Abstract. Aim: The aim of this study was to evaluate the pathological response of locally advanced rectal cancer after preoperative concurrent two-drug chemotherapy and intensified radiation therapy (RT) with concomitant boost. Patients and Methods: Patients with T4 tumor or local recurrence were included. A trial based on two-stage Simon’s design was planned. RT was performed with 3D-conformal technique. The dose to the mesorectum and pelvic lymph nodes was 45 Gy (1.8 Gy/fraction). A concomitant boost was delivered to Gross Tumor Volume (GTV) 2 cm margin to a total dose of 55 Gy (2.2 Gy/fraction). The following concurrent chemotherapy was administered: Raltitrexed (3 mg/m²) and oxaliplatin (130 mg/m²) on days 1, 17, and 35 of RT. Pathological response was evaluated according to the Mandard classification. Toxicities were scored according to the Common Terminology Criteria for Adverse Events v3.0 scale. Results: Eighteen patients (median age=64.5 years) were enrolled. The median follow-up was 22 months (range=2-36 months). After chemoradiation treatment, 16 patients underwent surgical resection (seven anterior resections and nine abdominal-perineal amputation); two patients did not undergo surgery due to early metastatic progression or refusal. R0 resection was achieved in all patients who underwent surgery. Five patients had pathological complete response [27.7%; 95% confidence interval (CI)=9.7-53.5%] and two patients showed only microscopic residual disease (11.1%; 95% CI=0.1-34.7%). Mandard grades 1 and 2 were detected in seven patients (38.9%; 95% CI=17.3-64.3%). Acute grade 3 or more toxicity was found in eight patients (44.4%; 95% CI=21.5-69.2%): one leucopenia-neutropenia, one liver, one skin and five cases of gastrointestinal toxicities. No patient had local tumor recurrence. One-, 2- and 3-year cumulative disease-free survival were 93.8%. One-, 2- and 3-year cumulative overall survival were 92.3%. Conclusion: Concurrent chemoradiation with concomitant boost in patients with advanced rectal cancer allows complete or near-complete pathological response in more than 38% of patients. However, severe acute toxicity was reported in more than one-third of patients.

Neoadjuvant chemoradiation (CRT), is considered standard treatment for locally advanced rectal cancer, with a positive impact on locoregional control and survival (1). However, patients with T4 rectal cancer have a high risk of local recurrence (LR) after conventional treatment (2). In these patients, even extended surgery with resection of adjacent organs is associated with poor local control rates and 5-year survival of less than 30% (3).

Local recurrence still represents a challenging problem in patients with rectal cancer because of poor outcomes. Surgical approach can be curative in these patients but frequently requires invasive procedures, with a high risk of...
complications (4). There is currently no standard treatment for LR, although multimodality treatment can be effective (5).

Several authors reported that pathological complete response (pCR) is strongly associated with improved long-term outcomes (1, 6, 7). Therefore, pathological response can be considered as a surrogate endpoint in neoadjuvant treatment. Radiotherapy (RT) with curative intent is traditionally used with conventional fractionation (1.8-2.0 Gy/fraction), however, the use of non-conventional fractionation schemes and multidrug chemotherapeutic regimens has improved the pCR rates (1, 8).

Only few studies have evaluated the feasibility and efficacy of neoadjuvant treatment combining intensified RT and concurrent multidrug chemotherapy. Data on the efficacy of combination chemotherapy regimens in terms of local control and reduction of distant metastases rate remain scant. (9-11)

In our previous phase II study, we assessed the feasibility and efficacy of a combined modality treatment based on concomitant boost RT plus multidrug concurrent chemotherapy in the neoadjuvant setting of locally advanced rectal cancer (12). In that study, patients with T3-4 N0-2 or T1-2 N1-2 rectal adenocarcinoma received RT with concomitant boost plus raltitrexed and oxaliplatin (Tom-Ox) chemotherapy. Results showed that this intensified treatment was effective in terms of pathological complete response (32%).

Based on these positive results, we planned a study on the efficacy in terms of response of concurrent CRT with multidrug chemotherapy plus concomitant boost, in patients with more advanced tumors (T4 and recurrences).

