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Nordic 5-Fluorouracil/Leucovorin Bolus Schedule Combined with Oxaliplatin (Nordic FLOX) as First-line Treatment of Metastatic Colorectal Cancer

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This study combined oxaliplatin with the Nordic bolus schedule of 5-fluorouracil (5-FU) and folinic acid (FA) as first-line treatment in metastatic colorectal cancer. Twenty-seven patients were treated every second week with oxaliplatin 85 mg/m^2 as a 2-h infusion on day 1, followed by a 3-min bolus injection with 5-FU 500 mg/m^2 and 30 min later a bolus injection with FA 60 mg/m^2 given on days 1 and 2. Seventeen patients achieved a complete (n = 2) or partial (n = 15) response, leading to a confirmed response rate of 63% (95% CI 45–81%). The estimated median times to progression and survival were 8.9 and 18.7 months, respectively. Neutropenia grade 3–4 toxicity was seen in 63% of patients, neuropathy grade 3 in one patient and grade 2 in 12 patients. Oxaliplatin combined with the bolus Nordic schedule of 5-FU/FA (Nordic FLOX) appears to be well tolerated, effective and feasible as first-line treatment of metastatic colorectal cancer yielding results comparable with those obtained by more complex schedules.

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5-Fluorouracil (5-FU) and folinic acid (FA, Leucovorin®) have an established role in the treatment of advanced colorectal cancer, and this has until the year 2000 been considered the standard combination for most patients. A wide variety of 5-FU regimens with either low-dose or high-dose FA have been used. 5-FU has been given either as a bolus injection or a continuous infusion or a combination of both (de Gramont schedule), as well as according to chronomodulated schedules (1). A plateau seems, however, to have been reached with fluorouracil, giving objective response rates of up to 30–40% with a variety of modulators. An adequate meta-analysis has elicited a statistically significant survival advantage, although of limited clinical relevance (1 month) for continuous infusion when compared to bolus administration of 5-FU in first-line treatment of colorectal cancer patients (2). However, subgroup analysis showed that when 5-FU was modulated by FA, no significant difference was found by comparing patients assigned to continuous infusion or 5-FU bolus. High-dose continuous schedules and hybrid regimens are commonly used in Europe, with consistently higher response rates and longer progression-free and overall survival times than the bolus regimens. Modulated bolus regimens have been the reference treatment in the US and in the Nordic countries. Bolus injection may represent a more feasible treatment given the limited difference in therapeutic benefit and the greater institutional burden of administering continuous schedules. The Nordic FLv regimen consists of a short (3 min) bolus injection of 500 mg/m^2 5-FU followed by a bolus injection of 60 mg/m^2 FA 30 min later (3). The Nordic FLv regimen usually shows a response rate (RR) of 25–30%, a progression-free survival (PFS) of 6 months and a median survival of 10–12 months (3, 4). However, the Nordic schedule has never been formally compared in a large randomized trial with either the US bolus regimens or any of the infused regimens.

Trials using oxaliplatin in combination with different 5-FU regimens and FA as first-line treatment of metastatic colorectal cancer have consistently demonstrated a doubling in response rate and a significant increase in PFS compared to 5-FU/FA alone (5–7). Overall survival has been between 16 and 20 months. 5-FU has then usually been given as a chronomodulated 12-h infusion for 4 days or as a de Gramont schedule (usually 2-h bolus leucovorin, 5-FU bolus and 22-h continuous 5-FU infusion given for 2 consecutive days). These schedules are time-consuming and require infusional pumps. We therefore decided to investigate whether the addition of oxaliplatin to the simple

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Nordic schedule (FLv) could give similar results as the infused schedules. Adding CPT-11 (irinotecan) to the same Nordic schedule has exhibited encouraging results (8).

MATERIAL AND METHODS

Patient selection

All patients had prior histologically confirmed adenocarcinoma of the colon or rectum, with non-resectable metastatic disease. No prior treatment with chemotherapy other than adjuvant 5-FU-based chemotherapy completed at least 6 months before study entry was allowed. The patients were required to have bidimensionally measurable disease (defined as the presence of at least one index lesion capable of two-dimensional measurement by abdominal computed tomography (CT) scan or chest x-ray outside any irradiated volume and above 2 cm in greatest diameter). Eligibility criteria also included age between 19 and 75 years, a WHO performance status of 0–2, absolute neutrophil count $> 1.5 \times 10^9$/L and a platelet count $> 100 \times 10^9$/L, serum creatinine $< 1.5 \times$ UNL (upper normal limit), bilirubin $< 2 \times$ UNL and ASAT (aspartate aminotransferase) or ALAT(alanine aminotransferase) $< 3 \times$ UNL, unless with known liver metastasis where no upper limits were set. The Regional Ethics Committee of Western Norway approved the study. All patients provided written informed consent.

