Original Clinical Research

Preoperative chemoradiation with oral capecitabine in locally advanced rectal cancers: An impact on sphincter preservation and pathologic response?

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Abstract

Background: Preoperative chemoradiotherapy with concurrent 5-flourouracil (5-FU) has shown superior results as compared to postoperative chemoradiation. Capecitabine, an oral flouropyrimidine, is converted to 5-FU in the body. Our aim was to evaluate the efficacy of capecitabine as radiosensitizer in preoperative chemoradiation of locally advanced rectal cancer.

Methods: From November 2008 to December 2009, 20 patients with locally advanced rectal cancers (≥ T3 or N +), were treated after written consent with concurrent capecitabine (825 mg/m^2 oral twice daily) with pelvic radiotherapy (dose 5 040 cGy in 28 fractions), followed by total mesorectal excision surgery and adjuvant chemotherapy. Primary endpoints were pathologic response rates, efficacy of capecitabine and its toxicity. Pathologic response rates and toxicities were summarized with 95% confidence intervals (95% CI).

Results: The predominant radiological stage was T3 N + in 40% followed by T4N0 in 35%. The complete pathologic response (pCR) was achieved in 3 patients (15%), the downstaging was observed in 17 patients (85%). Sphincter preservation was reported in 65% cases. The grade 3 hematological toxicities were lymphopenia (30%) and neutropenia (10%). The grade 3 non hematological toxicities observed were: diarrhea/proctitis (25%) and nausea/vomiting (25%). No hand foot syndrome or grade 3 skin toxicity was seen.

Conclusions: The capecitabine as radiosensitizer was well tolerated, more convenient than intravenous 5-FU and with similar response rates in locally advanced rectal cancer.

Key words: Preoperative radiotherapy; Capecitabine; Radiosensitizer; Locally advanced rectal cancer

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INTRODUCTION

The incidence of colorectal carcinoma in Pakistan is similar to Asian countries, but much lower than in the developed countries. The risk is equal in both sexes at present. However a 41 % rise in incidence was noted in the males between 1995 and 1999, whichmay indicate a higher risk in the males in future[1]. Most of the rectal cancers are presented at advanced stage, not amenable to upfront curative surgery. Recent prospective randomized rectal cancer studies with large sample sizes and long term follow up have reported that preoperative chemoradiotherapy

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was superior to postoperative chemoradiotherapy in terms of local control, feasibility and toxicity for locally advanced rectal cancer[2, 3].

The rationale for combining chemotherapy with radiation is believed that some agents enhance the effects of radiation, which are also called radiosensitizers or enhancers; among these 5-flourouracil (5-FU) is the most commonly used for rectal cancer radiotherapy. The protracted infusional 5-FU is better tolerated than bolus injections, with lower incidence of diarrhea and neutropenia, however risk of mucositis and hand foot syndrome increases[4].

The capecitabine is an oral flouropyrimidine that is converted to 5-FU in the body by the enzyme thymidine phosphorylase. Thymidine phosphorylase is more abundant in tumor cells than normal cells, leading to more intracellular concentration of 5-FU and more tumor cytotoxicity[5]. Further studies suggest that radiotherapy up-regulates the thymidine phosphorylase expression in tumor cells, making capecitabine suitable as radiosensitizer[6].

The optimal dose of capecitabine with radiotherapy was established in a phase I trial where maximal tolerated dose of capecitabine was 825 mg/m^2/day orally twice a day (bid), given throughout course of radiation[7]. Recent two phase II trials have achieved pathologic complete response rates (12% and 24%) and sphincter preservation (74% and 59%) with minimal toxicities[8,9]. Other potential benefits of oral capecitabine over 5-FU are: it avoids the intravenous lines and inconvenience.

With such encouraging outcomes, we started a single arm study of oral capecitabine concurrent with three dimensional conformal (3D-CRT) for locally advanced rectal cancer to evaluate (1) the response rate including complete pathologic response (pCR) rate and sphincter preservation for low lying rectal tumors and (2) tolerance and toxicity profile in our Pakistani population.

MATERIALS AND METHODS

Eligibility

After approval from institutional review committee and consent from patients with locally advanced rectal cancer for chemoradiation with oral capecitabine patients were selected on following criteria: (1) histologically proven rectal adenocarcinoma; (2) distal margin of tumor located within 10 cm from anal verge on endoscopy; (3) T stage ≥ T3 or nodes positive on preoperative imaging (CT, MRI) and M0; (4) Eastern Cooperative Oncology Group performance status 0-2; and (5) Normal hematology and biochemistry. The patients who had prior chemotherapy or pelvic radiotherapy, poor functional status or with severe co-morbidities were excluded. Treatment Protocol see Figure 1.

