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# Factors predicting for efficacy of oxaliplatin in combination with 5-fluorouracil (5-FU)±folinic acid (FA) in a compassionate-use cohort of 370 5-FU-resistant advanced colorectal cancer (CRC) patients☆

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**Abstract**

Univariate and multivariate analyses were performed on data from 370 5-fluorouracil (5-FU)-resistant advanced colorectal cancer patients treated with oxaliplatin (Eloxatin®)/5-FU±folinic acid (FA) to identify prognostic factors for oxaliplatin-based treatment. The response rate was 14.6% (95% confidence interval (CI): 11.0–18.2%), median time to progression was 4.3 months (95% CI: 3.9–4.7), and median overall survival 9.7 months (95% CI: 8.5–10.8). Multivariate analysis indicated $<2$ prior chemotherapy regimens, bi-weekly treatment administration schedule (versus tri-weekly) and continuous chronomodulated delivery (CCM) as significantly associated ($P<0.05$) with a higher overall response rate. Performance status (PS) $<2$, having only one involved organ, biweekly schedule and CCM were associated ($P<0.05$) with a longer time to progression. Good PS, one involved organ, low alkaline phosphatase (AP) serum levels, bi-weekly schedule and CCM were significantly correlated with longer overall survival, while confirming the efficacy of oxaliplatin/5-FU±FA in this indication. 

*Keywords:* Clinical resistance; Multivariate analysis; Salvage chemotherapy

## 1. Introduction

The prognosis for colorectal cancer (CRC) is generally poor, and although surgery is an effective treatment, 50% of patients either have metastatic or inoperable disease at the initial diagnosis, or else develop metastases and/or local recurrent disease within several months [1]. Although 5-fluorouracil (5-FU) is a moderately effective chemotherapeutic option, many patients either do not respond, or progress after a brief response, and therefore an effective second-line chemotherapy (CT) option is needed. Until 1990, the search for salvage therapies for CRC patients failing 5-FU-based CT regimens focused on new 5-FU administration modalities. Continuous infusion (CIV) and high-dose (HD) 5-FU were investigated, with studies suggesting that both CIV and HD 5-FU were partially effective in patients who had failed treatment with standard bolus 5-FU regimens [2,3]. Modulation using

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folinic acid (FA), although showing an improved response rate, presented no benefits in terms of survival [4].

The combination of 5-FU with other cytotoxic agents, such as cisplatin or interferon, was also explored, with no improvement in efficacy, and increased toxicity and morbidity [5–10]. Since 1990, the introduction of several new classes of antineoplastic agents active in CRC patients, including oxaliplatin and irinotecan, has opened up new therapeutic possibilities.

Oxaliplatin (*trans*-L-diaminocyclohexane[DACH] oxalatoplatinum) (Eloxatine®, Sanofi-Synthelabo, France), is a DACH platinum derivative that acts by forming DNA intrastrand adducts.

*In vitro* and *in vivo* data have shown oxaliplatin to be active against CRC cell lines and synergistic with 5-FU without cross-resistance [11,12]. It has also been shown not to be cross-resistant with cisplatin or carboplatin in various preclinical studies.

Oxaliplatin is the first platinum compound to show activity as a single agent when used in the treatment of advanced CRC patients [13]. In two phase II studies involving patients with fluoropyrimidine-resistant advanced CRC, treated with oxaliplatin given as a single agent at 130 mg/m$^2$ over a 2-h infusion every 3 weeks, the objective response rates (ORR) in both studies were 10% (95% confidence interval (CI) 3–21) with 31% (95% CI 19–46) of patients exhibiting disease stabilisation, and median overall survival times (OS) for the two groups of 8.3 and 10 months [14]. In a phase II trial by Bécouarn and colleagues involving previously untreated CRC patients, oxaliplatin used as a single agent produced a 27% ORR (95% CI: 13.8–44.1%), with a median response duration of 195 days (range: 126–364+), median time to progression (TTP) of 127 days (range: 22–364+), and median survival time of 395 days (range: 28–573+) [15].

Oxaliplatin was given to patients progressing on 5-FU-based regimens in phase II trials. Its addition to 5-FU + FA treatment produced objective response rates ranging from 11 to 58%, depending on patient characteristics and treatment scheme, with a median progression-free survival (PFS) ranging from 7 to 10 months, and median OS of 12–17 months [16–22].

