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Short-Time Infusion of Oxaliplatin (Eloxatin®) in Combination with Capecitabine (Xeloda®) in Patients with Advanced Colorectal Cancer

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Neuropathy exacerbated by exposure to cold is a dose-limiting toxicity of oxaliplatin. The incidence of this side effect is claimed to dependent on infusion rate and therefore a 2-h infusion is often recommended. For practical reasons and for the convenience of the patient, we used XELOX (Xeloda 2000 mg/m^2 orally on days 1–14 and oxaliplatin 130 mg/m^2 as a 30-min infusion on day 1) in patients with advanced colorectal cancer resistant to irinotecan and 5-fluorouracil. Thirty-four consecutive patients received a median of 5 courses of XELOX. Nine patients obtained partial response (PR) (response rate (RR) 26%), 11 patients no change (NC), 7 patients disease progression (PD) and 7 patients were not evaluable. Median time to progression was 4.7 (2.6–7.6) months and median survival was 7.4 (6.0–11.3) months. Sixteen patients had neuropathy grade 1, four patients grade 2 and two patients grade 3. Short-time infusion of oxaliplatin and capecitabine is an active and convenient second-line regimen with a safety profile similar to that of other oxaliplatin schedules.

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Until the early 1990s development of chemotherapy in colorectal cancer (CRC) proceeded very slowly and the only drugs available were fluorinated pyrimidines. Nevertheless, it is known that different schedules of 5-fluorouracil (5-FU), often combined with folinic acid (FA), prolong survival from approximately 6 months to 12 months and improve quality of life (1) in patients with advanced colorectal cancer (ACRC). The addition of irinotecan (Campto®) has prolonged survival even further, initially as second-line therapy (2) but subsequently also as first-line therapy in combination (3, 4) and therefore irinotecan and 5-FU/FA (in combination or sequentially) have been suggested as standard therapy in patients with ACRC.

Oxaliplatin (Eloxatin®) produces comparable results. First-line treatment with oxaliplatin and 5-FU/FA increases response rates, prolongs time to progression (TTP) and survival (5–7).

Oxaliplatin is a third-generation platinum compound in which the platinum atom is complexed with a 1.2 diaminocyclohexane and with an oxalate ligand as a leaving group. Oxaliplatin forms crosslinks that inhibit DNA replication and transcription, resulting in cell death in actively dividing cells. In addition, oxaliplatin in combination with 5-FU leads to synergistic antiproliferative activity in vitro as well as in vivo in several tumour models (8, 9).

Oxaliplatin has side effects that are distinct from those of other platinum-based drugs such as cisplatin or carboplatin, and lacks significant renal toxicity, ototoxicity, alopecia, or severe haematotoxicity. The dose-limiting toxicity consists of a cumulative sensory peripheral neuropathy exacerbated by exposure to cold.

Several drugs, or combinations of drugs, produce definite activity in patients with ACRC resistant to bolus 5-FU (e.g. 5-FU-infused regimens, irinotecan, oxaliplatin, mitomycin C, or combinations of these drugs) with response rates of 15 to 30%, median TTP of 4 to 6 months and median overall survival 6 to 9 months. In contrast, few studies have evaluated the efficacy of second-line therapy in patients with ACRC resistant to a combination of 5-FU and irinotecan (or 5-FU and oxaliplatin).

Capecitabine is a rationally designed, oral tumour-selective fluoropyrimidine which is converted to 5-FU preferentially in tumour tissue. Capecitabine mimics protracted fluoropyrimidine delivery without the shortcomings and problems of central venous access. Capecitabine is as effective as intravenous bolus 5-FU/FA (Mayo Clinic regimen) and has a superior safety profile (10, 11).

The Nordic Modulator Group has examined the Nordic 5-FU/FA bolus regimen (12) in combination with irinotecan (13). This bolus combination (FLIRI) is feasible, with mild

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and readily manageable toxicity with promising efficacy, response rate of 39% (complete response (CR)+partial response (PR)) and median survival of 15.6 months. The regimen is well tolerated and easy to administer, at least in relation to the de Gramont+irinotecan (FOLFIRI) schedule, which is presently most commonly used regimen in many European countries. Therefore it was considered relevant to compare the Nordic FLIRI with FOLFIRI in a large randomized study (NORDIC VI study, at present 380 randomized patients) aiming for inclusion of 450 patients.