Radiotherapy

Preoperative radiotherapy was delivered by using high energy multli-leaf collimator (MLC) linear accelerator (15 MV). All patients after written consent were virtually simulated in prone position using SOMATOM emotions6 CT scanner Siemens®, to displace small bowel (belly board). The whole pelvis was treated with three field technique up to 4 500 cGy in 25 fractions over 5 weeks. The superior border was at L5-S1 interspace, lower border was kept at least 3 cm below the tumor. The lateral borders of AP-PA fields were defined 1 cm away from lymph nodes using vessels as surrogate markers (Figure 2). Lateral portals covered the full sacrum and coccyx with a margin; anteriorly they were 3 cm from sacral promontory. Additional boost of dose 540 cGy in three fractions was given to gross tumor volume (GTV) and surrounding mesorectum. The wedges for lateral fields and appropriate shielding to organs at risk (OAR) were used for all patients.

Chemotherapy

The capecitabine was given at 825 mg/m^2 orally twice daily for duration of radiotherapy with initial dose starting 1 hour before radiotherapy. It was given during radiation days only (5 days/week). The dose modifications were as: if a patient experienced grade 2 hematologic toxicities, capecitabine was stopped until it resolved. For grade 2 or more non-hematologic

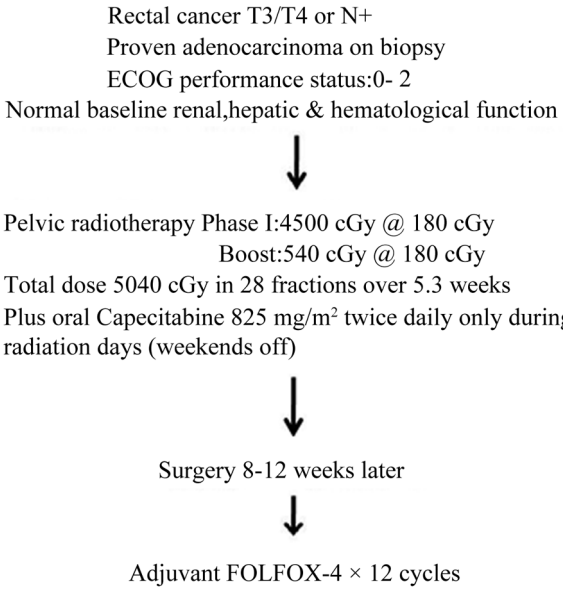

Figure 1 Treatment algorithm for study protocol

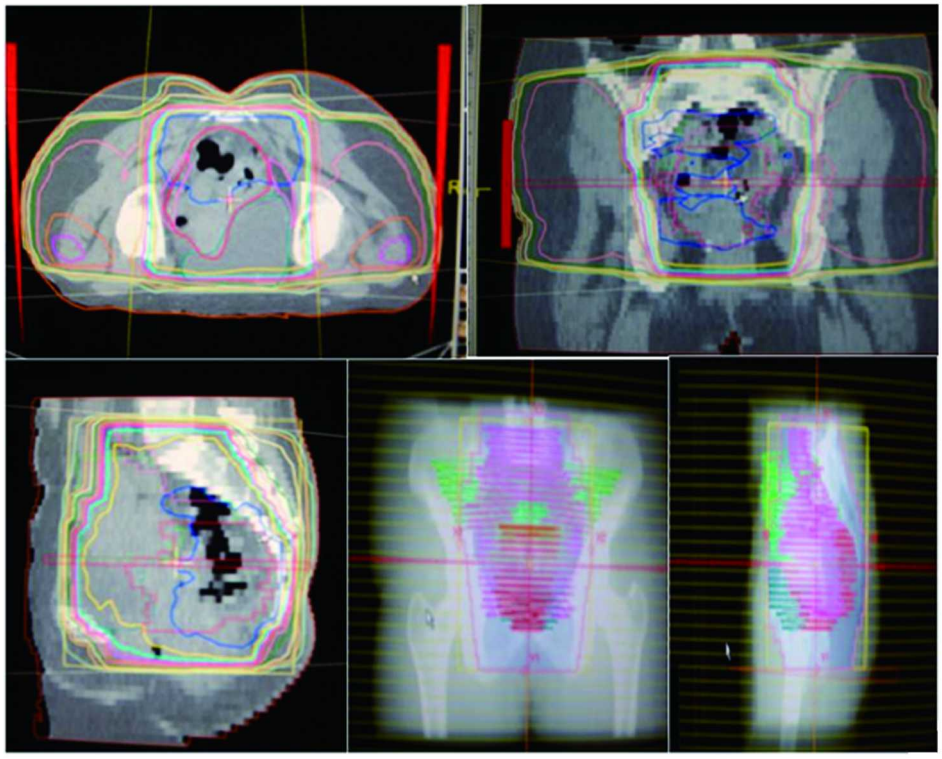

Figure 2 Treatment techniques used for radiotherapy (a) prone position with three field technique, (b) & (c) coronal and sagittal views of multi planar reconstructed (MPR) showing isodose distribution, (d) Posterior and lateral portals on digitally reconstructed radiographs (DRR) showing gross tumor volume, lymph nodes and boundaries.

toxicities, the drug was reduced to 50% of starting dose. For any reappearance of toxicity, the capecitabine was stopped until it resolved. Radiotherapy side effects were managed as per departmental protocols.