The compassionate-use programme which is the subject of this article included 490 patients treated with oxaliplatin in France on the basis of an ATU (*Autorisation Temporaire d'Utilisation*) granted by the French *Agence du Médicament* in September 1995. All requests were submitted to the programme's sponsor and monitored by the French *Agence du Médicament*. The patient cohort of 5-FU-resistant patients treated with oxaliplatin plus 5-FU±FA, which had already been the subject of safety assessments in pursuit of the primary regulatory objective, was analysed in order to identify factors predicting the efficacy of oxaliplatin when added to 5-FU±FA in a real-life prescription context, including patients with source-reviewed and third-party-assessed evidence for clinical 5-FU resistance. Efficacy has been analysed in terms of ORR, median TTP and OS.

## 2. Patients and methods

### 2.1. Patient selection

Between June 1995 and April 1996, a total of 490 advanced CRC patients were recruited in 148 French institutions in the context of a compassionate-use extended access programme (EAP). All the patients received oxaliplatin with 5-FU±FA.

### 2.2. Diagnosis and main inclusion guidelines

The main inclusion criterion for the compassionate-use EAP was histologically proven advanced/metastatic CRC. Patients were also to have objective, verifiable resistance to 5-FU±FA (on-treatment progression) or to have formal contraindications to 5-FU treatment, in which case they were given oxaliplatin as a single agent. There were no restrictions on age, performance status, or the number of prior lines of chemotherapy.

### 2.3. Data collection and patient classification

All cases were accurately reviewed on-site by a team of medical oncologists and all data were source-verified. Table 1 summarises the information requested for each patient in order for the physician and sponsor to identify which patients were to receive oxaliplatin. After source review, all case report forms (CRFs) were independently verified for completeness and consistency. For each patient, the team reviewed prior therapies,

Table 1
Information collected for each patient

| |
|---|
| Patient identification |
| Start date of oxaliplatin-based treatment |
| Age/sex |
| Performance status |
| Primary tumour site (colon or rectum) |
| Prior therapies, especially chemotherapy |
| Number of prior 5-FU chemotherapy regimens |
| Dose/schedule details of prior 5-fluorouracil (5-FU)-based treatment |
| Organs involved |
| Proof of progression while on prior 5-FU-based treatment |
| Dose/schedule of oxaliplatin + 5-FU±FA treatment |
| Safety of oxaliplatin treatment |
| Overall response while on oxaliplatin treatment |
| Progression, with proof, if applicable |
| Survival status at last visit |
| Cause of death, if applicable |

resistance to prior 5-FU treatment, dose and schedule of 5-FU±FA before and during oxaliplatin treatment, and tumour response to oxaliplatin-based treatment. In addition, an external panel of radiologists verified proof of progression during prior 5-FU-based treatment and reviewed all available imaging evidence for oxaliplatin-treated patients whose disease was reported to be responding or who showed stabilisation ($\geqslant$9 weeks or three planned cycles).

### 2.4. Identification of 5-FU-resistant advanced colorectal cancer patients

After verification of patients' characteristics, disease history and disease progression under prior 5-FU treatment, and after the external panel review, an algorithm was applied, based on treatment modality and clinical, radiological, biological or surgical evidence of 5-FU resistance, to reliably identify patients with 5-FU resistant disease (Fig. 1). As a result of this assessment, 370 5-FU-resistant advanced CRC patients were identified. These patients are the subject of the univariate and multivariate analyses presented in this article.

### 2.5. Administration of 5-FU-based chemotherapy

Administration and schedule modalities for 5-FU (and for FA when used as a modulating agent) were systematically recorded for every previous regimen. 5-FU was administered according to the preference of the individual prescribers, in line with the current practices of the institution in which the patient was treated, and hence in a wide variety of doses and schedules. The 5-FU was administered both as a single agent and in combination with various other cytotoxic or modulating agents. For the purposes of the present analysis, the administration types of 5-FU (with or without FA) were grouped according to acknowledged pharmacodynamic insights, as follows:

- Bolus/short infusion administration ($\leqslant$4 h)±FA: either daily (2–5 consecutive days), repeated weekly or every 3–4 weeks.
- High-dose intensity intermittent infusional schedule (HDI): this included all i.v. infusions $\geqslant$8 h and $\leqslant$48 h, given at weekly or bi-weekly intervals, usually involving high total doses of 5-FU ($\geqslant$1000 mg/m$^2$), ±FA. They were subdivided into: 8-h weekly infusion, 48-h bi-weekly infusion (±5-FU bolus), and 24-h infusion, given weekly.
- Continuous infusion (CVI): i.v. continuous infusion ($<$1000 mg/m$^2$), ±FA for 4–5 days every 2–3 weeks given at a flat rate of delivery or protracted continuous infusion lasting for more than 10 consecutive days ±FA.
- Chronomodulated delivery (CCM): 4–5 days continuous chronomodulated delivery, given every 2–3 weeks, ±FA.

