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Original Article

Comparison of 5FU-Base Chemoradiation with and Without Eloxatin on Pathologic Complete Response in Neoadjuvant Chemo-Radiation of Rectal Cancer

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ABSTRACT

Background and Objectives: To compare pathologic complete response (PCR) in patients with advanced rectal cancer receiving neoadjuvant chemoradiotherapy (NACT) by 5-FU or Xeloda (capecitabine) with and without Eloxatin (oxaloplatin injection).
Materials and Methods: Seventy-five consecutive patients with the diagnosis of advanced rectal adenocarcinoma were included. Two basic chemotherapy regimens were used: one drug (5-FU or Xeloda) or two-drug (5-U or Xeloda with Eloxatin). Endpoints were PCR and preservation of sphincter during surgery through low anterior resection (LAR). All analyses were done using SPSS software version 17.0 (SPSS Inc., Chicago, IL).
Results: There were no significant differences between the group of patients who received one-drug regimen with those who received two-drug regimen regarding the pCR (four cases (23.5%) versus 25 vases (43.1%)) state or the type of surgery performed [nine cases (52.9%) versus 36 cases (62.1%)].
Conclusion: Adding Eloxatin to the standard treatment of rectal adenocarcinoma (5-FU based) did not yield in a higher PCR or a higher chance to preserve the anal sphincter.

***Keywords*:** Eloxatin, 5FU, Rectum, Adenocarcinoma

Introduction

Colorectal cancer is the second most common cause of cancer-relate death in the United States (1). In recent years, efforts have been done to improve the survival of patients with locally advanced resectable rectal tumors. Some reports demonstrated better results of neoadjuvant chemoradiotherapy (NACT) than adjuvant method (2, 3). The use of chemoradiotherapy (CRT) before operation in locally advanced rectal tumors has been shown to result in a lower risk of local recurrence, easier resection because of tumor shrinkage, and allowance to preserve sphincter achieved by

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down-staging the tumor when compared with post-operative CRT (4-6). Currently, the standard therapy for patients with rectal adenocarcinoma is radiotherapy combined with 5-Fluorouracil-chemotherapy according to the recommendation of the National Institutes of Health Consensus Development Conference (7). However, different trials have been performed by administration of different methods of 5-FU or application of a second agent along with 5-FU to improve the clinical outcome and survival of patients with rectal cancer (8-10). For example, combinations of three agents including 5-FU, oxaliplatin, and irinotecan may give a high response rate of 75% (11).

One of the most common endpoints used in early follow-up of patients with rectal cancer, which has been associated with survival of the patients (12), is the pathological complete response (PCR). This is defined as the complete absence of intact tumor cells in the resected specimen (4). Rates of PCR by using a neoadjuvant approach range from 3% to 30% (13).

Regarding this data and lack of enough clinical trials comparing clinical efficacy of various CRT regimens in the treatment of rectal cancer, we decided to compare the effect of two NACT regimens [5-FU or Xeloda (capecitabine) with and without Eloxatin (oxaliplatin injection)] on PCR and the surgery type applied in patients with advanced rectal cancer.

Materials and Methods

This study was carried out from 2005-2008 at Imam Hossein Hospital affiliated to Shahid Beheshti University of Medical Sciences; which is a referral center for patients with rectal cancer. Inclusion criteria were patients from both genders, older than 18 and less than 70 years of age, advanced non-metastatic rectal adenocarcinoma accompanied by histological confirmation, clinical stage T3 or T4 with lymph node (LN) involvement, no prior history of chemotherapy or CRT, WHO performance status 0-1, life expectancy of more than 6 months, normal hematologic, hepatic and renal function.

Exclusion criteria included patients with hypersensitivity to 5-FU or those who had previously experienced a severe reaction to fluoropyrimidines, receiving radiotherapy or chemotherapy for the disease, those who had not fully recovered from a recent (within 4 weeks) major surgery, presence of a significant cardiac disease or a myocardial infarction within the previous 12 months, a serious uncontrolled infection. Patients were also not enrolled if screening evaluations revealed significant abnormalities in neutrophils (<1500), platelets (<100,000), serum creatinine or serum bilirubin (>1.5 times of upper normal limit), alanine aminotransferase (ALT), aspartames aminotransferase (AST) or alkaline phosphatase (>2.5 times of upper normal limit).