**Patients and Methods**

**Study design and aims.** This was a prospective phase II study on patients with locally advanced rectal cancer or locally recurrence to evaluate the efficacy in terms of pathological response and resectability of concomitant boost RT (55 Gy/5 weeks) with concurrent Tom-Ox chemotherapy. The primary aim was to assess the pCR rate. A key secondary aim was resectability. Secondary aims were evaluation of treatment-related acute and late toxicity, local control, disease-free survival and overall survival. The follow-up period of each patient started after the CRT treatment and ended after a maximum of 36 months of observation or until death. The trial was approved by the Local Ethics Committee and registered in an international public registry (ClinicalTrials.gov Identifier: NCT02723253).

**Elegibility criteria.** All the following inclusion criteria were to be fulfilled for inclusion in the trial: i) histologically-proven locally advanced (T4N0-2) or locally recurrent rectal adenocarcinoma; ii) age ≥18 years; iii) Eastern Eastern Cooperative Oncology Group performance status of 0-2. Patients with metastatic disease, those unfit for surgery, pregnant or breast-feeding females, and patients with clinically detectable ascites were excluded.

**Outcome measures.** Baseline evaluation included physical examination with a digital rectal examination, a complete pathological history and a complete blood count, liver and renal function. All patients were evaluated before RT with colonoscopy with biopsy, contrast-enhanced thorax-abdomen-pelvis computed tomography (CT) scan and pelvic magnetic resonance imaging (MRI).

Pathological responses of the primary tumors were defined according to the Mandard regression grading system (13): grade 1 was recorded when no tumor cells remained in the primary tumor and lymph nodes (pCR); grade 2 was characterized by the presence of rare residual cancer cells scattered through the fibrosis; grade 3 was characterized by an increase in the number of residual cancer cells, but fibrosis was still predominant; grade 4 showed residual cancer outgrowing fibrosis; and grade 5 was characterized by an absence of regressive changes. Good responders were defined those patients with a pathological response of Mandard grade 1 or 2 and poor responders were those with Mandard grade 3-5. The clinical response rate was assessed five to six weeks after completion of CRT, with clinical examination, contrast-enhanced thorax-abdomen-pelvis CT scan and pelvic MRI. Radiological restaging was evaluated according to the RECIST criteria (14), defined as complete response (CR), the disappearance of all target lesions; partial response (PR), 30% decrease in the sum of the longest diameter of target lesion; progressive disease (PD), 20% increase in the sum of the longest diameter of target lesions; and stable disease (SD) small changes that did not meet the above criteria. The overall response rate (ORR) was calculated as the sum of PR and CR.

Clinical examination and laboratory analysis were planned weekly during neoadjuvant treatment. Common Terminology Criteria for Adverse Events v 3.0 was used to score acute and late radiation toxicity (15). Follow-up examinations were performed 4 weeks after surgery and every 6 months until the established length of follow-up or death including physical examination and blood counts. CT scan or MRI were performed every 6 months as follow-up imaging studies. Disease-free survival was defined as the time from diagnosis to documented local or distant recurrence or last follow-up. Overall survival was defined as the time from the diagnosis until death from any cause, or the last follow-up.

**Radiotherapy.** During the simulation process and treatment, patients were immobilized in prone position on an up-down table, a personal device aimed to displace the small-bowel. An empty rectum and a full bladder were required before CT simulation and before every daily treatment fraction, in order to limit the physiological organ motion. Clinical target volume 1 (CTV1) included the gross tumor volume (GTV, both primary tumor and enlarged pelvic nodes) and the corresponding mesorectum plus 2 cm cranio-caudally. CTV2 included CTV1 plus the entire mesorectum, the pre-sacral space, the internal iliac nodes and the high-risk anatomical and nodal sub-sites, based on the distance of the tumor from the anal margin (16). Planning target volume (PTV) was generated by adding 0.8 cm margin to CTV in all directions. Organs at-risk were the small intestine, the femoral heads and the bladder. Radiotherapy was applied as conformal 3-D technique and was delivered with photon energies of 10-15 MV. The beams were delivered by an Elekta Precise Linac (Elekta, Crawley, UK) equipped with standard multi leaf collimators. A daily online check of isocenter position was performed using portal imaging, with set-up correction in case of displacement >0.5 cm in any direction (17). The RT dose delivered to PTV2 was 45 Gy (1.8 Gy/fraction) with a concomitant boost dose to PTV1 of 10 Gy with accelerated fractionation at 2.2 Gy/fraction, five consecutive days per week. Planning and delivery processes underwent systematic independent check procedures, as previously.
described (18). In patients with grade 3 or more acute toxicity (gastrointestinal, genitourinary or skin toxicity), RT was stopped until reaching at least grade 2 toxicity and then resumed as soon as possible. Chemotherapy was delayed similarly.

