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Concurrent Chemoradiation

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TOXICITY OF CONCURRENT CHEMORADIATION IN LOCALLY ADVANCED RECTAL CARCINOMA

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ABSTRACT

Objective: To evaluate treatment related toxicity of concurrent chemoradiation in locally advanced rectal carcinoma

Study Design: Cross sectional study.

Place and Duration of Study: Department of Oncology, Combined Military Hospital (CMH), Rawalpindi, from Jan 2017 to Jul 2017.

Methodology: Thirty-five patients with histopathologically diagnosed T3-4, N0-2, M0 adenocarcinoma rectum requiring neo adjuvant concurrent chemoradiation delivered using 3-D conformal technique with high-energy photon beams to were included. Patients were followed up weekly during concurrent chemoradiation to evaluate for any adverse events.

Results: Out of total 35 patient, only grade 3 radiation dermatitis developed in two patients. Grade 2 hematological toxicities i.e. anemia, leucocytopenia and neutropenia were noted in 11.4%, 17.14% and 5.71% of the patients, respectively. While grade 2 non-hematological toxicities including diarrhea, nausea, vomiting and radiation dermatitis were observed in 17.14%, 2.85%, 2.85% and 20% respectively. Grade 1 hematological toxicities i.e. anemia, leucocytopenia and thrombocytopenia were noted in 7 (20%), 12 (34.28%) and 6 (17.14%) of the patients, respectively.

Conclusion: Concurrent chemoradiation along with oral chemotherapy capecitabine in neoadjuvant setting was a well-tolerated and acceptable treatment option for locally advanced carcinoma of rectum.

Keywords: Chemoradiation, Capecitabine with radiation, Locally advanced rectal carcinoma.

INTRODUCTION

Rectal cancer represents the 2nd most common cancer in women and the 3rd most common cancer in men[1]. Globally rectal carcinoma is 4th common cause of cancer related deaths[2]. The most prominent risk factors include family history of colorectal carcinoma, diet, smoking and obesity[3]. Rectal carcinoma incidence is on the rise. Gastrointestinal cancers in males and females respectively represent 25% and 20% of malignant disease burdens in Pakistan[4]. Surgery, radiotherapy, chemotherapy and targeted therapy are the modalities used to treat rectal carcinoma. Neoadjuvant concurrent chemoradiation along with chemotherapy 5-fluorouracil has established cumulative attention in the management of resectable locally advanced disease. Concurrent chemoradiation is used in both neoadjuvant and adjuvant settings. Neoadjuvant radiotherapy is more favorable because of better tolerance, low toxicity and more dose-response relationship[5]. Toxicity of irradiation depends on treatment volume and dose[6]. In rectal cancer treatment, acute toxicity of chemo-radiotherapy mainly consists of hematological, genitourinary, gastrointestinal and neurological[7], while late radiotherapy adverse events occur in the genitourinary system, gastrointestinal tract, vascular, and skeletal system[8]. 5-flourouracil continuous infusion is preferred over bolus administration because of better tumor response, well tolerance and low adverse events. Capecitabine, a pro-drug of 5-flourouracil is an oral carbamate, which changes into 5-flourouracil within tumor via enzyme thymidine phosphorylase[9]. The capecitabine preferential activation in tumor cell reduces systemic acquaintance

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to 5-flourouracil and possibly enhances safety and efficacy[10]. Oral capecitabine could achieve dosing that approximates to continuous 5-florouracil infusional regimens. During radiation therapy, thymidine phosphorylase enzyme is up regulated within tumor cells leading to a synergistic effect of capecitabine with radiotherapy. The objective of this study was to observe the toxicity of radiation therapy along with capecitabine in our population.

