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FOLFOX3 in heavily pretreated patients with metastatic colorectal cancer

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ABSTRACT

Background: The combination of oxaliplatin, 5-fluorouracil (5FU) and leucovorin (LV) has shown to be active and safe as first- or second-line chemotherapy for metastatic colorectal cancer (MCC).

Patients and Methods: The outcome of patients with MCC who had progressive disease after at least two lines of palliative chemotherapy and who were subsequently treated with oxaliplatin, 5FU and LV was reviewed. Patients received FOLFOX3 consisting of oxaliplatin (85 mg/m²) on day 1, LV (500 mg/m²) as a two-hour infusion on days 1 and 2, and 5FU (3000 mg/m²) as a 46-hour infusion starting on day 1 in a cycle of two weeks.

Results: A total of 28 patients were treated with a median number of 9.5 cycles (range 1-24) at a mean dose intensity of 73%. Six patients discontinued treatment due to toxicity, of whom three had sensory neuropathy grade 2. Six patients experienced grade 3 toxicity: nausea (1), vomiting (1), diarrhoea (1), leucopenia (2) and thrombocytopenia (1); grade 4 toxicity was not observed. Twenty-five patients were evaluable for response, of whom four achieved a partial response (response rate 14%, based on intention to treat). The median progression-free survival was 5.8 months and the median overall survival was 8.5 months.

Conclusion: For heavily pretreated patients with MCC, the FOLFOX3 regimen is a fairly safe and effective treatment.

INTRODUCTION

In Western countries colorectal cancer is the second most common cause of cancer mortality. Approximately half of all colorectal cancer patients ultimately die of progressive metastatic disease. In the Netherlands, colorectal cancer was diagnosed in 8200 patients in 1998, resulting in 4200 deaths.[1] As compared with best supportive care, chemotherapy may result in improved survival and delay of onset of tumour-related symptoms of advanced colorectal cancer.[2] For decades, systemic treatment has consisted of 5-fluorouracil (5FU) and leucovorin (LV). Nowadays, the introduction of new agents, such as irinotecan, oxaliplatin and oral fluoropyrimidines, has expanded the therapeutic options for patients with metastatic colorectal cancer (MCC). Oxaliplatin is a member of the platinum family, inhibiting DNA replication and transcription through the formation of DNA adducts. Oxaliplatin is active in colorectal cancer both as a single agent and in combination with other anticancer agents. As a single agent in second-line therapy, partial responses and stable disease were reported in 10 to 11% and 24 to 42% of patients, respectively. Median progression-free survival (PFS) was 4.6 to 4.8 months and median overall survival (OS) was 8.5 to 10 months. Oxaliplatin in combination with 5FU and LV as first-line therapy resulted in promising response rates (RR) of 51 to 58%, a median PFS of 8.0 to 9.8 months, and a median OS of 16.2 to 19.9 months. The same combination as second-line therapy after 5FU showed an RR of 20 to 45%, a median PFS of 4.6 to 7 months and a median OS of 10 to 17 months.[3]

Thus far, various regimens with oxaliplatin, 5FU and LV have been investigated, consisting of weekly, two-weekly and three-weekly schedules, using different 5FU infusion schedules (bolus and/or continuous infusion) at constant or chronomodulated rates, and at different doses. The French group of De Gramont *et al.*[4] reported the results

of FOLFOX2, consisting of a regimen of oxaliplatin and LV as a two-hour infusion on day 1, followed by a 46-hour continuous infusion of 5FU, every two weeks.[4] Other groups have investigated various FOLFOX regimens in phase II studies, using a similar time schedule as in FOLFOX2, but at different doses.[3] A large randomised study by Goldberg *et al*. in 795 previously untreated MCC patients has recently shown improved survival for FOLFOX4 over the combination of irinotecan and bolus 5FU with leucovorin.[5] The optimal way of combining oxaliplatin with 5FU/LV has, however, not yet been established.[6]

Oxaliplatin was registered for MCC in the Netherlands in 1999. At that time, we started using oxaliplatin for pretreated MCC patients in a FOLFOX3 schedule, based on two studies by Andre *et al*.[7,8] To investigate the efficacy and safety of this regimen as (at least) third-line chemotherapy, we retrospectively reviewed the charts of patients treated at our institute.

