SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 1: 189-194, 2010

Chemoradiotherapy with 5-fluorouracil/leucovorin, surgery and adjuvant chemotherapy for locally advanced rectal cancer

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Received July 14, 2009; Accepted October 5, 2009

DOI: 10.3892/ol_00000035

Abstract. The aim of this study was to demonstrate a pathologic complete response (pCR) rate of at least 10% with an acceptable toxicity achieved by preoperative chemoradiotherapy with 5-fluorouracil (5-FU)/leucovorin in patients with locally advanced rectal cancer. Patients were treated by radiotherapy targeting 50 Gy and 5-FU/leucovorin intravenously during the 1st, 4th and 7th week after start of radiotherapy followed by surgery and adjuvant chemotherapy. In 71 evaluable patients, the pCR rate was 14.1% (95% CI, 6.0-22.2); the local relapse rate, 6.1%; the 5-year disease-free survival, 54% and the overall 5-year survival, 68%. The most severe adverse events were neutropenia (17%), diarrhoea (17%), infection (8%) and fatal cardiovascular function (1%). This therapy yielded a high rate of pCR, a low rate of local relapse and a long disease-free and overall survival. To increase its feasibility, radiation dose reduction to 45 Gy and administration of only two preoperative cycles of chemotherapy is recommended.

Introduction

In the 1990s adjuvant 5-fluorouracil (5-FU)-based chemotherapy combined with radiotherapy in patients with stage II and III rectal cancer after surgical resection was established as the new standard of care decreasing the rate of local recurrence and improving patient survival (1,2). A significant change in the treatment of rectal cancer occurred with the introduction of total mesorectal excision (TME) resulting in decreased local recurrences and improved survival (3). In 1995, when this trial started, preoperative therapy was applied to downstage tumors in order to increase sphincter-sparing surgery in distal rectal tumors and to decrease the overall toxicity.

We conducted a single centre phase II trial in order to investigate the feasibility and outcome of 5-FU-based preoperative chemotherapy combined with long-term irradiation followed by surgical treatment including TME, followed by postoperative 5-FU-based chemotherapy. The results, after a median follow-up of approximately three years (38.9 months; range 2.8-108.2 months), are presented and discussed within the context of the results published in the literature.

Patients and methods

Patients were enrolled between November 1995 and November 2004. Eligibility criteria included histopathologically confirmed adenocarcinoma of the rectum [according to the 1987 International Union Against Cancer (UICC) staging system] within 15 cm of the anal verge. The clinical TNM stage was assessed by clinical examination, rigid proctoscopy, endorectal ultrasonography, computed tomography scanning and nuclear magnetic resonance of the abdomen and pelvis. Patients with T3, T4 and with distal T2 (<4 cm from the anal verge) rectal cancers, respectively, were included irrespective of their nodal status. Patients with a single hepatic or lung metastasis were eligible. Patients were required to have a leukocyte level >3.0x10^9/l and a thrombocyte level >100x10^9/l, normal liver function with bilirubin values <2 mg/dl and normal renal function with creatinine values <1.5 mg/dl. Patients ≤85 years of age and with a performance status according to Karnofsky of >70% were accepted. Exclusion criteria were: prior pelvic irradiation, other uncontrolled severe disease precluding administration of irradiation, pregnancy or lack of contraception in women with childbearing potential, ileus, imminent perforation, evidence of fistules in the pelvic region, distant metastases or number of liver or lung metastases >1, synchronous or metachronous rectal or colonic

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Key words: locally advanced rectal cancer, distal rectal cancer, preoperative chemoradiotherapy, 5-fluorouracil, leucovorin, local relapse rate

tumors, previous other cancers except non-melanoma skin cancer. Written informed consent was obtained, and the trial was approved by the medical ethics committee.

