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Preoperative Treatment with Capecitabine, Cetuximab and Radiotherapy for Primary Locally Advanced Rectal Cancer – A Phase II Clinical Trial

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Abstract. *Background and Purpose: To study the feasibility and safety of preoperative capecitabine, cetuximab and radiation in patients with MRI-defined locally advanced rectal cancer (LARC, cT3/T4). Materials and Methods: 31 patients with LARC were treated with Cetuximab and Capecitabine concomitantly with radiotherapy of 45 Gy and resected by total mesorectal excision. Histopathological response and association with KRAS-status was evaluated. Results: R0-resection was possible in 27 of 31 (86%) patients. No complete pathological remission was observed. Radiochemotherapy with capecitabine and cetuximab was safe to administer, diarrhea was the main toxicity. KRAS-status did not correlate to downstaging or pathological response concerning T- or N-stage. Conclusion: Neoadjuvant therapy with Capecitabine and Cetuximab in combination with radiotherapy did not lead to complete pathological remission. Treatment tolerability was excellent and toxicity remained low. KRAS-status did not influence treatment outcomes. Capecitabine in combination with radiotherapy remains a standard therapy for locally advanced rectal cancer.*

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Key Words: Rectal cancer, radiochemotherapy, capecitabine, cetuximab, phase II.

Locally advanced rectal cancer (LARC) is a paradigm for multimodal management, as the combination of surgery, chemotherapy and radiotherapy is necessary to achieve the optimal outcome for patients (1). Preoperative radiochemotherapy (RCT) represents a standard treatment for patients with LARC. Since the introduction of total mesorectal excision, recurrence rates have been reduced significantly (<10% compared to 20%-45% with conventional surgery alone) (2, 3). Preoperative multimodality treatment of LARC is designed to improve survival, reduce local recurrence and increase the options for sphincter-saving surgery (4-6). The development of distant metastases is the predominant mode of failure. Efforts to improve preoperative treatment of LARC aimed to integrate more effective systemic therapy into combined-modality protocols.

Targeted therapies have rapidly gained attention in the treatment of advanced colorectal cancer and are under active investigation in the neoadjuvant and palliative settings. Cetuximab, an Immunoglobulin 1 monoclonal antibody directed against the epidermal growth factor receptor (EGFR), demonstrated efficacy with significant improvement in progression-free survival or overall survival in patients with metastatic colorectal cancer in first-, second- and third-line therapy (7-9). Cetuximab has been shown to be a potent

radiosensitizing agent in preclinical models of human cancer (10) and demonstrated its efficacy as a radiosensitizer in a phase III trial against head-and-neck cancer (11).

In this single-arm trial, we evaluated the feasibility, safety and efficacy of preoperative treatment with cetuximab in combination with capecitabine and concomitant radiotherapy in patients with LARC.

Patients and Methods

Study design. This single-arm multicenter phase II clinical trial undertaken by the Austrian Breast and Colorectal Cancer Study Group (ABCSG) evaluated the feasibility and safety of preoperative treatment with capecitabine, cetuximab and radiotherapy in patients with LARC. Secondary endpoints included pathological response and tumor down-staging. Analysis of the *Kirsten-RAS* (*KRAS*) status, which was not initially planned, was performed on available operative specimens after an amendment of the study.

Patient selection and evaluation. Previously untreated patients with locally advanced, histologically confirmed adenocarcinoma of the rectum, aged 18-80 years, with a World Health Organization performance status of zero to two, adequate hematological, renal and hepatic function were eligible for inclusion. The tumor had to be locally advanced by magnetic resonance imaging (MRI) (cT4, cT3) but potentially resectable. Initially, we only included cT4 tumors, but later amended the protocol to allow inclusion of cT3 tumors. Before registration, all patients were evaluated by a multidisciplinary team to determine potential resectability and general operability. A urine-based pregnancy test was required for all women with childbearing potential, and contraceptive use was required for patients of childbearing age. All patients were required to give their written informed consent. The study was approved by the local Ethics Committee (Eudract 2005-003740-62). Assessment of the clinical stage was based on flexible rectoscopy, computed tomographic scans of chest and abdomen, and obligatory pelvic MRI. Pre-treatment evaluation included a medical history, physical examination, complete blood cell count, serum chemistry within 28 days of starting treatment. The study was planned for 30 patients. Patients no. 30 and 31 were entered into the study on the same day and thus were allowed to stay on treatment according to the local data monitoring board. Recruitment took place from March 2006 to April 2008.