Despite progression to irinotecan, many patients are still in an excellent condition without or with only minor symptoms and there is definitely a need for further effective therapy. The combination of continuous 5-FU infusion (or oral 5-FU) and oxaliplatin might presently be the most promising regimen upon progression to 5-FU and irinotecan.

For practical and economic reasons, but also for the convenience of the patient, cytotoxic therapy is usually given as an outpatient regimen. It is recommended that oxaliplatin is given as a 2-h infusion but if acute neurotoxicity is observed, especially laryngopharyngeal dysaesthesia (LPD), prolonged infusion from 2 to 6 h may prevent recurrence of symptoms.

In a small, phase II trial, 35 patients with ovarian cancer received 100–130 mg/m^2 oxaliplatin, but as a 20–30 min infusion, and no extra neuropathy was reported (14). At least in Denmark an increasing number of patients with upper and lower gastrointestinal cancer are offered first- and second-line therapy, and a shorter infusion time will definitely ensure that more patients can be treated with the existing rather limited resources (staff and room at the hospital).

Inspired by the ovarian cancer study (14), we therefore started to treat patients with a combination of capecitabine (1 000 mg/m^2 twice daily, days 1 to 14) and oxaliplatin (130 mg/m^2 day 1) but as a 30-min infusion, with special attention to neurotoxicity. The dose was selected according to recommendations in recent phase I/II studies (8, 9, 15).

At the Department of Oncology, Odense University Hospital, we treated 34 ACRC patients from July 2001 to July 2002. These consecutive and unselected patients form the basis of this retrospective study.

MATERIAL AND METHODS

We included patients with histologically confirmed colorectal adenocarcinoma resistant to 5-FU and irinotecan and no longer amenable to surgical treatment. First-line therapy in our department during the inclusion period included irinotecan combined with bolus 5-FU and the FA Nordic schedule (13). The patients were treated with irinotecan at a dose of 180–210 mg/m^2 administered as a 30-min intravenous (iv) infusion on day 1, followed immediately by 5-FU at 500 mg/m^2 administered as an iv bolus, followed 30 min later by FA at 60 mg/m^2 iv bolus. The 5-FU/FA administrations were repeated on day 2. This treatment combination was repeated every 2 weeks until disease progression, or the occurrence of unacceptable toxicity.

Oxaliplatin was not approved in Denmark but therapy was given on a patient named basis according to the National Guidelines.

Other eligibility criteria were age above 18 years, a World Health Organization performance status of 0.1 or 2, adequate organ function and a life expectancy of at least 2 months. All patients received oral and written information, especially about the risk of neurotoxicity, before therapy was started.

Pretreatment evaluation included a complete medical history and physical examination, a complete blood count, chemistry profile, a chest X-ray, and a radiologic (CT scan) tumour parameter assessment. A complete blood count was obtained 10 to 12 days after initial cytotoxic treatment and before the start of each treatment cycle, together with a toxicity assessment with special attention to neurotoxicity. Patients had radiologic tumour parameter assessments every 8 weeks. Tumour response classification was made according to standard World Health Organization criteria.

Toxicities were assessed according to the NCI–CTC expanded common toxicity grading. Neuropathy was graded as 0–3 using the oxaliplatin-specific scale. Grade 1: paraesthesias/dysaesthesias of short duration with complete resolution prior to the next cycle; grade 2: paraesthesias/dysaesthesias persisting between two cycles without functional impairment; grade 3: functional impairment.

Hand–foot syndrome (palmar–plantar erythrodysaesthesia) was classified as grade 1 (numbness, dysaesthesia, painless swelling, erythema not disrupting normal activities), grade 2 (painful swelling, disrupting daily activities), or grade 3 (moist desquamation, ulceration, blistering, severe pain, inability to work or perform activities of daily living).