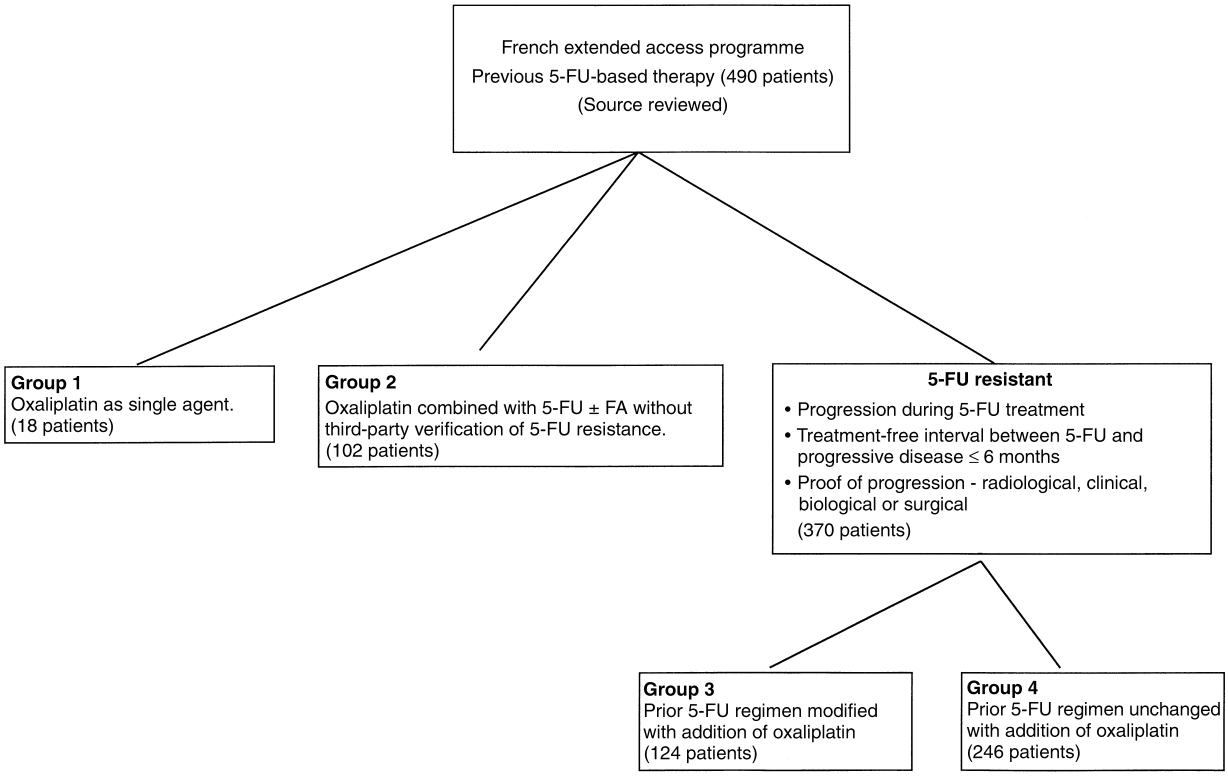


Fig. 1. Criteria used to identify patient resistance to 5-FU.

### 2.6. Oxaliplatin dosing

Oxaliplatin was administered either biweekly at doses ranging from 80 to 100 mg/m$^2$/cycle, usually associated with high-dose infusional intermittent schedules, or every 3–4 weeks at doses ranging from 100 to 130 mg/m$^2$/cycle, associated with a wide variety of 5-FU schedules and administration modalities. The treating physician chose the schedule of oxaliplatin he or she considered best adapted to the associated 5-FU-based regimen. Planned dose intensities for all the schedules of oxaliplatin administration were similar (33–42 mg/m$^2$/week).

