Long-term Results of Preoperative 5-Fluorouracil-Oxaliplatin Chemoradiation Therapy in Locally Advanced Rectal Cancer

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Abstract. *Aim: To evaluate the activity, safety and long-term survival of patients after preoperative oxaliplatin and 5-fluorouracil chemoradiation therapy in locally advanced rectal cancer (LARC). Patients and Methods: Patients with resectable, T3-4 and/or nodal involvement rectal adenocarcinoma were treated with oxaliplatin 60 mg/m^2 weekly and 5-fluorouracil 200 mg/m^2/d infused continuously for five days, over a period of five weeks, and radiotherapy (45 Gy/25 fractions). The primary end-point was pathological complete response (ypCR). Safety, overall survival (OS) and relapse-free survival (RFS) were secondary end-points. Results: Sixty-six patients were treated. Grade 1-2 diarrhea was the most common adverse event. The ypCR rate was 16.7% (95% confidence interval=7.7-25.7%). After a median follow-up of 73.5 months, 23 patients (34.8%) had experienced relapse. Five-year actuarial RFS and OS rates were 64% and 73%, respectively. Five-year actuarial RFS was 91.7% in the ypCR group versus 57.8% in non-ypCR cases. Conclusion: Long-term local control and survival after this very well-tolerated regimen appear encouraging.*

Since 1998, colorectal cancer incidence and mortality rates have been declining by approximately 2.5% per year as a result of early detection by screening and improvement in anticancer treatment (1). In the management of locally advanced rectal cancer (LARC), a multidisciplinary approach is mandatory in order to maximize patient outcome. Five-fluorouracil (5-FU)-based regimens in combination with preoperative radiation are considered the standard-of-care-treatment in LARC (2-4).

Different methods of chemoradiation therapy (CRT) administration have been described in the literature but the optimal CRT regimen is still debated. In 2005, in a meta analysis of phase II/III trials of preoperative CRT, Hartley *et al.* described a 13.5% overall pathological complete response (ypCR) rate for 3,157 studied patients (5). Statistically significant factors associated with higher ypCR rates were found to be the use of two-drug regimens, the continuous administration of 5-FU or capecitabine and doses of radiotherapy not lower than 45 Gy.

Oxaliplatin led to improved efficacy when combined with fluoropyrimidine agents in the treatment of colonic cancer, both in adjuvant and palliative settings (6-7). In addition, oxaliplatin also exhibited radiosensitizing properties in pre-clinical studies (8).

Based on this evidence, the aim of our study was to evaluate the combination of preoperative 5-FU-oxaliplatin- based CRT in a multicenter phase II trial in patients with cT3-T4, N0-1 rectal adenocarcinoma. The primary objective was to evaluate the activity of this regimen in terms of ypCR; safety, long-term survival and time-to-relapse were secondary end-points.

Patients and Methods

This multicenter, prospective phase II study was carried out by two Italian institutions. The protocol obtained approval by the Ethics Committee of the participating centers, and the study was performed in accordance with the Declaration of Helsinki and its subsequent

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amendments, as well as Good Clinical Practice Guidelines. Written informed consent was obtained from all patients before enrollment in the study.

Patients with a WHO performance status of 0-1 and age <75 years, with histologically-confirmed rectal adenocarcinoma and clinical stage T3-4 and/or nodal involvement, without evidence of distant metastases, were eligible for this trial. Inadequate bone marrow, liver or renal functions, others significant comorbidities, history of any other tumor (except for basal cell skin cancer) or prior chemo/radiotherapy treatments were exclusion criteria. Computed tomography (CT) of the thorax, abdomen and pelvis were required for each eligible patient at screening, to evaluate the stage of disease. Magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) of the pelvis were not mandatory.

After the implant of a subcutaneous intravenous access device, oxaliplatin was infused weekly over two hours, at the dose of 60 mg/m^2 and 5-FU was infused continuously at the dose of 200 mg/m^2/day for five days, over a period of five weeks. Concurrent radiotherapy consisted of 45 Gy in 25 fractions of 180 cGy, five days per week. Patients were monitored weekly by physical examination, hematological and non-hematological toxicity, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 2.0) (9).