Dose and schedule of XELOX

Patients received oxaliplatin at 130 mg/m^2 on day 1, given as a 30-min infusion in 250 ml of 5% dextrose, repeated every 3 weeks. Capecitabine was administered orally at a dose of 1 000 mg/m^2 b.i.d. as an intermittent regimen in 3-week cycles (2 weeks of treatment followed by a 1-week rest period). Patients received antiemetic prophylaxis with a 5-HT$_3$ antagonist (e.g. granisetrone 1 mg iv) and steroids (oral prednisolone 50 mg) immediately before each dose of oxaliplatin.

For practical reasons, capecitabine doses were rounded to the nearest dose that could be administered with 500-mg and 150-mg tablets of the drug. Capecitabine was given at intervals of approximately 12 h and taken orally with water within 30 min of ingestion of food. XELOX was adminis-

tered for a maximum of 6 months (9 cycles) unless there was evidence of disease progression or severe toxicity.

For NCI–CTC toxicity, grade 3 or 4 drug doses were reduced by 20% in the subsequent treatment cycles but because most patients were heavily pretreated, drug doses could also be reduced owing to toxicity grade 2. The oxaliplatin dose had to be reduced by 25% for neuropathy grade 2 or more. If laryngeal spasm syndrome occurred, the duration of the oxaliplatin infusion was increased from 30 min to 1–2 h, and if there were persistent problems, oxaliplatin was omitted.

RESULTS

Between July 2001 and September 2002, 34 patients (19 men and 15 women) were treated according to the above-mentioned guidelines in the same university department of oncology. Median age was 51 years (range 31–70 years) and median WHO performance status was 0 (range 0–2). All therapy was given on an outpatient basis. All but four patients had disease resistant to irinotecan and 5-FU/FA. These four patients had disease resistant to Nordic 5-FU/FA or de Gramont schedule and they did not receive irinotecan as second-line therapy because of coexisting bowel symptoms, which we thought was at variance with irinotecan therapy. In addition to irinotecan and 5-FU/FA, 11 patients also received a combination of oral uracil tegafur (UFT) and mitomycin and 3 patients received capecitabine prior to treatment with XELOX. Median survival from the diagnosis of metastases to first treatment with XELOX was 14 months (range 1–45 months). The median number of cycles of prior chemotherapy was 10 (range, 6–12).

Dose intensity

A total of 154 courses of XELOX were administered to 34 patients with a median number of cycles per patient of 5 (range 1–9). The median cumulative dose of oxaliplatin was 650 mg/m^2. In 11 patients the dose of XELOX was reduced to 80% after median 3 courses owing to LPD (n = 1), neurotoxicity (n = 2), nausea/vomiting and/or diarrhoea (n = 4), thrombocytopenia (n = 1) or handfoot syndrome (HFS) (n = 3).

Efficacy results

Of these 34 patients, 7 patients (21%) were not assessable for response owing to non-measurable disease or therapy of less than 3 months' duration. Nine patients (8 patients with disease resistant to irinotecan and 5-FU/FA) achieved a partial response (leading to an overall response rate of 26% in the ITT population), 11 patients had no change for at least 3 months and 7 patients had progressive disease within 3 months. Median TTP was 4.7 months (95% CI 2.6–7.6 months) and median survival was 7.4 months (95% CI, 6.0–11.3 months) in the ITT population.

Safety results

Haematological toxicity. Haematological toxicity was limited even in these pretreated patients. Four patients had leucopenia grade 1 or 2 and 8 patients had thrombopenia grade 1 or 2.

Non-haematological toxicity. The most common non-haematological adverse event was neurotoxicity. Median neurotoxicity was 1 (range 0–3); 12 patients were grade 0, 16 patients (47%) grade 1, 4 patients (12%) grade 2 and 2 patients (6%) grade 3. Two patients stopped oxaliplatin treatment because of acute neurotoxicity. In all cases neurotoxicity was at least partially reversible. Two transient cases of LPD were observed and therefore infusion time was increased to 60 min. In one patient LPD did not recur. Another patient complained of LPD when she was leaving the outpatient clinic in clear and frosty weather after having received the 5th infusion. Infusion time was increased to 60 min and LPD did not recur, except for one mild episode when the patient was at home, one week after the 7th course, and was drinking fluid at room temperature. This patient received 8 courses and was at that time feeling well with only mild sensory peripheral neuropathy.