PATIENTS AND METHODS

Patients

The charts of all patients with MCC at our hospital who were treated with FOLFOX3 after having progressed on at least two previous lines of palliative chemotherapy were reviewed. The diagnosis of MCC had been made by histological evidence of adenocarcinoma of the colon or rectum. The patient's history, a physical examination including the performance status, a chest X-ray, a CT scan of the abdomen, blood chemistry and a complete blood cell count were assessed at baseline.

Treatment

Chemotherapy consisted of oxaliplatin (85 mg/m^2) with LV (500 mg/m^2) as a two-hour infusion on day 1, immediately followed by 5FU (3000 mg/m^2) as a 46-hour continuous infusion and LV (500 mg/m^2) as a two-hour infusion on day 2 in a cycle of two weeks (the FOLFOX3 regimen). Treatment was given until progression or the occurrence of unacceptable toxicity. Standard antiemetics consisted of ondansetron and dexamethasone, both given intravenously at a dose of 8 mg 30 minutes prior to chemotherapy. In general, chemotherapy was postponed for one week if the leucocyte count was $<3.0 \times 10^9$/l, the platelet count was $<100 \times 10^9$/l or if toxicity was >grade 2. In case of persisting toxicity >grade 1, the oxaliplatin dose was reduced by 80% in further cycles.

Evaluation

Prior to each cycle of chemotherapy, a physical examination and a complete blood cell count were performed and toxicity was assessed. Blood chemistry, including renal and hepatic function and carcinoembryonic antigen (CEA), were measured in each cycle. CT scans of metastatic lesions were performed every two to three months and in case of clinical deterioration.

Tumour response was assessed according to the RECIST criteria. Toxicity was graded according to the Common Toxicity Criteria of the National Institutes of Health/National Cancer Institute, version 2.0.

RESULTS

This review identified 28 colorectal cancer patients at our institute who were treated according to the FOLFOX3 regimen after at least two lines of chemotherapy for metastatic disease. All patients started FOLFOX3 therapy between December 1999 and August 2002. Patient characteristics are shown in *table 1*. Of notice, all patients received 5FU as part of prior chemotherapy (25 received a 5-FU/LV regimen), while 26 patients were treated with irinotecan. None of the patients were pretreated with oxaliplatin. For three patients FOLFOX3 was the sixth line of therapy. In spite of extensive pretreatment, most patients (75%) had a World Health Organisation (WHO) performance status of 0 to 1.

Table 1
Characteristics of colorectal cancer patients treated with FOLFOX3

PATIENT CHARACTERISTICS	NUMBER OF PATIENTS
No. evaluable	
For response	25
For toxicity	28
Age	
Median	53 years
Range	32-72 years
Gender	
Male	18
Female	10
Primary tumour	
Colon	21
Rectum	7
Site of metastases	
Liver	25
Lung	14
Other	12
No. of involved sites	
1	10
2	8
>2	10
WHO performance score at start	
0-1	21
2	6
3	1
No. of lines of prior chemotherapy	
2	11
3	10
4	4
5	3

Toxicity

All patients were evaluable for toxicity. A total of 254 cycles was analysed with a median number of 9.5 cycles administered per patient (range 1-24). The maximum toxicities occurring per patient are listed in *table 2*. In six patients toxicity caused discontinuation of therapy. Three patients stopped because of grade 2 sensory neuropathy (after 9, 11 and 11 cycles, respectively), while one patient developed angina pectoris during the 5FU infusion. The infusion was aborted in this patient, who also suffered from pre-existing heart disease. At a second gift using a prolonged infusion time, a similar reaction prevented further therapy. One other patient developed an idiosyncratic reaction in the tenth cycle, and therapy was stopped. One patient developed a transient ischaemic attack, which might have been due to 5FU.

Table 2

Worst toxicities in 28 patients treated with FOLFOX3 (all cycles)*

	PATIENTS (N) PER GRADE			
TOXICITY	**0**	**1**	**2**	**3**
Nausea	10	13	4	1
Vomiting	15	10	2	1
Stomatitis	20	5	3	0
Diarrhoea	16	5	6	1
Sensory neuropathy	9	13	6	0
Alopecia	24	1	3	0
Laryngeal spasm	27	1	0	0
Anaemia	2	17	9	0
Leucopenia	14	4	8	2
Thrombocytopenia	6	19	2	1

**No grade 4 toxicity was observed.*

Grade 4 toxicities and neutropenic fever did not occur. Six patients experienced grade 3 toxicity: nausea (1), vomiting (1), diarrhoea (1), leucopenia (2) and thrombocytopenia (1). Myelosuppression was mild, with a grade 3 leucopenia occurring in only two patients after 11 and 9 cycles, respectively. One of these patients started with a grade 2 leucopenia due to previous chemotherapy. One patient developed grade 1 hand-foot syndrome during one cycle. Due to dose delay and/or dose reduction, only 21% of the patients received >90% of the scheduled oxaliplatin dose intensity during therapy. On average, patients received 73% of the scheduled oxaliplatin and 5FU dose.