Treatment plan (Figure 1). Radiotherapy: Three-dimensional conformal radiotherapy was planned using >4 MV X-rays in a 3-field irradiation technique. Clinical target volumes (CTVs) included the primary rectal tumoral lesions and the two end portions of the rectum, the perirectal tissues, the anterior sacral lymph, iliac lymph, obturator lymph and true pelvis internal iliac lymph drainage areas. For patients with stage T4 lesions or tumors invading the bladder, the CTV also included the external iliac lymph drainage area. The planned target volume (PTV) was defined as the CTV or gross tumor volume (GTV) plus 8 mm. The treatment was given in the prone position with a full bladder. Customized beam blocks or multileaf collimators were used to restrict the irradiation volume to the treated volume. A dose of 45 Gy was planned over five weeks, with 1.8 Gy per fraction, all fields being treated daily. The reference dose was specified at the intersection of the beam axis. The target absorbed dose was at least 95% and the maximum was not higher than 107% of the reference dose (ICRU62) (ICRU. International Commission on Radiation Units and Measurement, Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50). ICRU report 62, 1999) (12). Radiation was discontinued if grade 4 toxicity according to the NCI CTC guideline (13) occurred.

Capecitabine: Capecitabine was administered concurrently at 825 mg/m^2 *bid* on days of radiation during the first four weeks (days 1-5, 8-12, 15-19, and 22-26) (14, 15). Toxicities were assessed and recorded at every visit and graded according to NCIC CTC version 2.0. The capecitabine dose-modification scheme was applied if patients experienced grade 2-4 toxicity.

Cetuximab: The monoclonal antibody cetuximab was administered by a 90-minute intravenous infusion, with a loading dose of 400 mg/m^2 body surface on day 1, followed by 250 mg/m^2 body surface on days 8, 15, 22 and 29 (Figure 1). Premedication included an antihistamine and cortisone 30 minutes prior to cetuximab. Dose reduction for toxicity was not recommended but dosing with cetuximab was witheld or discontinued for defined adverse events such as grade 3 or more skin toxicity or hypersensivity reaction.

Surgery: Surgery followed 6-8 weeks after completion of preoperative treatment. The goal of surgery was complete removal of the primary tumor according to the principles of total mesorectal excision either by low anterior resection, abdomino-perineal excision, or intersphincteric resection.

Histological assessment. Tissue samples were embedded in paraffin, cut and stained with hematoxylin and eosin (H&E). The tumors were classified according to the WHO classification system and staged according to the TNM classification system using the y prefix for staging of rectal cancer after preoperative treatment (16).

Assessment of KRAS status. KRAS analysis was performed on 25 available tumor specimens of patients. Six tumor specimens were not forwarded for molecular analysis. After selection of representative tumor regions on H&E-stained slides, tumor areas were macrodissected from parallel unstained slides with a sterile needle. DNA was prepared using QIAamp® DNA Mini Kit, (Qiagen, Hilden, Germany) according to the manufacturer's recommendations. After spectrophotometric DNA evaluation (NanoDrop® ND-100 Spectrophotometer; NanoDrop Technologies, Wilmington, DE, USA). DNA was analyzed for KRAS mutations by pyrosequencing on a PyroMark™ Q24 MDx with PyroMark™ Q24 MDx Software using the PyroMark™ KRAS Kit (all Qiagen) according to the manufacturer's recommendations. Two pyrosequencing reactions were performed with products of 10 and 20 ng template DNA respectively.

Assessment of response to therapy. All patients were re-evaluated within two weeks before surgery by thoracic-abdominal CT scan, clinical examination and laboratory evaluations, consisting of hematology and serum biochemistry. Histopathological examination of the resected tumor followed the guidelines of the TNM system (17). *KRAS* status was correlated to tumor down-staging and pathological response.