Responses were evaluated according to WHO criteria (1981) (10). In patients without contraindications, surgery was planned three to six weeks from the end of the preoperative treatment; the choice of surgery (abdominoperineal resection or anterior resection of the rectum) was left to the surgeon. Four cycles of 5-FU-based adjuvant treatment were suggested, according to disease stage at diagnosis.

The specimens were managed according to the Quirke procedure (11). ypCR was defined as the complete absence of any viable tumor cells in the surgical specimen (primary tumor site, mesorectal fat and lymph nodes analyzed), regardless of the presence of mucin lake. The surgical resection was classified as R1 in cases of distance from any part of the tumor and the resection margins less than 1 mm, and R2 in cases of macroscopic residual tumor.

Simon's optimal two-stage design was used to calculate the sample size (12). Nineteen patients had to be enrolled in the first stage: if more then four ypCRs were observed, 35 additional patients would be recruited. This sample size would have allowed us to refute an activity lower than 20% and to retain as interesting a percentage of ypCR of 40%. If more than 15 ypCRs were observed out of the total of 54 evaluable patients, the regimen would be considered sufficiently active at a significance level of 0.05 and a power of 90%, to justify further evaluations.

Patients' characteristics, response to treatment and toxicity were reported as absolute numbers and percentages. Time-to-relapse (TTR) was defined as the interval between enrollment time and first relapse (local or distant), or death, or last follow-up visit, if disease had not progressed. Overall survival (OS) was defined as the interval between enrollment time and death for any cause or last follow-up visit. Median TTR and median OS were calculated according to the Kaplan Meier method (13); comparisons between survival curves were evaluated using the Log-rank test (14). The association between response-to-treatment and type of recurrence (local or distant) was analyzed with χ^2 test for categorical variables. Statistical analysis of the data was performed using the SPSS software, version 8.0 (SPSS Inc, Chicago, IL, USA).

Table I. *Patients and disease characteristics (N=69).*

Characteristic	No.	%
Age (years)		
Median	63	
Range	33-77	
Gender		
Male	49	71.0
Female	20	29.0
WHO performance status		
0	59	85.5
1	10	14.5
Radiological tumor stage		
T2	1	1.4
T3	55	79.7
T4	13	18.8
Radiological nodal stage		
N0	20	29.0
N 1-2	38	55.1
Undetermined N	11	15.9

Results

After enrollment of the first 19 evaluable patients, accrual proceeded into the second stage of the trial of up to 70 patients to compensate for possible drop-out. One patient was ineligible because of protocol violation (tumor was classified as squamous cell carcinoma of the rectum after histological reassessment). Three patients were lost to follow-up after preoperative treatment and were therefore considered only for safety and long-term outcomes.

The analysis of the primary end-point was performed on data for 66 evaluable patients. Approximately 80% of them had cT3 tumors; radiological evidence of lymph node involvement was reported in 44% of cases. Other characteristics are shown in Table I. Each patient was studied with colonoscopy and CT scan of the thorax, abdomen and pelvis with or without pelvic MRI or EUS.

Only one patient did not receive the full-planned dose of radiotherapy because of the development of sepsis that needed hospitalization and the omission of the second week of chemoradiation treatment. Regarding chemotherapy, 83% of patients completed the entire treatment program; 13% of patients omitted only the last week of treatment due to asthenia. In 17% of cases, dose reduction was performed and 15% of patients needed chemotherapy interval prolongation.

Grade 1-2 to 3-4 treatment-related adverse events (AEs) are shown in Table II. Mild to moderate diarrhea was the most common adverse event (26%) that reached grade 3 in 4.3% of cases. Neither grade 4 AEs nor treatment-related deaths were observed. Overall, grade 3 toxicity was observed in 12% of patients. No grade 3 toxicity was more frequent than 5%; 4.3% of patients experienced grade 3 vomiting and

Table II. *Reported acute toxicities*.