Other non-haematological adverse events were PPE (15 patients grade 1 or 2), nausea and vomiting (9 patients grade 1 or 2 and 3 patients grade 3), diarrhoea (10 patients grade 1 or 2) and fatigue (10 patients grade 1 or 2).

Four patients had severe adverse effects; 2 patients had grade 3 neurotoxicity and 2 patients had nausea/vomiting grade 3.

Patients stopped therapy because of disease progression (n = 16), completion of 6 months of therapy (n = 8), neurotoxicity (n = 2), gastrointestinal toxicity (n = 3), fatigue (n = 3), PPE (n = 1) and 1 patient continued therapy. Most of the deaths were due to progressive disease.

DISCUSSION

5-FU has been the backbone of cytotoxic therapy for patients with CRC for almost half a century. In recent years combination therapy has improved results considerably and, presently, CRC must be regarded as a chemosensitive malignancy. Several randomized studies have shown that a combination of 5-FU (bolus or infusion) and irinotecan or oxaliplatin increase response rates to approximately 50%, TTP to 7–9 months and median survival to 15–20 months (3–7) but presently it is not known which combination has the best therapeutic index, taking into account efficacy and toxicity.

The clinical use of infused 5-FU has been limited by the inconvenience and complications associated with central venous access. Therefore capecitabine might be a better

candidate for combination therapy, but more data are needed. Results of phase I and II studies suggest that XELOX is equivalent to infused 5-FU/oxalipatin (8, 9, 16, 17), but we must await the results from ongoing phase III studies before any final conclusions can be drawn. However, at least from a practical perspective, XELOX is a good candidate in ACRC.

We found a promising 26% response rate, a median TTP of 4.7 months and median survival of 7.4 months in these heavily pretreated patients. Few studies have examined the efficacy of second-line therapy in patients with ACRC resistant to 5-FU in combination with irinotecan or oxaliplatin.

In a large study conducted in the US (EFC 4584) the efficacy of infused 5-FU (de Gramont) vs. single agent oxaliplatin vs. the combination (FOLFOX4) was compared in patients with ACRC resistant to bolus 5-FU and irinotecan. Analysis of 821 patients, presented at ASCO 2003, showed that the combination (FOLFOX4) improved response rate (10%) and TTP (median 5.6 months) significantly and also reduced tumour-related symptoms (18).

In a French crossover study, 226 patients received FOLFOX or FOLFIRI and continued immediately upon progression with the opposite regimen (19). Median overall survival (20 and 21 months, respectively) was the longest ever reported in a randomized trial but without any difference in overall survival. Response rate to second-line therapy was 5% (FOLFIRI upon progression to FOLFOX) and 15% (FOLFOX upon progression to FOLFIRI), respectively.

These and our results indicate that patients progressing to a combination of irinotecan and FU should be offered further therapy. The ease and convenience of XELOX makes this combination an excellent candidate for standard therapy.

Toxicity, especially neurotoxicity, in our study is comparable with toxicity from other oxaliplatin regimens. A number of phase I, II or III studies have reported neurotoxicity grade 3 in 5–25% and grade 1–2 in 50–70% of cases (5, 6, 8, 9, 14, 15, 18). Thus it seems that a 30-min infusion does not increase the risk of severe neurotoxicity if the cumulative dose of oxaliplatin is less than 1 000 mg/m^2. To confirm the safety and efficacy of short-time XELOX, a Nordic phase II study (second-line treatment in patients with ACRC resistant to irinotecan and FU) was started in December 2002, aiming to include 50 patients.

CONCLUSION

A 30-min infusion of oxaliplatin in combination with capecitabine is an active, and very convenient regimen with an excellent safety profile similar to other oxaliplatin schedules.

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