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Original Research Article

Comparison of continuous infusional 5-fluorouracil and capecitabine in preoperative chemo radiotherapy for locally advanced rectal cancer: experience from a tertiary cancer centre from Southern India

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ABSTRACT

Background: Neoadjuvant concurrent chemoradiation (CTRT) is the recommended treatment for locally advanced rectal cancer. 5 Fluorouracil (5-FU) has been the standard chemotherapy drug, but recent studies have proved Capecitabine (CA) is as effective as 5-FU in terms of local response, distant recurrences and overall survival except toxicities. We conducted this study to evaluate acute toxicities and local response rates between 5-FU and CA as neoadjuvant treatment modality combined with radiation.
Methods: All patients with newly biopsy proven adenocarcinoma of rectum of TNM stage T3N0/ any T with N1,N2 and in whom curative treatment was planned with concurrent chemoradiation dose of 5040cGy in 28 fractions were included in the study. From January 2013 to June 2014, a total of thirty patients were enrolled in this study, fifteen patients received 5-FU (arm A) and fifteen patients received CA (arm B) during concurrent chemoradiation. All patients were evaluated for acute toxicities during treatment using RTOG criteria. Local response was assessed radiographically after four weeks of completion of CTRT utilising RECIST (Response Evaluation Criteria in Solid Tumors) criteria and also assessed for surgery simultaneously. Postoperatively adjuvant chemotherapy was considered in all patients.
Results: Grade III toxicities were more in 5-FU arm compared to CA arm. The local response rates were almost same in both the arms, partial response in 5-FU and CA arm were 53.3% and 60% respectively.
Conclusions: This is the first Indian study comparing Capecitabine and continuous Infusional 5FU in neoadjuvant CTRT of standard advanced rectal cancer patients. Oral Capecitabine had same efficacy when compared to 5-FU in terms of local response rates as neoadjuvant treatment modality in locally advanced rectal cancer, but CA was better tolerated with better patient compliance and was less toxic.

Keywords: 5-fluorouracil, Capecitabine, Neoadjuvant chemoradiation, Rectal carcinoma, Southern India

INTRODUCTION

According to GLOBOCAN 2012 analysis, worldwide, colorectal cancer is the third most common cancer in males and second most common cancer in females.[1] Worldwide, there were an estimated 1.4 million cases of colorectal cancer. The age-standardized rates of colorectal cancer in India have been estimated to be 4.2/1, 00,000 for males and 3.2/100,000 for females.[2] Incidence of colorectal cancer is increasing in India, this increasing incidence may partly be due to increasing prevalence of risk factors like sedentary lifestyle, smoking, unhealthy

diet and obesity. Most of the patients present in locally advanced stages or in metastatic stages due to various factors like poverty, illiteracy, lack of awareness and lack of facilities.

In spite of "curative" resections, 20-50% of rectal cancer patients develop local recurrence of disease.[3,4] In patients with resectable T3 N0 or any T N1-2 lesions, the standard of treatment is preoperative combined concurrent chemoradiation (CTRT) followed by surgery followed by adjuvant chemotherapy unless medically contraindicated. Locally advanced rectal cancer remains a major public health problem.

Local and systemic recurrences pose major problems in rectal cancer management. Various trials have established the role of preoperative chemoradiotherapy followed by surgery and adjuvant chemotherapy. The GITSG (GastrointestinalTumor study group) trial was a four-arm trial in which patients after being operated were randomized to observation, chemotherapy or radiation therapy alone. The GITSG study showed the significant overall survival benefit provided by adjuvant chemoradiation compared to observation or radiation alone.[5] Subsequently several trials confirmed the benefit of 5-Fluorouracil (FU) in concurrent chemoradiation.[6] Capecitabine is an oral, tumour-activated fluoropyrimidinecarbamate that delivers 5-FU preferentially to tumour cells via a three-step *in-vivo* enzymatic conversion. The final step is mediated by the enzyme thymidine phosphorylase (TP), which is upregulated in tumour tissue compared with adjacent healthy tissue. Due to its twice-daily oral administration, capecitabine approximates continuous infusions of 5-FU. Capecitabinehas proven activity as both adjuvant and first-line treatment for colorectal cancer. Several studies established that Capecitabine was well tolerated and was non-inferior to Infusional 5FU in preoperative chemoradiation.[7]

