Kasr El-Aini J. Clin. Oncol. Nucl. Med.
Vol. 8, No. 3-4, Jul.-Oct. 2012:49-55

Original article

Preoperative Concurrent Chemoradiation for Patients with Locally Advanced Rectal Cancer Experience of a Single Institute

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Background: Worldwide, colorectal cancer is the third most common cancer. In 2000, colorectal cancer accounted for 9.4% of the world's new cancers with 945,000 cases diagnosed and 7.9% of the world's cancer deaths with 492,000 deaths. Colorectal cancer affects men and women almost equally. Chemoradiation with surgical resection is considered standard treatment for operable rectal cancer, the optimal time to administer this therapy is not clear. Results from large clinical trial (National Surgical Adjuvant Breast and Bowel Project R-03) confirmed that preoperative chemoradiation significantly improved disease free survival and showed a trend toward improved overall survival.

Materials and Methods: A retrospective chart review of patients diagnosed with locally advanced rectal cancer at King Fahd Specialist Hospital-Dammam, Saudi Arabia, during period of January 2007 till December 2009. A total of 17 patients were included. Data extracted included age, gender, clinical presentation, tumor site, histopathological subtype, clinical stage, baseline imaging studies, details of therapy received and treatment related toxicities, type of surgery and pathological response. The primary end point was to assess the pathological response.

Results: There were 4 females and 13 males, median age of 57 years (29-76); all patients had adenocarcinoma pathology, 12 patients (70.6%) had grade II tumours and 8 patients (47.1%) had mid rectal tumours. All patients had baseline computerized tomography scans, 13 patients (76.5%) had magnetic resonance imaging, 3 patients (17.6%) had endoscopic ultrasound and 2 patients (11.8%) had PET/CT. Base line CT scan showed 12 patients (70.6%) with T3 lesions and 10 patients (58.8%) with N1 lesions, base line MRI showed 9 patients (52.9%) with T3 lesions and 10 patients (58.8%) with N1-2 lesions and EUS showed T3 lesions in 3 patients (17.6%). The main presenting symptom was bleeding per rectum which was seen in 15 patients (88.2%). Of patients who had surgery; 2 (11.7%) were done by colorectal surgeons, 14 (82.4%) by oncosurgeons and 1 (5.9%) by general surgeon. Ten patients (58.8%) had low anterior resection while 7 patients (41.2%) had abdominoperineal resection. All patients had concurrent chemoradiotherapy and completed their treatment. All patients completed radiation course of 50.4 Gy over 28 fractions. Four patients (23.5%) had to interrupt their radiotherapy course for more than 5 days for toxicity. Eleven patients (64.7%) received pre operative Xelox chemotherapy while 6 patients (35.3%) received only Xeloda with radiation. Two patients (11.8%) and 4 patients (23.5%) had grade III/IV neurotoxicity and diarrhea respectively. Four patients (23.5%) who received Xelox with radiation achieved complete pathological response.

Conclusion: Rectal cancer in Saudi Arabia is diagnosed at earlier age, staged according to guidelines. Combined preoperative chemoradiation using oxaliplatin-containing regimen is well tolerated and with no increase in surgical morbidity. Pathological complete response rate is comparable to what is reported in the literature.

Key words: rectal carcinoma, preoperative chemoradiotherapy

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INTRODUCTION

Locally advanced rectal cancer is comprised of tumors with extension beyond the muscularis propria (≥T3) and/or those with clinical or pathologic evidence for lymph node metastasis (N+); in these cases multimodality approaches are recommended[1].

Neoadjuvant chemoradiation (CRT) for locally advanced rectal tumors is more effective than adjuvant therapy in reducing local recurrence and in minimizing toxicity[2]. It is associated with tumor down staging, significantly higher rate of pathologic complete response (pCR), significantly less advanced pT and pN stage, and fewer cases with venous, perineural, or lymphatic invasion, increased tumor resectability[3]. Multivariate analyses confirmed that the response to neoadjuvant CRT was predictive of improved overall survival among the patients with locally advanced rectal cancer[4,5]. Taking advantage of tumor down staging after neoadjuvant CRT is supposed to increase the chance of sphincter saving surgery (SSS)[6].

