Addition of Oxaliplatin to Neo-adjuvant Radiochemotherapy for Irresectable Rectal Cancer, a Phase I Study

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Abstract. Background: The aim was to determine the maximum tolerable dose of oxaliplatin added to (oral) 5FU in irresectable rectal cancer. Patients and Methods: Nineteen patients were treated; 13 patients received 5FU/LV and 6 patients capecitabine. Oxaliplatin was administered on days 1 and 29 at dose levels 85 and 130 mg/m2. Four to seven weeks thereafter, surgery was performed. Results: In 6 patients treated with 85 mg/m2, one grade 3 elevation of liver transaminases occurred. Of 7 patients who received 130 mg/m2, 1 patient experienced a grade III thrombocytopenia and 1 patient died of neutropenic fever, probably due to an urosepsis. Six patients were treated with capecitabine, of whom 3 developed a grade III gastrointestinal toxicity. An R0 resection could be performed in 93%, a pT0-2N0 in 39%, with 2 pCR’s. Conclusion: The addition of oxaliplatin at 85 mg/m2 on days 1 and 29 to radiotherapy and 5FU/LV or capecitabine in irresectable rectal cancer is feasible.

The preoperative treatment of irresectable rectal cancer aims at a reduction of the tumor size by using radiotherapy alone or in combination with chemotherapy (neo-adjuvant treatment) (1) If successful, this strategy leads to resectability, resulting in a better local control rate and a better prognosis for survival. However, this combination treatment is not yet optimal. First, because some patients remain incurable after neo-adjuvant treatment with a median survival of compromised quality of only 12 months, and, secondly, the toxicity of this strategy may be considerable (2).

Oxaliplatin, a new platinum analog, shows promising results in the treatment of colorectal cancer, two phase III studies showed significant differences in progression-free survival and response rate with acceptable tolerability (3, 4). Other studies showed a synergistic antitumor activity also with 5FU (5, 6). Moreover, oxaliplatin can act as a radiosensitizer, as shown in a study by Cividalli et al. (7), who found an increased antitumor effect in the combination of radiotherapy with oxaliplatin. For this reason, the addition of oxaliplatin might improve the response rate of preoperative radiochemotherapy treatment for irresectable rectal cancer. During our study, intravenous 5FU was replaced by capecitabine, an oral 5FU drug. The reason for this change was the convenience of oral administration, combined with an efficacy and tolerability comparable to intravenous 5FU (8-12).

We tested the feasibility of the addition of oxaliplatin to (oral) 5FU and radiotherapy in the neo-adjuvant treatment of irresectable rectal cancer.

Patients and Methods

Eligibility criteria. Patients with histologically proven malignancy of the rectum with a clinical stage T3-4 (TNM UICC 1992, staging classification of colorectal cancer), not amenable to primary radical surgery with a tumor-free circumferential margin, were eligible. Patients with resectable liver metastases could also be included. The assessment of the tumor stage was performed by means of digital rectal examination and CT scan or MRI.

Patients who had received prior anticancer treatment (radio- and/or chemotherapy) or had another malignancy in the previous 10 years were excluded, with the exception of adequately treated in situ carcinoma of the cervix or non-melanomic skin cancer. Furthermore, pregnant or lactating women, patients with severe cardiac or lung failure, uncontrolled hypertension or angina pectoris were excluded. Patients with clinical signs of CNS metastases or a sensory neuropathy of NCI grade 1 were also excluded.

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Study design. In this study, oxaliplatin was added to an existing treatment strategy given with a curative intent. The additional study medication should not compromise this regimen. For this reason, any grade 4 toxicity was considered to be toxicity that would lead to adaptation of the dose or timing of the existing regimen, as dose-limiting. In our previous experience in 43 patients, dose reduction of 5FU/LV or radiotherapy was never required (2), neither was surgery postponed for reasons of toxicity of this neo-adjuvant treatment regimen. After the approval by our institutional review board, the use of i.v. 5FU was replaced with oral 5FU e.a. capecitabine after the treatment of 13 patients.