The study was conceived as a non-randomized phase II trial and was performed at a single centre in Vienna, Austria. Radiotherapy was delivered with a linear accelerator using 6- to 15-MV photons and a dorsal three-field technique achieving 50.4 Gy in daily fractions of 1.8 Gy after 3-D planning, 5 days/week. The planning target volume was designed to include all macroscopically identified disease and the internal iliac and presacral nodes up to the superior border L5. The distal border was the bottom of the obturator foramina or 5 cm below the distal extent of the primary tumor. The anal canal was irradiated in the case of tumors lying in the lower third of the rectum.

Preoperative chemotherapy was delivered in three 5-day courses during the 1st, 4th and 7th week after the start of radiotherapy. 5-FU was administered at a dose of 450 mg/m^2 intravenously (i.v.) bolus/day for 5 days and leucovorin at a dosage of 25 mg/m^2 i.v. bolus/day for 5 days. A dose reduction of 5-FU to 75% during radiotherapy was allowed. In addition, dose reduction was foreseen in case of toxicity ≥G3 according to the National Cancer Institute of Canada – Common Toxicity Criteria (4). The 5-FU and leucovorin doses were selected based on studies by Moertel *et al* (5) and Poon *et al* (6). Three cycles of the chemotherapy in combination with irradiation were administered to increase the downstaging effect. Surgery was scheduled after completion of chemoradiotherapy. TME was intended to be performed in all patients. Patients with a single hepatic metastasis were scheduled for additional liver resection, after R0 resection of the primary tumor. Postoperative chemotherapy started 4 weeks after surgery and was delivered in three cycles, every 4 weeks at the same doses that were used preoperatively.

During preoperative treatment, patients were monitored weekly and during postoperative treatment biweekly for signs of acute toxic effects. Toxicity was classified according to the National Cancer Institute of Canada - Common Toxicity Criteria (NCIC-CTC) (4) and the Radiation Therapy Oncology Group (RTOG) criteria (7). Toxicity was evaluated over the entire treatment period comprising chemoradiotherapy, the postoperative period and the following 3 months while receiving postoperative adjuvant chemotherapy.

Clinical tumor response was evaluated preoperatively according to the WHO (World Health Organisation) criteria (8). Patients were reviewed by one reference radiologist (B.H.). Time to progression was defined as the time interval from the start of treatment to progression or was censored at the last patient contact with proven freedom from progression. Tumor downstaging was defined by a comparison of the clinical pretreatment TN categories (determined by scanning with computed tomography, nuclear magnetic resonance or ultrasonography) to the histopathological TN categories. For this purpose, fresh resection specimens were transported unopened to the Department of Pathology. After opening of the rectum, the tumor or fibrotic area was identified and described macroscopically. Surgical specimens were fixed in 4% formaldehyde. If no tumor was visible, the suspicious area was sliced and embedded. If the tumor was visible, a minimum of four paraffin blocks was processed. For determination of the residual tumor, samples were taken from the lateral surface of the specimens as well as from the proximal and distal resection margins. Lymph nodes were dissected, and step sections were routinely performed. Histological typing and grading were performed according to the WHO criteria (9) and staging according to the UICC (10). The minimum requirement for tumor diagnosis was the presence of vital tumor cells or cell groups. The number of lymph nodes examined and involved was determined microscopically.

Table I. Characteristics of the 71 evaluable patients treated with preoperative chemoradiotherapy followed by surgical treatment and postoperative chemotherapy.

Age (years)	
Median	62
Range	39-84
Gender, no. (%)	
Male	43 (60.6)
Female	28 (39.4)
Distance of tumor from anal verge, no. (%)	
0-5 cm	33 (47.8)
>5-10 cm	28 (40.6)
>10 cm	8 (11.6)
Not evaluable	2
cT category, no. (%)	
T2	6 (8.5)
T3	50 (70.4)
T4	15 (21.1)
cN category, no. (%)	
N0	17 (29.3)
N1	27 (46.6)
N2	14 (24.1)
Not evaluable	13
cM category, no. (%)	
M0	63 (88.7)
Liver metastasis	6 (8.5)
Lung metastasis	2 (2.8)

Follow-up after completion of therapy was initially performed at 3 months, after 2 years at 6 months and after 5 years at 12-month intervals.

