Neoadjuvant Capecitabine and Oxaliplatin Before Concurrent Capecitabine and Radiation in Locally Advanced Rectal Cancers: Experience of a Cancer Hospital in Pakistan

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PURPOSE To report the toxicity and pathologic response rates after adding neoadjuvant capecitabine and oxaliplatin (CAPOX) followed by concurrent radiation and capecitabine (CAPRT) and surgery in patients with locally advanced rectal cancer.

MATERIALS AND METHODS We retrospectively analyzed medical records of 301 patients between January 2007 and December 2014. Patients were treated with four cycles of neoadjuvant chemotherapy comprising CAPOX, followed by radiotherapy at doses of 45-54 Gy in 25-30 fractions with concurrent capecitabine. A response assessment scan was performed at 4-6 weeks postradiation followed by surgical evaluation at 6-8 weeks. Pathologic tumor and nodal response rates as well as circumferential resection margin were assessed on surgical specimens.

RESULTS The median age of the patients was 43 years (range, 16-78). Overall, 227 (75.4%) patients were able to complete four cycles of CAPOX. Neoadjuvant chemotherapy was well-tolerated with no serious adverse effects. The most common toxicity was diarrhea (grade 2, n = 108; 35.8%; grade 3, n = 57; 18.9%; grade 4, n = 25; 8.3%) followed by neuropathy (grade 2, n = 132; 43.8%; grade 3, n = 54; 17.9%) and oral mucositis (grade 2, n = 108; 35.8%; grade 3, n = 47; 15.6%; grade 4, n = 9; 2.99%). A total of 229 (76.1%) patients underwent surgery. Pathologic complete response was seen in 52 (22.7%; 95% CI, 13 to 28), whereas 200 (87.3%; 95% CI, 82 to 99) patients had a negative circumferential resection margin on pathology.

CONCLUSION Neoadjuvant chemotherapy with CAPOX before CAPRT and planned total mesorectal excision surgery result in good tumor regression and substantial pathologic complete response rates with acceptable toxicity. With growing interest in organ preservation in rectal cancer, the strategy of completing all chemotherapy and chemoradiotherapy before planned surgery offers a favorable paradigm. However, further randomized clinical trials are needed to support this evidence.

INTRODUCTION

Colorectal cancer is the third leading cause of cancer death in the world, and its incidence is steadily rising in developing countries. According to GLOBOCAN 2018 statistics, rectal cancer is the eighth most commonly diagnosed malignancy across the globe.[1] In Pakistan, the prevalence of colorectal cancer ranges from approximately 4% to 6%.[2] The standard treatment for locally advanced rectal cancers (LARC) is trimodality comprising total mesorectal excision (TME), radiation therapy, and chemotherapy. The basic advantage of such multimodal treatment, particularly total mesorectal surgical excision, is reduction in local recurrence rates to < 10%.[3] The advantages of preoperative versus postoperative radiochemotherapy came from German randomized trial, which established the role of preoperative 5-fluorouracil–based chemoradiation in the treatment of rectal cancers.[4] Subsequently, the practice of administering neoadjuvant chemoradiation before TME and adjuvant chemotherapy was established in North America.[5]

Although local recurrences are the main concern, another challenge for the patients who undergo the radical treatment of rectal adenocarcinomas is the risk of distant metastases. One of the major factors affecting the long-term survival of patients with rectal cancer is distant recurrences, and their frequency is estimated to be 22.5% at 5 years.[6] Different strategies have been implemented to reduce the risk of distant metastases, which eventually increases the cure rate. One of them is to introduce systemic therapy before neoadjuvant concurrent chemoradiation in the treatment of LARC so that the dissemination of micrometastases is targeted early.

CONTEXT

Key Objective

Is upfront chemotherapy with capecitabine and oxaliplatin (CAPOX) well-tolerated and do CAPOX and radiation and capecitabine (CAPRT) result in improved pathologic responses in patients with rectal cancers?

Knowledge Generated

More than 75% of patients completed the recommended plan of CAPOX with acceptable toxicity. Nearly a quarter of patients had pathologic complete response, and a negative circumferential margin was achieved in more than 85% of patients.

Relevance

Neoadjuvant CAPOX is very well-tolerated. CAPOX and CAPRT probably result in better pathologic outcomes in patients with locally advanced rectal cancers.