When 3 patients had not required dose modification in the first dose step (85 mg/m²), the second dose step (130 mg/m²) was to be initiated. Six patients in the final dose step should be treated without compromising radiotherapy, surgery or 5FU dose. If dose-limiting events occurred in the final step, 3 additional patients were to be treated at the first dose level.

Radiotherapy. Preoperative radiotherapy was delivered by an isocentric three or four field technique, using mega voltage radiation produced by a linear accelerator with an energy ≥6 MV. Patients were positioned in the prone position with a full bladder to decrease the irradiated volume of the small bowel. All fields were treated on a daily basis. The radiation field extended superiorly to the L5/S1 junction and covered the obturator foramina inferiorly. The minimal inferior extent was 4-5 cm below the tumor. With carcinoma of the lower one-third of the rectum, the perineum was encompassed in the treatment field. The width of the anterior posterior portal covered the lateral pelvic inlet with a margin of 1.5 cm. The entire sacrum was included with a dorsal margin of 1.5 cm. Anteriorly, the lateral fields encompassed the tumor as determined by barium enema and pelvic CT scan and were positioned along the posterior border of the pubic bone. If there was clinical evidence of involvement of the bladder, the prostate, the cervix or the uterine body, not only the internal iliac nodes, but also the external iliac nodes were included in the radiation field. In that case, the anterior border of the lateral field was positioned along the upper border of the pubic bone. Patients received 25 daily fractions of 1.8 Gy up to a total of 45 Gy. After 45 Gy at the loco-regional treatment volume, the radiotherapy was continued with a boost dose of 3 fractions of 1.8 Gy each only encompassing the gross tumor volume with a 2-cm margin determined by barium enema and CT scan. The dose distribution was specified according to the rules of the ICRU 50 report. The dose homogeneity in the target volume was within 5% related to the dose specification point.

Chemotherapy. 5FU and leucovorin were administered during two cycles, on days 1 to 5 and days 29 to 33 as a 350 mg/m² bolus (intravenous injection over ≤20 min) immediately after the leucovorin bolus of 20 mg/m². Oxaliplatin was given at escalating doses (85 mg/m², 130 mg/m²) on day 1 and day 29 as a 2-h intravenous infusion prior to administration of 5FU and leucovorin. Oxaliplatin and 5FU were not combined in the same infusion bag, and the line was flushed between the administration of oxaliplatin and that of folinic acid.

Capcitabine was administered orally at a dose of 1000 mg/m², 2 x dd, days 1 to 14 and 25 to 38. This is 75% of the standard dose without radiotherapy and replaces the reduction in 5FU when combined with radiotherapy.

Surgery. The surgical procedure was performed between 4 to 7 weeks after preoperative treatment. The resection was carried out using sharp dissection to encompass the circumference of the mesorectum. The operation started with the transection of the inferior mesenteric vessels below the left colic artery and continued in the avascular plane between the mesentery and the parietal structures, thus preserving the pelvic plexus. In male patients, the anterior dissection was carried out in front of “Denonvilliers’ fascia.” The dissection was carried out in the so-called “holy plane” and both the rectum and the mesentery were transected at least 2 cm below the tumor. When a safe distal margin could be obtained without the need for a perineal phase, and the residual rectal stump was too short to warrant continence with a colorectal anastomosis, the rectal stump was either closed or left open. This, in fact, is a modified Hartmann procedure. Invaded contiguous structures on the primary assessment were resected en bloc with the rectum. If required, the posterior vaginal wall and/or uterus were excised.

Patient evaluation. We performed a weekly evaluation of toxicity during neo-adjuvant treatment. The toxicity scoring criteria of the NCI Common Toxicity Criteria version 2.0 were used. The evaluation of toxicity was performed until one month after the operation. The pathologist examined the surgical specimen for resection margin and pathological tumor stage (TNM UICC 1992, staging classification of colorectal cancer).