According to these criteria, 75 consecutive patients with advanced rectal cancer were included. At first, staging of the patients were done through spiral computed tomography (CT) scan of the thorax with and without intravenous (IV) contrast media, spiral CT scan of the abdomen with and without IV and oral contrast materials, and magnetic resonance imaging (MRI) of the pelvis with and without IV contrast media, and endoultrasonograph (EUS) of rectum. Distance of the tumor to anal verge was also measured.

In addition to the above mentioned methods, laboratory studies consisted of complete blood count (CBC diff), blood urea nitrogen, serum creatinine, ALT, AST, alkaline phosphatase, bilirubin (total and direct), and carcinoembryonic antigen (CEA).

Radiation therapy of pelvis was done with three doses in a range of 4500-5400 Gy (45 Gy, 50.4 Gy, and 54 Gy) five days a week for four weeks (four fields or initiating with anterior and posterior fields and continuation with lateral field). After this period, abdominal, pelvic, and thoracic CT scans were applied and in case of metastasis, the patent was excluded.

Chemotherapy was done with one of the four following regimens: infusional 5-FU,

Xeloda, Xeloda with Eloxatin, and infusional 5-FU with Eloxatin. Four weeks following CRT, the abdominal, pelvic, and thoracic CT scans were requested and no metastasis was found, the patient underwent surgery eight weeks after CRT. The surgeries performed for patients after NACT comprised low anterior resection (LAR) or abdomino-peritoneal resection (APR).

Down staging of the tumor was also determined according to pathologic stage (using the American Joint Committee on Cancer TNM Staging System) after surgery compared with pre-operative clinical stage achieved by EUS or MRI. Stable disease was described as no change in tumor stage after surgery, and PCR was defined as no evidence of viable tumoral cell.

This study was approved by Ethical Committee of Emam Hosein Hospital. For statistical analysis, descriptive indices such as frequency and percentage were used to express data. For categorical variables, the chi-squared test and for quantitative variables, parametric and non-parametric tests, as appropriate, were used. All analyses were done using SPSS software version 17.0 (SPSS Inc., Chicago, IL). Significance level was defined as $P<0.05$.

Results

Seventy-five (55 males and 20 females) patients were studied. Majority of patients (42.7%) were between 50 and 70 years old. LN involvement was observed in 50 cases (66.7%). Table 1 presents the characteristics of studied patients. Most patients (53 cases, 70.7%) were underwent radiation therapy with a dose of 50.4 Gy. Seventeen cases (22.7%) received radiation dose of 45 Gy and five patients received54 Gy. Chemotherapy with one drug and two drugs were applied for 17 (22.7%) and 58 (77.3%) patients, respectively. Different chemotherapy regimens were Infusional 5-FU (12 cases, 16%), Infusional 5-FU with Eloxatin (18 cases, 24%), Xeloda (5 cases, 6.7%), and Xeloda with Eloxatin (40 cases, 53.3%).

LAR and APR surgeries were performed for 45 (60%) and 30 (40%) patients, respectively. Regarding the response to the treatments applied, 29 patients (38.7%) showed PCR. However, 46 patients (61.3%) did not have pCR. The latter number consisted of 25 patients with down staging of the tumor, whereas 21 patients (28%) had stable disease.

In Table 2, pre-operative characteristics of patients according to the state of PCR are shown. There was no statistically significant difference regarding gender, T-stage of the tumor, LN involvement, CEA level, and distance of the tumor from anal verge between patients with PCR and those who did not have PCR. Only age showed a significant difference ($P = 0.024$) between the two groups. Of 11 patients, only one patient (9.1%) showed PCR and 10 patients (90.9%) did not have.

