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Clinical report

Phase II study of second-line oxaliplatin, irinotecan and mitomycin C in patients with advanced or metastatic colorectal cancer

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The aim of this phase II study was to investigate the therapeutic value of second-line treatment with oxaliplatin, irinotecan (CPT-11) and mitomycin C (MMC) in patients with metastatic colorectal cancer pretreated with 5-fluorouracil (5-FU)-based chemotherapy. A total of 10 patients with metastatic colorectal cancer, all of whom had developed progressive disease from advanced or metastatic colorectal cancer while receiving or within 6 months after discontinuing first-line chemotherapy with 5-FU and leucovorin, were entered in this study. At the time of relapse, cytotoxic chemotherapy consisting of oxaliplatin 80 mg/m^2 plus CPT-11 80 mg/m^2 given i.v. on therapeutic day 1, and MMC 6 mg/m^2 given i.v. on day 15, respectively, was initiated. Treatment courses were repeated every 4 weeks for a total of six courses unless there was prior evidence of progressive disease. The overall response rate was 30% with three partial responses for all 10 assessable patients. Two additional patients (20%) had stable disease and five patients (50%) progressed. The median overall survival duration has not been reached yet and is longer than 7.1 months (range 2–23.5+) from the beginning of second-line therapy. Four patients are currently alive with progressive disease. The tolerance of second-line treatment was generally mild to moderate and easy to treat. Our data suggest that the combination of oxaliplatin, CPT-11 and MMC in patients with metastatic colorectal cancer pretreated with 5-FU-based chemotherapy is feasible and has substantial antitumor activity. Further evaluation of this regimen seems warranted.

Key words: Colorectal cancer, irinotecan, mitomycin C, oxaliplatin.

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Introduction

Advanced colorectal cancer remains a therapeutic challenge to clinicians involved in the management of this common malignant disease, which continues to be the second leading cause of cancer death in the Western world.[1] Despite intensive efforts to improve the poor prognosis of patients with advanced colorectal cancer, therapeutic progress has been hampered by its apparent chemotherapeutic refractoriness. Although randomized trials have established with reasonable certainty that 5-fluorouracil (5-FU)/leucovorin (LV)-based chemotherapy results in substantive therapeutic gain when compared to either best supportive care[2,3] or treatment with 5-FU alone,[4,5] there is considerable room for further improvement in terms of response rates and tolerability of treatment. Until now, it has not been possible to define an optimal second-line chemotherapy in patients with advanced colorectal cancer after progression under or after 5-FU-based first-line chemotherapy.

Recently, new drugs have been developed, some of which have demonstrated promising activity not only in chemotherapy-naive, but also in 5-FU-pretreated patients.[6,7] Most notable among these new drugs are oxaliplatin and irinotecan (CPT-11). In treating patients with advanced or metastatic colorectal cancer, the third platinum complex oxaliplatin has not been associated with renal toxicity or with alopecia, and has produced minimal hematotoxicity. Nausea, vomiting and diarrhea are the main acute side effects, and dose-limiting toxicity consists of a cumulative sensory peripheral neuropathy exacerbated by exposure to cold.[8,9] When used as a single

agent, oxaliplatin was described to achieve a 10% objective response rate in three phase II trials involving a total of 139 patients with metastatic colorectal cancer previously treated with 5-FU.[10,11]

CPT-11, a semi-synthetic camptothecin derivative, is now available in many countries for second-line therapy in metastatic colorectal cancer. The response rate in the European study of patients with metastatic colorectal cancer was found to be 14% with a median duration of response of 8.5 months.[12] There was also a high rate of disease stabilization (44%), with a median duration of 4.8 months. Median survival time was 10.4 months.[12] Dose-limiting toxicities (DLT) for CPT-11 are delayed diarrhea and neutropenia, both of which are schedule-dependent and non-cumulative.[12]