Treatment protocol

The study patients were given the Nordic 5-FU/FA bolus schedule combined with oxaliplatin (Nordic FLOX) as first-line treatment on a compassionate use basis. Eloxatin® was generously provided by Sanofi Winthrop. Patients received oxaliplatin 85 mg/m^2 as a 2-h infusion on day 1 followed by a 3-min bolus injection with 5-FU 500 mg/m^2 and 30 min later a bolus injection with FA 60 mg/m^2. 5-FU and FA were given days 1 and 2. The treatment was repeated every second week. Treatment was delayed if neutrophils were $< 1.5 \times 10^9$/L or platelets $< 100 \times 10^9$/L or until recovering from other grade 2 toxicity. In cases of febrile neutropenia, grade 4 thrombocytopenia or treatment delay > 2 weeks due to toxicity, the 5-FU dose was reduced by 20%. If paresthesias persisted between cycles, the next oxaliplatin dose was reduced by 25% and stopped if no improvement took place. Oxaliplatin was discontinued if paresthesia was associated with pain or functional impairment. Ondansetron 8 mg was given routinely on days 1 and 2 of each schedule. Subjective symptoms, body weight, physical examination, performance status, complete blood cell counts and all adverse reactions were recorded before the start of the next treatment cycle. Measurable lesions were reassessed by abdominal CT scan and chest x-ray after every fourth cycle or every second month in patients without treatment until progression was documented. Treatment was continued until disease progression, the occurrence of unacceptable toxicity, secondary surgery or the patient's own withdrawal.

Study endpoints

Response was calculated according to WHO criteria (9). A complete response (CR) required the complete disappearance of all objective evidence of the disease. A partial response (PR) was defined as reduction by $> 50\%$ in the sum of the products of the greatest perpendicular dimensions of measurable, bidimensional lesions. Progressive disease (PD) was defined as the enlargement of existing, measurable lesions by $> 25\%$ in the sum of the products of the greatest perpendicular dimensions or the development of new metastatic lesions. Stable disease (SD) was defined as any measurement that did not fulfil the criteria for CR, PR or PD. Toxicity grades were evaluated according to WHO criteria (9). The neurological toxicity induced by oxaliplatin was graded as follows: grade 1, paresthesias/dysesthesias of short duration with complete resolution prior to the next cycle; grade 2, paresthesias/dysesthesias persisting between two cycles without functional impairment; grade 3, paresthesias with functional impairment.

Statistical analyses

The analysis was performed with the Medlog Datapackage (Information Analyse Corporation, Crystal Bay, NV). The primary endpoint was response rate, calculated with the 95% confidence interval (CI). The secondary efficacy criteria were time to progression (TTP) and overall survival (OS). The times to event were analysed by the Kaplan–Meier method. Response rate, TTP, OS and safety analyses were performed on all patients according to the intention-to-treat principle.

RESULTS

Patient characteristics

The demographic and baseline disease characteristics are listed in Table 1. All patients were evaluable for response and toxicity assessment. Two of the patients had brain metastases, three had bone metastases. Four patients had received prior adjuvant treatment, six had prior surgery for metastatic disease. Median carcinoembryonic antigen (CEA) level was 78 µg/L (range 3–4120 µg/l).

Response to therapy

All 27 patients were evaluable. The overall response rate was 70% (95% CI 50.0–80.6%) including 3 CR (11%, 95% CI 8.8–32.9%) and 16 PR (59%, 95% CI 40.8–73.1%). Seven patients showed SD and one patient had PD. Seventeen of the 19 objective responses were confirmed by a second examination at least 4 weeks later, giving a confirmed response rate of 63% (95% CI 45–81%). Median TTP (from first day of treatment to progression) was 8.9

Table 1

Patients characteristics

	No. of patients
Gender	
Male	17
Female	10
Age (years) Median 59 (range 34–74)	
WHO performance status	
0	18
1	6
2	3
Primary site	
Right colon	7
Left colon	11
Rectum	9
Sites of metastases	
Liver	22
Lung	9
Soft tissue	10
Other	9
No. of metastatic sites	
1	12
2	9
≥3	6

(range 1.2–48+) months. Median survival (from first day of treatment to death) was 18.7 (range 1.8–48+) months. Two years after start of treatment, 48% of the patients were still alive (Fig. 1). Six patients (22%) who were initially unresectable became, after the chemotherapy, surgically resectable and underwent secondary curative surgery or radiofrequency ablation. The median survival of patients with an objective response was 26.5 months, significantly higher than the median survival of 12 months in patients with SD ($p = 0.03$).