**Chemotherapy.** Adequate neutrophil and platelet count parameters (>1.5x10^9/l and >75x10^9/l respectively) were required before each chemotherapy infusion. The concurrent chemotherapy consisted of 15 min intravenous infusion raltitrexed (Tomudex®) 3 mg/m^2 and a 2-h intravenous infusion of oxaliplatin (Eloxatin®) at 130 mg/m^2, 20 min after raltitrexed, on days 1, 17, 35. Antiemetic prophylaxis with 5-hydroxytryptamine antagonists was administered only the day of chemotherapy delivery. In case of grade 3 or more liver, renal or hematological toxicity, chemotherapy was delayed until grade 2 toxicity resumed. In this case, a 25% dose reduction of chemotherapy was prescribed in the subsequent cycles. The choice of adjuvant chemotherapy was recommended for patients with positive nodes at pathological examination and left at the oncologist's discretion.

**Surgery.** Independently of clinical response, patients underwent surgery 8 weeks after CRT. The choice of surgical procedure [abdominoperineal resection (APR) versus low anterior resection (LAR)], was left at the surgeon's discretion on the basis of restaging. Total mesorectal excision TME was recommended and performed in all resected cases.

**Sample size determination and statistical analysis.** The sample size was determined using the two-stage design by Simon (19). The study required the enrollment of 9-17 patients in order to test the null hypothesis that the pCR for this population would improve from ~5% to the clinically relevant alternative of 25%, (error probability limits 0.05/0.2). Nine patients were to be recruited in the first step: if there were no pCR, the study would be closed. Assuming a possible non-participation rate of 5%, we raised the sample size of the second step to nine patients. Hence, if at least one pCR detected, the study would enroll nine new patients up to a total of 18 patients. The regimen would be considered inactive if fewer than 2/18 pCR were recorded.

Continuous variables are reported as the median with range. Categorical variables are reported as the proportion and percentage. Survival curves were calculated with the Kaplan–Meier method (20). Statistical analysis was performed with SYSTAT, version 11.0 (SPSS, Chicago, IL, USA) and SPSS v. 22 (IBM Corp., Armonk, NY, US).

**Results**

Nine patients were enrolled in the first phase of this study and underwent surgical resection. Four patients showed pCR. Therefore, the study continued with the recruitment of nine additional patients in the second part of the study for a total of 18 patients (10 females; median age 64.5±years, range=45-80 years). The median follow-up was 22 months (range=2-36 months). Baseline patient characteristics are detailed in Table I.

**Pathological response of the primary tumor.** A pCR was observed in five patients [27.7%; 95% confidence interval (CI)=9.7-53.5%] and two patients (11.1%; 95% CI=0.1-34.7%) showed only microscopic residual disease. According to the Mandard criteria, seven patients (38.9%; 95% CI=17.3-64.3%) were good responders (i.e., grade 1 and 2).

**Resectability.** Sixteen patients (88.9%; 95% CI=65.3-98.6%) underwent surgical resection: seven patients (38.9%; 95% CI=17.3-64.3%) with LAR approach and nine patients (50%; 95% CI=26.0-74.0%) with APR approach. A complete locoregional resection (R0) was achieved in all patients who underwent surgery. One patient did not undergo surgery due to early metastatic progression and one patient refused surgical intervention.

**Tumor response.** According to RECIST criteria, PR was observed in 17 patients (94.4%; 95% CI=72.7-99.9%) and one patient (5.6%; 95% CI=0.1-27.3%) had a CR.