Mitomycin C (MMC) is a cytotoxic antibiotic and was found to achieve a 10–15% objective response rate as a single agent in patients with metastatic colorectal cancer.[13,14] DLT for MMC is hematotoxicity and nausea/vomiting.[13,14]

On the basis of synergistic activity observed *in vitro* with oxaliplatin and an active metabolite of CPT-11[15] termed SN-38, a number of phase I studies using these two chemotherapeutic agents have been initiated which have produced encouraging response responses. Recently, a phase II evaluation of the activity and tolerance of oxaliplatin and CPT-11 in patients who had prior palliative 5-FU-based first-line chemotherapy[16] was conducted. The data suggested that the two-drug combination had substantial antitumor activity with an overall response rate of 42% combined with modest overall toxicity.

Due to *in vitro* synergistic activity of platinum analogs, SN38 and MMC,[17] and preliminary encouraging response data in our own pilot phase I series, we have now performed a phase II study to evaluate the activity and tolerance of a three-drug combination consisting of oxaliplatin, CPT-11 and MMC in patients with advanced or metastatic 5-FU/LV-resistant colorectal cancer.

Patients and methods

Patient population

This phase II study is a prospective evaluation including patients who had to have developed progressive disease from advanced or metastatic colorectal cancer while receiving or within 6 months of discontinuing first-line chemotherapy with 5-FU plus LV. As defined in the original study protocol, patients eligible for second-line treatment with oxaliplatin, CP-11 and MMC had to have histologically confirmed metastatic or recurrent colorectal cancer with at least one bidimensionally measurable lesion, a WHO performance status score of 0–3, an adequate bone marrow reserve (leukocyte count $>3500/\mu l$ and platelet count $>100\,000/\mu l$), adequate renal (serum creatinine concentration $<132\ \mu mol$) and hepatic functions (serum bilirubin level $<34\ \mu mol/l$ and serum transaminase level <100 IU/l). Informed consent according to institutional regulations was obtained from all patients before study entry. Patients with serious or uncontrolled concurrent medical illness or with central nervous system metastases were not eligible for treatment.

Treatment protocol

Cytotoxic chemotherapy consisting of oxaliplatin (Eloxatin®; Debiopharm, Charenton le Pont, France) 80 mg/m^2 administered as a 2 h i.v. infusion on therapeutic day 1 followed by CPT-11 (Campto®; RPR, Paris/Antony, France) 80 mg/m^2 given as a 1.5-h i.v. infusion also on therapeutic day 1. MMC ('Kyowa'®; Ebewe, Unterach, Austria) 6 mg/m^2 was administered as 20 ml i.v. bolus injection on day 15. Treatment courses were repeated every 4 weeks for a total of six courses unless there was prior evidence of progressive disease. All cytotoxic agents were given at the time of relapse (defined as progression of measurable tumor of at least 25% in size or the appearance of new metastases). Concomitant medications routinely given before cytotoxic drug administration included 8 mg ondasetrone and 8 mg of dexamethasone. Specific guidelines for treatment of delayed diarrhea were provided which recommended 2 mg of loperamide every 2 h if more than 12 h had passed after the last loose stool. If severe cholinergic symptoms were observed during or after irinotecan infusion, 0.25 mg of atropine given as a s.c. injection was recommended and prophylactically administered during subsequent course. In patients who had experienced WHO grade 3 or 4 toxicity during second-line treatment, dosage was reduced by 20%. Treatments were to be delayed weekly if patients had not recovered from toxicity.

