Phase I study of weekly oxaliplatin plus irinotecan in previously treated patients with metastatic colorectal cancer


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Background: In vitro synergy between Oxal (oxaliplatin) and CPT-11 (irinotecan) has been reported. Oxaliplatin exerts its antineoplastic activity through the formation of platinum–DNA adducts. Resistance to oxaliplatin is through repair of these adducts, which is inhibited by irinotecan.

Patients and methods: Oxaliplatin and irinotecan were administered weekly for 4 weeks followed by a 2-week rest period. The dose of oxaliplatin was escalated first, starting at 30 mg/m². Once a dose of 60 mg/m² was attained, the weekly dose of irinotecan was escalated, from 40 mg/m² to 85 mg/m². A total of 49 previously treated patients with metastatic colorectal cancer were entered in order to establish the maximum tolerated dose. Pharmacokinetics of oxaliplatin and irinotecan were analyzed.

Results: Forty-nine patients were evaluable for toxicity. The recommended phase II doses for this combination are oxaliplatin 60 mg/m² and irinotecan 50 mg/m², weekly × 4 q 6 weeks. Diarrhea was the most common dose-limiting toxicity. No pharmacological interactions were noted between oxaliplatin and irinotecan. Twelve of the 47 evaluable patients (26%) achieved a partial response.

Conclusion: Weekly combination of oxaliplatin and irinotecan appears to be a well tolerated and active regimen in patients previously treated for metastatic colorectal cancer. Further investigations of this regimen are warranted.

Key words: colorectal cancer, irinotecan, oxaliplatin

Introduction

Colorectal cancer is one of the most common malignancies in the United States and Europe, and only half the patients with the disease will be cured by surgery. Those who develop metastatic disease have a median survival of 12–14 months. For decades, the only chemotherapeutic drug that was useful in this disease was 5-fluorouracil (5-FU) [1]. Strategies developed to enhance the antiproliferative effects of 5-FU have included changing treatment schedules, biochemical modulation, and the addition of synergistic drugs [2–4], but no therapy has produced an increase in survival over 5-FU alone [5]. In the last few years, however, a number of new drugs have become available. Of these, the topoisomerase inhibitors [6] and a new class of platinum drugs exemplified by Oxal (oxaliplatin) [7] are particularly exciting. The topoisomerase I inhibitor, CPT-11 (irinotecan), has produced response rates of 19–32% in previously untreated patients [8, 9]. When irinotecan is combined with 5-FU and leucovorin (LV) there is an increase in response rate and survival compared with 5-FU and LV alone [10, 11]. Oxaliplatin is a third-generation platinum characterized by a 1,2-diaminocyclohexane (DACH) platinum-carrier ligand. It has in vitro activity in several cisplatin-refractory tumors [12]. Response rates of 24% have been reported using oxaliplatin as a single agent in previously untreated patients [13]. Additive/synergistic activity has been observed with the combination of irinotecan and oxaliplatin [14].

Oxaliplatin functions as an antineoplastic agent by forming platinum–DNA adducts which, if not excised, prevent further DNA synthesis and/or transcription and thereby lead to cell death [15]. A major mechanism of resistance is through rapid repair of these platinum–DNA adducts. This repair process requires DNA synthesis, which, in turn, requires uncoiling of the damaged section of DNA and this uncoiling is facilitated by topoisomerase I [16]. Therefore, the use of a topoisomerase I inhibitor such as irinotecan in conjunction with oxaliplatin may decrease the resistance to oxaliplatin. Preliminary reports demonstrated that combinations of oxaliplatin and irinotecan every 3 weeks were tolerable [17]. In order to increase exposure to the two agents simultaneously and thereby
perhaps optimize synergy, we initiated a weekly schedule of oxaliplatin and irinotecan.