Sixteen patients (60%) received second-line irinotecan-based chemotherapy at the time of progression. Six patients were alive at the time of this report, one of them without evidence of disease.

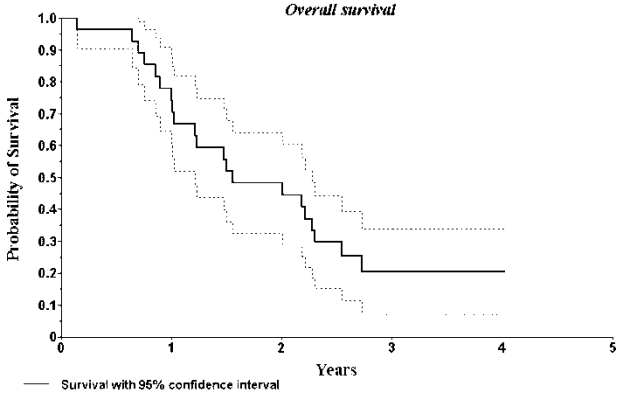

Fig. 1. Survival of patients treated by the Nordic FLOX regimen for metastatic colorectal cancer.

Toxicity

A total of 274 courses of chemotherapy with oxaliplatin were given (median 9 courses, range 2–16). Another 61 courses were given without oxaliplatin (range 0–14). Seventy-two (21%) courses were delayed, 21 patients had one or more delays of treatment, usually due to low-grade neutropenia or thrombocytopenia. Toxicity data are given in Table 2. Grade 4 neutropenia developed in seven patients (26%) and in 25 cycles (7%). Grade 3 neutropenia developed in another 10 patients (37%) and in 22 cycles (7%). Accumulated sensory neuropathy grade 2 was seen in 14 patients and grade 3 in one patient (totally 56%). Seven patients were hospitalized due to treatment-related toxicity (total admissions 10). The reasons for withdrawal from treatment were neuropathy (eight patients), progressive disease (seven patients), secondary surgery (six patients), lethargy (one) and acute transient dysartry (one). In four patients treatment had to be stopped because of an allergic reaction towards oxaliplatin after 8–10 courses of chemotherapy. Two of these allergic reactions consisted of an immediate severe thrombocytopenia and haemolysis (10). No treatment-related deaths occurred.

DISCUSSION

The objective of this study was to evaluate the efficacy of oxaliplatin combined with 5-FU plus low-dose FA, administered according to the Nordic schedule (3-min bolus injection for 2 days, every 2 weeks). This regimen is commonly used in Nordic patients with advanced colorectal cancer. Oxaliplatin was administered in a 85 mg/m^2 dose every 2 weeks as with the de Gramont schedule (6). The present study showed the combination regimen to be highly active with a confirmed response rate of 63%, a median TTP of 8.9 months and a median survival of 18.7 months. Our results are comparable with even the best results recorded when 5-FU and oxaliplatin are given chronomodulated or according to the de Gramont schedule. In phase III studies the chronomodulated schedule has shown a response rate of 47–53%, TTP of 6.4 months, PFS 7.8–8.7 months and OS of 15.9–19.4 months (5, 7). The FOLFOX-regimen based on the de Gramont schedule has in phase III

Table 2

Grade 2–4 toxicity data in 335 cycles after WHO criteria

	Grade 2	Grade 3	Grade 4
Thrombocytopenia	5 (2%)	1	
Neutropenia	2	25 (7%)	22 (7%)
Diarrhoea	5	1	
Neuropathy (accumulated)	14 (52%)	1	
Anaemia	4		
Stomatitis	1		
Nausea	2	1	
Allergic reaction	2	2	
Febrile neutropenia		1	

studies shown a response rate of 51%, PFS 9.0 months and OS 16.2 months (6). In attempts to avoid infusion pumps oxaliplatin has been combined with raltitrexed and capecitabine in phase II studies. Raltitrexed plus oxaliplatin exhibited an RR of 54%, PFS 6.3 and OS 14.6 (11). Capecitabine combined with oxaliplatin produced a response rate of about 50%, PFS 6–10 months and a median survival of 17.1 months (12, 13).