The study was carried out to determine the toxic effects of concurrent chemoradiation using 50.4 Gy in 28 fractions with capecitabine 825 mg/m^2 in patients of rectal adenocarcinoma

METHODOLOGY

This cross sectional study was conducted at oncology department Combined Military Hospital, Rawalpindi and was completed in six months, form January to July 2017. Sample size was calculated by WHO sample size calculator, using 95% confidence level, 15% absolute precision and population proportion of 10%. Consecutive (non-probability) sampling technique was used for data collection. A total of thirty five diagnosed cases of T3-4, N0-2, M0 rectal adenocarcinoma were enrolled from Oncology department Combined Military Hospital, Rawalpindi with prior permission from the hospital ethical committee and other concerned authorities. A written consent from all the patients was obtained. Inclusion criteria were newly diagnosed T3-4, N0-2, M0 rectal adenocarcinoma patients with no history of oncological treatment, age ≥18 years, eastern cooperative oncology group performance status (ECOG PS) <2, hemoglobin >10g/dl, WBC >3500/ul and platelet count >150000/ul with normal liver and renal functions. Patients with history of synchronous malignancies, hemorrhoids and those previously exposed to chemotherapy and or radiotherapy before the diagnosis of rectal carcinoma were excluded.

Patients' complete history, physical examination and clinical evaluation were done. Local examination and colonoscopy was conducted for the local extension of tumor. Basic biochemical profile was carried out. CT scan chest, abdomen and MRI pelvis were done for staging workup.

All patients were given neoadjuvant concurrent chemo radiotherapy i.e. 50.4 gray in 28 fractions using 3D conformal technique with high-energy photons and concurrent oral capecitabine. Radiation was given in two phases with radiation dose of 45 Gy in 25 fractions in phase 1 to the pelvis. Gross tumor volume (GTV) was defined as primary tumor and involved lymph nodal extent demonstrated on pelvic MRI. CTV included the primary tumor, regional lymph nodes, mesorectum from the sacral promontory to insertion of levatorani and the posterior presacral space. PTV was created by adding a margin of 1.5 cm to the CTV. Phase II boost radiation dose of 5.4gy/3fx was given to the GTV plus 2 cm margin. Radiotherapy was delivered in 6 weeks with 5 days/week treatment.

Concomitant Capecitabine 825mg/m^2 twice a day was given 5 days a week (Monday to Friday) i.e. only on radiotherapy treatment days. Morning dose of Capecitabine was given before each radiation fraction and evening dose taken 12 hours after. Before starting the regimen, the adverse effects of the concurrent chemoradiation were explained to the patients.

Hematological and non-hematological toxic effects (genitourinary, gastrointestinal and neurological acute toxicities) were assessed weekly. Clinical adverse events were graded according to the Common Toxicity Criteria for Adverse Event (CTCAE) version 4.0.

Data analysis was done using SPSS version 20. Mean and standard deviation (SD) were calculated for quantitative variables. Frequencies and percentages were calculated for qualitative variables.

RESULTS

A total of 35 patients with T3-4, N0-2 rectal adenocarcinoma were enrolled (twenty nine male and six female patients between the age of 29 and 72 years). All of the patients received chemoradiation (table-I). Generally, neoadjuvant

concurrent chemoradiation was very well tolerated. No grade 3 or 4 hematological adverse events nor treatment-associated death were observed however Grade 3 radiation dermatitis was observed in two (5.7%) patients. Grade 2 hematological toxicities i.e. anemia, leucocytopenia and neutropenia were noted in 11.4%, 17.14% and 5.71% of the patients, respectively. While grade 2 non-hematological toxicities including diarrhea, nausea, vomiting and radiation dermatitis were observed in 17.14%, 2.85%, 2.85% and 20% respectively. Grade 1 hematological toxicities i.e. anemia, leucocytopenia and thrombocytopenia were noted in 7 (20%), 12 (34.28%) and 6 (17.14%) of the patients, respectively. While grade 1 non-hematological toxicities including nausea, diarrhea, radiation dermatitis, cystitis, vomiting, hand foot syndrome and oral mucositis were observed in 9 (25.71%), 8 (22.85%), 4 (11.4%), 4 (11.4%), 2 (5.71%), 2 (5.71%) and 1 (2.85%) respectively (table-II). Subset analyses revealed hematological toxicity to be the most commonly observed toxicity. Leucocyte and platelet counts started decreasing third week onward of chemoradiation. Likewise, platelet count started to decline during the initial 3 weeks of treatment. All adverse events were easily managed and generally ameliorated with supportive medications when required. None of the patients required radiotherapy interruption.

Table-I: Patient characteristics.

Number of patients (n=35)		
Age (years)	**n**	**%**
Male	29	82.85
Female	6	17.15
Median age	58	-
Range	29-72	-
ECOG Performance Status		
1	32	91.4
2	3	8.6
Histopathology	**Adenocarcinoma Rectum**	
TNM Clinical Stage		
T3, N0, M0	14	40
T3, N1/N2, M0	16	46
T4, N0, M0	1	3
T4, N1/2, M0	4	11

Table-II: Toxicity profile.

