A PROSPECTIVE STUDY ON PREOPERATIVE CONCURRENT CHEMORADIATION WITH CAPECITABINE IN STAGE II/III CARCINOMA OF RECTUM

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ABSTRACT

BACKGROUND

Fluorouracil (5-FU) based chemoradiotherapy represents the standard treatment option for the preoperative treatment of advanced rectal cancer. Capecitabine is an oral precursor of 5-FU with the advantage of delivering the chemotherapy in an outpatient setup. NSABP R-04 & a German phase 3 trial by Hofheinz et al showed that Capecitabine was equivalent to 5-FU.

The primary objective of this study was to evaluate pathological response (PR), clinical & surgical outcomes of stage II & III patients treated with chemoradiation with Capecitabine. The secondary objective was to evaluate toxicity and compliance to treatment.

MATERIALS AND METHODS

This single arm prospective study included 35 patients with stages II & III adenocarcinoma of rectum who after evaluation were treated with pelvic radiotherapy and concurrent Capecitabine. Toxicities were graded using RTOG scoring criteria. Clinical response was assessed after EBRT completion, and patients were referred for surgery after 4-6 weeks. Pathologic response and completeness of resection were assessed from the histopathology report.

RESULTS

Growth located within 5 cm from anal verge was seen in 24 (68.5%) patients and 6 were inoperable upfront. All patients completed the intended preoperative treatment and 88.6% did not have any toxicity related break in RT. Clinical response was seen in 80% of patients after Chemoradiation. Out of 35 treated 80% of them underwent surgery. APR was performed in 64.2% and 35.7% had LAR. Out of 6 upfront inoperable patients, 3 were converted to operable. Out of 23 APR cases, 7 were converted to anterior resection (30.4%, p=0.046). 96% of operated patients had an R0 resection, including all the 3 upfront inoperable patients. Minimal pathologic response was seen in 89.2% of patients and 7.14% had complete pathologic response. There were no Grade 4 or 5 toxicities. Only 2.9% had a Grade 3 event. 45.7% had maximum of Grade 1 events and 48.6% had maximum of Grade 2 events.

CONCLUSION

Chemoradiation with concurrent Capecitabine in Stage II and III Ca rectum results in good clinical response and modest pathologic response. It provides good surgical outcome in terms of complete resection and conversion to operability and results in sphincter-sparing resection for low lying tumours. Treatment is well tolerated with good patient compliance and acceptable levels of toxicity and also facilitates treatment on an outpatient basis.

KEYWORDS

Locally Advanced Ca Rectum, Capecitabine, Neoadjuvant Concurrent Chemoradiation.

HOW TO CITE THIS ARTICLE: Soman AK, Thomas BT, Lekshmikutty RP, et al. A prospective study on preoperative concurrent chemoradiation with capecitabine in stage II/III carcinoma of rectum. J. Evid. Based Med. Healthc. 2017; 4(76), 4492-4496. DOI: 10.18410/jebmh/2017/895

Financial or Other, Competing Interest: None.
Submission 31-08-2017, Peer Review 06-09-2017,
Acceptance 19-09-2017, Published 21-09-2017.
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DOI: 10.18410/jebmh/2017/895

BACKGROUND

Colorectal cancer is the 3rd most common cancer and 3rd leading cause of cancer related deaths in both males & females, constituting 10% of all cancers.[1] Whereas, it is the 10th most common cancer in Indian population and constituted 4% of all cancer deaths.[2] Rectal cancer remains a significant oncologic problem, with approximately 34,700 new cases diagnosed each year with an expected overall 5-year survival of 50%. Prognosis appears to be worse when tumours arise in the distal rectum (<3 cm from the anal

verge) and in an advanced stages (T3, T4, N+ - stage-II/III).

Combined modality treatment with surgery, chemotherapy and radiation is the standard treatment for locally advanced rectal cancer.[3] Preoperative radiotherapy has the advantage of potential downstaging of the tumour and the theoretical conversion of patients who were destined for Abdominoperineal resection (APR) to those who are amenable for sphincter-saving procedures. Studies have shown significant improvement in local control of tumour with addition of chemotherapy to radiation.

