or more measurable lesions, evidence of new lesions, death from disease progression within eight weeks after the first administration of oxaliplatin, or lack of formal disease evaluation after three cycles of treatment.

Time-related parameters

Follow-up information to determine TTP and OS were collected for the 5-FU-refractory patients. TTP and OS were calculated from the beginning of the treatment containing oxaliplatin until either disease progression or death, respectively.

Statistical analysis

A descriptive analysis of disease and patient characteristics, previous therapy, oxaliplatin treatment schedule, time-related parameters, response, and toxicity was carried out (mean, median, standard deviation, 95% confidence interval (95% CI), and range of values) using the STATISTICA system (STAT SOFT, Tulsa, OK, USA). Response rate was characterized using descriptive statistics (mean, median, standard deviation, 95% CI, and range of values) and the Pearson χ^2 test for univariate analysis. TTP and OS were analyzed according to the Kaplan–Meier method and log-rank test for univariate analysis.

Results

Cohort characteristics

After source verification, 206 out of the 234 registered ACRC patients were considered eligible for analysis, with 28 failing to fulfill the accrual guidelines or missing the deadline for inclusion. Out of these 206 patients, 29 had received single-agent oxaliplatin. Of the remaining 177, all of whom received oxaliplatin + 5-FU ± FA, 111 (63%) were source verified as being 5-FU refractory.

Table 1. Patient and disease characteristics.

Characteristics	Subgroups of 5-FU-refractory patient					
	B+ (n=33)	B− (n=16)	C+ (n=35)	C− (n=27)	Total (n=111)	Percentage (%)
Sex						
Male	15	7	25	11	58	52
Female	18	9	10	16	53	48
PS (WHO)						
0–1	27	12	32	21	92	83
2–3	6	4	3	6	19	17
Primary tumor						
Colon	25	8	18	18	69	62
Rectum	8	8	17	9	42	38
Number of metastatic sites						
1	17	5	19	7	48	43
2	8	6	12	5	31	28
⩾3	8	5	4	15	32	29
Metastatic sites						
Liver	31	13	27	22	93	84
Lung	8	5	16	14	43	39
Lymph nodes	7	5	6	13	31	28
Peritoneum	3	3	1	7	14	13
Bone	2	1	0	2	5	5
Others	2	1	0	6	9	8
Elevated markers[a]						
CEA	23	9	25	20	77	69
CA 19 9	15	9	17	18	59	53
Prior surgery	33	16	35	27	111	100
Prior radiotherapy	7	4	12	8	31	28
Prior chemotherapy	33	16	35	27	111	100
Adjuvant	5	6	4	8	23	21
Palliative	28	10	31	19	88	79
Number of prior chemotherapy regimens						
1	23	6	20	10	59	53
2	4	4	10	8	26	23
⩾3	6	6	5	9	26	23
Prior cisplatin–CBDCA	2	2	1	2	7	6
Treatment-free interval						
⩽2 months	30	10	26	17	83	75
⩽3 months	0	2	5	5	12	11
⩽6 months	2	4	4	4	14	13
6 months	1	0	0	1	2	2

B, verified 5-FU-refractory patients receiving oxaliplatin q 2 weeks + 5-FU ± FA regimen; C, the same as B, except receiving oxaliplatin q 3 weeks, B+, C+, prior 5-FU ± FA regimen unmodified; B−, C−, prior 5-FU ± FA regimen modified.
[a] > 2× upper normal limit.

Patient and disease and prior treatment characteristics at inclusion are listed in Table 1.

The 5-FU-refractory population included 58 men and 53 women. Most of these patients had good performance status (PS), with 83% reporting a WHO grade 0 or 1 PS, and 63 (57%) had 2 or more sites involved.

Twenty-three of the 5-FU-refractory patients (21%) had received prior chemotherapy in the adjuvant setting. When the pre-oxaliplatin treatments were considered, eight different main modalities of 5-FU ± FA doses/schedules were identified, with the three most common modalities being daily (× 4–5 days) or weekly bolus or continuous infusion, biweekly bolus and/or continuous infusion, and protracted infusion.

Eighty-three 5-FU-refractory patients (75%) had received their last chemotherapy within two months of the first oxaliplatin dose.

Safety

A total of 1026 oxaliplatin-containing treatment cycles were administered in combination with 5-FU ± FA to 177 patients. A total cumulative dose of >520 mg/m^2 oxaliplatin was given to 94 of 177 patients (53%). One hundred twenty-two patients (69%) received between four and nine cycles. Toxicities are presented in Table 2 by patient and by cycle.

