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Phase II Study of Weekly Oxaliplatin and High-dose Infusional 5-Fluorouracil plus Leucovorin in Pretreated Patients with Metastatic Colorectal Cancer

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Abstract. *Background: Chemotherapy with oxaliplatin, fluorouracil (5-FU) and leucovorin (LV) has proven efficacy in patients with advanced colorectal carcinoma (CRC), although the optimal dosage and administration schedule are still unclear. This phase II trial investigated the tolerability and activity of weekly oxaliplatin, high-dose infusional 5-FU and LV in pretreated patients with metastatic CRC. Materials and Methods: Patients received weekly courses of i.v. oxaliplatin 50 mg/m^2 (1-h infusion), LV 100 mg/m^2 (1-h infusion) and 5-FU 2100 mg/m^2 (24-h infusion) until disease progression or unacceptable toxicity. NCI-CTC criteria were used for assessment of side-effects (at each cycle) and WHO criteria for assessment of tumour response (every 8 cycles). For descriptive purposes, time to progression, overall survival and duration of objective response were also calculated. Results: Forty-four patients were enrolled and received a total of 606 cycles (median 13/patient, range 4-33), and 70% of courses (421/606) were delivered at 100% of the planned dose. The most frequent side-effects were gastrointestinal and neurological and incidence rates were: diarrhoea 66% (grade III: 29%), nausea/vomiting 54%, neurotoxicity 34% (grade III: 2%), fatigue 27%, mucositis 22%, leucopenia 14%. No grade IV toxicity was observed. Objective response rates were: partial response 23% (10 patients), stable disease 59% (26) and progressive disease 11% (5). Median time to progression was 7 months, overall survival 13 months and the duration of partial response and stable disease were 9 and 6 months, respectively. Conclusion: The study demonstrated that this regimen has a favourable tolerability profile and is an active combination in the pretreated metastatic CRC patient, deserving further evaluation in phase III trials.*

For the last five decades, fluorouracil (5-FU) has been the mainstay of chemotherapy for colorectal carcinoma (CRC), both in the treatment of metastatic disease and in the adjuvant setting. However, when administered as a single agent for first-line treatment of advanced disease, 5-FU has produced only modest response rates, with no major impact on survival (1). The addition of leucovorin (LV) was found to improve the response rate (by up to 2-fold) but not overall survival (2). More recently, a meta-analysis of 6 studies comparing different methods of 5-FU administration has demonstrated improved response rates with continuous infusion compared with bolus injection (22 *vs.* 14%), as well as decreased toxicity. Survival rates, however, remained poor (12.1 *vs.* 11.3 months, respectively) (3). Different types of administration also appear to affect the pattern of toxicity of 5-FU, with haematological side-effects being more frequent with bolus administration and hand-foot syndrome with continuous infusion (4,5). In our experience too, LV modulation of weekly short-term continuous infusion of high-dose 5-FU has proved to be a well tolerated and highly active regimen in both untreated and 5-FU-resistant patients with advanced CRC (6).

With the recent introduction of novel agents with activity against 5-FU-refractory tumours, such as oxaliplatin, there has been considerable progress in the therapy of advanced CRC. Oxaliplatin, a third-generation platinum derivative with a thymidylate synthase-independent mechanism of action, has

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demonstrated synergistic effects with 5-FU/LV *in vitro* and *in vivo* (7) and has been widely used in the treatment of CRC, both in combination regimens and, to a lesser extent, as single agent. As reviewed by Culy *et al.*, administration of oxaliplatin plus 5-FU/LV to patients who had failed first-line chemotherapy was associated with objective response rates of 13-45%, median progression-free survival of 5-10 months and median survival of approximately 9-17 months (8). When evaluated as first-line treatment in two large randomised trials, oxaliplatin plus 5-FU/LV combination therapy resulted in response rates of 53% compared with 16% in patients receiving 5-FU/LV ($p<0.001$) (9), and 50.7% *vs.* 22.3%, respectively ($p<0.001$) (10). In both studies, median progression-free survival was also significantly longer in patients receiving oxaliplatin (approximately 9 *vs.* 6 months), with no significant differences in overall survival. Despite the large number of trials, the optimal dosing schedule of oxaliplatin has not yet been defined. In combination regimens with fluoropyrimidines this compound is generally used at dosages of 85 mg/m^2 once every 2 weeks or 130 mg/m^2 every 3 weeks, but different dosing regimens have been tried in order to increase dose intensity and minimise toxicity, including weekly administration schedules (11,12). Pharmacokinetic studies have demonstrated that oxaliplatin has a slow plasmatic clearance and also reduces the plasma clearance of 5-FU (which could be an important factor in the synergy between these 2 agents) (13,14). Therefore, it has been suggested that weekly oxaliplatin regimens may have a better chance of optimising the benefits of this pharmacokinetic interaction than schedules based on administration every 2 or 3 weeks.