Treatment evaluation

Prior to initiating second-line therapy with oxaliplatin, CPT-11 and MMC, all patients were assessed by physical examination, routine hematology and biochemistry analyses, chest X-ray, and computed tomographic scan of the abdomen and pelvis. Complete blood cell counts were repeated every 14 days during chemotherapy; all other adverse reactions were recorded and graded for severity before the

next treatment cycle. Measurable disease was reassessed every 12 weeks according to WHO standard criteria.[18] Objective responses on second-line therapy had to be confirmed in one subsequent examination after a 4 week interval, and were reviewed by an independent panel of oncologists and radiologists. The primary efficacy endpoint was response rate, and second efficacy endpoints included the duration of response (measured from the onset of the best response to the date of disease progression), time to treatment failure (defined as the time from start of second-line therapy to progression or relapse) and overall survival. Data were calculated using the Kaplan–Meier method.[19]

Results

Patients' characteristics

Between March 1998 and August 1999, a total of 10 patients were entered into this protocol. Patients' characteristics at the time of initiating second-line therapy are shown in Table 1. The patients' (two female and eight male) median age was 58 (range 38–63 years). Eight patients had WHO performance status of 2 or 3. The primary tumor site was colon in nine patients and rectum in one. The predominant sites of metastases were liver in nine, lung in five, abdominopelvic mass in one and lymph nodes in two patients. Six patients had multiple metastases involving two or more organ systems. All patients had developed progressive disease from advanced or metastatic colorectal cancer while or after receiving i.v. continuous first-line chemotherapy with 5-FU/LV (n=9) or 5-FU/LV/mitoxantrone (n=1). One patient with rectal cancer had received prior pelvic radiation therapy (20 Gy). Second-line treatment with oxaliplatin, CPT-11 and MMC was started within 2 months after first-line treatment failure (n=3), and within 6 months after discontinuing first-line treatment in case of disease progression after achieving partial response (PR) (n=3) or stable disease (SD) (n=4), respectively. A total of 42 (median 3.5; range 2–6) treatment cycles were administered for second-line therapy. All 10 patients were evaluable for response and toxicity.

Table 1. Patient characteristics

	N
No. of patients	10
Sex	
male	8
female	2
Age (years)	
median	57.9
range	38–63
WHO performance status	
0–1	2
2–3	8
Location of primary tumour	
colon	9
rectum	1
Histologic grading	
1	1
2	2
3	7
Location of metastases	
liver	9
lung	5
abdominopelvic mass	1
lymph nodes ± bone	2
No. of metastatic sites	
single	4
multiple	6
Surgery	
right hemicolectomy	4
sigma-resection	4
abdominoperineal resection	2
Radiotherapy	
20 Gy	1
First-line chemotherapy	
5-FU + LV	9
5-FU + LV + Novantron	1

Table 2. Response by prior treatment response

Response to first-line treatment	No. of patients	PR	NC	PD
		No. (%)	No. (%)	No. (%)
CR	–	–	–	–
PR	3	2 (20)	1 (10)	–
SD	4	1 (10)	1 (10)	2 (20)
PD	3	–	–	3 (30)
Total	10	3 (30)	2 (20)	5 (50)

Antitumor responses

Three patients had a PR after second-line chemotherapy with a median duration of 4.6 (range 2–9.7) months yielding an overall response rate of 30%. Two patients (20%) had a SD with a duration of 3 and 5 months, respectively, and five patients (50%) had progressive disease (PD). As shown in Table 2, second-line chemotherapy in the three patients who had achieved complete remission (CR) under previous first-line 5-FU/LV-based chemotherapy resulted in two PR and one SD, respectively. Among the four patients who had experienced SD after first-line chemotherapy, one presented with another PR, one had SD and two patients were rated progressive. Three patients with

PD after first-line therapy displayed also PD after second-line therapy. The median time to second treatment failure (indicated by progression of disease) was 7.1 (range 2–12.2) months.

Survival

Median overall survival duration has not been reached yet, and exceeds 14.4 (range 11.7–50.9+) months from the start of palliative first-line chemotherapy and 7.2 (range 3–23.5+) months measured from the beginning of second-line chemotherapy which is the subject of the current report. Currently, four patients are alive with PD.