The most common adverse events amongst the patients receiving the combination treatment were mucositis, diarrhea and hematological toxicities. Diarrhea was the most frequent acute toxicity, severe episodes being observed in 28% of patients and 8% of cycles. Severe (grade 3–4) nausea/vomiting was reported in 17% of patients but only 3% of cycles were associated with grade 3–4 toxicity. Severe (grade 3–4) neutropenia and thrombocytopenia were uncommon, being observed in only 10% and 7% of patients or 5% and 1.6% of cycles, respectively.

Eighty-two percent of patients receiving oxaliplatin + 5-FU ± FA reported some signs and/or symptoms of neuropathy. Characteristic oxaliplatin-related neurotoxicity may occur early in treatment, presenting as transient acute, cold-triggered dysesthesias, and/or later, as a cumulative toxicity characterized by proprioceptive impairment [20]. Overall, 29 patients (18%) reported neurological grade 3–4 toxicity (old version of oxaliplatin-specific grading scale), with only 6 (3%) reporting a grade 4 toxicity (persistent functional impairment, usually minor and slowly reversible upon treatment discontinuation). The incidence of severe neurotoxicity was correlated with the cumulative oxaliplatin dose.

No renal or ototoxicity was reported. The three deaths that occurred within a month of the last oxaliplatin + 5-FU ± FA combination chemotherapy were all from characteristic 5-FU-related toxic effects.

Antitumor activity

Out of 111 verified 5-FU-refractory patients, 98 were found to be assessable for objective anti-tumor activity. Reasons for non-evaluability were: inadequate assessment documentation or disease considered not measurable/evaluable, patient refusal, and early treatment discontinuation. Responses achieved for the subgroups of 5-FU-refractory patients are detailed in Table 3.

Overall, there were 25 objective responses and 31 disease stabilizations ⩾4 months among the 5-FU-refractory patients treated with oxaliplatin + 5-FU ± FA, giving an ORR of 25.5% (95% CI: 17%–35%).

With each patient acting as his or her own control (addition of oxaliplatin to unchanged 5-FU ± FA regimen), evidence for the contribution of oxaliplatin to the antitumor activity of the combined salvage regimen is provided by the results for the B+ (ORR: 32%) and C+ (ORR: 31%). No substantial difference in response rate was observed between the subgroups of patients who received oxaliplatin every two weeks (B) vs. every three weeks (C) (26.7% vs. 24.5%, respectively).

Table 2. Toxicity by patient and cycle.

Toxicity	Oxaliplatin + 5-FU ± FA					
	n = 177 patients			*n* = 1026 cycles		
	Evaluable patients	Grades 1–4 (%)	Grades 3–4 (%)	Evaluable cycles	Grades 1–4 (%)	Grades 3–4 (%)
Gastrointestinal[a]						
Nausea/vomiting	168	115 (68)	27 (16)	922	328 (36)	31 (3)
Mucositis	166	57 (34)	10 (6)	923	153 (17)	13 (1)
Diarrhea	166	111 (67)	47 (28)	923	294 (32)	72 (8)
Hematological[a]						
Leukopenia	168	92 (55)	17 (9)	940	261 (28)	22 (2)
Neutropenia	166	91 (55)	34 (10)	923	245 (26)	48 (5)
Thrombopenia	167	57 (34)	12 (7)	936	144 (15)	15 (2)
Anemia	167	81 (48)	6 (4)	939	245 (26)	8 (1)
Peripheral neurotoxicity[b]	165	136 (82)	29 (18)	920	653 (71)	49 (5)

[a] WHO criteria.
[b] Oxaliplatin-specific scale [19].

Table 3. Response to treatment.

Patient sub-group	Oxaliplatin + 5-FU ± FA treatment regimen	Number treated/ evaluable	Antitumor response				Response rate (95% CI)	TTP in months (95% CI)	Survival in months (95% CI)
			CR	PR	SD	PD			
B+	q 2 wk (unchanged 5-FU ± FA schedule)	33/31	1	9	7	14	32% (17–51)	5.7 (4.8–6.6)	10.4 (7.7–73.1)
B−	q 2 wk (modified 5-FU ± FA schedule)	16/14	0	2	6	6	14% (2–43)	3.2 (1.4–5.0)	10.6 (4.3–16.9)
C+	q 3 wk (unchanged 5-FU ± FA schedule)	35/29	0	9	4	16	31% (15–51)	3.5 (2.2–4.8)	7 7 (1.4–14.1)
C−	q 3 wk (modified 5-FU ± FA schedule)	27/24	0	4	12	8	17% (5–37)	4.5 (3.8–5.2)	6.9 (4.7–9.0)
B & C	All 5-FU-refractory patients	111/98	1	24	29	44	25.5% (17–35)	4.1 (3.2–5.0)	9.6 (8.2–10.9)

Abbreviations: CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease; TTP – time to disease progression; CI – confidence interval.