In the light of the results of these preliminary studies, we investigated the tolerability and activity of a combination regimen consisting of weekly administration of oxaliplatin plus high-dose infusional 5-FU (over 24 hours) and LV in pretreated patients with metastatic CRC.

Patients and Methods

Adult patients aged 18-75 years, with histologically proven adenocarcinoma of the colon or rectum, who had become refractory or had progressed following first-line chemotherapy, had bidimensionally measurable lesions, life expectancy >3 months and WHO performance status ≥ 2, were eligible for inclusion. Prior radiotherapy was allowed if measurable lesions were outside the radiation field. Patients were also required to have adequate bone marrow, renal and liver function (neutrophil count >2000/mm^3, platelet count >100 000/mm^3, serum creatinine <1.5 mg/dl and serum bilirubin <1.25 the upper normal limit). Ineligibility criteria included prior chemotherapy based on infusional 5-FU, a history of a second malignancy other than colorectal adenocarcinoma (excluding non-melanoma skin carcinomas and adequately treated *in situ* carcinomas of the uterine cervix), serious concomitant diseases, pregnancy or lactation or concomitant therapy with investigational agents.

Pre-treatment evaluation included assessment of hepatic, haematopoietic and renal function, ECG, chest X-ray/computerised tomography (CT) and abdominal-pelvic ultrasound/CT scan. Every 2 months (8 cycles of chemotherapy) a re-evaluation of the patient was planned for assessment of tumour response. This study was conducted in conformity with Good Clinical Practice Guidelines and the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was required at study entry.

Therapy consisted of oxaliplatin 50 mg/m^2 administered as a 1-h intravenous infusion and LV 100 mg/m^2 1-h infusion followed by 5-FU 2100 mg/m^2 24-h continuous infusion. This regimen was repeated every week. Subcutaneous port insertion and a portable external infusion pump allowed chemotherapy to be administered in an outpatient setting. $5HT_3$ receptor antagonists were administered before each cycle for emesis prevention. There was no prophylactic use of haemopoietic colony-stimulating factors.

Toxicity was graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC; Version 2.0, 1998), and evaluated after each cycle. Therapy was continued until disease progression, the occurrence of unacceptable toxicity or patient refusal. In case of grade II toxicity the treatment was discontinued until complete resolution of the symptoms and then re-instituted without changes in drug dosages, while in case of grade III toxicity there was a 20% dose reduction of all chemotherapy agents when treatment was restarted. Patients with grade II diarrhoea received loperamide and were instructed to take it without delay if the symptom recurred during subsequent courses.

Tumour responses were evaluated every 8 cycles according to WHO criteria (15). Complete response (CR) was defined as complete disappearance of all symptoms and signs of disease for ≥ 4 weeks; partial response (PR) as a >50% reduction in tumour area (sum of the products of the greatest length and maximum perpendicular width of all measurable lesions) with no new lesions; stable disease (SD) as no change or <25% increase in indicator lesions with no new lesions; progressive disease (PD) as > 25% increase in ≥ 1 indicator lesions or appearance of new lesions. Time to event curves were estimated by means of the Kaplan-Meier method. Survival was defined as the period of time from start of chemotherapy until death from any cause. Time to progression was determined by calculating the interval between the start of therapy and the time when disease progression or death or treatment interruption was first documented. The duration of complete response was defined as the interval between first documented CR and first documented PD; the duration of partial response as the time between treatment initiation and first documented PD.

The study was a phase II trial designed to investigate the response rate of a combination of drugs given as second-line chemotherapy in CRC patients with metastatic disease. The sample size was calculated according to the Simon' s two-stage design (16). Having set $\alpha = \beta = 0.10$ and $\delta = 15\%$ (considering 10% response rate as clinically not interesting), a sample of 27 patients was required in the first stage. If more than 2 patients had a clinical response, a further 13 patients were enrolled in the second stage and up to 5 more patients could be accrued to correct for attrition. The treatment under investigation could be considered interesting for further trials if more than 6 patients presented a clinical response out of the total number of enrolled patients. Confidence intervals were used to determine the 95% upper and lower confidence limits of response rate. Analyses were conducted according to the intention-to-treat method.