**Patients and methods**

**Patient eligibility**

Patients with measurable metastatic colorectal cancer histologically confirmed at Memorial Sloan-Kettering Cancer Center (MSKCC) were eligible. Prior chemotherapy regimens were permitted except for cisplatin, oxaliplatin, nitrosoureas or mitomycin. No more than two prior regimens were permitted including prior adjuvant therapy. Patients were not permitted to have received cytotoxic therapy for at least 3 weeks before initiation of treatment. Prior radiation therapy was permitted if completed >4 weeks before enrollment, and sites of tumor measurement were required to be outside of the radiation port. Patients who had received previous radiation to ≥30% of bone marrow were not eligible. Other requirements included Karnofsky performance status (KPS) ≥70%, white blood cell count (WBC) ≥5000 cells/µl, absolute neutrophil count (ANC) ≥1500/µl, platelet count ≥125 000 cells/µl, total serum bilirubin <1.5 mg/dl, and creatinine ≤1.5 mg/dl within 14 days of registration. Exclusion criteria included patients with current symptomatic peripheral sensory neuropathy, gastrointestinal or genitourinary obstruction, central nervous system metastases, and pregnant or lactating women.

Pretreatment evaluation included tumor measurements by computed tomography (CT) scan, magnetic resonance imaging (MRI), and/or chest X-ray, ECG, medical history and physical examination, complete blood count (CBC) with differential and platelet count, liver function tests, creatinine, lactate dehydrogenase (LDH), serum electrolytes and carcino-embryonic antigen (CEA).

**Treatment plan**

All patients received oxaliplatin and irinotecan on an out-patient basis as a 120 min infusion of oxaliplatin, followed by a 30 min infusion of irinotecan. A cycle comprised 4 weeks of treatment followed by 2 weeks of rest. Chemotherapy continued on this schedule until there was evidence of disease progression or dose-limiting toxicity (DLT). The starting dose of oxaliplatin was 30 mg/m²; the dose was escalated in 10 mg/m² increments until 60 mg/m² was reached. The starting dose of irinotecan was 40 mg/m² intravenously (i.v.), with escalations of irinotecan to 85 mg/m², initiated only after the oxaliplatin dose of 60 mg/m² was reached. When a cohort of three patients completed one course of therapy (4 weeks followed by a 2-week rest) without a DLT, a new cohort was entered at the next higher dose level. Dose escalation continued in this manner until the maximum tolerated dose (MTD) was established. The dose escalation schedule used is outlined in Table 1. Cholinergic symptoms (diarrhea, sweating, salivation, abdominal cramping) that occurred during or within 1 h after receiving irinotecan were treated with atropine (0.5–1 mg i.v.). All patients were instructed to begin taking loperamide at the first sign of diarrhea: 4 mg at the first onset of diarrhea, then 2 mg every 2 h around the clock until diarrhea-free for at least 12 h. Grade 1 diarrhea did not exclude retreatment. If patients experienced grade 2 diarrhea on the day of treatment, treatment was held until diarrhea resolved to a level of grade 1 or less.

Patients had to meet all hematological and blood chemistry criteria outlined in the above Patient eligibility section before beginning the first cycle of therapy. For subsequent cycles, patients had to have: WBC ≥3000 cells/µl, ANC 10000/µl, platelet count ≥100 000 cells/µl, and creatinine ≤1.8 mg/dl. If counts did not meet these requirements on the date of scheduled treatment, therapy was delayed by 1 week.

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Oxaliplatin weekly dose (mg/m²)</th>
<th>Irinotecan weekly dose (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
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<tr>
<td>3</td>
<td>50</td>
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<tr>
<td>4</td>
<td>60</td>
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</tr>
<tr>
<td>5</td>
<td>60</td>
<td>50*</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>75*</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>85*</td>
</tr>
</tbody>
</table>

*Recommended phase II dose.

When three patients completed one cycle of therapy without a DLT, the next three patients were entered on the next higher dose level. Dose escalation continued until the MTD was established. Evaluation during study included weekly toxicity assessment, vital signs, CBC, platelet count, blood urea nitrogen and creatinine (weekly); liver function tests and CEA before each cycle; CT or MRI and chest X-ray were performed every other cycle to determine response.