### 2.7. Efficacy criteria

Tumour response was assessed in conformity with World Health Organization (WHO) criteria [23]. Nevertheless, as this was a compassionate-use programme, the frequency and thoroughness of the assessment of antitumoral efficacy was not as uniform as in a formal clinical trial. The responses were defined according to the following modified WHO criteria (modifications in italics):

- Complete response (CR): complete regression of all evidence of tumour, where possible assessed in two evaluations at least one month apart.
- Partial response (PR): a $\geqslant$50% decrease in the sum of the products of the two longest perpendicular diameters of all measurable lesions with no increase in size of tumour or appearance of any new lesion.

*As long as patients showed no clinical or biological signs of progression in the 8 weeks following their determination of either CR or PR, they were maintained in this category.*

- Stable disease (SD): $<$25% decrease of measurable disease and $\leqslant$25% progression of measurable lesion, *as well as no clinical, biological or radiological evidence of any new lesion.*
- Progressive disease (PD): $\geqslant$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 8 weeks of introduction of oxaliplatin or lack of formal disease evaluation after three cycles of treatment.*

SD is a clinically relevant category in this analysis, as most patients treated under this compassionate-use programme exhibited PD under their previous treatment regimen. SD represents a positive change in disease status for such patients, who have a similar median OS to those exhibiting PR [24].

Time-related parameters were also calculated, with median TTP and OS being defined as the time elapsed between the start of oxaliplatin-based treatment and the date when evidence of tumour progression was first obtained and the date of patient's death, respectively.

### 2.8. Methods for statistical analysis

TTP and OS curves for the various groups were computed using the Kaplan–Meier method. Both univariate and multivariate analyses were used to assess potential prognostic factors. For univariate analyses, dichotomous (objective responses) and censored (TTP and OS) data were compared by means of Pearson's $\chi^2$ test and the log-rank test, respectively. The variables included in the univariate analysis were: sex, PS (0–1 or 2–3), primary tumour site (colon or rectum), number of disease sites (1, 2 or $\geqslant$3), number of prior lines of chemotherapy for CRC (1, 2 or $\geqslant$3), haemoglobin level ($<$100 g/l or $\geqslant$100 g/l), serum alkaline phosphatase (AP) level ($<2\times$ULN (upper limit of normal laboratory values), or $\geqslant2\times$ULN), oxaliplatin schedule (bi-weekly or tri-weekly), change of 5-FU scheme (yes or no), and mode of 5-FU delivery in combination with oxaliplatin (bolus, HDI, CVI or CCM). For the multivariate analysis, dichotomous and censored data were compared by means of a multivariate logistic model [25] and a Cox proportional hazards model [26], respectively. A forward stepwise procedure was used, based on the Wald statistic. The significance level used as a criterion for retaining variables from the univariate analysis for inclusion in the multivariate analysis was $P\leqslant0.10$.

## 3. Results

### 3.1. Cohort characteristics

Out of the 490 patients recruited, 370 (76%) were considered, after source-data review and third-party verification, to have evidence of 5-FU-resistant advanced colorectal cancer. In this 5-FU-resistant group 230 (62%) were men, and 211 (57%) were at least 60 years old. The majority of these patients (312; 84%), had a PS of 0 or 1 (88% of patients with PS available). The median number of metastatic sites was 1 (range: 1–4). Liver involvement predominated, being found in 292 patients (79%), followed by the lung in 112 patients (30%), the peritoneum in 56 patients (15%) and lymph nodes in 51 patients (14%). There were 115 5-FU resistant patients (31%) who had received three or more lines of chemotherapy prior to treatment with oxaliplatin, 132 (36%) who had received two and 123 (33%) who had received only one prior line of chemotherapy. The time interval between the last regimen and the beginning of oxaliplatin treatment was less than 2 months for 291 of the patients (79%), between 2 and 6 months for 67 (18%) and 6 months or more for the

remaining 12 patients (3%). These characteristics are summarised in Table 2.

### 3.2. Antitumour activity

Out of the 370 5-FU-resistant patients, an objective response to the oxaliplatin-based treatment was reported in 54 patients, resulting in a 14.6% ORR (95% CI: 11.0–18.2%). Response rates and time-related parameters according to various variables analysed are presented in Table 3, and the results of the multivariate analysis are presented in Table 4.