MATERIALS AND METHODS

During the period between January 2007 to December 2009, 17 patients with locally advanced rectal cancer who received neoadjuvant CRT were retrospectively reviewed. Data extracted included age, gender, clinical presentation, tumor site, histopathological subtype, clinical stage, baseline imaging studies, details of therapy received and treatment related toxicities, type of surgery and pathological response. The primary end point was to assess the pathological response. Residual tumor mass, fibrotic changes, and irradiation vasculopathy after preoperative CRT semi quantitatively evaluated according to a 5-point rectal cancer regression grading established by Dworak *et al*.[7], Table 1. A pathologic complete response (pCR) was defined as the absence of viable tumor cells in the primary tumor and in the lymph nodes (ypT0N0).

RESULTS

Patients characteristics' is shown in Table 2. A total of 17 patients were reviewed. The median age was 57 years (29-76). There were 4 females and 13 males, all patients had adenocarcinoma pathology and 12 patients (70.6%) had grade II tumors. Four patients (23.5%) had low rectal tumors, while 8 (47.1%) and 5 (29.4%) patients had mid and low rectal tumors, respectively. The main presenting symptom was bleeding per rectum which was seen in 15 patients (88.2%). All patients had baseline computerized tomography scans, 13 patients (76.5%) had magnetic resonance imaging, 3 patients (17.6%) had endoscopic ultrasound and 2 patients (11.8%) had PET/CT. Base line CT scan showed 12 patients (70.6%) with T3 lesions and 10 patients (58.8%) with N1 lesions, base line MRI showed 9 patients (52.9%) with T3 lesions and 10 patients (58.8%) with N1-2 lesions and EUS showed T3 lesions in 3 patients (17.6%). Eleven patients (64.7%) received weekly pre operative Xelox (Xeloda 625 mg/m^2 and oxaliplatin 50 mg/m^2) chemotherapy while 6 patients (35.3%) received only Xeloda (825 mg/m^2) with radiation. Of patients who had surgery; 2 (11.7%) were operated by colorectal surgeons, 14 (82.4%) by oncosurgeons and 1 (5.9%) by general surgeon. Ten patients (58.8%) had low anterior resection while 7 patients (41.2%) had abdominoperineal resection. All surgical margins of the resected specimens were negative. Lymph node dissection ranged from 0-19 with a mean of 7 lymph nodes. pT2 and pN0 lesions were seen in 5 (29.4%) and 14 (82.4%) patients, respectively.

All patients completed the course of neoadjuvant concurrent chemoradiation (50.4 Gy / 28 fractions, 180 cGy per fraction) without any modification in the radiation dose. Radiation was delivered in two phases, phase I was a whole pelvic irradiation 45Gy/25 fractions while phase II was confined to the primary tumor bed with 3cm margin in all direction to a dose of 540 cGy / 3 fractions. The most frequently encountered acute toxicities were grade III diarrhea in 4 patients (23.5%), anorectal discomfort in 9 patients (53%) and vague abdominal pain in 6 patients (35.2%). Neoadjuvant radiotherapy does not seem to be a significant risk factor for anastomosis dehiscence, even after resection of low-sited tumours, but proximal diversion with temporary stoma were used in such patients.

Four patients (23.5%) had to interrupt their radiotherapy course for more than 5 days for toxicity. Two patients (11.8%) and 4 patients (23.5%) had grade III/IV neurotoxicity and diarrhea respectively. Five patients (29.4%) had grade III/IV skin toxicity, table 3.

Four patients (23.5%) who received Xelox with radiotherapy achieved complete pathological response. None of the patients developed grade III/IV hematological toxicity.