Results

Between July 1999 and December 2000, forty-four patients were enrolled in the trial. The patients' characteristics are shown in Table I. All patients had received first-line chemotherapy prior to this study: 9 patients had progressed during treatment and were considered refractory, 25 were resistant (no response to therapy) and the other 10 progressed after achieving an objective response to first-line chemotherapy. Twenty-seven patients (61%) had metastases at the moment of first diagnosis. Fourteen out of the remaining 17 patients had undergone adjuvant chemotherapy after primary surgery, thus having received 2 regimens before entering the present study. The majority of patients (61%) presented with liver metastases, 73% had one metastatic site while in 27% ≥ 2 metastatic sites were documented. First-line chemotherapy consisted of irinotecan in combination with raltitrexed (50%), 5-FU/LV bolus combination (41%), and single-agent capecitabine or raltitrexed (9%). The majority of patients had been included in clinical trials.

A total of 606 cycles were administered, with a median of 13 courses/patient (range 4-33) and 70% of courses (421/606) were delivered at 100% of the planned dose of the 3 agents.

Tolerability. No grade IV toxicity occurred during the 606 observed cycles (Table II). Seven patients (16%) experienced haematological toxicity: grade I neutropenia (6 patients) and grade II anaemia (1 patient). Anaemia was treated with erythropoietic growth factor and did not require discontinuation of chemotherapy.

Diarrhoea was the main non-haematological toxicity. Thirteen patients (29%) developed grade III diarrhoea: a 20% dose reduction of all 3 agents and early treatment with loperamide allowed continuation of therapy (after a temporary interruption) in all but 4 patients, who refused further chemotherapy. Sixteen patients (36%) developed grade I or II diarrhoea. Nausea and vomiting occurred in twenty-four patients (54%), being rated grade I or II in 22 patients (50%) and grade III in 2 (4%).

Grade III peripheral sensory neuropathy (paraesthesia interfering with activities of daily living) occurred in one patient (2%) at the cumulative oxaliplatin dose of 560 mg/m^2, making interruption of treatment necessary. Grade I or II neuropathies developed in 14 (32%) patients. Grade II neurotoxicity (4 patients) was associated with a median cumulative dose of 250 mg/m^2 (range 200-550). No objective response was documented in the 5 patients with grade II-III toxicity. No acute neurotoxic manifestations were observed.

Hand-foot syndrome occurred in 3 (7%) patients; in one case, long-lasting (>3 weeks) grade III hand-foot syndrome was associated with diarrhoea and it was therefore necessary to discontinue therapy, in spite of the dosage reduction. Ten patients experienced mucositis, which was rated grade I in 4 (7%), grade II in 5 (11%) and grade III in 1(2%). Five (11%) patients developed grade I fever.

Overall, 16 (36%) patients underwent a 20% dose reduction. Thirty (68%) patients had their treatment temporarily interrupted because of chemotherapy-related grade II or III toxicities. Three of them needed a 2-week interruption to allow recovery from symptoms, while for the remaining 13 patients a 1-week rest was sufficient. Overall, 33 cycles were delayed but chemotherapy was resumed at full dosage, while 185 courses were resumed at 20% of the planned dosage. Seven (16%) patients stopped treatment permanently due to toxicity: grade III diarrhoea (n=4); grade III paraesthesia (n=1); grade III hand-foot syndrome associated with grade II diarrhoea (n=1); grade II mucositis combined with grade II paraesthesia (n=1).

Activity. Evaluation of response was performed in 41 patients. Three patients were not evaluable (1 because of early progression of the disease, 2 because of their refusal to continue chemotherapy after one month of treatment). Responses are shown in Table III. Overall, the response rate was 22.7% (95% C.I.=12%-38%) corresponding to 10 partial responses. No complete responses were observed. Twenty-six patients (59%) had stable disease, including 4 with minor response (tumor decrease < 50%), while 5 (11.3%) patients had disease progression. Two out of 9 (22%) patients who were refractory to first-line chemotherapy demonstrated objective response to this second-line treatment. The median time to progression was 7 months and the median overall survival was 13 months. (Figure 1). The median duration of partial response was 9 months (range 6-26) and the median duration of stable disease was 6 months (range 3-28).

Discussion

In the present study we investigated a dose-intensive weekly schedule of oxaliplatin 50 mg/m^2 administered in combination with LV 100 mg/m^2 and 5-FU 2100 mg/m^2 24-h continuous infusion. This regimen demonstrated a manageable toxicity profile, without grade IV toxicity and with recovery from grade III side-effects in the majority of patients. Discontinuation of chemotherapy occurred in only 7 patients, 4 of whom refused subsequent courses after having experienced grade III diarrhoea.