### 3.3. Univariate and multivariate analyses of response rates

Both the univariate and multivariate analyses showed the schedule of oxaliplatin administration to be the most significant factor in terms of response rate with an ORR of 36.1% on the bi-weekly schedule versus 13.3% on the tri-weekly schedule (univariate: $P < 0.00037$ and multivariate: odds ratio = 0.14). Another significant factor was the number of prior lines of chemotherapy, with ORRs of 20.3%, 15.9% and 7.0% for patients who had received 1, 2 and 3 or more prior lines of chemotherapy, respectively (univariate $P = 0.012$, while for the multivariate, the odds ratio for likelihood of response in patients who had received $\geqslant 2$ prior lines of chemotherapy versus 1 was 0.61). Other factors which were correlated with a higher ORR, even though not reaching significance levels in the univariate analysis, were having a higher haemoglobin level ($\geqslant 100$ g/l, ORR = 15.9% versus $< 10$ g/l, ORR = 4.9%, $P = 0.061$) and having a lower serum AP level ($< 2$ ULN, ORR = 16.7% versus $\geqslant 2$ ULN, ORR = 9.1%, $P = 0.070$). Neither of these factors was significant for ORR according to the multivariate analysis. The mode of 5-FU delivery was also identified as a statistical trend in the univariate analysis (bolus, ORR = 12.5%; HDI, ORR = 12.2%; CVI, ORR = 15.2%; CCM, ORR = 23.2%; $P = 0.16$), which was found to be an independent prognostic factor in the multivariate analysis (taking bolus 5-FU administration as the standard, the odds ratio associated with HDI, CVI and CCM were found to be 0.62, 1.96 and 2.31, respectively).

### 3.4. Univariate and multivariate analyses of time-related parameters

Both the univariate and multivariate analyses showed patients' PS to be the most significant factor in terms of TTP and OS (PS 0–1; TTP = 4.4 months, OS = 10.5 months versus PS 2–3; TTP = 1.8 months, OS = 3.8 months, $P < 0.00001$ for TTP and OS, and, according to the multivariate analysis, the relative risk associated with PS $\geqslant 2$ was 1.56 for TTP and 1.66 for OS). The number of disease sites was also a significant factor for TTP and OS in both the univariate and multivariate analyses (one site; TTP = 4.7 months, OS = 11.4 months versus two sites; TTP = 4.3 months, OS = 9.2 months versus three or more; TTP = 2.8 months, OS = 6.3 months, $P = 0.0002$ for TTP and $P < 0.00001$ for OS.) The relative risk associated with $\geqslant 2$ disease sites was found to be 1.31 for TTP and 1.69 for OS (a highly significant factor). Low haemoglobin levels were found to be a statistically significant factor for shorter TTP and OS ($\geqslant 100$ g/l, TTP = 4.5 months and OS = 10.1 months versus $< 100$ g/l, TT = 2.3 months and OS = 6.7 months, $P = 0.011$ for TTP and 0.012 for OS) according to the univariate analysis, but according to the multivariate was only a significant factor for TTP. Serum AP level was found to be a highly significant factor for OS ($< 2$

Table 2
Characteristics of 5-FU-resistant patients ($n = 370$)

| Characteristic | *n* of patients (%) |
|---|---|
| Sex | |
| Male/female | 23 (62)/140 (38) |
| Age | |
| $< 60/\geqslant 60$ years | 159 (43)/211 (57) |
| WHO PS | |
| 0/1/2/3/MD | 144 (39)/168 (45)/39 (11)/4 (1)/15 (4) |
| Primary tumour site | |
| Colon/rectum | 259 (70)/111 (30) |
| Initial Dukes' stage | |
| A/B/C/D/MD | 3 (1)/48 (13)/118 (32)/193 (52)/8 (2) |
| Number of metastatic sites | |
| $1/2/\geqslant 3$/MD | 188 (51)/127 (34)/51 (14)/4 (1) |
| Organs involved | |
| Liver | 292 (79) |
| Lung | 112 (30) |
| Lymph nodes | 51 (14) |
| Peritoneum | 56 (15) |
| Other | 24 (6) |
| No. of prior chemotherapy lines | |
| $1/2/\geqslant 3$ | 123 (33)/132 (36)/115 (31) |
| Interval between diagnosis of recurrence and oxaliplatin treatment | |
| $0–\leqslant 12$ months | 182 (49) |
| $> 12–\leqslant 24$ months | 107 (29) |
| $> 24$ months | 81 (22) |
| Interval between last chemotherapy cycle and oxaliplatin treatment | |
| $< 1$ month | |
| $\geqslant 1–< 2$ months | 291 (79) |
| $\geqslant 2–< 6$ months | 67 (18) |
| $\geqslant 6$ months | 12 (3) |

MD, missing data; PS, performance status; WHO, World Health Organisation.