**Toxicity and response assessment**

Toxicities were graded according to the Common Toxicity Criteria version 2.0 of the National Cancer Institute. The definition of a DLT was:

(i) any grade 3 or 4 diarrhea, despite aggressive loperamide therapy; (ii) any other grade 3 or 4 non-hematological toxicity (except nausea, vomiting and alopecia); (iii) grade 2 gastrointestinal toxicity or stomatitis that did not completely resolve within 1 week from the time of causing a treatment delay; (iv) serum creatinine ≥1.8 mg/dl that did not recover to <1.5 mg/dl within 2 weeks from the time of causing a treatment delay; (v) WBC <3000/µl, ANC <1000/µl, or platelet count <100 000/µl that does not recover to above these levels within 1 week from the time of causing a treatment delay; (vi) any grade 4 granulocytic toxicity or neutropenic fever. If a dose level produced any DLT, then that dose level was expanded to treat up to a total of six patients to characterize more fully the toxicities at that level.

The MTD was the dose level immediately preceding the dose level at which two or more patients in a cohort of three to six patients experienced a DLT. Following identification of the MTD, additional patients were enrolled at this dose level so that a minimum of 10 patients received the MTD. Pharmacokinetic data were obtained on 10 patients at the MTD.

Neurosensorial toxicity was graded as follows: grade 0, no symptoms; grade 1, paresthesias or dysesthesias of short duration without complete resolution before the next cycle; grade 2, paresthesias or dysesthesias persisting between two cycles without functional impairment; grade 3, paresthesias or dysesthesias with functional impairment. If paresthesias persisted during cycles, the oxaliplatin dose was reduced 25%. If there were paresthesias with functional impairment, oxaliplatin was held until improvement. If laryngopharyngeal dysesthesia occurred, the next dose of oxaliplatin was administered as a 6-h infusion.

Tumor responses were assessed with CT or MRI and chest X-ray obtained every other cycle. A reference radiologist confirmed all responses. Scans were repeated every other cycle. A partial response (PR) denoted a
reduction of ≥50% in the sum of the products of the greatest perpendicular diameters of tumor nodules measured on any follow-up CT compared with baseline. A minor response was a reduction of <50% but ≥25% in the sum of the products of the greatest perpendicular diameters of tumor nodules. Confirmatory scans were not necessary. A reduction or growth of <25% was considered stable disease (SD). Tumor measurements of >25% increase over baseline or the point of maximal regression in the summed products of the perpendicular diameters were considered progression.

Pharmacokinetic studies
Pharmacokinetic analyses were performed only on patients at the MTD level. On week 1 of cycle 1, irinotecan pharmacokinetic analyses were conducted over 24 h at 0, 0.5, 1, 3, 5, 7 and 24 h after irinotecan infusion. On week 4 of cycle 1, one sample was collected before oxaliplatin infusion (for platinum baseline only). Additional samples were collected for both irinotecan and oxaliplatin analyses at the end of oxaliplatin infusion and coinciding with the start of irinotecan infusion and 0.5 h after oxaliplatin infusion (coinciding with the end of irinotecan infusion); samples were also collected at 1, 3, 5 and 24 h after the oxaliplatin infusion.

All blood samples (~5 ml each) were collected into heparinized containers and kept on ice throughout the procedure and underwent ultrafiltration within 1–2 h of sample collection. Ultrafiltrable platinum was obtained from plasma after centrifugation with a Centrifree 30/000-Da micropartition device (Amicon Bioseparations, Millipore Corporation, Bedford, MA, USA) and shipped to Sanofi Synthelabo Pharmaceuticals for platinum analysis. Another sample was analyzed for irinotecan and irinotecan metabolites (SN38 and SN38G) at MSKCC. The pharmacokinetics of platinum were evaluated in plasma ultrafiltrate samples by an inductively coupled plasma mass spectrometry method [18]. Irinotecan, SN-38, and SN-38G were assayed using high-performance liquid chromatography with fluorometric detection, according to previously published techniques [19, 20].

Biostatistics
A phase I study was conducted, which had three major objectives: (i) to determine the MTD of oxaliplatin in combination with irinotecan in patients with metastatic colorectal cancer; (ii) to evaluate the toxicities of the combination treatment; and (iii) to characterize the pharmacokinetics at the MTD of this combination chemotherapy regimen.