Results

Between December 2000 and July 2003, 19 patients were treated in this study. The median age of the patients was 60 years (range 30-69 yr.). Eleven patients were male and eight were female.

Thirteen patients were treated with intravenous 5FU, eleven of these had primary irresectable rectal adenocarcinoma and one a recurrence 4 years after a low anterior resection for a pT3N0 tumor. One patient had a cT2N0 cloacal carcinoma. This patient was treated with a higher radiotherapy dose of 61.2 Gy in 29 fractions. No surgery was performed after this treatment schedule, because of results published by Mitchell et al. (13) demonstrating that radiochemotherapy alone is a sufficient treatment for this type of tumor. One of the patients with rectal adenocarcinoma had 2 liver metastases at the start of the treatment. Resection of the liver metastases took place during the same operation as the abdominoperineal resection. Six patients were treated with capcitabine instead of intravenous 5FU. Five of these patients had a primary rectal adenocarcinoma and one a recurrence 3 years after a low anterior resection for a pT3N1 tumor.

Toxicities in the first cohort of three patients at a dose level of 85 mg/m² oxaliplatin consisted of elevated liver transaminases grade III, mild leucopenia and anemia (Table I). The dose was therefore escalated to 130 mg/m². At this dose level, seven patients were treated. One patient discontinued the treatment after 1 chemotherapy cycle and 27 Gy radiotherapy, because of grade 4 mucositis, diarrhoea.
and leucopenia. Subsequently, this was found to be due to a dihydropyrimidine dehydrogenase (DPD) deficiency, a germ line mutation known to intensify toxicity to 5FU (14). The DPD activity in this patient was 21% of the normally expected activity in controls. As this patient was considered not to be evaluable, a replacement patient was treated. However the sixth evaluable patient treated in the oxaliplatin dose group of 130 mg/m² experienced a grade V toxicity with a leucocyte count of 0.10 x 10⁹/l and died, probably of septicemia related to urosepsis. DNA analysis excluded common DPD deficiencies. After the treatment related-death of this patient, nine additional patients were treated in the regime with 85 mg/m² oxaliplatin without any dose-limiting toxicity, of whom six received capecitabine instead of intravenous 5FU. Two patients in the capecitabine group experienced grade III diarrhea. One of these was hospitalized for 11 days because of dehydration due to vomiting and diarrhea grade III. Neurosensory toxicity grade III was found in one patient. She complained of an objective weakness of the left arm lasting for 3 hours after which it resolved spontaneously. Table I lists the toxicities of the patients treated in both oxaliplatin dose schedules.

The median period between the last day of radiotherapy and surgery was 5.5 weeks (range 3.5-21.5 weeks). The median duration of admission after surgery was 17 days (range 9 days-7.5 months). Surgery performed after neo-adjuvant treatment consisted of 6 low anterior resections, 7 abdominoperineal resections and 2 exenterations. Two patients treated with 85 mg/m² oxaliplatin were found to have progressive disease at laparotomy. One of these patients underwent a palliative tumor resection, while in the other patient no resection was performed.

<table>
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<tr>
<th></th>
<th>Oxaliplatin 85 mg/m² and 5FU/LV(i.v.) (n=6)</th>
<th>Oxaliplatin 130 mg/m² and 5FU/LV(i.v.) (n=6)</th>
<th>Oxaliplatin 85 mg/m² and capecitabine (n=6)</th>
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<td><strong>Hematological</strong></td>
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<td>Leucopenia</td>
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<td>Nausea/vomiting</td>
<td>3 3</td>
<td>1 3</td>
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<tr>
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<td>Peripheral</td>
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The pathological tumor stage in the patients treated in the 85 mg/m² group showed three patients with stage pT3 tumors and two patients with stage pT2 N0-1. One patient had a pT0 stage but still showed few tumor cells in 2 lymph nodes. In the group treated with 130 mg/m² oxaliplatin, two patients had a stage pT3 tumor, one patient a stage pT2, one patient a pT1 stage and one a pT0N0 stage. In the six patients undergoing resection after 85 mg/m² oxaliplatin and capecitabine, there was one patient with a pT3 stage, one patient with pT2, two patients with pT1 and one with a pT0 N0 stage. Microscopic radical resection (R0) was performed in fourteen (78%) of the fifteen operated patients. A summary of these results is listed in Table II.