ULN, OS = 11 months; ⩾2 ULN, OS = 8.8 months) in both the univariate and multivariate analyses. The number of prior lines of chemotherapy was found to be marginally significant with respect to TTP in the univariate analysis, but this significance was not confirmed by the multivariate analysis. The mode of 5-FU delivery was found to be a statistically significant factor for both TTP and OS (bolus, TTP = 4.6 months and OS = 9.7 months; HDI, TTP = 3.7 months and OS = 8.7 months; CVI, TTP = 4.7 months and OS = 11.1 months; CCM, TTP = 5.2 months and OS = 13.6 months; $P = 0.014$ for TTP and 0.016 for OS). The multivariate analysis also identified the mode of delivery as a highly significant factor both for TTP ($P = 0.0007$) and OS ($P = 0.0021$). Taking bolus administration to be 1 for both TTP and OS the odds ratios were as follows: HDI, 1.21 for TTP and 1.02 for OS; CVI, 0.70 for TTP and 0.58 for OS; CCM, 0.62 for TTP and 0.54 for OS.

Table 3
Univariate analysis of objective response rate (ORR), time to treatment progression (TTP), and overall survival (OS) following the addition of oxaliplatin to a 5-FU±FA regimen in 5-FU-resistant colorectal cancer patients

| | | ORR | | | TTP | | OS | |
|---|---|---|---|---|---|---|---|---|
| Parameter | *n* of pts (%) | % | 95% CI | *P* value | Median (mo) | *P* value | Median (mo) | *P* value |
| All patients | 370 (100) | 14.6 | 11–18.2 | | 4.3 | | 9.7 | |
| Sex | | | | | | | | |
| Male | 230 (62) | 14.8 | 10.2–19.4 | 0.90 | 4.1 | 0.089 | 9.9 | 0.60 |
| Female | 140 (38) | 14.3 | 8.5–20.1 | | 4.5 | | 9.6 | |
| Performance status | | | | | | | | |
| 0–1 | 312 (84) | 14.7 | 10.7–18.6 | 0.17 | 4.4 | $<10^{-5}$ | 10.5 | $<10^{-5}$ |
| 2–3 | 43 (12) | 7.0 | 0–14.6 | | 1.8 | | 3.8 | |
| MD | 15 (4) | | | | | | | |
| Primary tumour site | | | | | | | | |
| Colon | 259 (70) | 14.3 | 10–18.5 | 0.80 | 4.1 | 0.092 | 9.3 | 0.27 |
| Rectum | 111 (30) | 15.3 | 8.6–22 | | 4.6 | | 10.7 | |
| No of disease sites | | | | | | | | |
| 1 | 188 (51) | 13.8 | 8.9–18.7 | 0.53 | 4.7 | 0.0002 | 11.4 | $<10^{-5}$ |
| 2 | 127 (34) | 13.4 | 7.5–19.3 | | 4.3 | | 9.2 | |
| ⩾3 | 51 (14) | 19.6 | 8.7–30.5 | | 2.8 | | 6.3 | |
| MD | 4 (1) | | | | | | | |
| No of prior lines of chemotherapy | | | | | | | | |
| 1 | 123 (33) | 20.3 | 13.2–27.4 | 0.012 | 4.7 | 0.037 | 11.3 | 0.28 |
| 2 | 132 (36) | 15.9 | 9.9–22.1 | | 4.5 | | 9.1 | |
| ⩾3 | 115 (31) | 7.0 | 2.3–11.7 | | 3.2 | | 9.9 | |
| Haemoglobin | | | | | | | | |
| <100 g/l | 41 (11) | 4.9 | 0–11.5 | 0.061 | 2.3 | 0.011 | 6.7 | 0.012 |
| ⩾100 g/l | 315 (85) | 15.9 | 12.8–19 | | 4.5 | | 10.1 | |
| MD | 14 (4) | | | | | | | |
| Serum AP | | | | | | | | |
| <2×ULN | 233 (63) | 16.7 | 11.9–21.4 | 0.070 | 4.3 | 0.13 | 11.0 | 0.0002 |
| ⩾2×ULN | 99 (27) | 9.1 | 3.4–14.7 | | 3.8 | | 8.8 | |
| MD | 38 (10) | | | | | | | |
| Oxaliplatin schedule | | | | | | | | |
| Bi-weekly | 36 (10) | 36.1 | 20.4–51.8 | 0.00037 | 5.4 | 0.19 | 11.1 | 0.11 |
| Tri-weekly | 308 (83) | 13.3 | 9.5–17.1 | | 4.2 | | 10.0 | |
| MD | 26 (7) | | | | | | | |
| Change of 5-FU scheme | | | | | | | | |
| Yes | 124 (34) | 15.3 | 8.9–21.6 | 0.78 | 4.4 | 0.42 | 10.6 | 0.35 |
| No | 246 (66) | 14.2 | 9.8–18.6 | | 4.1 | | 9.5 | |
| 5-FU modality | | | | | | | | |
| Bolus | 53 (14) | 12.5 | 3.6–21.4 | 0.16 | 4.6 | 0.014 | 9.7 | 0.016 |
| High-dose | 196 (53) | 12.2 | 7.6–16.8 | | 3.7 | | 8.7 | |
| Continuous infusion | 46 (12) | 15.2 | 4.8–25.6 | | 4.7 | | 11.1 | |
| Chronomodulated | 69 (19) | 23.2 | 13.2–33.2 | | 5.2 | | 13.6 | |
| MD | 6 (2) | | | | | | | |