The primary aim of this study was to determine the histopathological response rate of patients who underwent surgery after chemoradiation. Secondary aims included evaluation of the feasibility of this preoperative regimen, determination of the clinical objective response rate after completion of the chemoradiotherapy preoperatively, evaluation of the rate of local and distant relapses, and calculation of the disease-free and overall survival.

To determine the sample size as a minimum requirement, the number of evaluable patients was set to 62. Such a sample size allowed for the estimation of confidence intervals for histopathological complete remissions given an *ex ante* expectation of roughly 10% with a precision of ±7.5%.

Table II. Postoperative pathological tumor stage, type of surgery and completeness of resection of the 71 evaluable patients.

Lymph nodes, no. operated	
Mean	17.51
Range	2-55
Lymph nodes, no. positive	
Mean	0.79
Range	0-18
Degree of resection histopathologically, no. (%)	
R0	61 (88.4)
R1	3 (4.3)
RX	5 (7.2)
Not evaluable	2
Distance from tumor to resection margin, no. (%)	
<1 cm	10 (15.6)
≥1 cm	54 (84.4)
Not evaluable	7
Histopathological stage according to UICC, no. (%)	
0	9 (12.9)
I	15 (21.4)
II	27 (38.6)
III	15 (21.4)
IV	4 (5.7)
Not evaluable	1
ypT category	
ypT0	10 (14.1)
ypT1	1 (1.4)
ypT2	18 (25.4)
ypT3	38 (53.5)
ypT4	4 (5.6)
ypN category	
ypN0	53 (74.6)
ypN1	15 (21.1)
ypN2	3 (4.2)
ycM category	
M0	66 (94.3)
M1	4 (5.7)
Not evaluable	1
ypL facultative descriptor	
ypL0	45 (72.6)
ypL1	17 (27.4)
Not evaluable	9
ypV facultative descriptor	
ypV0	58 (95.1)
ypV1	3 (4.9)
Not evaluable	10
Grade	
G1	1 (1.5)
G2	49 (75.4)
G3	15 (23.1)
GX	6
Sphincter infiltration	
Yes	3 (4.3)
No	67 (95.7)
Not evaluable	1
Definitive colostomy	
Yes	18 (25.7)
No	52 (74.3)
Not evaluable	1
Type of resection	
Abdominoperineal resection	18 (25.4)
Low anterior resection	53 (74.6)

UICC, International Union Against Cancer.

Disease-free interval and overall survival were estimated using the Kaplan-Meier method. The log-rank test was used to calculate influence of gender, age, clinical tumor stage, presence of distant metastasis, distance of the primary tumor from the anal verge, presence of sphincter infiltration, response to therapy, total dose of radiotherapy, dose of chemotherapy, number of cycles of chemotherapy, histopathological tumor stage, number of lymph nodes investigated, tumor grade, residual tumor, resection margin, degree of downstaging of the tumor, requirement of definitive colostomy and type of surgical procedure on disease-free survival and overall survival. Statistical analyses were performed using SPSS software 15.0.

Results

Patients. Of the 101 patients enrolled only 75 were eligible. The reasons for excluding the remaining 26 patients were: T2 and distance from the anal verge >4 cm (n=5), unknown number of hepatic metastases or >1 hepatic metastasis (n=7), presence of simultaneous liver and lung metastases (n=1), presence of ≥2 lung metastases (n=2), presence of liver and peritoneal metastases (n=1), synchronous rectal and colonic carcinoma (n=3), metachronous rectal and colonic carcinoma (n=1), multiple liver and lung metastases and another malignancy (n=1), presence of a second malignancy (n=2), TME not performed (n=2) and deviation from the chemotherapeutic regimen (n=1). Out of the 75 eligible patients, 2 patients withdrew their informed consent, 1 patient relocated and 1 patient was lost to follow-up. Therefore, 71 patients were considered to be evaluable for the primary endpoint. The baseline characteristics of these 71 patients are listed in Table I.