In multivariable analysis, performance status and previous number of chemotherapy regimens were the only two variables to show statistical significance ($P < 0.004$ and $P < 0.03$, respectively) for their independent predictive value of response likelihood in the 5-FU-refractory patients.

Time-related parameters

The 5-FU-refractory patients were assessed for TTP and OS, with follow-up until December 1996 (17–18 months after the accrual of the last patient). The median TTP and OS for the 111 5-FU-refractory patients in subgroups B and C were 4.1 months (95% CI: 3.3–5.0) and 9.6 months (95% CI: 8.2–10.9), respectively. Both parameters were higher for the patients treated with a biweekly administration schedule for the oxaliplatin than with the 3-week schedule (category B vs. category C; TTP: 5.4 vs. 4.0 months and OS: 10.6 vs. 7.7 months), although this difference was not statistically significant.

Discussion

This analysis provides further evidence for the efficacy and safety of oxaliplatin when added to a 5-FU ± FA treatment for metastatic/recurrent colorectal cancer patients, notably in patients verified as 5-FU refractory. These results were obtained in a large, heterogeneous cohort of patients receiving oxaliplatin in a compassionate-use program, rather than in a clinical trial. This analysis gives valuable information because the attribution of drug therapy in a compassionate-use framework is less selective than in phase II–III studies, and patients entering such a program have clinical, treatment and disease characteristics closely reflecting those encountered in everyday practice. The characteristics of the present cohort attest to the lack of patient selection for oxaliplatin treatment in this program. Numerous 5-FU regimens were administered, either unchanged or modified with respect to those given prior to the addition of oxaliplatin. Such diversity allowed us to assess the con-

tribution of oxaliplatin in the context of different 5-FU treatment regimens. The analysis was intended to examine the efficacy of oxaliplatin and to determine its contribution to any observed antitumor activity in this heterogeneous patient cohort with more precision.

This study supports the view that oxaliplatin is both active and exhibits synergistic antitumor activity with 5-FU in 5-FU-refractory ACRC patients. This observation is consistent with previously reported phase II experiences [14, 16, 17, 21, 22]. We applied strict criteria to define resistance to prior treatment including verified, documented evidence of disease progression while on 5-FU ± FA treatment. In many studies the assessment of such status has either not been provided or else the guidelines for defining it have been less strict or unspecified [23]. All clinical and radiological charts of patients allocated to the 5-FU refractory categories (B and C) were reviewed by independent external experts. Under such conditions, the efficacy data reported in patients with 5-FU-refractory disease can be considered a reliable indicator of oxaliplatin's contribution to efficacy. The response rate of 25.5%, the median TTP of 4.1 months, and the median OS of 9.6 months calculated for the patients in groups B and C are within the range of those reported in formal phase II–III trials. Oxaliplatin activity was also consistently noted whatever 5-FU ± FA regimen it was combined with, including the weekly, biweekly and triweekly schedules, as well as bolus and infusional administration.

The safety profile of oxaliplatin given alone or combined with 5-FU ± FA presented here is consistent with previously reported data [14, 22, 24–26]. A higher frequency of diarrhea, mucositis, and neutropenia was reported when combined with 5-FU ± FA. In this heterogeneous patient cohort, oxaliplatin was combined in the majority of cases with high-dose-intensity 5-FU ± FA regimens. Accordingly, we noted more severe hematotoxicity and diarrhea when compared to other oxaliplatin + 5-FU ± FA experiences [14, 21]. Although peripheral neuropathy is the limiting toxicity for oxaliplatin, the most frequent neurological manifestations observed were grades 1 or 2 (transient dysesthesias and/or paresthesias). Clinical experience has shown that laryngopharyngeal dysesthesias are more frequent when the drug is given in a short (two-hour) infusion; prolonging the infusion ($\leqslant 6$ hours) in such cases can prevent the recurrence of this adverse event. In the present population, grade 4 neurotoxic effects (persistent paresthesia causing functional impairment) occurred in 3% of patients. This sensory neuropathy was clearly related to the cumulative oxaliplatin dose and is consistent with those previously observed [27]. Overall, oxaliplatin can safely be given at the recommended dose and schedule in combination with a wide variety of 5-FU ± FA regimens.

Finally, our results failed to elicit any evidence that the synergistic activity of oxaliplatin when used in combination with 5-FU ± FA is dependent on the modality of administration, dose or schedule of the 5-FU-containing regimen.

Acknowledgement

This work was sponsored in part by grants from Debiopharm and Sanofi-Winthrop.

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Received 28 June 1999; accepted 13 September 1999.

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