Results

A total of 31 patients (11 women and 20 men) were enrolled (Figure 2). Their median age was 61 years (range=41-80

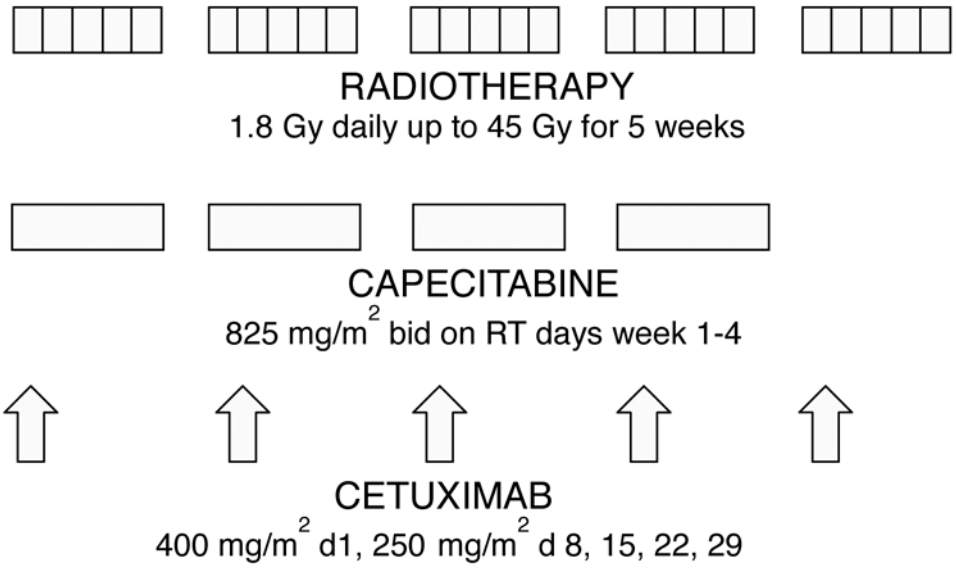

Figure 1. *Overview of the concomitant radiochemotherapy regimen.*

years) and Eastern Cooperative Oncology Group performance status (EGOG PS) was 0, 1 and 2 in 71%, 26% and 3%, respectively. Patients' characteristics and pre-treatment diagnostic tests are shown in Table I. The majority of patients (68%) had cT4 tumors and positive lymph nodes (LN) were detected by imaging in 25 patients (81%).

All patients received preoperative treatment. The dose intensity of capecitabine and cetuximab was 92% and 99%, and that of radiotherapy was 99%. Major side-effects of RCT were mostly diarrhea (grade 3: 10%; grade 4: 3%), skin rash (grade 3: 6%) and rectal itching/pain (grade 3: 3%). All toxicities occurring during RCT and before surgery are listed in Table II.

Surgery was performed on 28 patients. Three patients did not undergo surgery: one patient developed peritoneal metastases during the preoperative treatment and received palliative medical treatment; one patient was judged unfit for general anesthesia due to cardiac disease at pre-surgical re-evaluation; and one patient suffered a cerebrovascular stroke and eventually died while on study. total mesorectal excision was performed on 28 patients (low anterior resection n=16, abdominoperineal extirpation n=10, intersphincteric resection n=1, not stated n=1), R0 resection was possible in 27 out of 28 patients (96%). Of 12 patients presenting with cT4 tumors, down-staging to ypT3 occurred in seven cases, to ypT2 in four and to ypT1 in one case comparing clinical stage to pathological stage. Six patients with cT4 tumors remained at ypT4 after RCT and resection. Only one patient out of 10 presenting with cT3 tumors showed down-staging to ypT2, the others (n=9) remained at ypT3. Of 25 patients which were LN-positive at screening, three did not undergo surgery, 10 were LN-negative after RCT and 11 patients remained LN-positive (ypN1=6, ypN2=5). Lymph node status of one patient could not be determined (ypNX). No complete pathological response was observed in the 28 resection specimens.