It is considered to be the most frequently explored attractive approach, as it not only addresses the risk of distant metastases by introduction of early systemic treatment but also reduces the risk of local recurrence. Many British and Spanish investigators have evaluated the role of neoadjuvant infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) or capecitabine plus oxaliplatin (CAPOX) before chemoradiation. These trials have demonstrated that increased chemotherapy exposures lead to high response rates and more favorable outcomes.[6-8] Similarly, another well-known study has used the same strategy of using neoadjuvant CAPOX for around 12 weeks followed by radiation and capecitabine (CAPRT) for LARC and reported a pathologic complete response (pCR) rate of 20% and a rate of negative resection margin (R0) of about 88%.[9] One study quoted the rate of sphincter preserving R0 resection of about 75% and a pCR rate of about 25% following preoperative four cycles of FOLFOX plus short-course radiation treatment.[10]

On the basis of the available scientific evidence, we started treating patients with rectal cancer at Shaukat Khanum Memorial Cancer Hospital and Research Centre with upfront chemotherapy in 2007. The purpose of this study is to report toxicity and pCR in patients treated at our institution. The relevant information acquired from this study will also enable us to compare our results with contemporary international literature and may also be used in the future as a part of evidence for changing treatment protocols to provide better local control and improved disease-free survival to our patients.

MATERIALS AND METHODS

After being granted of exempt status by institutional review board, records of all the patients' treated for LARC between January 2007 and December 2014 with CAPOX followed by CAPRT and surgery were reviewed retrospectively. LARC was defined as tumor size T3-4 with or without nodal involvement or T2 with node-positive disease without any evidence of distant metastasis.[11] All patients with histologically proven malignancy of rectum, age above 16 years,

Eastern Cooperative Oncology Group performance status 0-2, and adequate renal and liver functions were included in the study. Patients with poor performance status, metastatic disease, and recurrent tumors were excluded.

All patients had a full clinical history and physical examination including digital rectal examination, complete colonoscopy, magnetic resonance imaging (MRI) of pelvis, and computed tomography of chest and abdomen followed by multidisciplinary team discussion.

Treatment

Patients were planned for induction chemotherapy comprising four cycles of capecitabine 850 mg/m^2 given twice daily for 14 days and oxaliplatin 130 mg/m^2 given once on day 1 only, repeated every 3 weeks. Patients were assessed before each cycle of chemotherapy for local clinical response and adverse effects. Chemotherapy-induced toxicity was graded and documented using Common Terminology Criteria for Adverse Events Version 4.[12]

Three weeks after the last course of induction chemotherapy, patients were planned for concurrent CAPRT. Radiotherapy was delivered using conformal planning at a dose of 45-54 Gy using 6-15 MV photons. All patients underwent a planning computed tomography scan with 3 mm slices. The clinical target volume included the postchemotherapy gross primary tumor and entire mesorectum together with presacral, obturator, and internal iliac and external iliac lymph nodes.

Patients were treated with three-dimensional conformal radiation therapy using three to four coplanar fields. Weekly online imaging was performed to verify the treatment and planning positions. These patients received concurrent capecitabine at a dose of 825 mg/m^2 twice daily during the days of radiation.

Pelvic MRI was performed 6 weeks after the end of CAPRT to assess the local clinical response using response evaluation criteria in solid tumors version 1.1, and TME was performed at 7-12 weeks by specialist

TABLE 1. Patient and Disease Characteristics

Characteristic	No. (%)
Age, years	
Mean ± SD (range)	43 ± 14.417 (16-78)
≤ 50	206 (68.4)
> 50	95 (31.6)
Sex	
Male	204 (67.8)
Female	97 (32.2)
Performance status (ECOG)	
0	214 (71.1)
1	84 (27.9)
2	3 (1.00)
T stage (pretreatment)	
T2	8 (2.70)
T3	227 (75.4)
T4	66 (21.9)
Lymph node status (pretreatment)	
N0	19 (6.30)
N1	52 (17.3)
N2	230 (76.4)
Tumor histology	
Adenocarcinoma	229 (76.1)
Signet-ring or mucinous carcinoma	72 (23.9)
Tumor grade	
Well-differentiated	58 (19.3)
Moderately differentiated	134 (44.5)
Poor or undifferentiated	101 (33.6)
Unknown	8 (2.70)
Distance from anal verge	
< 5 cm low	170 (56.5)
> 5 cm high	129 (42.9)
Unknown	2 (0.70)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; N, nodal; SD, standard deviation; T, tumor.

colorectal surgeons. The choice of the surgical procedure, abdominoperineal resection, or low anterior resection was at the surgeon's discretion and tumor location from anal verge.