Surgery

After the completion of chemoradiation, patients underwent assessment (repeat CT/MRI, endoscopy, ± exploratory laparotomy) for surgery at 8th and 10th week. The choice of procedure (low anterior resection or abdominoperineal resection) was left on the discretion of the surgeon.

Postoperative chemotherapy

The choice was left on the discretion of medical oncologist.

Study endpoints

Pathologic response rate

After surgery, the pathologic tumor staging was determined according to TNM classification system by International Union against Cancer and American Joint Committee on Cancer (UICC, AJCC) [10]. Downstaging was applied for T stage and was defined as "yp", where "y" was after chemoradiotherapy and "p" for postoperative pathologic examination. All resected specimens were evaluated for pathologic response with careful inspection of tumor, mesorectal fat and circumferential margins. The pathologic complete response (pCR) was defined as the absence of cancer cells in resected specimen.

Toxicity profile

The adverse events were graded according to National cancer Institute Common Toxicity Criteria (CTC) version 2.0[11] and were weekly recorded during follow up. Hematology and serum chemistry was checked on weekly basis and after completion of chemoradiation at 4 and 8 weeks.

Statistical analysis

The pathologic complete response was a binary variable and was scored as 0 or 1 based on presence of tumor cells. This study design was planned using Simon's optimal two stage design12. According to this, in first stage to document ≥ 2 pCR, 19 patients were required, otherwise to close study prematurely. The descriptive data (mean, median, range and frequency) were calculated using SPSS version 16.0. The response rates and toxicities were summarized with 95% confidence intervals (95% CI).

RESULTS

From November 2008 to July 2009, a total 25 patients were considered eligible for the study. Five patients could not complete treatment protocol (2 lost to follow up/ 3 refused for surgery). Patient characteristics for 20 patients are described in Table 1. The study population and was predominantly male (14 males and 6 women). The majority of tumors (55%) were within 5 cm of anal verge. The predominant clinical stage was T3N + in 8 patients (40%) followed by T4N0 in 7 patients (35%).

Table 1 Characteristics of study patients

Variable	Number
Median Age	34.7 years (range 17-55)
Gender	
Male	14 (70%)
Women	6 (30%)
Site of primary tumor	
Upper rectum	9 (45%)
Lower rectum	11 (55%)
Clinical/radiological Stage	
T2 N +	1 (5%)
T3 N0	3 (15%)
T3 N +	8 (40%)
T4 N0	7 (35%)
T4 N +	1 (5%)
Performance Status (ECOG)	
0	12 (60%)
1	8 (40%)

ECOG = Eastern Cooperative Oncology Group.

The pathologic response data were available for 20 patients who underwent surgery. Complete pathologic response was found in 3 patients (15%) in primary

tumor as well in retrieved lymph nodes. T downstaging was found in all remaining 17 patients (85%). No progression or stable disease was found at time of analysis.

The scheduled radiotherapy was completed in all patients without any treatment break (mean duration was 40 days [37-50]).

All patients were evaluable for toxicity. No treatment related death neither life threatening event were seen. The toxicity profile is mentioned in (Figure 3).

Grade 3 hematologic toxicities were lymphopenia in 6 patients (30%) and neutropenia in 2 patients (10%). Grade 3 non-hematologic toxicities were diarrhea in 5 (25%), nausea/vomiting in 5 (25%), proctitis in 5 (25%) and voiding problems in 3 (15%). No hand foot syndrome or grade 3 skin toxicity noticed. Capecitabine dose interruption was reported in 6 patients (diarrhea 2, neutropenia 1, nausea and vomiting 3) until symptoms resolved.

After chemoradiotherapy, 13 patients (65%) had sphincter preservation surgery while abdominoperineal resection (APR) in 7 patients (35%). All excisions were total mesorectal excisions (TME). Postoperative complications were seen in 2 patients (wound infection and abscess).