Toxicity

Table 3 shows worst-ever toxicity patterns noted in all 10 patients who received second-line therapy. The most common treatment-associated toxic effect was myelosuppression. Leukopenia and granulocytopenia occurred both in seven (70%) patients, but grade 3 leukopenia in one (10%) patient only. The median nadir WBC count was 6.233 (range 1.900–32.700)/μl. The variations in granulocyte counts paralleled those of WBCs, and the median nadir count was 3.050 (range 1.200–15.800)/μl. Thrombocytopenia was noted in a total of two patients, but was rated severe (grade 3) in only one (10%). No bleeding episodes occurred. Mild anemia was recorded in three patients (30%). Non-hematologic side effects were generally mild to moderate, always fully reversible and easy to treat. Severe adverse reactions included grade 3 emesis and diarrhea, in two patients and one patient, respectively. Minimal alopecia was noted in three cases (30%). No treatment-related deaths were observed.

Three patients (30%) had at least one treatment delay of 1 week at some time during therapy and the total of delayed courses was three (7%). The reasons for treatment delay were patients' request unrelated to disease or treatment (one cycle), leukocytopenia/thrombocytopenia (one cycle) and diarrhea (one cycle). Only two patients had a 20% dose reduction of cytotoxic drugs during treatment according to the study protocol, because of grade 3 granulocytopenia plus thrombocytopenia plus emesis (n=1) and emesis plus diarrhea (n=1).

Table 3. Toxicity during second-line therapy (n=10)

Toxicity	WHO grade			
	1	2	3	4
Leukopenia	–	6	1	–
Granulocytopenia	4	3	–	–
Thrombocytopenia	1	–	1	–
Anemia	1	2	–	–
Nausea/emesis	–	5	2	–
Diarrhea	–	6	1	–
Alopecia	3	–	–	–

Discussion

Recent results of controlled trials have overcome the controversial issue whether patients with advanced colorectal cancer should be treated by palliative chemotherapy. This is due to observations that despite a low objective response rate, about half of patients seem to derive benefit from 5-FU/LV-based chemotherapy in terms of progression-free and total lifetime, but foremost in quality of life.[2,3] It seems obvious that this improvement should be achieved with minimal toxicity and time spent in the hospital.

Thus, several recent trials have evaluated the therapeutic value and toxicity of new agents including oxaliplatin, CPT-11, raltitrexed and capecitabine as single agents or as part of polychemotherapeutic regimens in patients with advanced colorectal cancer progressing under or within 6 months after first-line 5-FU-based chemotherapy.[16,20–25] Objective responses were achieved in 20 and 24% of patients, respectively, in two small trials of first-line oxaliplatin monotherapy and in about 10% of patients given the drug as a second-line option.[20] Another oxaliplatin-based second-line treatment for advanced colorectal cancer consisted of oxaliplatin (50 mg/m^2 by 2 h i.v. infusion) followed by LV (500 mg/m^2 as 2 h i.v. infusion) and 5-FU (2500 mg/m^2 as 24 h continuous i.v. infusion) on days 1, 8, 15, 22, 29 and 36.[21] The regimen was repeated every 50 days. Out of 32 patients, 53% developed grade 3 or 4 diarrhea. Due to this side effect, only 29% of cycles were given with at least 90% of the planned dose of 5-FU. Hematologic toxicity included grade 3 neutropenia and thrombocytopenia (10% for each) and grade 4 thrombocytopenia (3%). Two patients (6%) died of septicemia, one related to neutropenia and one to urinary tract infection, respectively. The objective response rate was 13%, median time to progression only 3 months and median survival only 9 months from the start of second-line therapy. The efficacy of combination chemotherapy with oxaliplatin (85–140 mg/m^2) and raltitrexed (3 mg/m^2) administered on therapeutic day 1 and repeated every 3 weeks has been evaluated in 69 patients with measurable metastatic colorectal cancer in a phase I/II trial.[22] This regimen resulted in an

objective response rate of 42% with an additional 48% of patients achieving SD. Median response duration, time to progression (longer than 7.5 months) and survival time (with 84% of all 69 patients currently being alive) have not been reached, yet. Overall, dose-limiting toxicities included grade 3 increase in transaminases, diarrhea, stomatitis, grade 3 infection and polyneuropathy, grade 3 asthenia, amaurosis fugax, and neutropenia grade 4. Toxicities were most often observed in patients treated with the highest dose level.