Table 1: Grades of pathological response according to the Dworak method.

Grade	Description
1	No viable cancer cells, only fibrosis
2	Very few cancer cells(difficult to find microscopically) in fibrotic tissue with or without mucous substance
3	Dominantly fibrotic changes with few tumor cells easy to find microscopically
4	Dominant tumor mass with fibrosis
5	Tumor mass

Table 2: Patient characterisitics.

Patient characteristic	No of patients
Age, years	
Median	57
Range	29-76
Sex	
Male	13
Female	4
Pathological grade	
1	4
2	12
3	1
T stage by CT	
T1	1
T2	1
T3	12
T4	3
N stage by CT	
N0	5
N1	10
N2	2

Table 3: Grade III/IV toxicity.

Toxicity	No	%
Neuropathy	2	11.8
Diarrhea	4	23.5
Skin	5	29.4

DISCUSSION

Globally, nearly 800,000 new colorectal cancer cases believed to occur each year all over the world. They account for 10% of all incident cancers. The mortality from colorectal cancer is estimated to be nearly 450,000 per year[8].

The treatment of rectal cancer has evolved dramatically through the last three decades. Until the 1970's and 1980's, surgery was often the only therapeutic modality employed in the treatment of rectal cancer patients. However, local recurrence with surgery alone was significant resulting in patient morbidity and death[9,10]. Neoadjuvant chemoradiotherapy has become the standard of care for stages II and III rectal cancer since the CAO/ARO/AIO trial[2].

Preoperative radiotherapy with continuous 5-FU infusion has the biologic advantage of prolonging exposure of tumor cells to 5-FU and improving antitumor activity. However, its disadvantages include the requirement of central venous access with potential complications, such as bleeding, thrombosis, infection and pneumothorax[11]. Most patients receiving chemotherapy prefer oral therapies to intravenous regimens because of their possibility to receive treatment without attending clinics, to continue daily activities and to maintain a relatively normal lifestyle. There is evidence that, with regular patient education and monitoring, adequate patient compliance to oral medications can be achieved, although issues of compliance and safety remain a concern[12].

Capecitabine is an oral fluoropyrimidine carbamate prodrug of 5-FU designed to generate 5- flurouracil (5-FU) preferentially in tumor cells[13], as concentration of the key enzyme thymidine phosphorylase (TP) is higher in tumor cells compared with normal tissue. In preclinical studies, irradiation with thymidine phosphorylase was found to be upregulated in tumor tissue resulting in a selective synergistic effect of capecitabine on radiotherapy[14-16]. Capecitabine is administered daily to mimic a continuous infusion of 5-FU[17]. This continuous regimen is likely to have a more constant cytotoxic action, thereby limiting tumor regrowth. The side-effect profile of capecitabine is similar to that observed when 5-FU is given as a protracted infusion and consists mainly in diarrhea. The dose-limiting toxicity is the hand–foot syndrome, occurring as the capecitabine dose reaches 1000 mg/m^2 twice daily. Other toxicities were generally mild to moderate[18,19]. The recommended dose of capecitabine to be 825 mg/m^2 twice daily, administered 7 days/week during a conventional RT period of about 6 weeks for preoperative therapy in locally advanced rectal cancer[20]. Capecitabine is an adequate substitute for continuous infusional 5-FU in preoperative chemoradiation regimens with regards to the favorable toxicity profile, considerable down staging effect and pathologic complete response on the tumor, and could increase the possibility of sphincter preservation in distal rectal cancer[21-24].

In terms of timing of capecitabine and radiotherapy, in the xenograft experiments capecitabine was administered 1 h before radiotherapy. However, the tmax for capecitabine and its metabolites (including 5-FU) are identical at 2 h post-ingestion[16,25]. For this reason, authors recommend administering capecitabine a minimum of 2 h before morning radiotherapy in the clinic.