Preoperative chemoradiotherapy using continuous intravenous infusion of Fluorouracil (5-FU), represents a standard option for the initial treatment of locally advanced rectal cancer (LARC). This study is conducted to find out the treatment response and toxic profile of oral Capecitabine, a rapidly absorbed oral compound, which is converted into 5-FU in body as preoperative and concurrent chemoradiation therapy in stage II/III Carcinoma of the Rectum in Indian patients.

The primary objective of this study was to evaluate pathological response (PR), clinical & surgical outcomes of stage II & III patients treated with chemoradiation with Capecitabine. The secondary objective was to evaluate toxicity and compliance to treatment.

MATERIALS AND METHODS

This prospective single arm study was to evaluate the outcome in 35 patients with biopsy proven stage II/III Ca rectum, treated with preoperative concurrent chemoradiation with capecitabine followed by surgery from November 2015 to October 2016.

Eligibility criteria included patients of 18 to 75 years and ECOG[4] Performance Status = 0 or 1 with clinically stage II/III with histologically confirmed Adenocarcinoma of the Rectum, located within 15 cm from anal verge which is resectable or expectation of being resectable after preoperative chemoradiation were included.

Treatment protocol included a detailed history, clinical examination including per rectal digital examination and routine blood investigations were done and results obtained were recorded for all patients. MRI or CECT abdomen with pelvis and sigmoidoscopy were done in all patients for assessing the clinical extent of tumour and staged according to AJCC staging. All eligible patients after taking informed consent received pelvic radiotherapy and concurrent chemotherapy with oral Capecitabine. Radiotherapy was given at a dose of 50.4 Gy in 28 fractions, 5 days per week along with Capecitabine orally at a dose of 825 mg/m^2 BD on the days of radiation. Thin patients with IFD less than 18 cm were given RT in Cobalt and others treated in LINAC. CT-based simulation was used for all patients. RT was delivered using SAD technique in 2 phases of 45 Gy in 25 fractions to the whole pelvis, followed by boost of 5.4 Gy in 3 fractions. Target volumes for the initial phase included primary tumour with margin, entire mesorectum, iliac, obturator & presacral lymph nodes. Boost was given to the primary tumour with margin & mesorectum. RTOG contouring guidelines were used for target delineation in patients treated in LINAC. Patients were monitored once a week during treatment for toxicities. Toxicities were assessed and noted down and appropriate supportive care was provided. After 4-6 weeks of completion of preoperative concurrent chemoradiation, patients were sent for surgical resection. Clinical response was assessed prior to surgery by clinical examination or imaging. Decrease in the tumour size in thickness or length on imaging was taken as clinical response.

Patients were followed up after surgery and surgical outcome & pathological response was assessed from the histopathology report. Downstaging was defined as reductions in T and N stages by at least one level. Pathologic response was assessed according to CAP protocol[5] from histopathology report of resected surgical specimen. RTOG grading criteria was used for assessing the toxicity profile.[6] All patients were started on adjuvant chemotherapy with FOLFOX regimen for 12 cycles as per our department protocol.

Data management and statistical analysis was entered in Excel Sheet and analysis was done using IBM SPSS software.

RESULTS

All 35 patients received preoperative chemoradiation therapy of 50.4 Gy in 28 fractions, 5 days per week, with oral Capecitabine concurrently at dose 825 mg/m^2 BD on the days of radiotherapy. On evaluation, prior to surgery 28 patients (80%) had clinical response on either clinical examination or imaging. Out of 6 initially inoperable patients, 3 of them became operable. Initially, 2 patients considered operable were found inoperable. Total 5 patients (14.3%) were found to be inoperable on preoperative evaluation after chemoradiation. Abdominoperineal resection was performed in 18 patients (51.4%) and 10 patients (28.6%) had anterior resection with sphincter preservation. Out of remaining 12 patients, 4 (11.4%) were initially suitable for anterior resection, 6 (17.1%) were inoperable and 2 were not willing for any surgery. 25 patients (71.4%) would have needed APR upfront. After chemoradiation, 7 out of the 23 APR candidates were converted to anterior resection (30.4% p=0.046).

Of the 28 operated patients, 27 patients (96.4%) had an R0 resection and 1 (3.6%) had R1 resection. There were no R2 resections. All the 3 upfront inoperable patients converted to operable by chemoradiation achieved R0 resection.