Table I. *Patient characteristics.*

Characteristic	No. of patients (%)
Total	31
Male	20 (65%)
Female	11 (35%)
Age (years)	
Median	61
Range	41-80
ECOG performance status	
0	21 (71%)
1	9 (26%)
2	1 (3%)
Clinical TN stage	
cT3	10 (32%)
cT4	21 (68%)
cN0	2 (6%)
cN1	25 (81%)
cNX	4 (13%)
KRAS status	N=25
Wild-type	14 (56%)
Mutated	11 (44%)
Missing	6

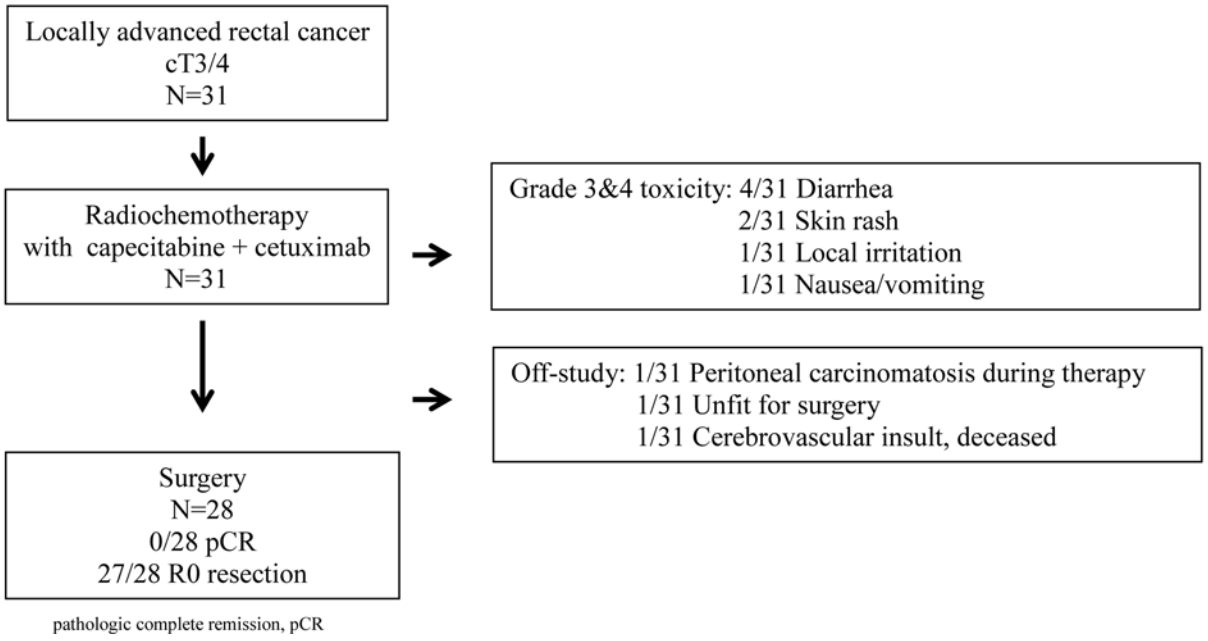

Figure 2. *Accrual and treatment summary.*

Tumor specimens for analysis of *KRAS* mutation were available for 25 patients. Fourteen patients (56%) were *KRAS* wild-type, while tumor in 11 patients (44%) had a *KRAS* mutation. *KRAS* status did not correlate to down-staging by T-stage (chi square=0.12, p=0.729) nor by N-stage (chi square=0.1125, p=0.737) (Table III).

Discussion

Preoperative 5-Fluorouracil (5-FU) based RCT and total mesorectal excision is considered a standard treatment for patients with stage II/III rectal cancer. Despite optimized treatment, with local recurrence rates of 5-10%, subsequent distant metastasis still occurs in 25-30% of patients (18, 19). In order to enhance the efficacy of RCT, the role of radiationsensitizing agents has been studied in several trials. Capecitabine, oxaliplatin, and irinotecan, as well as targeted therapies such as cetuximab, have improved results for patients with colorectal cancer when treated in the metastatic setting (20, 21). In recent years, our study group designed and conducted clinical trials to improve the efficacy in terms of local recurrence and prevention of metastasis in rectal cancer (14, 15).

In this phase II study, the preoperative therapy included capecitabine, cetuximab and external beam radiotherapy. The mean dose intensities of capecitabine, cetuximab and radiotherapy were high (92%, 99% and 99%, respectively), indicative of excellent treatment tolerability. The main toxicities were diarrhea and skin rash, which were managed adequately. R0 resection was possible in 27 out of 31 (87%) patients. Comparing clinical stage to pathological stage, we observed tumor down-staging by T-stage in 42%, and by N-stage in 40% of the LN-positive patients. However, no pathologic complete remission was observed for the resected patients.