Pathologic Assessments

TME specimens were evaluated using rectal cancer regression grading (RCRG) system.[13] All lymph nodes were examined, and circumferential resection margin (CRM) was measured. A pCR was defined as no tumor cells in entire specimen, and involved CRM was defined when the tumor cells were located at 1 mm or less from the CRM.[14]

RESULTS

A total of 301 patients were given CAPOX before CAPRT at Shaukat Khanum Memorial Cancer Hospital and Research Centre. The mean age of the patients at presentation was 43 years. Of 301, 227 (75.4%) patients had T3 disease. Most common histology was adenocarcinoma (n = 229 [76.1%]), and a majority of tumors were moderately differentiated (n = 134 [44.5%]). Regional lymph node metastasis was found in 282 (93.7%) patients, with N1 disease in 52 (17.3%) and N2 disease in 230 (76.4%) patients. One hundred seventy (56.5%) patients had lower rectal cancer starting within 5 cm of anal verge. Further details of disease are shown in Table 1.

Neoadjuvant CAPOX was offered to all patients, and most of them completed four cycles of chemotherapy (n = 227 [75.4%]). Most common toxicity was diarrhea, with grade 2 and grade 3 diarrhea observed in 108 (35.8%) and 57 (18.9%) patients. Grade 2 oral mucositis was found in 108 (35.8%) patients, whereas 47 (15.6%) developed grade 3 oral mucositis. Neuropathy was seen in 186 patients, with 132 (43.8%) and 54 (17.9%) developing grade 2 and grade 3 neuropathy. Only 98 (32.6%) patients had grade II hematologic toxicity. Hand-foot syndrome was found in 91 (29.5%) patients, with 65 (20.9%) and 26 (8.63%) developing grade 2 and grade 3 toxicity. The only grade 4 toxicity observed was diarrhea (n = 25 [8.3%]) and oral mucositis (n = 9 [2.9%]). Details of the toxicity associated with neoadjuvant CAPOX are shown in Table 2. Toxicity during chemoradiation was not reviewed.

A radiation dose of 5,040 cGy in 28 fractions was given to 290 (96.3%) patients, whereas 9 (3%) received 4,500 cGy in 25 fractions. Doses of 5,400 cGy in 30 fractions were given in two (0.7%) patients. All the fractions were delivered as a part of once daily fractionation scheme, 5 days a week.

Concurrent chemotherapy with capecitabine was given in all patients. The radiation treatment was completed in a mean duration of 45 days, with a range of 35-70 days.

TABLE 2. Severity and Frequency of Various Toxicities Associated With Neoadjuvant Capecitabine and Oxaliplatin

Toxicity	Grade 1, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)	Grade 5, No. (%)
Hand-foot syndrome	210 (69.7)	65 (20.9)	26 (8.63)	0 (0)	0 (0)
Neuropathy	115 (38.2)	132 (43.8)	54 (17.9)	0 (0)	0 (0)
Hematologic	203 (67.4)	98 (32.6)	0 (0)	0 (0)	0 (0)
Diarrhea	111 (36.8)	108 (35.8)	57 (18.9)	25 (8.30)	0 (0)
Oral mucositis	137 (45.5)	108 (35.8)	47 (15.6)	9 (2.99)	0 (0)

TABLE 3. Treatment Characteristics

Characteristic	No. (%)
No. of neoadjuvant chemotherapy cycles	
≤ 3	40 (13.3)
4	227 (75.4)
≥ 5	34 (11.3)
Radiation dose and fractionation	
45 Gy in 25 Fr	9 (3.00)
50.4 Gy in 28 Fr	290 (96.3)
54 Gy in 30 Fr	2 (0.70)
Radiologic response assessment after CAPRT	
Yes	294 (97.7)
No	7 (2.30)
Surgery	
Yes	229 (76.1)
No	72 (23.9)
No. of lymph nodes removed	
< 12	74 (32.3)
≥ 12	155 (67.6)
Pathologic complete response	
Yes	52 (22.7)
No	177 (77.3)
CRM	
Negative	200 (87.3)
Positive	29 (12.6)

Abbreviations: CAPRT, capecitabine and radiation; CRM, circumferential resection margin; Fr, Fractions.