Capecitabine is being increasingly used in neoadjuvant chemoradiation of rectal carcinoma. Addition of oxaliplatin in preoperative chemoradiation of rectum cancer has no added benefit.[8,9] Few retrospective studies from regional cancer centres in India have been published regarding Capecitabine in preoperative chemoradiation of rectum cancer patients, however till date to the best of our knowledge, a formal comparison of Capecitabine vs Infusional 5FU in preoperative chemoradiation of rectum cancer patients has not yet been published from India. We conducted a study to compare the efficacy and safety of Capecitabine versus Infusional 5FU in chemoradiation of locally advanced rectal cancer patients.

METHODS

A comparative single institutional pilot prospective study was conducted from January 2013 to June 2014. This study included a total of thirty patients with fifteen patients in each arm i.e. 5-FU arm and CA arm.

Inclusion criteria

Newly diagnosed, biopsy proven adenocarcinoma: AJCC 2010 TNM stage T 3/4 and/or N+ M0; Eastern Cooperative Oncology Group(ECOG) performance status 0 to 2; No prior pelvic surgery; in whom curative treatment is planned.

Exclusion criteria

Metastatic disease; previous radiation to pelvis; unfit for anaesthesia; contraindications to chemotherapy.

Pre-treatment examination included clinical history, digital rectal examination, proctoscopy and colonoscopy with biopsy, contrast enhanced computerised tomography (CECT)/ magnetic resonance imaging (MRI) of abdomen and pelvis. In females, per vaginal examination was carried out to look for anterior spread. Baseline investigations including complete blood count (CBC), renal function tests (RFT), liver function tests (LFT), echocardiography, electrocardiogram, viral serology HIV and HBsAg (ELISA) were done.

In Arm A (n = 15): Injection 5-Fluorouracil was given as a continuous intravenous infusion at the dose of 225 mg/m2 through a central line (subclavian or an internal jugular venous central venous double lumen catheter) on the days of radiation.

In Arm B (n = 15): Tablet Capecitabine 825mg/m2 twice daily was given on the days of radiation. Radiation was delivered with linear accelerator using three-dimensional conformal radiation therapy (3DCRT). The patients were positioned and treated in supine position with full bladder, no immobilization devices were used. Three fiducial markers on lower abdomen were used as reference and to define isocentre using lasers. Radiotherapy planning scan was performed on GE Helical CT with 5 mm slice thickness. Scanned images were imported to planning system Varian Eclipse 11. Volumes were contoured and planned with dose: 5040cGy in 28 fractions, 180cGy per fraction. During treatment patients were assessed every weekly with CBC, RFT and LFT. Toxicity grading was done according to Radiation Toxicity Oncology Group (RTOG) criteria.

Local response assessment was done in all the patients after completion of neo adjuvant CTRT and also after four weeks. Patients were examined clinically and radiological assessements were done with CECT/MRI abdomen and pelvis. Response assessment was done using RECIST criteria. After the assessment was done by surgical oncologists, operable cases were taken for surgery. For upper one third and middle third rectal cancers, low anterior resection with restoration of intestinal continuity and sphincter preservation was performed. For lower third rectal cancers, total mesorectal excision or abdominoperineal resection with permanent colostomy was performed. After recovery

from surgery, patients received adjuvant chemotherapy. Later all patients were advised regular follow up once in three months for first two years, then six monthly for next three years, and then annually.

RESULTS

The study population had a total number of thirty cases, fifteen cases in each arm. The characteristics of the patients enrolled are listed in Table 1.

Table 1: Patient characteristics treatment (N = 30).