Females had better results with regard to completeness of resection. R0 resection was 78.6% in females compared to 76.2% in males; inoperability was 7.1% in females and 19% in males with a P value of 0.489. Of the 28 operated patients, 53.5% had downstaging in T status after chemoradiation, 18 out of 28 operated patients (64.2%) had downstaging of nodal status. Complete pathologic response was seen in 2 patients (7.1%) and 25 patients (25- 89.2%) had minimal response and 1 (3.5%) had poor pathologic response.

Inoperable tumours and patients with poor tumour regression were considered to have absent pathologic

response. There were 6 patients (18.1%) under this category and 27 patients (81.8%) had pathologic response though majority had minimal response. Female gender had better pathologic response (78.6%) compared to males (76.2%) with a P value of 0.869. Moderately differentiated tumours had better clinical response in females (85.7%) compared to males (78.6%). P value was 0.849. Similarly female patients showed better pathologic response (85.7%) than males (75%) with P value 0.546. Moderately differentiated tumours showed better response to chemoradiation than well differentiated tumours. Capecitabine related skin toxicity was not seen in any patients. RT related grade 1 skin toxicity was seen in 20 patients (57.10%) and 13 patients (37.10%) had a maximum of grade 2 toxicity. There was no grade 3 or grade 4 skin toxicities.

Only 4 out of 35 patients (11.4%) had anaemia of which only 1 patient (2.9%) had Grade- 2 anaemia and rest were Grade- 1 anaemia. There was no Grade- 3 or 4 anaemia. Only 1 patient (2.9%) had Grade- 2 neutropenia and 5 patients (14.3%) had only Grade- 1 neutropenia. There were no Grade- 3 or 4 haematologic toxicities.

Lower GI toxicity as diarrhoea was the most common type of toxicity. Incidence of diarrhoea was seen in 27 patients (77.1%), at least once during the entire treatment. Grade 3 diarrhoea was seen in 1 patient (2.9%). Grade- 2 in 5 patients (14.3%) and Grade-1 diarrhoea in 21 patients (60%).There was no Grade 4 toxicity. On the whole in this study, only 1 patient (2.9%) was free of any form of toxicities for the entire study. There were no Grade 4 events and 16 patients (45.7%) had only Grade 1 events and 17 (48.6%) had Grade 2 events at least once during their entire treatment. Only 1 patient (2.9%) required hospitalisation for blood transfusion once during the entire course of study and all other patients were treated on an outpatient basis.

Total (n)	35
Mean age	57
Gender (%)	
Male	60
Female	40
Tumour related	
Distance from anal verge (cm) (%)	
<5	68.5
6-10	28.6
>10	2.9
Pathological grade (%)	
Well differentiated	80
Moderately differentiated	20
T stage (%)	
T2	5.7
T3	60
T4	34.3
N stage (%)	
N0	17.1
N1	51.4
N2	31.4
Table 1. Patient Characteristics	

Treatment Outcomes	**Percentage**
Days of RT break due to toxicity	
0	88.6
1 to 2 days	11.4
Dose reduction of capecitabine	
No	94.3
Yes	5.7
Type of resection	
LAR	28.6
APR	51.4
Inoperable	14.3
Operable; not willing for surgery	5.7
Pathologic T stage	
0	5.7
T2	25.7
T3	31.4
T4a	14.3
T4b	2.9
Pathologic nodal stage	
N0	48.6
N1	28.6
N2	2.9
Table 2. Treatment Outcomes	

DISCUSSION

After the completion of chemoradiation, 28 patients (80%) showed clinical response. Of the 6 patients with fixed inoperable tumour initially, 3 became operable and 2 T3 lesions became inoperable and in total 5 (14.3%) were found to have inoperable tumour. Out of clinically responded operable cases, 2 (5.7%) patients refused surgery.

Growth was located within 5 cm from anal verge in 24 (68.5%) patients at presentation. Out of 28 patients (80%) who underwent surgery, 19 (67.8%) of them had growth within 5 cm from anal verge. APR was performed in 18 patients (64.2%) and rest of them had LAR (35.7%). The major studies which have evaluated preoperative chemo RT in Ca rectum are the French FFCD 9203,[7] EORTC 22921,[8] NSABP R-03,[9] German Rectal Cancer Study Group,[10] NSABP R-04,[11] & a phase 3 trial[12] by Hofheinz et al at 35 German institutions. The last 2 studies evaluated Capecitabine as the concurrent chemotherapeutic agent. All others were 5-FU based studies. All of these studies had included only patients who were able to undergo upfront surgical resection.