Hematological			
Toxicity	**Grade 1**	**Grade 2**	**Grade 3**
Anemia	7 (20%)	4 (11.4%)	-
Leucopenia	12 (34.28%)	6 (17.14%)	-
Thrombocytopenia	6 (17.14%)	-	-
Neutropenia	-	2 (5.71%)	-
Non Hematological			
Diarrhea	8 (22.85%)	6 (17.14%)	-
Nausea	9 (25.71%)	1 (2.85%)	-
Vomiting	2 (5.71%)	-	-
Cystitis	4 (11.4%)	-	-
Radiation dermatitis	4 (11.4%)	3 (8.57%)	2 (5.71%)
Hand food syndrome	2 (5.71%)	-	-
Oral mucositis	1 (2.85%)	-	-

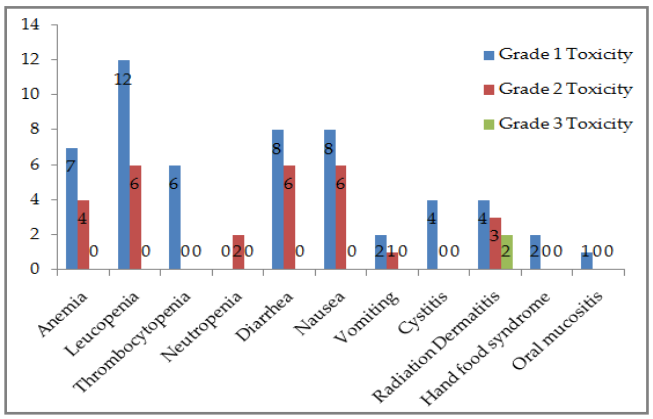

Figure: Toxicity profile.

DISCUSSION

Concurrent chemoradiation is the current standard approach in the management of locally advanced rectal cancer[11-13]. Discovery of newer drugs like capecitabine, tegafur and as raltitrexed which mimic mechanism of 5-flourouracil, have served as new window to explore role of these drugs in combination with radiotherapy. The avoidance of intravenous line is the major advantage of capecitabine. Secondly during radiation therapy, up regulation of thymidine phosphorylase in tumor cells results in a radio-sensitizing effect of capecitabine[9,14].

In one of capecitabine escalating doses concurrent chemoradiation phase 1 studies reported by Dunst *et al*, in which hand foot syndrome was found as dose limiting toxicity with capecitabine dose of 1000mg/m^2 twice a day during radiotherapy[14]. Another phase 1 study by Ngan *et al*, has shown grade 3 diarrhea and skin reaction as dose limiting toxicity with capecitabine 1000mg/m^2 twice a day concurrent with radiotherapy[15]. In

current study, Leucopenia, nausea and vomiting were the most commonly observed toxicities. This difference in observed toxicity profile in our study may be attributed to the lower dose of capecitabine i.e. 825mg/m^2 twice daily, used in our study. Current study delivered 50.4 Gy in 28 fractions, combined with capecitabine 825 mg/m^2 twice daily on radiotherapy days. Treatment was very well tolerated by patients and no dose reduction was required. The observed incidence of acute toxicities during treatment was very low. In addition, no grade 4 toxicity was reported while grade 3 toxicity was observed only in two (5.71%) patients however grade 1 and 2 toxicities were common. With the currently accepted standard dose of capecitabine i.e. 825 mg/m^2 twice daily with radiation, a number of phase II trials have reported low toxicity rates[15]. NSABP R-04 studied toxicity profiles of 5 fluorouracil and capecitabine in neo adjuvant setting concurrent with radiation. This study revealed comparable toxicity profiles for both in terms of grade 3-4 adverse events in a similar target patient population to our study with respect to disease stage, age, eastern cooperative oncology group performance status (ECOG PS)[16-18]. These data verify the feasibility of our treatment that concurrent chemoradiation with capecitabine is safe and well tolerated.

CONCLUSION

Concurrent chemoradiation along with oral capecitabine was well-tolerated and feasible treatment option for locally advanced rectal adenocarcinoma.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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