Characteristics	5-FU	CA	*P*
Age (years)	Median 38 (Range 23-65)	Median 44 (Range 23-70)	0.179
Sex			1.0
Female	5(33.3%)	5(33.3%)	
Male	10(66.7%)	10(66.7%)	
Tumour location			0.705
Middle 3rd	5(33%)	6(40%)	
Lower 3rd	10(66.7%)	9(60%)	
Clinical stage			1.0
T3N1	8(53.3%)	8(53.3%)	
T3N2	3(20%)	3(20%)	
T4N1	3(20%)	426.7%)	
T4N2	1(6.7%)	0(0%)	
Histology			1.0
Adenocarcinoma	13(86.7%)	12(80%)	
Mucinous	2(13.3%)	3(20%)	
Grading			0.740
Well differentiated	6(40%)	4(26.7%)	
Moderately differentiated	5(33.3%)	6(40%)	
Poorly differentiated	4(26.7%)	5(33.3%)	
Duration of treatment(days)			0.001**
< 40	6(40%)	15(100%)	
>40	9(60%)	0(0%)	
Treatment interruption			0.020*
Present	8(53.3%)	2(13%)	
Absent	7(46.7%)	13(86.7%)	
CEA level			
<5ng/mL	6(40%)	3(20%)	
>5 ng/ mL	9(60%)	12(80%)	

Patients in both the study arms were well matched with respect to age, sex, stage, site of disease. Both the study arms had 10 male and 5 female patients. Majority of the patients had lower 1/3rd involvement (10 in 5FU infusion arm vs 9 in CA arm) Table 1. 83% of the patients in both study arms had T3N1 disease Table 1. 12 (80%) of the patients in the Capecitabine arm had high CEA (>5ng/mL) when compared to the 5FU arm. The pre-treatment characteristics were compared using chi-square test, and the accrual in both the arms was comparable.

Grade III haematological toxicity (arm A versus arm B: 40% vs 6.7%), gastrointestinal toxicity (arm A vs arm B : 46.7% vs 0%), skin toxicity (arm A vs arm B : 13.3% vs 6.7%) were more in arm A compared to arm B. (Table 2, 3, 4).

No patient in arm B had grade III diarrhoea. All patients in arm B completed treatment within 40 days duration, whereas only 40% of patients in Arm A completed in 40 days. Majority of the patients (53%) in 5FU infusion arm had treatment interruption compared to only 13% of patients in the Capecitabine arm having treatment interruption Table 2.

Table 2: Bone marrow toxicity.

BM toxicity	5 Fluorouracil arm		Capecitabine arm	
	N	%	No	%
Grade 0	0	0.0	5	33.3
Grade1	2	13.3	6	40.0
Grade 2	5	33.3	4	26.7
Grade 3	7	46.7	0	0.0
Grade 4	1	6.7	0	0.0
Total	15	100.0	15	100.0

Table 3: Gastrointestinal toxicity.

GI toxicity Grades	5 Fluorouracil Arm		Capecitabine Arm	
	No	%	No	%
0	0	0.0	8	53.3
1	2	13.3	5	33.3
2	2	13.3	1	6.7
3	6	40.0	1	6.7
4	5	33.3	0	0.0
Total	15	100.0	15	100.0

Table 4: Skin toxicity.

Skin toxicity	5 Fluorouracil Arm		Capecitabine Arm	
	No	%	No	%
Grade 0	11	73.3	13	86.7
Grade1	2	13.3	0	0.0
Grade 2	2	13.3	1	6.7
Grade 3	0	0.0	1	6.7
Total	15	100.0	15	100.0

None of the patients had complete response. Partial response was better in patients on Capecitabine, though not significant (arm A versus arm B: 53% vs 60%, P value = 1.0). (Table 5) 3 patients on 5-Fluorouracil vs 2 patients on Capecitabine had progression after CTRT Table 5.

Table 5: Response evaluation post CTRT.

Response Evalution post CTRT	5 Fluorouracil Arm		Capecitabine Arm	
	No	%	No	%
Partial response(PR)	8	53.3	9	60.0
Stable disease(SD)	4	26.7	4	26.7
Progressive disease	3	20.0	2	13.3
Total	15	100.0	15	100.0