Relationships between gastrointestinal and hematological toxicities, blood values and pharmacokinetic parameters of both drugs were assessed. Initial assessment included examination of scatter plots and summary. If these exploratory analyses suggested a relationship, rank-based tests were used to evaluate their statistical significance. Exact permutation distributions were used to obtain p values. Survival probabilities were estimated using Kaplan–Meier methods.

Statistical methods for pharmacokinetic data
Non-compartmental analysis included the following: the area under the plasma concentration-versus-time curve from time 0 to the last measurable concentration (AUC0–t) calculated by the linear trapezoidal method; the area under the plasma concentration-versus-time curve from time 0 to infinity (AUC0–INF) calculated as the sum of the AUC0–t plus the ratio of the last measurable plasma concentration to the elimination rate constant; the maximum measured plasma concentration over the time span specified (Cmax); the terminal half-life (t1/2); the volume of distribution at steady-state; and the total body clearance rate, calculated as the dose divided by the AUCinf. The data were analyzed using WinNonlin, standard version 3.1 (Pharsight Corporation, Mountain View, CA, USA). The data on days 1 and 4 were compared using a paired two-sided Student’s t-test using Microsoft Excel Software version 9.0 (Microsoft Corporation, Redmond Hills, WA, USA).

Results
Forty-nine patients were entered (26 males and 23 females). Patient characteristics are listed in Table 2. The median age was 61, median KPS was 80. All patients had prior chemo-therapy and 49% had received two prior regimens. Twenty-five (51%) had received prior irinotecan; eight (16%) had prior adjuvant therapy. Four patients (8%) had prior radiation to the liver (in 38 patients) followed by metastases in the lung (21 patients).

Toxicity
Forty-nine patients were evaluable for toxicity and 47 for response. One patient at the first dose level died at home 2 weeks after starting therapy. The patient was evaluated after

Table 2. Patient characteristics

<table>
<thead>
<tr>
<th>Total number</th>
<th>49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: median, years (range)</td>
<td>61 (40–81)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>26/23</td>
</tr>
<tr>
<td>KPS: median (range)</td>
<td>80 (70–100)</td>
</tr>
<tr>
<td>CEA: median, mg/ml (range)</td>
<td>65.3 (1.4–3965)</td>
</tr>
<tr>
<td>LDH: median, U/l (range)</td>
<td>177 (107–867)</td>
</tr>
<tr>
<td>Alkaline phosphatase: median, U/l (range)</td>
<td>101 (51–503)</td>
</tr>
<tr>
<td>Bilirubin: median, mg/dl (range)</td>
<td>0.6 (0.2–1.4)</td>
</tr>
<tr>
<td>Previous oxaliplatin therapy</td>
<td>25 (51%)</td>
</tr>
<tr>
<td>One prior regimen</td>
<td>25 (51%)</td>
</tr>
<tr>
<td>Two prior regimens</td>
<td>24 (49%)</td>
</tr>
<tr>
<td>Colon/rectal primary</td>
<td>46/3</td>
</tr>
<tr>
<td>One site of metastasis</td>
<td>16</td>
</tr>
<tr>
<td>Two sites of metastasis</td>
<td>22</td>
</tr>
<tr>
<td>Three sites of metastasis</td>
<td>11</td>
</tr>
<tr>
<td>Sites</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>21</td>
</tr>
<tr>
<td>Liver</td>
<td>38</td>
</tr>
<tr>
<td>Abdomen</td>
<td>10</td>
</tr>
<tr>
<td>Nodes</td>
<td>12</td>
</tr>
<tr>
<td>Other (rib, pelvis, kidney, adrenal)</td>
<td>5</td>
</tr>
</tbody>
</table>

‡Institutional upper limits of normal: LDH, 200 U/l; alkaline phosphatase, 88 U/l (20–55 years), 115 U/l (55+ years); bilirubin, 1.0 mg/dl.

CEA, carcinoembryonic antigen; KPS, Karnofsky performance status; LDH, lactic dehydrogenase.
1 week of therapy with no toxicity but died at night with no reported toxicity from therapy, and no known cause of death. Another patient was not evaluable for response because she received one cycle of therapy and never had a repeat scan.