AP, alkaline phosphatase; mo, months; ULN, upper limit of normal; 5-FU, 5-fluorouracil; FA, folinic acid; pts, patients; MD, missing data.

## 4. Discussion

The aim of the present statistical analysis was to identify factors that could serve as prognostic indicators for patients receiving oxaliplatin/5-FU±FA after having progressed on a prior 5-FU-based therapy. The addition of oxaliplatin to treatment offers a valuable option for salvage therapy, once the first-line 5-FU regimen has failed, as before the only alternatives with some evidence of activity were the modulation of the 5-FU regimen by adding FA or interferon, or else administering the 5-FU-containing treatment using different doses and/or schedules [2,9,27,28].

We should stress that 67% of the patients had already received two or more lines of chemotherapy for their advanced CRC prior to the administration of the oxaliplatin-containing treatment. Furthermore, the number of prior lines of chemotherapy was correlated with another possibly relevant variable: the interval between the diagnosis of metastatic disease and the introduction of the oxaliplatin treatment. These two observations suggest that the reported population was characterised by less aggressive and/or more responsive disease, allowing multiple treatment attempts.

When considering baseline patient and disease characteristics, it is interesting to note that while PS is a highly significant factor in terms of both TTP and OS, it is not a significant predictive factor for ORR, raising once again the problem of the limited surrogate value of the objective response assessment current definition as an indication of a patient's survival time is in this indication [24].

Although low haemoglobin levels were significantly associated with poorer ORR, TTP and OS, the high significance of abnormally elevated serum AP levels for shortened OS makes this a more useful indicator for determining patient prognosis. As far as administration regimens and schedules are concerned, the multivariate analysis suggests that bi-weekly as opposed to tri-weekly oxaliplatin/FU±FA administration schedules may be significantly correlated with improved rate of response and, more importantly, longer TTP and OS. Chronomodulated administration was significantly correlated with longer TTP and longer OS in both the univariate and multivariate analyses and higher ORR in the multivariate analysis. The fact that any given accrual centre tends to use one particular schedule and mode of administration, and that different centres also perform response assessment with different frequencies might suggest that the better efficacy parameters that appear related to mode of administration and schedule are in fact the result of a bias in favour of the centres that use these modes of administration or schedules. However, when treatment centre is added as a variable into the multivariate analysis, it is not retained in the final model, which remains the same as that generated before entering treatment centre. We conclude that the value of the higher dose density bi-weekly schedule and the chronomodulated mode of delivery, as has been validated in prior controlled trials [29,30] is supported by this study.

Interestingly, the change of 5-FU regimen upon addition of oxaliplatin to the treatment had no bearing on any of the efficacy parameters, calling into question the value of any specific strategy that might be pursued when associating oxaliplatin with a prior 5-FU regimen.

When the data from this study are compared with the efficacy data obtained in formal phase II studies in 5-FU-pretreated CRC patients, which necessarily enforce positive selection through restrictive eligibility criteria, the time-related efficacy parameters are similar, but the ORR is lower (14.6% versus 24%–55%) [16–22]. This difference in ORR is very possibly due to both the lack of eligibility criteria and the lack of enforced regular evaluations in the compassionate-use programmes, which contrast with the uniform method of evaluation required in clinical trials [31]. Other factors resulting in the different ORRs may well be the lack of accrual restriction on PS and the number of prior lines of chemotherapy for patients included in the present analysis.