Treatment administration. Preoperatively 206 cycles (median 3 cycles) of 5-FU/leucovorin and postoperatively, 149 cycles (median 3 cycles) were delivered. Seventy-seven percent of the patients received at least 50 Gy and 3 preoperative cycles of chemotherapy, 87% at least 45 Gy and 3 cycles of preoperative chemotherapy and 94% received at least 45 Gy and 2 preop-

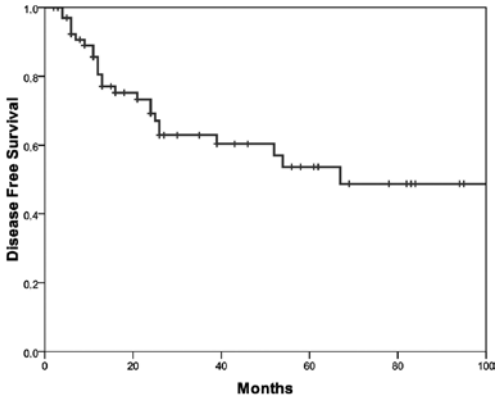

Figure 1. Disease-free survival of the 71 evaluable patients treated with preoperative chemoradiotherapy followed by surgical treatment and postoperative chemotherapy.

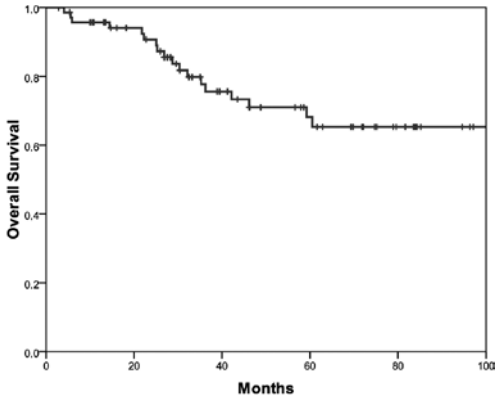

Figure 2. Overall survival of the 71 evaluable patients treated with preoperative chemoradiotherapy followed by surgical treatment and postoperative chemotherapy.

Table III. Maximal non-haematotoxic adverse effects/patient graded by NCIC-CTC or RTOG in the 71 evaluable patients treated with preoperative radiotherapy and chemotherapy with 5-FU and leucovorin followed by surgical treatment and postoperative adjuvant chemotherapy for locally advanced and distal T2 rectal cancer.

	NCIC-CTC category for severity, no. (%)	
Adverse effect	3	4
Bowel obstruction/paralytic bowel	2 (3)	1 (1)
Diarrhoea	5 (7)	7 (10)
Stomatitis	1 (1)	2 (3)
Nausea	1 (1)	0
Vomiting	0	1 (1)
Infection	6 (8)	0
Neutropenic fever	2 (3)	0
Skin necrosis	0	1 (1)
Cardiovascular function	0	1 (1) (fatal)
Venous thromboembolism	2 (3)	1 (1)
Fainting	3 (4)	0
Confusion	1 (1)	0
Vaginitis	2 (6)[a]	0
Urinary incontinence	1 (1)	0
Proctitis	2 (3)	0
Skin toxicity - RTOG	2 (3)	0

5-FU, 5-fluorouracil; NCIC-CTC, National Cancer Institute of Canada - Common Toxicity Criteria; RTOG, Radiation Therapy Oncology Group. [a]Percentage of females.