	Grade 1-2 No. (%)	Grade 3-4 No. (%)
Neutropenia	5 (7.2)	2 (2.9)
Febrile neutropenia	0 (0)	1 (1.4)
Anemia	11 (15.9)	1 (1.4)
Thrombocytopenia	3 (4.3)	1 (1.4)
Nausea	13 (18.8)	1 (1.4)
Vomiting	5 (7.2)	3 (4.3)
Diarrhea	18 (26.1)	3 (4.3)
Neurotoxicity	10 (14.4)	1 (1.4)
Oxaliplatin reaction	4 (5.8)	0 (0)
Asthenia	3 (4.3)	1 (1.4)
Skin toxicity	0 (0)	3 (4.3)
Increased SGPT/SGOT	1 (1.4)	1(1.4)
Mucositis	2 (2.9)	0 (0)
Local complications	3 (4.3)*	3 (4.3)**

* Rectal pain and inflammation; **Rectal bleeding, n=2, gluteal abscess, n=1. SGPT: serum glutamic pyruvic transaminase; SGOT: serum glutamic-oxaloacetic transaminase.

14.4% experienced peripheral neurosensory toxicity, which reached grade 3 in 1.4% of cases. Four cases (5.8%) of allergic reaction to oxaliplatin were observed.

Surgery was performed in 66 patients at a median interval from the end of the preoperative treatment of 38 days. Sphincter preservation was possible in 82% of cases, while 18% of patients underwent abdominoperineal resection according to the Hartmann procedure. Ninety-seven percent of patients had R0 resection; one patient (1.5%) had macroscopic residual disease (R2 resection) and one patient had a positive resection margin (R1 resection). About 90% had neither surgical nor medical postoperative complications; no perioperative deaths were encountered in this study. 5-FU-based adjuvant treatment was performed in 75% of cases; out of these, 43% received the 5-FU and oxaliplatin combination regimen. Further information concerning treatment compliance are shown in Table III.

Antitumor activity, the primary objective, is summarized in Table IV. Among the 66 patients included in the analysis, 11 did not have any residual tumor in the pathological specimen (ypCR), two patients had residual tumor only in a few lymph nodes (ypT0-N1) and one patient had very few residual cancer cells in the primary site (ypTmic-N0).

Another 28 patients had a partial remission of disease; 23 patients had a stable disease and only one patient experienced local tumor progression.

At a median follow-up of 73.5 (range=46-116) months, 23 patients (33.3%) experienced relapse. Two patients (2.9%) had local recurrence; nineteen patients (27.5%) had distant metastases, and two patients (2.9%) had both local and distant recurrences. The lungs were the most frequent metastatic site, followed by the liver, lymph nodes, brain, bone and peritoneum, as shown in Table V. Two patients developed primary breast cancer and one patient developed primary breast and endometrial cancer during the follow-up period.

Table III. *Treatment compliance (N=69)*.

	No.	%
Full radiotherapy dose	68	98.6
Preoperative chemotherapy		
Weeks of infusion		
5	57	82.7
4	9	13.0
3	2	2.9
2	1	1.4
Dose reductions (at least one cycle)	12	17.4
Chemotherapy interval prolongation	10	14.5
Surgery and adjuvant chemotherapy (N=66)		
Type of surgery		
Anterior resection	54	82
Abdominoperinael resection	12	18
Postoperative surgical complications		
None	56	85
Local fistula	2	3
Intestinal occlusion	2	3
Wound-healing complication	2	3
Ureteral dissection	1	1.5
Postoperative medical complications		
None	59	89.5
Myocardial infarction	1	1.5
Atrial fibrillation	2	3
Pneumonitis	1	1.5
Adjuvant chemotherapy		
None	17	26
De Gramont	10	15
FOLFOX	21	32
5FU/LV	16	24
Capecitabine	2	3

FOLFOX: Infusional 5-fluorouracil, leucovorin and oxaliplatin; 5FU: 5-fluorouracil; LV: leucovorin.