Comparison of PCR state according to the treatment methods is presented in Table 3. Of 30 patients who underwent APR, only five patients (16.7%) had PCR and 25 subjects (83.3%) did not have PCR. The state of PCR was not different according to the radiation dose or chemotherapy regimen.

In Table 4 comparison of pre-operative characteristics of patients according to the type of surgery performed is presented. Only CEA and distance of the tumor from anal verge showed significant differences between two groups of surgical method.

Comparison of surgery method according to the treatment modalities is presented in Table 5. Neither radiation dose nor chemotherapy regimen had differences between surgical methods.

Side effects which were documented during the study period were grade 1-2 diarrhea (40 cases, 53.3%), grade 3-4 diarrhea (17 cases, 22.7%), grade 1-2 neuropathy (15 cases, 20%), delay RT (31 cases, 41.3%), and grade 3-4 neuropathy (2 cases, 2.7%).

Table 1- Characteristics of 75 patients with rectal cancer studied

	Frequency	Percentage
Gender		
Male	55	73.3
Female	20	26.7
Age, year		
< 40	7	9.3
40-50	25	33.3
50-70	32	42.7
> 70	11	14.7
T-stage		
T3	54	72
T4	21	28
Lymph node involvement	50	66.7
Carcinoembryonic antigen (CEA), ng/ml		
< 10	58	77.3
10-50	13	17.3
50-100	1	1.3
>100	3	4
Distance of the tumor to anal verge, cm		
< 6	48	64
6-10	24	32
>10	3	4

Table 2- Comparison of pre-operative characteristics of patients according to pathological complete response (PCR) (NS: not significant)

	PCR (29 cases) Number (percent)	No PCR (46 cases) Number (percent)	*P* value
Gender			
Male	20 (69)	35 (76.1)	NS
Female	9 (31)	11 (23.9)	
Age			
< 40	2 (6.9)	5 (10.9)	0.024
40-50	15 (51.7)	10 (21.7)	
50-70	11 (37.9)	21 (45.7)	
>70	1 (3.4)	10 (21.7)	
T-stage			
T3	21 (72.4)	33 (71.7)	NS
T4	8 (27.6)	13 (28.3)	
Lymph node involvement			
Yes	19 (65.5)	31 (67.4)	NS
No	10 (34.5)	15 (32.6)	
CEA, ng/ml			
< 10	25 (86.2)	33 (71.7)	NS
10-50	3 (10.3)	10 (21.7)	
50-100	0	1 (2.2)	
>100	1 (3.4)	2 (4.3)	
Distance, cm			
< 6	15 (51.7)	33 (71.7)	NS
6-10	12 (41.4)	12 (26.1)	
>10	2 (6.9)	1 (2.2)	

Table 3- Comparison of pathological complete response state according to the treatment methods

	PCR (29 cases) Number (percent)	No PCR (46 cases) Number (percent)	*P* value
Radiation therapy dose, Gy			
45	4 (13.8)	13 (28.3)	NS
50.4	24 (82.8)	29 (63)	
54	1 (3.4)	4 (8.7)	
Chemotherapy regimen			
Infusional 5-FU	4 (13.8)	8 (17.4)	NS
Infusional 5-FU with Eloxatin	5 (17.2)	13 (28.3)	
Xeloda	0	5 (10.9)	
Xeloda with Eloxatin	20 (69)	20 (43.5)	
Surgery			
Low anterior resection	24 (82.8)	21 (45.7)	0.002
Abdomino-peritoneal resection	5 (17.2)	25 (54.3)	
Chemotherapy			
One drug	4 (13.8)	13 (28.3)	NS
Two-drug	25 (86.2)	33 (71.7)	

NS = Not significant

Table 4- Comparison of pre-operative characteristics of patients according to the type of surgery (low anterior resection (LAR) vs. abdomino-peritoneal resection (APR) performed