As expected, the most frequently reported side-effects were gastrointestinal disorders and neurotoxicity. Approximately one-third of our patients (29%) complained of grade III diarrhoea, which usually resolved with loperamide treatment and did not require hospitalisation. In these patients, a reduction of the dosages of all 3 chemotherapy agents during subsequent courses was sufficient to avoid further episodes of

Table I. *Patients' characteristics.*

No. of patients enrolled	44
Age	
median	63
range	45-78
Sex [no. (%)]	
M	27 (61%)
F	17 (39%)
WHO performance status [no. (%)]	
0	34 (77%)
1	10 (23%)
Primary tumour site [no. (%)]	
colon	21 (48%)
rectum	23 (52%)
Sites of metastatic disease [no. (%)]	
liver	27 (50%)
lung	12 (22%)
peritoneum	10 (18%)
pelvis	2 (4%)
other	3 (5%)
No. of metastatic sites [no. (%)]	
1	32 (73%)
≥2	12 (27%)
Adjuvant chemotherapy	
Yes	14 (32%)
No	30 (68%)

Table II. *Toxicity per patient (maximum NCI-CCT grade).*

Adverse event [no. (%) of pts.]	Overall incidence	Grade I	Grade II	Grade III
Diarrhoea	29 (65.9%)	12 (27.3%)	4 (9.1%)	13 (29.5%)
Nausea/vomiting	24 (54.5%)	22 (50.0%)	-	2 (4.5%)
Neurotoxicity	15 (34.1%)	10 (22.3%)	4 (9.1%)	1 (2.3%)
Fatigue	12 (27.3%)	11 (25.0%)	-	1 (2.3%)
Mucositis	10 (22.3%)	4 (9.1%)	5 (11.4%)	1 (2.3%)
Leucopenia	6 (13.7%)	6 (13.7%)	-	-
Fever	5 (11.4%)	5 (11.4%)	-	-
Hand-foot syndr.	3 (6.8%)	2 (4.5%)	-	1 (2.3%)
Anaemia	1 (2.3%)	-	1 (2.3%)	-

Table III. *Objective response.*

Complete response	-
Partial response	10 (22.7%) [95% CI 12-38%]
Stable disease	26 (59%)
Progressive disease	5 (11.3%)
Not evaluable	3 (6.8%)

severe diarrhoea. Peripheral sensory neuropathy was experienced by 34% of patients and, as expected, the severity of symptoms was correlated with increasing cumulative doses of oxaliplatin (8). However, the severity of neurotoxic symptoms was mild in the majority of cases, being rated grade I in 23% of patients and grade II in 9%. Even though oxaliplatin was infused over 1 hour (rather than the more commonly used 2-hour period), no acute laryngopharyngeal dysaesthesia was observed. Since this side-effect seems to depend on the oxaliplatin dose, the lower dosage of drug utilised at each dosing time in our weekly regimen (compared with bimonthly regimens) may have contributed to minimising the risk of this distressing symptoms in our patient population (17). At the dosage employed, haematological toxicities were not a matter of concern and did not require treatment delay or dosage reductions.

The response rate in our patients was 23% and stable disease was recorded in 59%. These results and data for overall survival and progression-free survival demonstrated the activity of this oxaliplatin plus 5FU/LV weekly schedule, with efficacy-related parameters matching those of phase II trials (FOLFOX regimens) in patients progressing after treatment with fluoropyrimidines (18-20).

Several regimens of oxaliplatin plus 5FU-LV combination chemotherapy have been used, and some authors have proposed schedules based on weekly administration in an attempt to intensify the dose (which is thought to improve response rate) (21) without increasing and, hopefully, minimising toxic burden. In a phase I dose-finding study conducted in a limited number of patients, Rosati *et al.* suggested the use of weekly cycles of oxaliplatin 65 mg/m^2, LV 500 mg/m^2 and 5-FU 2300 mg/m^2 (48-h infusion) for 4 consecutive weeks, followed by a 1-week rest period. Diarrhoea and neutropenia were the dose-limiting toxicities in this study, and transient peripheral neuropathy was reported by 14 (66%) patients, reaching grade II intensity at a cumulative oxaliplatin dosage of 720-1170 mg/m^2 (12). Janinis *et al.* tested a weekly regimen of oxaliplatin 50 mg/m^2, LV 500 mg/m^2 and 5-FU 2500 mg/m^2 (24-h infusion) for 6 consecutive weeks (to be repeated every 50 days) in 32 patients with metastatic CRC (11). However, due to toxicity problems, only 50% of the cycles could be administered at ≥90% of the planned dosage, and the median dose intensities of oxaliplatin and 5-FU were 33 mg/m^2/week (range 24-43) and 1517 mg/m^2/week (range 974-2252), respectively. The response rate was lower than expected (13%) and the incidence of adverse events was high: over half of the patients (53%) developed grade III or IV diarrhoea and haematological toxicities (grade III or IV)