An important consideration is the relevance of disease stabilisation as a positive therapeutic outcome in the treatment of 5-FU-resistant advanced CRC patients (25% in this analysis). This could explain why the TTP and OS are very close to those found in other studies, while the ORR is lower. Indeed, the patients treated in this compassionate-use programme who would have satisfied the inclusion criteria for phase II second-line CRC trials (good PS, $\leqslant 2$ prior lines of chemotherapy, normal blood counts, adequate liver and renal function, etc.), show time-related progression parameters strictly similar to those reported in other studies [16,17,32].

The present analysis confirms the view of the oxaliplatin/5-FU±FA combination as an active treatment for progressive 5-FU-resistant CRC patients. Although not strictly comparable, the results obtained in this heterogeneous, non-restricted cohort of 5-FU-resistant CRC patients, especially with respect to time-related parameters (median TTP and OS) compare favourably with those published for single-agent irinotecan following formal phase II–III trials including patients with similar disease characteristics profiles [33]. The formal comparison between irinotecan and oxaliplatin/5-FU in 5-FU-pretreated and/or refractory CRC patients may be warranted, but may also be a moot academic issue in light of several reports showing their combination to be feasible and active in the same patient population [34–36].

The patient's prognosis in such cases depends significantly on several factors discussed in this paper. The interest of oxaliplatin/5-FU as a therapeutic option in 5-FU-resistant cancer appears well supported by the

Table 4
Multivariate analysis of objective response rate (ORR), time to treatment progression (TTP), and overall survival (OS) following the addition of oxaliplatin to a 5-FU + FA regimen in 5-FU-resistant colorectal cancer patients

| | ORR ($n=393$) | | TTP ($n=408$) | | OS ($n=412$) | |
|---|---|---|---|---|---|---|
| Parameter | *P* value | Odds ratio | *P* value | Odds ratio | *P* value | Odds ratio |
| Sex | NA | | NS | | NA | |
| Male | | | | | | |
| Female | | | | | | |
| Age | NA | | NA | | NA | |
| Performance status | NS | | 0.026 | | 0.025 | |
| 0–1 | | | | 1 | | 1 |
| 2–3 | | | | 1.56 | | 1.66 |
| Primary tumour site | NA | | NS | | NA | |
| No of disease sites | NA | | 0.0002 | | $<10^{-5}$ | |
| 1 | | | | 1 | | 1 |
| $\geqslant 2$ | | | | 1.31 | | 1.69 |
| No of prior lines of chemotherapy | $<10^{-5}$ | | NS | | NA | |
| 1 | | 1 | | | | |
| $\geqslant 2$ | | 0.61 | | | | |
| Haemoglobin level | NS | | 0.033 | | NS | |
| $<100$ g/l | | | | 1 | | |
| $\geqslant 100$ g/l | | | | 0.64 | | |
| Serum alkaline phosphatase level | NS | | NS | | 0.001 | |
| $<2\times$ULN | | | | | | 1 |
| $\geqslant 2\times$ULN | | | | | | 1.71 |
| Oxaliplatin frequency | $<10^{-5}$ | | 0.017 | | 0.0043 | |
| Bi-weekly | | 1 | | 1 | | 1 |
| Tri-weekly | | 0.14 | | 1.63 | | 2.17 |
| Change of 5-FU scheme | NA | | NA | | NA | |
| 5-FU modality | 0.022 | | 0.0007 | | 0.0021 | |
| Bolus | | 1 | | 1 | | 1 |
| High-dose | | 0.62 | | 1.21 | | 1.02 |
| Continuous infusion | | 1.96 | | 0.70 | | 0.58 |
| Chronomodulated | | 2.31 | | 0.62 | | 0.54 |

NS, non significant; NA, not analysed; ULN, upper limit of normal value.

results of the analysis of this 'real-life' prescription context. Its value appears enhanced when patients are treated earlier in their disease development and before the general deterioration of the patient's condition.

To conclude, this experience confirms the preclinical and clinical data reported in phase II–III studies concerning the synergy and activity of oxaliplatin in combination with 5-FU±FA in 5-FU-resistant patients. Finally, the efficacy of oxaliplatin-based combination treatment in this population is dependent on well-recognised factors related to patients' general status and pretreatment history as well as the extent of disease, and may vary as a function of the modality of drug delivery.

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