At the time of analysis, the median time-to-relapse was not reached. After five years' follow-up, the five-year actuarial relapse-free survival (RFS) was 64% and OS was 73%, as shown in Figure 1.

For descriptive purposes only, we analyzed TTR and OS according to the type of response (ypCR *vs*. other responses): five-year actuarial RFS was 91.7% (ypCR group) *vs*. 57.8% (non-ypCR cases) (p=0.047); only one patient who achieved a ypCR experienced a recurrence of disease. The five-year overall survival probability was 91.7% and 69%, in the ypCR group *vs*. other responses, respectively.

Discussion

During the past ten years, several trials have been conducted to investigate the role of preoperative treatment in LARC. The

Table IV. *Pathological findings (N=66).*

	No.	%
Pathologic response		
Complete	11	16.7
Partial	31	46.9
Stable disease	23	34.8
Progression	1	1.5
ypT-stage		
0	13	19.7
Mic	1	1.5
1	3	4.5
2	19	29
3	28	42.5
4	2	3
ypN-stage		
0	43	65
1	16	24
2	7	11
Residual disease		
None (R0)	64	97
Microscopic (R1)	1	1.5
Macroscopic (R2)	1	1.5

ypT: Post-therapy pathological primary tumor size; Mic: very few residual cancer cells in the primary site; ypN: post-therapy pathologic lymph nodes involvement.

Table V. *Disease recurrences (N=69).*

	No.	%
Patients with relapsed disease	23	34.8
Site of recurrence		
Local	2	2.9
Distant	19	27.5
Local and distant	2	2.9
Site of distant recurrence		
Bone	1	1.4
Brain	3	4.3
Lymph nodes	3	4.3
Liver	9	13.0
Lungs	14	20.3
Peritoneum	1	1.4

evidence so far suggests that preoperative CRT reduces local relapse and is superior and less toxic than postoperative adjuvant treatment (3, 4, 15, 16). Currently, preoperative CRT followed by surgical resection with total mesorectal excision (TME) and adjuvant chemotherapy represents the standard treatment option for T3-T4 and/or N-positive rectal cancer (2, 17). However, there is still uncertainty concerning the optimal radiotherapy schedule and the chemotherapy regimen to be used in combination with radiation (18). In current practice, a fluoropyrimidine-based regimen is considered the standard-of-care chemotherapy to be combined with radiation. The potential benefit of adding to a fluoropyrimidine a second chemotherapy agent, such as oxaliplatin, irinotecan, bevacizumab or cetuximab, is still under investigation (19-27).

Preoperative treatment in our study was designed in order to find a more active regimen that could be safely employed in LARC. Based on results achieved with the combination of oxaliplatin and fluoropyrimidines in metastatic and adjuvant colorectal cancer settings (6, 7), this study was designed to demonstrate an optimistic 40% ypCR rate. We obtained ypCR of 16.7%, which is lower than that originally pre-defined as a positive outcome of this study. However, ypCR rate achieved in the present study is consistent with results of recent phase III randomized trials, including similar oxaliplatin-fluoropyrimidine regimens, where the ypCR rate ranged from 13% to 20% (24-27). When this study was designed, ypCR rate was chosen as the primary end-point since, at that time, this was believed to be an important early surrogate end-point. However, the results of a recent pooled analysis of two large phase III trials have questioned the validity of ypCR as a surrogate parameter for local control, progression-free survival (PFS) and OS (28). In contrast with this finding, despite the limitations of a retrospective analyses of a phase II study, in our study patients that reached ypCR clearly had a better outcome compared to those without. The real role of ypCR as a surrogate marker of long-term outcome in LARC treated with preoperative CRT would probably require further elucidation.