**Toxicity.** All patients had at least one temporary and reversible grade 1-2 acute symptom: diarrhea/proctitis were the most frequent acute symptoms. Five patients (27.8%; 95% CI=9.7-53.5%) developed acute grade 3 or more toxicity gastrointestinal toxicity, one (5.6%; 95% CI=0.1-27.3%) had grade 3 or more leucopenia-neutropenia, one (5.6%; 95% CI=0.1-27.3%) had grade 3 or more skin toxicity and one (5.6%; 95% CI=0.1-27.3%) had grade 3 or more liver toxicity, with an overall incidence of eight patients (44.4%; 95% CI=21.5-69.2%) with grade 3 or more acute symptoms (Table II). Ten patients (55.6%; 95% CI=26.0-74.0%) were required before each chemotherapy delivery. In case of grade 3 or more liver, renal or hematological toxicity, chemotherapy was delayed until grade 2 toxicity resumed. In this case, a 25% dose reduction of chemotherapy was prescribed in the subsequent cycles. The choice of adjuvant chemotherapy was recommended for patients with positive nodes at pathological examination and left at the oncologist's discretion.

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Table II. Acute toxicity (Common Terminology Criteria for Adverse Events, CTCAE, Version 3.0) (15).

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>0 (n=18)</th>
<th>1 (n=18)</th>
<th>2 (n=18)</th>
<th>3 (n=18)</th>
<th>4 (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>5</td>
<td>1</td>
<td>11</td>
<td>1</td>
<td>5.6</td>
</tr>
<tr>
<td>Proctitis</td>
<td>13</td>
<td>2</td>
<td>1</td>
<td>5.6</td>
<td>11.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>3</td>
<td>4</td>
<td>22.2</td>
<td>16.7</td>
</tr>
<tr>
<td>Urinary frequency/urgency</td>
<td>13</td>
<td>4</td>
<td>1</td>
<td>5.6</td>
<td>61.1</td>
</tr>
<tr>
<td>Hematuria</td>
<td>17</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dysuria</td>
<td>12</td>
<td>5</td>
<td>1</td>
<td>5.6</td>
<td>0</td>
</tr>
<tr>
<td>Urinary</td>
<td>6</td>
<td>10</td>
<td>2</td>
<td>11.1</td>
<td>0</td>
</tr>
<tr>
<td>Liver</td>
<td>15</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>14</td>
<td>3</td>
<td>1</td>
<td>5.6</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>11.1</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>13</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14</td>
<td>3</td>
<td>1</td>
<td>5.6</td>
<td>0</td>
</tr>
</tbody>
</table>

*Same patient.

CI=30.8-78.5%) discontinued therapy for at least one day because of toxicity (median=1 day; range=0-16 days).

After a median of 14 months (range=2-36 months), one patient (5.6%; 95% CI=0.1-27.3%) had late grade 3 or more urinary incontinence and another one (5.6%; 95% CI=0.1-27.3%) had a gastrointestinal late grade 3 or more toxicity due to an anastomotic stenosis. Four patients (22.2%; 95% CI=6.4-47.6%) had grade 1-2 skin late toxicity and two patients (11.1%; 95% CI=0.1-34.7%) had a grade 2 gastrointestinal late toxicity. No patient had local tumor recurrence. One-, 2- and 3-year cumulative disease-free survival were 93.8% (Figure 1). One-, 2- and 3-year cumulative overall survival were 92.3% (Figure 2).

Discussion

Main findings of this phase II prospective study were that neoadjuvant treatment with concomitant boost RT plus concurrent multidrug chemotherapy of patients with advanced rectal cancer or local recurrences achieved a complete or near-complete pathological response in more than one-third of cases and the resectability in almost all cases. However, a grade 3 toxicity was reported in more than 44% of cases. Our results substantially confirmed the efficacy of this treatment regimen also in patients with more advanced stage of rectal cancer (T4 and recurrences) and not only in all those with locally advanced stages (12).

In literature, other previous studies tried to improve the pCR rate by using a concomitant boost RT and some phase II clinical trials reported promising results (21-23). In most of these studies, concurrent chemotherapy was based on 5-FU or oral fluoropyrimidines (23, 24), whereas some authors did not these agents (25).

Furthermore, various efforts have been made to improve standard neoadjuvant CRT by intensifying the chemotherapy schedule. Most of them were based on use of oxaliplatin, assuming a real benefit compared to fluoropyrimidine-based treatment (26-28), even if recent phase III trials (29, 30) did not support the inclusion of oxaliplatin in neoadjuvant schedule. A phase III, multicenter, randomised trial (31), reported a high 3-year disease-free survival rate in patients undergoing CRT with the addition of oxaliplatin to fluorouracil-based chemotherapy compared to those receiving standard fluorouracil-based combined modality regimen (75.9% vs. 71.2%; p=0.03%).