In the first four cohorts, there were no DLTs during the first cycle. At the fourth cohort, oxaliplatin 60 mg/m² and irinotecan 50 mg/m², one patient experienced neutropenic fever, and therefore three more patients were entered at this dose without further DLTs. Escalation continued until the dose of oxaliplatin 60 mg/m² and irinotecan 75 mg/m², when three patients had DLTs; one grade 3 diarrhea and two grade 4 diarrhea with grade 3 ANC in one of these patients. Therefore, the MTD was initially determined to be oxaliplatin 60 mg/m² and irinotecan 65 mg/m². Fifteen patients were then treated at this dose and pharmacokinetic data were obtained on 10 of these patients. Three of these 15 patients had grade 3 or 4 diarrhea during the first cycle and nine had grade 3 or 4 toxicity if all cycles are considered. Due to these toxicities, a recommended phase II dose was considered to be the next lower level (oxaliplatin 60 mg/m² and irinotecan 50 mg/m²). At this dose, there were two DLTs during the first cycle in 12 patients. During the next cycles two other patients developed grade ≥3 diarrhea (Table 3). At this dose level, grade 4 ANC was not common, with only one patient (8%) developing grade 4 ANC.

Neurotoxicity was usually mild and was related to cumulative dose. The peripheral sensory neuropathy (grade 1) was characterized by dysesthesia and/or distal paresthesia (fingers, toes and, less frequently, peri-oral region and pharyngo-laryngeal tract), induced or exacerbated by cold and generally regressing between cycles of treatment. Acute laryngopharyngeal dysesthesias did not occur in these patients. Twenty-four patients received oxaliplatin at a cumulative dose of >1000 mg/m². Grade 2 neurotoxicity occurred in eight patients (16%). In six patients this occurred only after a cumulative oxaliplatin dose of 960 mg/m² had been delivered. In the remaining two patients it occurred after oxaliplatin doses of 540 and 720 mg/m², respectively. In all patients with grade 2 neurotoxicity, the dose of oxaliplatin was lowered by 25%. In three patients (6%), grade 3 neurotoxicity occurred; in one patient this was manifested as pain in the fingers and hands with some difficulty in walking because of numbness in the feet, and the other two patients developed severe pain in the hands causing difficulty in movement. These three patients required cessation of oxaliplatin therapy. In two patients the neurotoxicity abated in 3 and 6 months; in the third patient the functional impairment improved after 6 months but paresthesias continued. In the patients with grade 3 neurotoxicity, it occurred only after a cumulative oxaliplatin dose of 1110 mg/m². Neurotoxicity is outlined in Table 3.

Less common toxicities included thrombocytopenia: three patients developing grade 3 platelet toxicity, and five developed grade 2 thrombocytopenia. Alopecia was rare and there was no renal toxicity. Among other non-hematological...
adverse events were grade 2 or 3 asthenia (seen in nine and four patients, respectively), nausea (in 10 and one patients, respectively) and vomiting (in three and one patients, respectively).

Baseline blood values such as alkaline phosphatase, bilirubin and LDH and KPS did not correlate with toxicity. Seven of nine patients with intra-abdominal disease (i.e. peritoneal or abdominal lymph nodes) developed grade 3 or 4 toxicity, while 14 of 31 patients with liver metastases developed grade 3 or 4 toxicity.

Response and survival

Twelve of the 47 evaluable patients had a PR, resulting in a response rate of 26% [95% confidence interval (CI) 14% to 40%]. Median duration of response was 5.5 months (range 3.5–10 months). Minor responses were seen in three patients, with a median duration of response of 5.5 months (range 4.5–14 months). Fourteen patients had SD, for a median of 6 months (range 2–11 months). Eighteen patients had tumor progression.

Five of 25 (20%) patients who had prior therapy with irinotecan had a PR. Four of the five patients were progressing on prior therapy with irinotecan. The fifth had been off irinotecan for 5 months and then progressed. Two of the minor responses and nine of the stable patients had also received prior irinotecan. The median survival from entry to the study is 10.5 months (95% CI 8.1–12.9 months) and 1 year survival was 38% with five patients still alive.