	LAR (45 cases) Number (percent)	APR (30 cases) Number (percent)	*P* value
Gender			
Male	30 (66.7)	25 (83.3)	NS
Female	15 (33.3)	5 (16.7)	
Age			
< 40	5 (11.1)	2 (6.7)	NS
40-50	16 (35.6)	9 (30)	
50-70	19 (42.2)	13 (43.3)	
>70	5 (11.1)	6 (20)	
T-stage			
T3	33 (73.3)	21 (70)	NS
T4	12 (26.7)	9 (30)	
Lymph node involvement			
Yes	31 (68.9)	19 (63.3)	NS
No	14 (31.1)	11 (36.7)	
CEA, ng/ml			
< 10	40 (88.9)	18 (60)	0.01
10-50	5 (11.1)	8 (26.7)	
50-100	0	1 (3.3)	
>100	0	3 (10)	
Distance, cm			
< 6	20 (44.4)	28 (93.3)	< 0.001
6-10	22 (48.9)	2 (6.7)	
>10	3 (6.7)	0	

NS = Not significant

Table 5- Comparison of the surgery type (low anterior resection (LAR) vs. abdomino-peritoneal resection (APR) according to the treatment methods

	LAR (45 cases) Number (percent)	APR (30 cases) Number (percent)	*P* value
Radiation therapy dose, Gy			
45	8 (17.8)	9 (30)	NS
50.4	34 (75.6)	19 (63.3)	
54	3 (6.7)	2 (6.7)	
Chemotherapy regimen			
Infusional 5-FU	8 (17.8)	4 (3.3)	NS
Infusional 5-FU with Eloxatin	12 (26.7)	6 (20)	
Xeloda	1 (2.2)	4 (13.3)	
Xeloda with Eloxatin	24 (53.3)	16 (53.3)	
Chemotherapy			
One drug	9 (20)	8 (26.7)	NS
Two-drug	36 (80)	22 (73.3)	

NS = not significant

Discussion

In recent years, multiple clinical trials have been done to find new treatments to increase the survival rate of patients with the diagnosis of advanced rectal cancer. Appropriate response to preoperative CRT has increased the probability of preservation of sphincter, which in turn can influence on disease process and the survival rate of patients with rectal cancer (12, 14, 15). One important target in these studies is the rate of PCR. Combination of 5-FU, as the basic chemotherapy agent in resectable rectal tumors, with other drugs aims to increase the rate of PCR and to preserve the anal sphincter.

According to the obtained results, there were no significant differences between the group of patients who received 5-FU with those who received Eloxatin in addition to 5-FU or its oral metabolite (Xeloda) regarding the PCR state or the type of surgery performed. For better interpretation of the results, patients who received infusional 5-FU or Xeloda were considered as "one-drug" group. Those who received Eloxatin in addition to one of the previous agents were categorized as "two-drug" group. Patients who were older than 70 years had more cases with no PCR. However, radiation dose and the chemotherapy regimen (one-drug vs. two-drug) were not different between PCR and non- PCR patients.

Oxaliplatin is a platinum analog and radiosensitizer active in colorectal cancer. Several studies have been performed to evaluate the efficacy of this drug. Rodel *et al*. (16) studied the feasibility and efficacy of preoperative radiotherapy with concurrent capecitabine and oxaliplatin (XELOX-RT) in 32 patients with locally advanced (T3/T4) or low-lying rectal cancer. Down staging of the tumor, histopathologic tumor regression, resectability of T4 disease and sphincter preservation in patients with low-lying tumors were endpoints. According to their results, preoperative XELOX-RT is a feasible and well-tolerated treatment. They proposed this regimen for phase III evaluation comparing standard fluorouracil-based therapy with XELOX chemoradiotherapy. In some other studies, the clinical efficacy of Eloxatin has been demonstrated. Rosenthal *et al*. (17) examined the safety and preliminary efficacy of adding oxaliplatin to standard preoperative CRT for T3 to T4 rectal adenocarci-

noma. Based on their results, oxaliplatin was well tolerated at 85 mg/m2 given every 2 weeks in combination with standard preoperative chemoradiation for rectal cancer.

Conclusion

Adding Eloxatin to the standard treatment of rectal adenocarcinoma did not yield in a higher PCR or more chance to preserve the anal sphincter.

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