Postoperative complications within 1 month consisted of the need for a suprapubic catheter in five patients for a maximum period of 4 weeks. Operation techniques in these patients were 3 abdominoperineal resections and 2 low anterior resections. In three patients, a second laparotomy was needed to reconstruct a dehiscence of the fascia. One patient developed an ileus, which was treated conservatively. Pelvic exenteration in one patient, treated in the 85 mg/m² dose level, was complicated postoperatively by severe bleeding episodes.

**Discussion**

In our study, the addition of oxaliplatin to the radiochemotherapy treatment regime with 5FU and leucovorin in primary irresectable rectal cancer was safe in the 85 mg/m² group. In the next dose step (130 mg/m²), one patient experienced a dose-limiting toxicity, a grade 4 leucopenia of 0.1 x 10⁹/l, and died. Because of this DLT, the advisory dose to treat patients in this regime is 85 mg/m².
toxicity in the 130 mg/m² dose step in this study (18). A smaller irradiated volume might explain the acceptable dose was recommended. Continuous infusion of 5FU and a cycles of 5FU/LV (continuous infusion) were given patients who were treated in a phase II study (19). Two (80, 100 to 130 mg/m²) (17). This study used a treatment radiotherapy, 5FU/LV and oxaliplatin in escalating dose steps performed a phase I study treating seventeen patients with oxaliplatin to 5FU/LV and radiotherapy. Freyer neurosensory toxicity was the main dose-limiting toxicity studies with a higher cumulative dose of oxaliplatin, manageable grade III diarrhea (2/6 patients). In other 5FU by capecitabine resulted in a more frequent but attributed to the addition of oxaliplatin. The replacement of leucopenia and thrombocytopenia, which might be toxicity in the treatment with 5FU/LV and radiotherapy treatment with 5FU and oxaliplatin was comparable to the oxaliplatin. The gastrointestinal toxicity in the combination toxicity of our schedule (22). However, this schedule is more difficult because of different radiation fields and chemotherapy regimens. The patients in our study were treated for primary irresectable rectal cancer. Of the nineteen patients treated, one went off study due to a DPD deficiency, one was not operated on because of a cloacal carcinoma (and had a clinical complete response) and one died during the neo-adjuvant treatment. Two patients had progressive disease at laparotomy 5 weeks after neo-adjuvant treatment. From fifteen patients who underwent a tumor resection, fourteen (78%) had a microscopic radical resection (R0). Down-staging towards a pT0-2 N0 stage was found in 7/18 patients (39%), two of whom had a pathologic complete response (pT0 N0).

To optimize the neo-adjuvant regimen, a protracted infusion of 5FU might improve the effect and lessen the toxicity of our schedule (22). However, this schedule is more difficult to administer on an outpatient basis. Therefore, a treatment regime with radiotherapy, oxaliplatin and an oral 5FU like capecitabine, which mimics a protracted infusion of 5FU, might be the optimal regimen.

References


Table II. Surgery and pathology results of patients per treatment group.

<table>
<thead>
<tr>
<th>oxaliplatin dose level</th>
<th>Resection after neo-adjuvant treatment</th>
<th>R0 resection</th>
<th>pT0-2 N0</th>
<th>pCR</th>
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<tbody>
<tr>
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<td>6</td>
<td>5</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Oxaliplatin 130 mg/m² and 5FU/LV(i.v.) (n=6)</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Oxaliplatin 85 mg/m² and capecitabine (n=6)</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total (n=18)</td>
<td>15 (83 %)</td>
<td>14 (78 %)</td>
<td>7 (39 %)</td>
<td>2 (11 %)</td>
</tr>
</tbody>
</table>

Abbreviations: R0: microscopic radical resection, pCR: pathologic complete resection


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