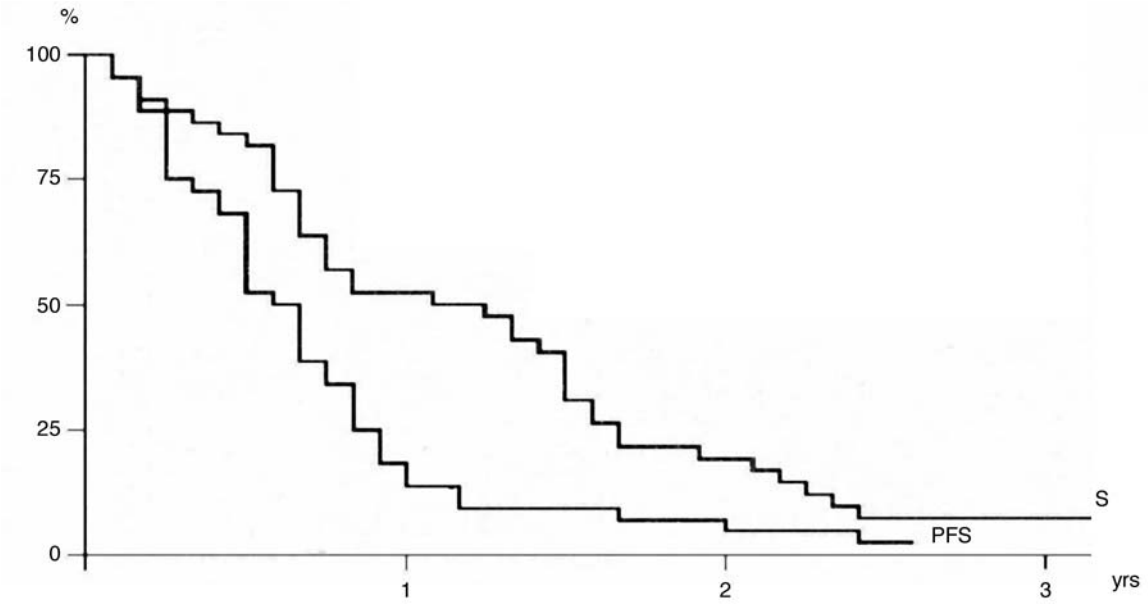

Figure 1. *Overall survival (S) and progression-free survival (PFS).*

affected 22% of patients. On the basis of these negative results, the authors urged caution when using weekly regimens of oxaliplatin and high-dose 5-FU although, clearly, factors other than the chemotherapy regimen used may have influenced the outcome. In our patients, we obtained a more favourable tolerability profile, associated with a response rate of 23%, at median dose intensities of 50 mg/m^2/week (range 40-50) for oxaliplatin and 2100 mg/m^2/week (range 1680-2100) for 5-FU. There were no grade IV toxicities or grade III haematological toxicities and a lower percentage of patients experienced grade III diarrhoea (29%). Moreover, 70% of courses (421/606) were delivered at 100% of the planned dosage. Our data on incidence and severity of neurotoxicity are fairly similar to those reported by Janinis *et al.* and compare favourably with the findings of trials which have tested the FOLFOX regimens (bimonthly oxaliplatin 85 or 100 mg/m^2 plus 5-FU/LV at different doses). Overall, these regimens were associated with a higher incidence and severity of neurotoxicity (18-20). Reduction of this side-effect in the present trial was probably correlated to the weekly schedule, since the dose intensity of oxaliplatin was similar. We also observed a lower haematological toxicity rate compared with FOLFOX regimens, without any case of febrile neutropenia, suggesting that the weekly regimen may also be suitable for pretreated or aged patients.

Our toxicity data are comparable with the preliminary findings of a large-scale trial evaluating weekly oxaliplatin 50 mg/m^2, 5-FU 2000 mg/m^2 (24-h infusion) and LV 500 mg/m^2 *vs.* bolus 5-FU/LV (Mayo regimen) in advanced CRC. In this trial, incidence rates of grade III/IV haematological toxicity, diarrhoea and sensory neuropathy were 6.7%, 21.2 % and 12.7%, respectively, in the oxaliplatin arm (22).

In conclusion, weekly oxaliplatin, LV and high-dose infusional 5-FU demonstrated a manageable toxicity profile and a satisfactory therapeutic response in pretreated patients with advanced CRC. This schedule deserves further evaluation in both pretreated and chemotherapy-naive patients.

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