Baseline CEA and LDH values were significantly associated with response (P <0.01 for both, Wilcoxon test). Those who responded to treatment had lower values (n = 12, mean CEA = 95 mg/ml, mean LDH = 155 U/l) when compared with those who did not respond (n = 35, mean CEA = 660 mg/ml, mean LDH = 287 U/l). No other variables correlated with response.

Pharmacokinetic analysis

Pharmacokinetic analysis was performed on samples obtained from 10 patients at the dose level of oxaliplatin 60 mg/m² and irinotecan 65 mg/m². Platinum concentrations in plasma ultrafiltrate were only analyzed on week 4 of cycle 1 following oxaliplatin administration. The results for ultrafiltrable platinum were comparable with those of historical controls [21].

The mean platinum concentrations in ultrafiltrate were plotted against time. The t½ beta (31.7 ± 34.2 h), volume of distribution (552 ± 243 l) and clearance (19.1 ± 10 l/h) of platinum in the presence of irinotecan were similar to the values obtained following single-agent oxaliplatin, indicating that irinotecan did not modulate the kinetics of oxaliplatin. There did not appear to be a significant variation in the values for AUC and C×max for irinotecan, SN-38 or SN38G when given alone (week 1) or after oxaliplatin (week 4). The median AUCs (ng·h/ml) at weeks 1 and 4 for irinotecan were 3835 ± 1079 and 4282 ± 974; for SN-38, 145 ± 71 and 143 ± 55; and for SN38G, 395 ± 139 and 435 ± 169. The c×max (ng/ml) for weeks 1 and 4 were 900 ± 256 and 787 ± 145 for irinotecan; 7 ± 8 and 15 ± 4.6 for SN-38; and 40 ± 16 and 36 ± 16 for SN-38G. There did not appear to be a significant pharmacokinetic interaction between oxaliplatin and irinotecan.

There was a strong relationship between SN38 AUC values and high values for alkaline phosphatase (r = 0.78). Biliary index, calculated as (irinotecan AUC)×(SN38 AUC)/(SN38-G AUC), was used to measure the irinotecan exposure of liver. Our pharmacokinetic data indicated a strong relationship between percent reduction from baseline in ANC and biliary index (r = 0.68). None of the other pharmacokinetic parameters correlated with reduced ANC levels.

Discussion

Historically, the treatment of metastatic colon cancer after progression on first-line therapy has yielded poor results. However, the discovery of new chemotherapeutic agents has expanded therapeutic options for these patients. Colorectal cancer cells have generally been resistant to platinum drugs, which have been successful drugs in other tumor types. Burchenal et al. [22] stimulated interest in DACH–platinum complexes by demonstrating their efficacy in cisplatin-resistant mouse cell lines. In the L1210 cell line, oxaliplatin was 20–100 times more active than cisplatin. In human xenograft modules, oxaliplatin showed good activity in HT-29 and DLD-2 colon models [21]. In vivo antitumor studies demonstrated additive or better activity of oxaliplatin when combined with irinotecan [14], mitomycin, cisplatin and 5-FU [23, 24]. The initial work with oxaliplatin combinations were with 5-FU and LV. In randomized studies comparing oxaliplatin and 5-FU/LV with 5-FU/LV alone there was a significant increase in response rate (34% versus 12%, respectively) and median disease-free survival (7.7 versus 4.6 months, respectively) [25]. The combination of oxaliplatin and irinotecan needed to be tested because of demonstrated synergism in colon cancer cell lines, and non-overlapping toxicity.

The combination of oxaliplatin and irinotecan was first tested by Wasserman et al. [17]. Using oxaliplatin 85–120 mg/m² and irinotecan 150–250 mg/m² on an every 3-week schedule, they treated 24 patients with colorectal cancer, all of whom had been previously treated with 5-FU and LV (58% were 5-FU-refractory but none had received prior irinotecan). Grade 3/4 toxicity included neutropenia (36%), diarrhea (31%), peripheral neuropathy (26%) and nausea and vomiting (33%). Six patients required granulocyte colony-stimulating factor (G-CSF). Their recommended dose for the combination on this schedule was oxaliplatin 110 mg/m² and irinotecan 200 mg/m². The response rate was 7/24 (29%), with a median survival of 15.8 months.