In the past, other studies showed the efficacy of oxaliplatin, not only in association with standard chemotherapy, but also in combination with new chemotherapeutic agents. An Italian phase II study, based on Tom-Ox, showed similar efficacy and tolerability to conventional 5-hydroxytryptamine based regimens (32). Likewise, in our previous study, we investigated and demonstrated the feasibility and efficacy of a chemoradiation treatment with the use of Tom-Ox in a preoperative setting for locally advanced rectal cancer (9). Despite the use of the same chemotherapy scheme of our current study, we used a standard radiotherapy schedule (50.4 Gy). To confirm the excellent pCR observed in this phase II trial, a randomized multicenter study was performed to assessed the tumor down-staging after two different schedules of preoperative chemoradiotherapy, TOMOX arm vs. cisplatin and 5-fluorouracil (PLAFUR) arm. The study included 164 patients...
with locally advanced rectable rectal cancer and evaluated the tumor down-staging rate and the acute toxicity rate into the two arms. The results demonstrated a greater percentage of down-staging in the TOMOX arm (35.8% vs. 24.1%) despite a greater acute grade 3 toxicity (16% vs. 7%) (33).

Subsequently, the question arose as to whether intensified radiotherapy could play a positive role in the final outcome of this combined treatment. In a recent dose-escalation study, four cohorts of patients were compared to determine the safety dose of preoperative radiotherapy with concomitant two-drug chemotherapy. The treatment schedules of chemoradiation included standard RT (50.4 Gy) plus raltitrexed as monotherapy, accelerated RT (55 Gy) plus raltitrexed-based chemotherapy, standard RT plus Tom-Ox regimen and, finally, accelerated RT plus Tom-Ox. The overall pathological response rate for the intensified regimen plus Tom-Ox cohort was 31.25% with an acceptable rate of grade 3 or more toxicity. The authors concluded that the use of accelerated RT plus Tom-Ox could be carefully administered in a preoperative setting in patients with locally advanced rectal cancer (34).

The association of intensified RT plus multidrug chemotherapy was also previously investigated in our previous experience (12) and in the Lyon R-02-01 phase I trial. (35). In the French study, 12 patients underwent chemotherapy based on capecitabine, irinotecan and oxaliplatin administered during RT (46 Gy in 2.3 Gy daily fractions and a boost of 4 Gy in two fractions to a reduced field). The trial showed efficacy in terms of local control (66.7%) but with an unacceptable rate of grade 3/4 toxicities in two-thirds of the patients after addition of oxaliplatin.

Compared to these studies, our results showed that 11 patients (61.1%) had grade 1-2 gastrointestinal toxicity, especially diarrhea and proctitis, and five patients (27.8%) had grade 3 gastrointestinal toxicity. No grade 4 toxicity occurred. Furthermore, one patient had reversible hypertransaminasemia and one patient grade 3 leucopenia-neutropenia, resulting in a reduction of chemotherapy dose. As in our previous study (12), this combination treatment resulted in relatively higher rates of toxicity compared to standard CRT and this effect was probably, at least partially, due to the use of multidrug chemotherapy. Despite this, in line with our previous studies, in the current study there was an impressively high disease-free and overall survival rate. No patient had local tumor recurrence at the time of the last follow-up.

The idea of a treatment with a multidrug scheme in association with preoperative RT is thus debated, as it may allow potentiation of the latter, providing beneficial effects on the local and systemic disease. Like our study, several randomized trials (36, 37) have indeed established that preoperative CRT reduces the rate of local recurrence, with a higher percentage of disease-free and overall survival, but a standard safe combination is still lacking.

In conclusion, our study suggests that combined treatment with intensified RT by concomitant boost plus multidrug chemotherapy induces a high pCR rate, despite increased severe toxicity. Further studies are required to investigate whether the implementation of different treatment protocols and drugs regimens together with advanced RT techniques might improve treatment tolerability, reducing the overall toxicity. Consequently, we planned a phase I-II study based

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Figure 1. Kaplan–Meier plot estimates of the cumulative disease-free survival.

Figure 2. Kaplan–Meier plot estimates of the cumulative overall survival.
on a different treatment scheme delivered concurrently to intensity-modulated RT with simultaneously integrated boost.

**Conflicts of Interest**

No actual or potential conflicts of interest exist regarding this paper.

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