Raltitrexed (2 mg/m^2 administered as 15 min infusion on therapeutic day 2) was also combined with CPT-11 (180 mg/m^2 administered as 90 min infusion on day 1) in 23 heavily pretreated patients enrolled in a bi-weekly regimen by Garcia *et al.*[23] Adverse events consisted of toxicity grade 3–4 nausea and vomiting, diarrhea, anemia, and neutropenia but no objective responses were observed, although treatment led to SD in 45% of patients. However, median time to progression was only 13 weeks. Raltitrexed (3.0 mg/m^2) and MMC (6 mg/m^2), both given on day 1 repeated every 28 days in 13 patients, resulted in PR in 16% and SD in 39% of patients, respectively, and median response duration and overall survival in this well-tolerated regimen were 7 and 8 (3–13+) months, respectively.[24]

Hoff *et al.* evaluated the efficacy of orally administered capecitabine (2500 mg/m^2/day in two equally divided doses × 14d, q3 weeks) in patients with metastatic colorectal cancer who had failed treatment with i.v. bolus 5-FU.[25] Six of 19 (32%) patients experienced SD. Serious therapy-related adverse events included nausea, vomiting, abdominal pain and diarrhea.

In agreement with the study rationale and *in vitro* evidence of a synergistic activity of oxaliplatin and CPT-11[15] as well as cisplatin, SN-38 (an active metabolite of CPT-11) and mitomycin C,[17] therapeutic results and toxicities achieved in this phase II study compare favorably with the above results and suggest an encouraging antitumor activity of oxaliplatin, CPT-11 and MMC in patients with advanced or metastatic colorectal cancer pretreated with 5-FU/LV-based chemotherapy. Three patients had PR after second-line chemotherapy with a median duration of 4.6 (range 2–9.7) months, yielding an overall response rate of 30%. Two patients (20%) had SD with a duration of 3 and 5 months, respectively, and five patients (50%) had PD. The median overall survival duration has not been reached yet, and currently exceeds more than 14.4 (range 11.7–50.8+) months from the start of palliative first-line chemotherapy and more than 7.1 (range 3–23.5+) months from the beginning of second-line therapy. A possible advantage of the investigated combination regimen might represent its fairly good tolerance, when compared with another clinical trial using oxaliplatin 85 mg/m^2 on days 1+15 and CPT-11 80 mg/m^2 on days 1+8+15 every 4 weeks.[16] Myelotoxicity was commonly observed in the latter study necessitating the use of granulocyte colony stimulating factor which was administered to 31 out of 36 patients during 81 out of 174 chemotherapy courses depending on absolute neutrophil count, thus resulting in only few cases of granulocytopenia grade 3 or 4 which occurred in five and two cases, respectively.

In the present study, the most frequent non-hematologic adverse reactions were nausea/emesis and diarrhea which were rated as severe in 17 and 19%, respectively. In contrast, severe hematologic and non-hematologic side effects were noted in only two patients (20%) who required a 20% dose reduction of cytotoxic drugs during treatment according to the study protocol. This was probably due to the lower total dose of oxaliplatin and CPT-11 per course when combined with MMC.

Conclusion

In conclucion, our results suggest that this regimen may be recommended and used as effective regimen in patients with advanced or metastatic colorectal cancer pretreated with 5-FU-based chemotherapy. This combination chemotherapy consisting of oxaliplatin, CPT-11 and MMC should be investigated further in a randomized trial in patients with refractory disease.

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