Response

Twenty-five out of 28 patients were evaluable for response (*table 3*). Within two weeks after the start of therapy, one patient developed symptomatic brain metastases. Two patients had to discontinue treatment early because of a transient ischaemic attack (after one cycle) and recurrent pectoral angina (after two cycles), respectively.

A total of four partial responses were observed (RR 14%, 95% CI 4-33%, based on intention to treat), while stable disease occurred in 14 patients (50%). The median PFS was 5.8 months (95% CI 4.8-6.7) and the median OS was 8.5 months (95% CI 6.4-10.5).

Table 3

Response rates of colorectal cancer patients treated with FOLFOX3

TUMOUR RESPONSE	**N**	**%**
Partial response (PR)	4	14
Stable disease (SD)	14	50
Progressive disease	7	25
Nonevaluable	3	11
Responses	4	14
In patients with 2 prior lines of CT	1	
In patients with 3 or more lines of CT	3	

CT = chemotherapy.

DISCUSSION

The results of this retrospective analysis of the FOLFOX3 regimen indicate that the combination is well tolerated and modestly active in heavily pretreated patients with advanced colorectal cancer. All patients had previously received a 5FU-containing regimen, and all but two had received irinotecan as another line of therapy. Of notice, most patients in this study had a good performance status, which may account for the observed feasibility of this regimen in the third line. Thus far, only one preliminary Spanish study has described the outcome of FOLFOX3 as third-line chemotherapy.[9] This Spanish study reported an RR of 8.6% in 23 treated patients, stable disease in 43% of patients and a median OS of 8.0 months. These results are quite similar to our series. Likewise, a majority of 76% of the patients had a good performance status. In contrast, 14 grade 3-4 toxicities (61%) and one toxic death were reported.

FOLFOX3 as second-line therapy has been investigated in two studies in patients with MCC refractory to 5-FU/LV.[7,8] Andre *et al.* treated 30 patients who had progressed on 5FU/LV after which oxaliplatin was added to the same regimen.[7] They reported an RR of 20% and stable disease in 50%. The median PFS was 6.1 months and the median OS was 13.3 months. Neutropenia grade 3-4 occurred in 20% of the patients. The main toxicity was sensory neuropathy (90%), of which 13% was grade 2. In another study, the same authors treated 40 patients with second-line FOLFOX3

after 5FU/LV.[8] They reported an RR of 18.4%, stable disease in 37% of patients, a median PFS of 4.6 months, and a median OS of 10.6 months.[8] Again, the main toxic effects were sensory neuropathy (95%), of which 27.5% were grade 3. Grade 3-4 neutropenia was rare (15%). Grade 1-2 skin toxicity (hand-foot syndrome) was observed in three patients. As can be expected, the outcome of FOLFOX3 after pretreatment with only 5FU/LV is slightly better in terms of RR and OS when compared with data from FOLFOX3 as third-line treatment in our patients. The median PFS and toxicity scores, however, were similar to our results.