Our study included 6 patients who were inoperable upfront. After the completion of chemoRT, 80% had clinical response. Of the 6 patients with fixed inoperable tumour initially, 3 became operable but 2 T3 lesions became inoperable and in total 14.3%[5] were found to have inoperable tumour. 2 patients (5.7%) were not willing for surgery although they were operable and had clinical response. 68.5% of our patients had growth located within 5 cm from anal verge at presentation. 28 patients (80%) underwent surgery. 19 out of these 28 (67.8%) had growth within 5 cm from anal verge. 18 patients had APR (64.2%) and rest LAR (35.7%).

The reported anterior resection rates in the concurrent chemoradiation arms were 69% (German study); 52.4% (French FFCD 9203); 55.6% (EORTC); 47.8% (NSABP R-03) and 59.3% (NSABP R-04). But all of these studies had lesser

no. of patients with growth located within 5 cm from anal verge compared to our study. Only 30% in German study, 49.4% in EORTC and 51.2% in French study were within 5 cm from anal verge in the chemoradiation arm.

In this study, initially 4 patients (11.4%) were suitable for anterior resection, 6 (17.1%) were inoperable and 25 patients (71.4%) would have needed APR. In the present study, the resections were carried out by different surgeons. Hence, surgical standardisation was not present. After chemoradiation, 3 of the 6 inoperable patients were converted to operable, 7 out of the 23 APR candidates were converted to anterior resection (30.4%; p=0.046). The German, EORTC and NSABP studies had also shown conversion to sphincter-sparing surgery following chemoradiation in low lying tumours although the differences were not significant in the latter 2 studies. In the current era of organ preservation, the role of sphincter preservation surgeries is paramount and it has the potential to improve the quality of life of the patients drastically without worsening treatment outcomes.

This study showed better operability and good resection status. CRM was adequate in majority of the patients. There were no R2 resections and 96.4% of patients who underwent surgery had an R0 resection. All the 3 upfront inoperable patients converted to operable by chemoradiation also achieved R0 resection. Resection rates were 94.2% (R0 & R1) in French FFCD 9203 study and 91% for the German study. Out of 473 patients, 10 had an incomplete (R2) resection in EORTC study. A radical surgical resection is one of the most important factors in preventing recurrences and no improvements in any other treatment techniques will substitute for a radical surgery.[13] With good communication between the radiation and surgical oncologists regarding patient referral and appropriate combined modality treatment, results of international trials can be reproduced with the same efficacy in any institution. A retrospective analysis of 504 patients reported by Bail and colleagues showed a higher local recurrence rate (35% versus 11%) and lower 5-year survival (27% versus 73%) for patients with positive radial margins compared with those with negative radial margins.[14]

Pathologic response was seen in 29 (81.8%) and 27 (75.7%) had minimal response (75.7%). 2 patients (7.14%) had pathologic complete response. The historic studies have excluded patients who were inoperable after chemoradiation while assessing pathologic response. After preoperative chemoradiation, the reported pathologic complete response rates were 11.4% (French FFCD 9203), 13.7% (EORTC 22921), 155 (NSABP R-03), 8% (German Rectal Cancer Study Group) and 20.7% (NSABP R-04). Whereas, pathologic complete response seen in our study was only in 7.14%. This decrease in pathologic complete response might be due to the predominance of well-differentiated tumours (80%) in our study. The historic studies had almost equal proportion of well differentiated and moderately differentiated histology. The French study had 45.3% well differentiated and 40.8% moderately differentiated tumours in the chemoradiation arm, the EORTC study had 37.2% and 39.7% respectively.

Downstaging could be achieved in 53.5% of Tumours and in 64.2% in nodal status. In 28 operated patients, 17 (60%) had ypN0 status. It was 66.6% for French FFCD 9203, 71.9% in EORTC study and 66.7% for NSABP R-03. Retrieval of fewer lymph nodes after chemoradiation treatment may be a marker of a higher tumour response and better prognosis.[15,16]

In the subset analysis, it was seen that females showed improved clinical response of 92.9% vs. 71.4% (p=0.285); R0 resection 78.6% vs. 76.2%; inoperability 7.1% vs. 19% (p= 0.489); pathologic response 78.6% vs. 76.2% (p = 0.869) and less toxicities though the results were not statistically significant. Moderately differentiated tumours showed better clinical response of 85.7% vs. 78.6% (p=0.849) and pathologic response of 85.7% vs. 75% (p=0.546) to chemoradiation compared to well-differentiated tumours.