Data on oxaliplatin combined with a strict 5-FU bolus schedule (i.v. push) as first-line treatment in metastatic colorectal cancer are sparse. Oxaliplatin (130 mg/m^2) was administered together with daily × 5 bolus 5-FU and FA (Mayo Clinic regimen) in first-line treatment of colorectal cancer patients (14). The response rate was 45%, PFS 3.9 months, but the regimen was highly toxic and unfeasible due to a high level of myelosuppression and gastrointestinal toxicity. In the Intergroup N9741 study, a similar treatment arm was closed due to excessive toxicity (15). Ravaioli et al. (16) used a modified Machover schedule consisting of oxaliplatin 130 mg/m^2 every third week combined with 5-FU 350 mg/m^2 and leucovorin 20 mg/m^2 as a daily bolus for 5 days, every 21 days. Because of toxicity the 5-FU dose had to be reduced to 300 mg/m^2. They report an RR of 40%, PFS 5.9 months and median survival 14 months. Recently, Hochster et al. (17) combined biweekly oxaliplatin with weekly bolus fluorouracil and low-dose leucovorin in 42 patients, showing a response rate of 63%, a TTP of 9.0 months and a median survival of 15.9 months (17).

Patients obtaining an objective response in our study had longer overall survival compared to patients obtaining stable disease (26.5 months vs. 12 months). This is in accordance with prior observations. In patients with advanced colorectal cancer receiving 5-FU alone or modulated by FA or methotrexate, the survival advantage was median 11 months after a complete response, 6 months after a PR and 4 months after stable disease (18). An increase of 10–11% in response rate usually corresponds to 1 month increase in PFS and OS (19).

The combination of oxaliplatin with a bolus 5-FU/folic acid according to the Nordic schedule was well tolerated, safe and effective, and may offer the advantage of increased convenience and lower cost by the use of low doses of leucovorin. The main dose-limiting toxicity was cumulative sensory peripheral neuropathy, and more patients had to stop treatment because of neuropathy rather than actual progression of disease. Grade 2–3 neuropathy was seen in 56%, but this toxicity usually appeared after 8–10 courses of treatment and is more likely to reflect the number of courses given. In future, an intermittent strategy with a treatment break after eight courses may prove favourable (20). Grade 3–4 neutropenia was reported in 63% of the patients, but only one case exhibited neutropenic fever. The main consequence of neutropenia (and of a low-grade thrombocytopenia) was delay in treatment seen in 21% of the treatment cycles, usually of 1 week. Grade 3 diarrhoea was only seen in one patient and no grade 4 diarrhoea was seen. In the modified Machover schedule with oxaliplatin, grade 3–4 diarrhoea was observed in 29% of the patients, and grade 3–4 neutropenia in 20% (16). In the oxaliplatin groups incidences of grade 3–4 diarrhoea were reported in 35% of the constant rate treatment arm and 29% of the chronomodulated arm in the study of Levi et al. (7), 43% in the chronomodulated study of Giacchetti et al. (5) and 12% by de Gramont et al. (6). Grade 3–4 neutropenia was reported by Levi in 3% of the constant rate arm, and 8% of the chronomodulated arm, by Giachetti in 2% and by de Gramont in 42%. Neurotoxicity grade 2–3 was reported by Levi in 31% in the constant arm and in 16% in the chronomodulated arm, by Giacchetti in 46% and by de Gramont in 47%. The toxicity profile of the bolus Nordic FLOX compares favourably in many aspects.

The Nordic 5-FU and FA schedule was developed to be an active, but at the same time a highly tolerable and practical, palliative bolus regimen. The schedule has shown an RR of 25% and an OS of 12 months. Adding oxaliplatin to this schedule doubled the RR and increased survival, as has been observed by adding oxaliplatin to other 5-FU/FA schedules. Oxaliplatin is usually given as a 2-h infusion. Only a few studies have tried to give the oxaliplatin infusion in 30 min, without any increase in observed toxicity (21, 22). If oxaliplatin could be given in 30 min without compromising effect or toxicity, the schedule would constitute an even more attractive regimen suitable for outpatient practice.

In conclusion, the Nordic FLOX regimen is a well-tolerated, effective and simple bolus schedule suitable for first-line treatment of metastatic colorectal cancer. An ongoing large, multicentre phase II study by the Nordic Gastrointestinal Tumour Therapy Group is largely confirming our results.

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