Scheithauer et al. [26] tried an alternative schedule of oxaliplatin 85 mg/m² every other week with irinotecan 80 mg/m² given on days 1, 8 and 15. Thirty-six patients who had progressed on 5-FU/LV (received only one prior regimen and no
prior irinotecan) were treated. G-CSF was given to 86% of patients. With the use of G-CSF in 31 of 81 courses, grade 3/4 granulocytopenia was seen in 7 of 36 patients (19%) and grade 3 diarrhea in 19%, grade 3 neuropathy in 8% and nausea/vomiting in 17%. Forty-two percent of patients achieved a PR with a median response duration of 6.5 months.

In the current study, utilizing a weekly combination schedule, there was a response rate of 26%. All patients in this study had received previous 5-FU/LV treatments and 50% of the patients had received previous irinotecan treatments. While the activity of this regimen may be due to oxaliplatin alone, synergism between oxaliplatin and irinotecan is likely since oxaliplatin alone has a 10% response rate in previously treated patients with no prior exposure to irinotecan. The dose of oxaliplatin used in this trial, 60 mg/m² × 4 weeks in a 6-week period, is similar in intensity to the accepted dose of oxaliplatin, 130 mg/m² every 3 weeks.

Our pharmacokinetic data suggested that this level of oxaliplatin does not affect the metabolism of irinotecan, since the AUCs of irinotecan and SN38 did not change from week 1 to week 4 (without and with oxaliplatin co-administration). This result is consistent with the lack of cytochrome p450 inhibition observed with oxaliplatin when co-incubated with human liver chromosomes [21]. This is not surprising since the mechanisms of elimination of the two drugs are quite different, irinotecan by esterase and cytochrome P450–3A4, and oxaliplatin by renal elimination and non-enzymatic bio-transformation. Therefore, as expected, irinotecan did not appear to modulate the pharmacokinetics of oxaliplatin, and oxaliplatin pharmacokinetic data are in line with historical values [21]. We observed a relationship between the SN38 exposure and elevated alkaline phosphatase levels, as well as a relationship between biliary index and reduction in ANC from baseline.

The toxicity profile of this regimen is similar to that of the irinotecan plus 5-FU/LV regimen with 14 (29%) of the entire group including 3 of 12 patients (25%) at the MTD developing grade 3 or 4 diarrhea. Four patients (8%) developed grade 4 neutropenia, only one of whom was receiving the MTD dose. There were eight (16%) admissions for toxicity and another five for disease-related problems. Forty-nine percent of these patients were receiving third-line therapy, therefore five admissions for disease-related problems is not high. While a 16% admission rate for toxicity is high, reports of the irinotecan, 5-FU and LV combination have admission rates of 11–31% [10, 11].

Grade 3 neurotoxicity was seen in three patients (6%). Two of these patients experienced more pain and discomfort after having surgery. It is possible that tourniquets applied to hands and feet during surgical procedures may aggravate neurotoxicity. There was no correlation with baseline blood values of alkaline phosphatase, bilirubin and LDH with toxicity. There may be a correlation between site of disease and toxicity.

Our recommended phase II dose for the combination of oxaliplatin and irinotecan is oxaliplatin 60 mg/m² and irinotecan 50 mg/m², both administered weekly for 4 weeks followed by a 2-week rest. The promising activity of this regimen, even as third-line therapy, together with its acceptable toxicity profile indicates that this regimen should undergo further evaluation.

Acknowledgements
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References
12. Machover D, Diaz-Rubio E, de Gramont A et al. Two consecutive phase II studies of oxaliplatin (L-OHP) for treatment of patients with advanced colorectal carcinoma who were resistant to previous treatment with fluoropyrimidines. Ann Oncol 1996; 7: 95–98.
13. Becouarn Y, Ychou M, Ducreux M et al. Oxaliplatin (L-OHP) as first-line chemotherapy in metastatic colorectal cancer (MCRC)