DISCUSSION

The preoperative radiotherapy for locally advanced rectal cancer has been found superior in terms of local control rates and toxicity to postoperative use[13]. However, there remains controversy about effectiveness of protracted and bolus 5 FU with radiation. Protracted infusion of 5-FU prolongs the exposure of tumor cells to the drug and more cytotoxicity[14]. However, protracted infusion of 5-FU requires continuous venous access and an ambulatory infusion pump, which increases the cost and complexity. Recently, data has shown superior overall response rate and safety profile of capecitabine when compared to bolus 5-FU[15, 16].

Our study aimed to evaluate the efficacy of concurrent capecitabine with preoperative radiotherapy in locally advanced cancer. We obtained pathologic complete response (pCR) 15%, downstaging 85% and sphincter preservation 65% with the manageable toxicity. The results of similar phase II trials shown are shown in Table 2.

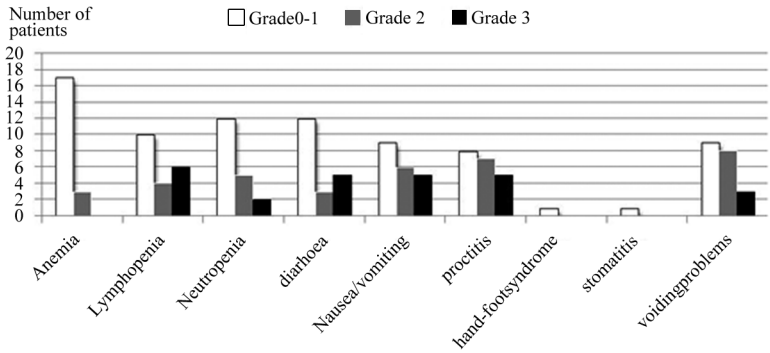

Figure 3 Hematologic and non-hematologic toxicities according to CTC-NCI (Common toxicity criteria-National Cancer Institute)

Table 2 Selected phase II trials of preoperative capecitabine and radiotherapy in patients with locally advanced rectal cancer

Study(Reference)	PCR (%)	Sphincter preservation (%)	Hematologic ≥G3 toxicity	Non-hematologic ≥G3 toxicity (%)
Kim JC, et al[8]	12%	74%	2%	3%
De Paoli A, et al[9]	24%	59%	10%	12%
Krishnan, et al[18]	18%	67%	6%	17%
Slampa P, et al[23]	21%	76.5%	3%	15%
Kim DY, et al[24]	16.9%	88.7%	6.3%	3%
Zampino MG, et al[19]	18%	62%	2%	14%
DeBriun AF, et al[25]	13 %	25%	0%	5%
Our study	15%	65%	10%	25%

pCR = Pathologic complete response

Our study showed higher incidence of non hematological toxicities (nausea/vomiting and diarrhea) 25%. The possible explanation could be (1) different study population, (2) lack of patient education, and (3) different eating habits. It is advisable to give antiemetics prior to oral capecitabine. Our study showed better sphincter preservation (65%) like other studies for low rectal cancers. Krishnan, *et al*[17]. used concomitant boost during last week of radiotherapy; no added benefit was seen by concomitant boost. Further, Zampino, *et al*[18]. used further two courses of 1 250 mg/m^2 bid after concurrent chemoradiation before the surgery. But no additional benefit of capecitabine monotherapy was found in this study. Contrary, Elwanis MA, *et al*. found relatively lower pathologic complete (pCR) 4% and sphincter preservation procedures 46.5% with similar regimen for low lying rectal cancer[19]. Our previous study of concurrent 5-FU with radiation in locally advanced rectal cancer showed pCR of 15 % comparable with present study[20].

In present study we did not see any severe skin toxicity or hand foot syndrome which has been documented around 8%-35% in above mentioned trials. Explanation could be dark skinned Asian population and comparatively lower doses (825 mg/m^2) in our study. We did not see any treatment related death or hospitalization. Post surgical complications in present study were similar to other studies.

Our study had few limitations; first, the primary endpoint was limited to pathologic response rate and short term toxicity profile, so no futher statistical tests were applied. The sample size was low, with more advanced unresectable stages and capecitabine was given only during radiation days, rather in continuous fashion. The lower sample size is justified by poor referral to tertiary care centers, lack of multidisciplinary approaches and lack of patient education. Other additional result in our study was that, predominant study population was young male. Cause is unknown and attention is required of epidemiologists and oncologists.

CONCLUSION

The results of our single center experience were similar to other published studies, but with higher but manageable gastrointestinal toxicity. Capecitabine was found more convenient and with satisfactory response rates, can be safely used concurrent with preoperative radiotherapy especially in busy oncology centers. However, a multicenter randomized trial is warranted to evaluate long term local control and survival benefit.

Conflicting Interest: Authors have not potential conflict of interest. No grant received for this study.

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