Inclusion of 6 inoperable cases initially in this study was the major deviation from other large international trials. Even though this might have negatively influenced the overall pCR rate and percentage of operable tumours, the fact that we could convert 3 out of these 6 tumours to R0 resection proves the efficacy of this regime and advantageous to patients.

Acute toxicities were assessed weekly. It was seen that only 13 patients (37.1%) had a maximum of Grade 2 skin toxicity and 20 patients (57.1%) had Grade 1 skin toxicity. No patients had Grade 3 or 4 skin toxicity. Whereas 2.5% Grade 3 skin toxicity was reported by NSABP-R-04 study in their Capecitabine arm.

Only 11.4% had maximum of Grade 1 anaemia and 2.9% had maximum of Grade- 2 anaemia. One patient required blood transfusion to correct the anaemia. Grade 1 neutropenia was seen in 14.3% and 2.9% had maximum of Grade 2. Whereas, Hofheinz et al reported leucopenia in 25% of his patients and in 2% of cases Grade 3 to 4. There were no Grade 3 or 4 haematologic toxicities in this study.

Diarrhoea was the most common lower GI toxicity seen with Grade 3 toxicity in 2.9%, Grade 2 in 14.3% and Grade 1 in 60% of cases. There was no Grade 4 toxicity seen. Hofheinz et al reported diarrhoea as the most common adverse event in the capecitabine arm with 9% Grade 3 & 4 and 53% with any Grade diarrhoea. NSABP-R-04 study reported 6.9% cases with Grade 3 & 5 diarrhoea. No patient in our study had Grade 3 or 4 UGI toxicity. Whereas NSABP-R-04 study had 1.3% Grade 3 & 5 UGI toxicity.

The toxicity profile of the patients in our study was more favourable. There was no Grade 4 or 5 events. Grade 3 in 1 patient (2.9%), Grade 1 in 16 patients (45.7%) and Grade 2 events in 17 (48.6%) patients were seen during their entire treatment. One patient (2.9%) was free of any form of toxicities for the entire study. In the NSABP R-04 study, the capecitabine containing arm had 2.2% Grade 4 events, 26.6% Grade 3 and 1.3% Grade 5 events.

The difference in toxicity profile of this study compared to international studies will be emphasising the involvement

of multiple factors influencing the toxicity profile of regional population. The impact of this can only be studied by data from multiple small trials conducted based on international studies. This study as a regional trial included almost most all parameters as recommended by international studies but showed reduced levels of toxicity with almost similar end results.

In the management of Ca Rectum, preservation of organ and avoidance of APR drastically improves the patient's quality of life. Unlike in the Western countries where there is extensive supporting systems for patient with stoma, in a developing country like India, the avoidance of stoma, if possible without compromising on the treatment results is more important.

In this study, there was a statistically significant conversion rate from APR to LAR and the fact that most of the patients underwent an R0 resection, is encouraging and predicts better recurrence-free survival in these patients without undergoing a permanent colostomy.

CONCLUSION

Preoperative concurrent chemoradiation with capecitabine in stage II and III Ca Rectum results in better surgical outcome in terms of complete resection and conversion to operability. It can result in sphincter-sparing resection for low lying tumours. There is a good clinical and modest pathological response. With good patient compliance, manageable toxicity, good results and easy administration (oral route) ensuring OP based treatment, the encouraging results of treatment and improved sphincter preservation rates suggest that concurrent preoperative chemoradiation with Capecitabine is an excellent treatment modality for Locally advanced Carcinoma of Rectum in Indian patients.

ACKNOWLEDGMENT

We are extremely thankful to Dr. Rema P. L., Professor, Head of the Department of Radiotherapy for the valuable suggestions and guidance. We also thank faculty members of Radiation Physics Department and all the patients who participated in the study. We also express our sincere thanks to Mrs. Ancy Joseph, Statistical Assistant Department of Radiotherapy.

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