DISCUSSION

Many randomized trials have proved that neo adjuvant chemoradiation is beneficial over adjuvant chemoradiation in terms of tolerability, sphincter preservation and overall survival rates and hence has become the standard of care for locally advanced rectal cancer. German Rectal Cancer Study Group has established 5-FU based preoperative chemoradiation as the standard modality for locally advanced rectal cancers.[10] Various Phase II and Phase III trials have used 5-FU as both bolus (5-FU/ LV) and as continuous infusion during preoperative chemoradiation.[11,12] 5-FU/LV in neoadjuvant chemoradiation causes significant toxicities leading to treatment delays and prolongation of treatment duration.5-FU is the most commonly used chemotherapeutic agent in concurrent chemoradiation protocols in pelvic irradiation. Infusional 5-FU has been compared to Capecitabine in various trials.[13,14] The addition of oxaliplatin in neoadjuvant chemoradiation of rectal cancer has only added to the toxicity without any added benefit.[15] The published literature with respect to preoperative chemoradiation of rectal cancer is very scanty from India. Engineer et al have published a retrospective study of 182 patients who received Capecitabine during preoperative chemoradiation of advanced rectal cancer.[16] In another Indian retrospective study, the concurrent chemotherapy (infusional 5-FU) was delivered in two courses during the first and fifth week of radiotherapy.[17] Saha et al have published their single center small pilot study comparing capecitabine-oxaliplatin and 5-FU/LV in neoadjuvant chemoradiation of advanced rectal cancer.[18]

In our institute this study was undertaken to compare local response and toxicity between continuous infusional 5-FU (5 days a week) and Capecitabine in the neoadjuvant chemoradiation of advanced rectal cancer. Fifteen patients were assigned to each chemo radiation arm. The local response was assessed in both the arms at the end of four weeks of neo adjuvant chemo radiation using CECT/ MRI abdomen pelvis with contrast.

66% of the patients in our study were males and majority (66%) were below 40 years of age, whereas other Indian studies have noted majority of patients being more than 40 years of age.[16,18] Patients in 5-FU arm: 8 out of 15 (53.3 %) and in CA arm: 9 out of 15 (60%), had partial response, 20% patients in 5-FU arm and 13.3% in CA arm had progression of disease, and 26.7 % patients in both the 5-FU and CA arms had stable disease. The difference was not statistically significant.

In our study, all patients in 5-FU arm had greater bone marrow toxicity (neutropenia) and gastrointestinal toxicity (diarrhoea). Grade III toxicity in 5-FU arm was seen in 7(46%) patients compared to none (0%) in capecitabine arm. Grade III and IV diarrhoea were seen in 6(40%) and 5(33.3%) patients receiving 5-FU, compared to 1(6.7%) patient in CA arm. Both bone marrow and GI toxicity were less in CA arm which was statistically significant. Saha et al noted Grade III haematological and genitourinary toxicity in 19% of the patients receiving FU/LV in preoperative chemoradiation.[18] Other Indian studies have noted similar excellent tolerance of Capecitabine in preoperative chemoradiation of rectal cancer.[16,17] Yerushalmi et al have published a retrospective study of their experience with Capecitabine and continuous Infusional 5-FU. They noted Grade 3 and Grade 4 haematological toxicities in 5FU arm whereas hand foot syndrome was seen in Capecitabine arm.[19] There are no Indian studies published regarding efficacy or tolerance of continuous infusion of 5FU in this setting.

In our study, 9 (60%) patients in 5-FU arm had a treatment time of more than 40 days. In CA arm, all patients completed chemoradiation within 40days. Eight patients in 5-FU arm had a major treatment interruption compared to only two patients in CA arm. Central line related bloodstream infection related fever was noted in 8 patients, however culture did not grow any specific organism. During the course of treatment, 5 patients needed removal of central line due to complications and another central venous catheter was inserted. No case of procedure related pneumothorax was noted during this study. In India, where patients have limited financial resources for medical treatment, continuous infusional 5-FU administration adds to cost because of need for admission, central venous catheter care, administration of antibiotics in case of fever etc. Capecitabine in neoadjuvant chemoradiation seems to be the way forward in resource poor setting like India.

CONCLUSION

Capecitabine when used concurrently with radiation in locally advanced carcinoma rectum has almost same local response rate when compared to 5 FU. Bone marrow toxicity, gastrointestinal toxicity and radiation treatment interruption were less in CA arm.

Overall capecitabine was well tolerated with better compliance and equal local response rate and reduced toxicity compared to 5 FU arm. More literature needs to be published regarding continuous infusional 5-FU and capecitabine in neoadjuvant CTRT in rectal cancer from Indian cancer centres.

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