erative chemotherapy cycles, respectively. Due to toxicity in 16/71 (23%) patients, the planned preoperative chemoradiotherapy (3 cycles of chemotherapy and ≥50 Gy) could not be administered due to ileus (n=1), diarrhoea (n=7), local reaction or proctitis (n=4), neutropenia and/or neutropenic fever (n=3) and mucositis (n=1). Chemotherapy was performed in 54/71 (76%) patients postoperatively. In 17/71 (24%) patients the planned postoperative treatment was not administered due to cardiomyopathy G4 (fatal) (n=1; 1%); reduced performance status (n=1; 1%); eight (11%) patients requested <6 cycles of treatment; 2 (3%) were lost to follow-up after surgical treatment; 3 (4%) had a reduction to 3 cycles due to having achieved pT2N0 or pT0pN0, respectively and in 2 (3%) patients chemotherapy was changed to FOLFOX following surgical treatment comprising curative local and hepatic resection. In 3 patients, chemotherapy was discontinued due to toxicity (skin necrosis due to the cytostatic agent, n=1; diarrhoea, n=1; fever and mucositis, n=1).

Efficacy. The clinical response rate in the evaluable patients reached 79.7% (51/64) (95% CI, 69.8-89.5; CR, n=3; PR, n=48; NC, n=11 and PD, n=2). The reasons for non-evaluability were occurrence of an ileus on day 39 (n=1) and loss of radiographic films (n=6). Tumor downstaging occurred in 48% of the T-categories (T3, 44% and T4, 80%), in 53% of the N-categories and in 74% of the UICC stages, respectively. Patients with downstaged tumors located ≤4 cm from the anal verge did not undergo more frequent sphincter sparing operations than patients with non-downstaged distal rectal carcinomas.

All patients underwent a TME. A histopathologic complete remission (pCR), ypT0ypN0, was found in 14.1% of the patients (95% CI, 6.0-22.2; Table II). Curative liver resection was performed in 4 patients.

Four (6.1%) patients developed local recurrences only, and 2 (3%) more patients also had distant metastases. A total of 13 (19.7%) patients developed distant metastases exclusively.

The 5-year disease-free survival was 53.7% (Fig. 1) and the 5-year overall survival was 68% (Fig. 2). Younger patients had a longer disease-free (p=0.02) and overall survival (p=0.01). Female patients survived longer (p=0.04). The presence of a singular liver or lung metastasis influenced the length of both the disease-free (p=0.008) and overall survival (p=0.02) significantly. The clinically assessed preoperative N-category after completion of combined chemoradiotherapy was associated with a significant impact on survival (p=0.011). Patients with 6 cycles of chemotherapy, i.e., patients who had received

the complete postoperative adjuvant chemotherapy survived longer (p=0.054).

Side effects. The following severe (grade 3 and 4) haematological toxicities were observed: leukopenia 27% (15% grade 3, 12% grade 4), neutropenia 17% (8% grade 3, 9% grade 4) and thrombocytopenia 6% (6% grade 4), respectively. The neutrophil nadir was reached after a median of 43 days (range 0-214). The acute severe non-haematologic toxicities are listed in Table III. Postoperatively, an anastomotic leakage with a consecutive abscess occurred in 1 patient, an abscess in the anastomotic region in 1 patient, a fistula with consecutive abscess in the anastomotic region in 1 patient and a stenotic anastomosis in a fourth patient. A delay in wound healing was observed in 1 patient and ejaculation dysfunction in 3 patients.

Discussion

A pCR was found in 14.1% of our patients thereby meeting the primary endpoint of our study. It is known from other studies that the ability to accurately predict the pathologic stage by clinical staging following preoperative chemotherapy and concurrent radiation remains suboptimal. Thus, only by ascertaining a pathologic complete response can a correct result be achieved (11,12). The high pCR of 14.1% was highly comparable to the median percentage of 11% (range 8-27%) observed in other studies administering 5-FU ± leucovorin in combination with preoperative irradiation in locally advanced rectal cancer (13-18). Two recently published multicentric randomized phase III trials treating patients with locally advanced rectal cancers with preoperative chemoradiation yielded an equally high pathological complete sterilization rate independent of whether oxaliplatin was added to 5-FU or not, thus indicating that 5-FU-containing preoperative chemotherapy in combination with irradiation remains the actual standard of care unless long term follow-up in the future reveals differences in efficacy (19,20). Since pCR was shown to be of prognostic significance in independent investigations, it is speculated whether or not pCR should be used as a basis for subsequent postoperative adjuvant therapy (15,21,22).