In contrast to the FOLFOX3 schedule, the FOLFOX4 regimen consists of a similar dose of oxaliplatin (85 mg/m^2) with LV (200 mg/m^2) as a two-hour infusion, followed by 5FU 400 mg/m^2 bolus intravenously and 5FU (600 mg/m^2) as a 22-hour infusion on day 1, and the same therapy, without oxaliplatin, on day 2 of a two-weekly schedule. In a recent study by Rothenberg *et al.*, FOLFOX4 was administered to 152 patients with progressive MCC after first-line treatment consisting of the combination of irinotecan and bolus 5FU/LV (IFL schedule).[10] The group reported an RR of 9.9%, stable disease in 59.9% of patients and a median PFS of 4.6 months. Of note, 73% of patients treated with FOLFOX4 developed grade 3-4 adverse events, including 44% grade 3-4 neutropenia and 6% neutropenic fever. Although the efficacy of the FOLFOX4 schedule was similar to the results observed in our patients, the toxicity profile of FOLFOX4 was much more pronounced. We observed a grade 3-4 adverse event in only six patients (21%). Although the total dose of 5FU is lower than in FOLFOX3, the higher incidence of toxicity in the less pretreated FOLFOX4 group might be due to bolus 5FU infusion and/or a higher administered dose intensity (88% of the planned dose). As previously mentioned, the best FOLFOX regimen in terms of safety and efficacy has not yet been established. In a nonrandomised fashion, FOLFOX3 and FOLFOX4 after prior 5FU/LV therapy were compared by Andre *et al.*[7] FOLFOX4 resulted in an RR of 23.5%, a median PFS of 5.1 months and a median OS of 11.1 months, which did not differ significantly from FOLFOX3. With regard to toxicity, however, neutropenia was observed more frequently in FOLFOX4 than in FOLFOX3, with grade 3-4 neutropenia in 36.9 *vs* 15% of patients, respectively (p=0.02). Of notice, any differences in toxicity as observed in various phase II studies may be due to patient selection and FOLFOX3 and FOLFOX4 have never been compared head to head in a randomised trial.

In the palliation of heavily pretreated patients the choice of chemotherapy should not only be based on efficacy, but on the toxicity profile as well. This retrospective analysis shows that FOLFOX3 is a fairly safe and effective regimen for heavily pretreated MCC patients who have a good performance score. Currently, the oral 5FU prodrug capecitabine (Xeloda) is being combined with oxaliplatin (XELOX),[11,12] which might replace FOLFOX3 in those patients without gastrointestinal symptoms from MCC.

REFERENCES

1. Dijck JAAM van, Coebergh JWW, Siesling S, Visser O (editors): Trends of cancer in the Netherlands 1989-1998. Utrecht: Vereniging van Integrale Kankercentra, 2002.
2. Colorectal Cancer Collaborative Group. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. Br Med J 2000;321:531-5.
3. Carrato A, Gallego J, Diaz-Rubio E. Oxaliplatin: results in colorectal carcinoma. Crit Rev Oncol Hematol 2002;44:29-40.
4. Gramont A de, Vignoud J, Tournigand C, et al. Oxaliplatin with high-dose leucovorin and 5-fluorouracil 48-hour continuous infusion in pretreated metastatic colorectal cancer. Eur J Cancer 1997;33:214-9.
5. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluouracil plus leucovorin, irinotecan and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004;22:23-30.
6. Maindrault-Goebel F, Louvet C, Andre T, et al. Oxaliplatin added to the simplified bimonthly leucovorin and 5-fluorouracil regimen as second-line therapy for metastatic colorectal cancer (FOLFOX6). Eur J Cancer 1999;35:1338-42.
7. Andre T, Louvet C, Raymond E, Tournigand C, Gramont A de. Bimonthly high-dose leucovorin, 5-fluorouracil infusion and oxaliplatin (FOLFOX3) for metastatic colorectal cancer resistant to the same leucovorin and 5-fluorouracil regimen. Ann Oncol 1998;9:1251-3.
8. Andre T, Bensmaine MA, Louvet C, et al. Multicenter phase II study of bimonthly high-dose leucovorin, fluorouracil infusion, and oxaliplatin for advanced metastatic colorectal cancer resistant to the same leucovorin and fluorouracil regimen. J Clin Oncol 1999;17:3560-8.
9. Abon G, Munoz, A, Rubio I, et al. Third line oxaliplatin with leucovorin and continuous infusion 5-fluorouracil in metastatic colorectal cancer. Ann Oncol 2000;11(Suppl 4):48 (abstract).
10. Rothenberg ML, Oza AM, Bigelow RH, et al. Superiority of oxaliplatin and 5-fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. J Clin Oncol 2003;21:2059-69.
11. Borner MM, Dietrich D, Stupp R, et al. Phase II study of capecitabine and oxaliplatin in first- and second-line treatment of advanced or metastatic colorectal cancer. J Clin Oncol 2002;20:1759-66.
12. Scheithauer W, Kornek GV, Raderer M, et al. Randomized multicenter phase II trial of two different schedules of capecitabine plus oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2003;21:1307-12.