Study design, treatment schedule and toxicity in our trial are comparable with other phase I/II trials of preoperative chemoradiation in combination with cetuximab for LARC (22-30), although we included a higher proportion of cT4 tumors (68%). Two studies employed a combination of capecitabine, oxaliplatin, and radiation plus cetuximab (22, 23), while in four additional studies, capecitabine, irinotecan and radiation was combined with cetuximab (24-26, 30); in the remaining studies, all patients received capecitabine/5-FU, and radiation plus cetuximab (27-29). The radiation dose was 33 Gy in one study (29), 45 Gy in three studies (27, 28, 30) and 50.4 Gy in eight studies (22-26, 31-33). Out of a total of 356 patients, complete pathological response was observed in only 10.6% and was less than expected with fluoropyrimidine-based RCT, which lies in the range of 13%-17% (18, 19). The main toxic effects of these regimens were grade 3/4 diarrhea at 14%, which is comparable with 13% in the present study.

It is now well known from the treatment of metastatic colorectal cancer that patients with *KRAS* mutations do not benefit from anti-EGFR-directed therapies. The frequency of

Table II. *Maximum toxicity grade (number of patients).*

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hand-foot syndrome	2	0	0	0
Skin toxicity	14	10	2	0
Fever	0	2	0	0
Local toxicity	1	0	1	0
Loss of weight	3	1	0	1
Hypertension	1	2	0	0
Bleeding	1	0	0	0
Hypotension	1	0	0	0
Infection	3	1	0	0
Neurotoxity, sensory	1	0	0	0
Nausea	6	0	0	0
Vomiting	1	0	0	0
Diarrhea	8	4	3	2
Neurotox. cerebellar	1	0	0	0
Stomatitis	2	0	0	0
Neurotox. psyche	1	0	0	0
Neuroteox. headache	1	0	0	0
Neurotox. constipation	1	0	0	0
Lung	1	0	0	0
Neutropenia	1	2	0	0
Anemia	2	5	0	0
Thrombopenia	1	0	0	0

Each patient is counted once with the maximal grade she/he reported during the study per that toxicity.

Table III. *Tumor down-staging* and association with KRAS-status .*

	cT3/T4		cN1/N2	
KRAS status	With down-staging	Without down-staging	With down-staging	Without down-staging
Wild-type	n=6	n=8	n=5	n=8
Mutated	n=4	n=6	n=3	n=4
Not tested	n=3	n=1	n=2	n=1

*Tumor in three patients was not resected.

KRAS mutation in rectal cancer has been reported to be between 13% and 32% (26, 30-32). In our analysis, rectal carcinomas from 11 patients (44%) harboured a *KRAS* mutation. KRAS status did not influence treatment outcome in our study. Despite the limited number of patients, this is in accordance with three phase II studies (26, 30, 32) in which no association of *KRAS* status and efficacy of cetuximab was demonstrated. Only one study reported a better outcome in patients with wild-type KRAS while receiving capecitabine, cetuximab and radiation (31). A recently published randomized phase II study using induction chemotherapy with capecitabine and oxaliplatin followed by RCT with capecitabine and adjuvant chemotherapy *versus* the same therapy plus cetuximab did not show improvements in histological response or progression-free survival in those with *KRAS/B-rat fibrosarcoma* (*BRAF*)-wild-type tumors (33). Whether the addition of cetuximab to a fluoropyrimidine-based RCT protocol leads to antagonistic effects is open to speculation. One explanation for such effects could be that cetuximab causes G_1 or G_2/M cell-cycle arrest and prevents the additive effect of 5-fluorouracil and radiation (34). This might also affect the chance of achieving complete pathological respons.

In summary, our trial of capecitabine, cetuximab and radiation for LARC showed excellent tolerability, few toxicities and a high R0 resection rate. Comparing clinical stage to pathological stage, we observed some form of down-staging, but no complete pathological response. Comparable to other trials on rectal cancer, *KRAS* status was not associated with response or pathological remission. While continuing to investigate additional approaches and drug combinations in order to improve the efficacy and long-term outcome of neoadjuvant multi-modality treatment in patients with LARC, capecitabine or infusional 5-fluorouracil in combination with radiotherapy remains a standard therapy.

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Conflicts of Interest

None.

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