A phase II study conducted at the MD Anderson Cancer Center in the USA included 54 patients who received preoperative radiotherapy (45 Gy given in 25 fractions to the pelvis with a boost to deliver 52.5 Gy given in 30 fractions to the primary and perirectal nodes) plus continuous oral capecitabine (825 mg/m^2 twice daily) for 5 weeks. Overall response rate after chemoradiation was 90%. Fifty-two patients underwent surgery with pCRs in 17% and microscopic residual disease in a further 15%. Tumour and nodal downstaging was observed in 62% of patients. Again a low rate of grade 3/4 adverse events was observed[26]. Other prospective phase I/II studies of capecitabine chemoradiation have been conducted in China[27], the Czech Republic[28], France[29], Greece[30], Italy[31,32], Thailand[33], the UK[34] and the USA[35], with results being similar to those from the earlier German and US trials.

The third-generation platinum analogue oxaliplatin is a good candidate for inclusion into neoadjuvant chemoradiation regimens. Preclinical and clinical studies have demonstrated oxaliplatin to be a potent radiosensitising agent[36]. In preclinical models of combined radiotherapy and oxaliplatin, an 8-h oxaliplatin exposure has been associated with a dose-related cell kill rate[37]. Synergistic effects with radiation in colon cancer cells were observed when oxaliplatin was administered both before and after radiation. In mouse xenograft models of colorectal cancer, tumour

growth has been shown to be inhibited by combined oxaliplatin and radiation[38]. Preclinical studies have also shown that combination of capecitabine and oxaliplatin is capable of inhibiting the *in vivo* growth of a CXF280 human CRC xenograft more effectively than either capecitabine or oxaliplatin alone, which is probably due to the upregulation of TP expression by oxaliplatin observed in the same xenograft model[39].

Capecitabine/oxaliplatin combinations have demonstrated efficacy and tolerability comparable to that of 5-FU/oxaliplatin in the first-line treatment of metastatic colorectal cancer. Several studies have investigated the combination of capecitabine, oxaliplatin, and radiation in the neoadjuvant treatment of rectal cancer in hopes of improving both local and systemic disease control.

In a phase I/II study, daily capecitabine (including weekends) was combined with a fixed dose of oxaliplatin at 130 mg/m^2 on days 1 and 29 concurrently with RT 45 Gy (25 fractions) in patients with borderline or unresectable rectal cancer. A total of 96 patients were enrolled and there was a pCR in 19% of patients and only 22% experienced grade 3/4 adverse events, the most common being gastrointestinal[40].

A phase II neoadjuvant study of capecitabine and oxaliplatin (XELOX) plus radiation in 110 patients with locally advanced rectal cancer. The regimen consisted of capecitabine at 825 mg/m² twice daily on days 1 to 14 and 22 to 35 along with oxaliplatin 50 mg/m² on days 1, 8, 22, and 29, plus RT (50.4 Gy in 28 fractions). Grade 3 toxicity, mainly diarrhea, occurred in 14% of patients. Of the resected specimens 15% showed a pCR[41].

The Capecitabine Oxaliplatin Radiotherapy and Excision (CORE) study investigated a variant regimen of capecitabine twice daily on Mondays through Fridays and weekly oxaliplatin at 50 mg/m^2 concurrently with radiation at 45 Gy in patients with threatened or positive circumferential margins by magnetic resonance imaging. Initial results from this multicenter phase II study showed an R0 resection rate of 67% and a pCR rate of 13%[42].

Other researchers have investigated a capecitabine/oxaliplatin regimen similar to the one used in the CORE study[43-47]. These studies were associated with pCR rates of 14% to 24%, tumor-downstaging rates of 52% to 78%, and grade 3/4 diarrhea rates of 8% to 30%. The current recommended dose for capecitabine given twice daily on radiation days with weekly oxaliplatin and RT (1.8 Gy × 25–28 fractions) is 825 mg/m^2 twice daily and 50 mg/m^2 weekly for capecitabine and oxaliplatin, respectively.