No data concerning the survival impact of a two-drug preoperative regimen from phase III randomised trials are yet available in the literature to our knowledge. With the limitations of a phase II non-randomized trial but with the strength of a long follow-up period, RFS and OS in our study compare favourably to those observed in single-agent CRT phase III trials (3, 4, 15, 16, 29). Moreover, the long-term local recurrence rate in our study was particularly low.

The schedule of our chemotherapy regimen was similar to the one employed from Aschele *et al*. (5-FU at 225 mg/m^2/d plus oxaliplatin at 60 mg/m^2/week), which achieved a ypCR rate of 16% (25). With the limits of a phase II sample size, our regimen obtained similar results with some favourable aspects. For example, the total 5-FU dose administered was lower and the schedule allowed patients two days per week without 5-FU infusion. Moreover, the dose of radiotherapy was also lower than that usually employed in other recent CRT regimens because of the omission of the boost dose (45 Gy *vs*. 50.4 Gy) (24-27). These aspects could explain the excellent adherence to the treatment, as shown by the high rate of patients that completed the whole program, and the good tolerance, with a low incidence of side-effects. The incidence of G3-4 toxicities reported in our study was half the one reported for phase III trials with oxaliplatin (24-27). In particular, grade 3-4 diarrhea, which is usually the most frequent side-effect, was observed in

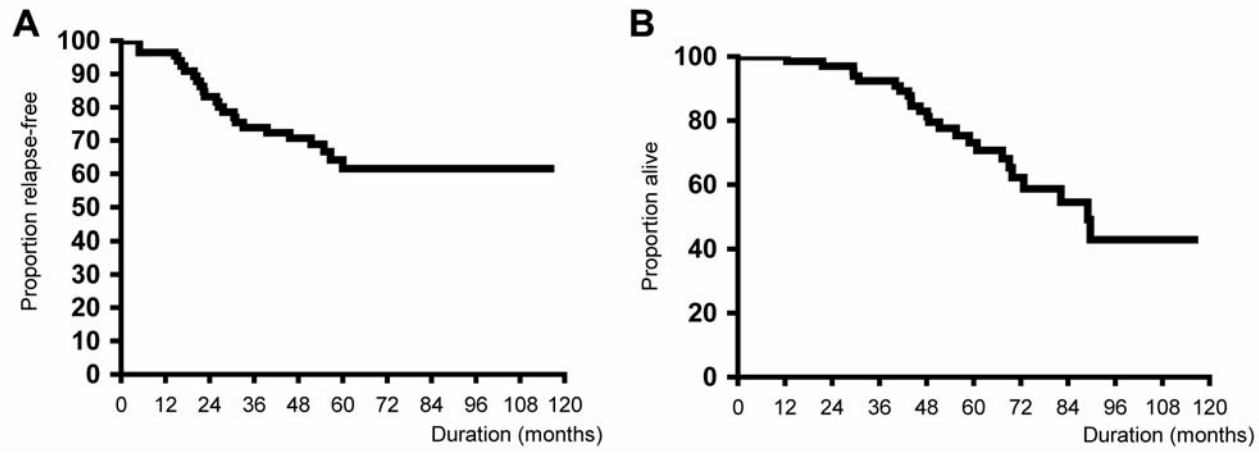

Figure 1. *Five-year actuarial relapse-free survival (A) and overall survival (B) of all studied patients.*

only 4.3% of patients compared to about 15% reported in the above mentioned phase III trials.

In conclusion, we report on long-term results of a feasible and active preoperative CRT in LARC. This regimen was well-tolerated, without, however, reaching the primary objective, in terms of ypCR. Considering the demand of employing oxaliplatin in the adjuvant setting in patients affected by LARC and waiting for definitive RFS and OS data from randomized phase III trials, we believe that earlier administration of oxaliplatin during preoperative treatment, while not adding significant toxicities, may shorten the duration of postoperative chemotherapy and contribute to long-term systemic disease control. In addition, considering the excellent toxicity profile of this regimen, it could be regarded as a valid option when high-dose radiation therapy is not feasible, or when 5-FU dose reduction is needed.

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