In this single centre trial, high median 5-year disease-free and 5-year overall survival rates were obtained, especially when one considers that 11% of our patients had a singular pulmonary or hepatic metastasis and in view of our observation that the presence of a singular distant metastasis influenced the disease-free and overall survival. The length of the disease-free interval and the overall survival in our study was nearly identical to that found by Bosset et al (23), although in their study a lower percentage of T4 tumors was included and patients with distant metastasis were excluded; both results were also in line with those of Sauer et al (17). The low local relapse rate of 6.1% observed in our study was highly comparable to that found in other studies (17,23), although we included a four-time higher percentage of T4 tumors compared to Sauer et al and a two-time higher percentage of T4 tumors than Bosset et al. Apart from T-categories, other independent prognostic factors such as the TME technique (24), or the skills and training of the surgeon (25) may influence the rate of local recurrences in rectal cancer. In addition, preoperative in contrast to postoperative chemoradiation per se was confirmed to be an independent prognostic variable for predicting local recurrences in a randomized controlled study (17). Long-term versus short-term irradiation continues to be the preferred treatment in our patient cohort, since it has been shown in distal rectal tumors ≤5 cm from the anal verge that short-term irradiation fails to reduce the rate of local relapses (26). Additionally, the equieffectiveness of short- and long-term irradiation has only been shown for patients with resectable T3 and T4 rectal carcinomas (11).

The rate of distant relapses was highly comparable to that reported by Bosset et al (23) and Sauer et al (17). Using 5-FU plus leucovorin we achieved a more effective chemotherapy in comparison with other investigators who used 5-FU alone (6). Furthermore, an association between the number of cycles of chemotherapy and survival was shown in our study. The subgroup analysis indicated a survival advantage for the patients undergoing postoperative treatment. This result may influence the treatment decision after surgery in daily practice. Also Bosset et al (23) and Janjan et al (27) observed a reduction in mortality in patients who received postoperative chemotherapy. Presumably, further intensification of chemotherapy by its combination with newer cytostatic and biologic agents will substantially change the prognosis of locally advanced rectal cancer (28-30).

Acute toxicity observed in our trial was high and highly comparable to other studies (13,17,31). However, the higher haematologic toxicity observed in our study and in that of Bosset et al was certainly caused by the intravenous bolus administration of 5-FU in contrast to the continuous infusion of 5-FU reported by Sauer et al (32). The high overall severe toxicity found in our study was mainly attributed to both the high dose of radiotherapy ≥50 Gy and to the administration of three preoperative cycles of chemotherapy. If the treatment of our patients had been terminated at the lower threshold of irradiation of 45 Gy and after only two cycles of the chemotherapy, preoperative chemoradiation would have been completed in 94% of our patients. Our theory is in line with Bosset et al (23) who completed chemoradiation in 96% of their patients with a dose of 45 Gy of irradiation and two preoperative cycles of chemotherapy. Therefore, we recommend a dose reduction of irradiation to 45 Gy in combination with only two cycles of chemotherapy consisting of 5-FU and leucovorin, followed by four postoperative cycles of this chemotherapy using the same doses as in our study. The maintenance of the total number of six cycles of chemotherapy seems important in light of the longer survival of the patients in our study.

In conclusion, this treatment is very effective and yields a high pCR rate, a low local relapse rate and long disease-free and overall survival. The comparable high pCR rate obtained in studies adding oxaliplatin to 5-FU in comparison to 5-FU monotherapy indicates that the treatment used in our study can be further used as a standard of care. The proposed preoperative combined modality treatment consisting of only two preoperative 5-FU-containing cycles of chemotherapy concurrently administered with 45-Gy irradiation followed by surgery including, TME and postoperative adjuvant 5-FU-containing chemotherapy of four cycles, represents an effective and feasible treatment for locally advanced rectal cancer.

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