The recommended doses of capecitabine, oxaliplatin, and radiation therapy may tend to be lower in the United States than in Europe, because higher rates of toxicity have been reported in the US for capecitabine monotherapy or capecitabine/oxaliplatin combinations[48]. The exact etiology for the discrepancy in toxicity at equal capecitabine dosing may be related to increased folic acid supplementation in the American diet. The phase III trial ACCORD 12/0405 – Prodige 2 randomly assigned patients to receive 5 weeks of RT 45Gy/25 fractions with concurrent capecitabine 800 mg/m^2 twice daily 5 days/week (CAP45) or RT 50Gy/25 fractions with same dose of capecitabine plus oxaliplatin 50 mg/m^2 once weekly (CAPOX50). More preoperative grade 3 to 4 toxicity occurred in the CAPOX50 group (25% vs 1%, P<0.001). The ypCR rate was 13.9% with CAP45 and 19.2% with CAPOX50 (P = 0.09). In this trial, a benefit of oxaliplatin was not demonstrated and they concluded that this drug should not be used with concurrent irradiation[49].

A German Group performed a phase I study to determine the maximum tolerated dose of oxaliplatin when administered with capecitabine and standard radiotherapy, and extended to a phase II neoadjuvant study in 32 patients with LARC or low-lying rectal cancer[50]. Patients received an intermittent schedule of capecitabine (825 mg/m^2 twice daily on days 1–14 and days 22–35) plus oxaliplatin (50 mg/m^2 on days 1, 8, 22 and 29) in combination with pelvic radiotherapy (50.4 Gy in 1.8 Gy daily fractions) for 5 weeks. Adverse events observed at the recommended oxaliplatin dose level (50 mg/m^2/day) were generally mild, with only two cases of short-lived grade 3 diarrhoea. Myelosuppression, mainly leukopenia, was no higher than grade 2 in 19% of patients. A Belgian trial has used capecitabine 5 days per week given on weekdays only (i.e. capecitabine 825 mg/m^2 twice daily on weekdays plus weekly low-dose oxaliplatin 50 mg/m^2 on days 1, 8, 15, 22 and 29 plus radiotherapy 45 Gy in 1.8 Gy daily fractions for 5 weeks). A high rate of grade 3/4 diarrhoea (30%) has been reported, but toxicity has been generally manageable with dose interruptions/reductions and the dose intensity of both capecitabine and oxaliplatin remained high. The pCRs were identified in 14% of the resected specimens[51].

Despite the limitation of the analysis in our review due to inconsistency in the neoadjuvant chemotherapy regimen given at our hospital, as 11 patients and 6 patients received Xelox and Xeloda chemotherapy respectively and small sample size, pathological

complete response was achieved in 23.5% of patients. All the patients who achieved complete pathological response received preoperative Xelox with radiation. Our results are comparable to other studies that used the same regimen and reported complete pathological response ranging from 14-24%[43-47].

In our study, the acute toxicity profiles of neoadjuvant concurrent chemoradiation were comparable to those achieved in other studies as grade III acute diarrhea developed in 23.5% of our patients compared to grade 3 or 4 acute toxic effects that occurred in 27 percent of the patients in the preoperative-treatment arm of Sauer *et al.* study[2].

The degree of pathological response by preoperative chemoradiation could be used to stratify patients to individualize the postoperative adjuvant chemotherapy. Patients who showed pathologically complete response might not require adjuvant therapy[52], and that was not considered in the current study as all patients received adjuvant chemotherapy irrespective of the degree of pathological response.

CONCLUSION

The preoperative chemoradiotherapy regimen used in our center seems to be well tolerated and of very acceptable toxicity profile. Preoperative chemoradiotherapy incorporating capecitabine with oxaliplatin achieved a high rate of complete pathological response. Phase III studies of large number of patients are needed for better evaluation and assessment of this group of patients.

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