Treatment was interrupted in only seven patients. Following completion of CAPRT, a response assessment by MRI of pelvis was performed in 294 (97.7%) patients. The extent of response by digital rectal examination or endoscopy was not reviewed and could not be correlated with the radiologic or pathologic response. About 229 (76.1%) patients underwent surgery, with 137 (59.8%) undergoing lower abdominal resection and 92 undergoing abdominoperineal resection (40.2%). In 72 (23.9%) cases, TME was not performed as disease was technically unresectable (n = 52 [72.2%]) or because of medical comorbidities or extrapelvic metastases rendering patient inoperable (n = 9 [12.5%]) or either refused by patients (n = 11 [15.3%]). The details of various treatment-related characteristics are shown in Table 3. The frequency of various radiologic and pathologic responses is shown in Figure 1. For an easy comparison, RCRG 1 specimens with only microscopic foci of tumor are labeled as partial response. RCRG 2 and 3 specimens are labeled as stable disease and disease progression.

Tables 4 and 5 show pathologic tumor and nodal responses, respectively, in patients who underwent TME. In 4 (1.7%) patients, lymph nodes were not identified in the surgical specimen. A pCR (ypT0N0) was observed in 52 patients (22.7%; 95% CI, 13 to 28), whereas another 11 (4.8%) had near complete response (ypT1N0). CRMs turned out to be negative in 200 patients (87.3%; 95% CI, 82 to 99).

DISCUSSION

The concept of neoadjuvant chemotherapy before chemoradiation in LARC was initially explored by Chau et al[15] in 2003 in which 5-fluorouracil and mitomycin were given before chemoradiation, and they reported R0 resection in 82% of patients. Another single-institution trial conducted at Memorial Sloan Kettering Cancer Center used neoadjuvant FOLFOX and bevacizumab without radiation for patients with stage 2 and 3 rectal cancer, which also reported a high rate of R0 resection and a pCR of 27%.[16]

In our experience, a majority of patients who underwent surgery postinduction CAPOX and CAPRT achieved negative CRM and pCR. Furthermore, treatment was well-tolerated as 75.4% of the patients completed four cycles of CAPOX given initially. Although progression during initial CAPOX is rare, there remains a possibility as it has already

FIG 1. Radiologic and pathologic responses after neoadjuvant chemotherapy followed by concurrent chemoradiation.
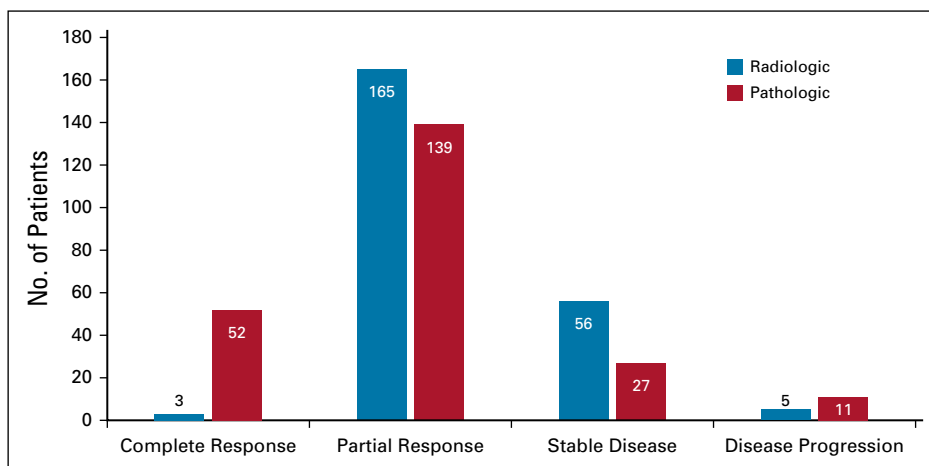
TABLE 4. Pathologic Tumor Response

		Post-Treatment T Staging					
		ypT0	ypT1	ypT2	ypT3	ypT4	Total
Pretreatment T staging, No. (%)	cT2	2 (0.9)	1 (0.4)	4 (1.7)	1 (0.4)	0 (0)	8 (3.5)
	cT3	45 (19.7)	11 (4.8)	41 (17.9)	77 (33.6)	8 (3.5)	182 (79.5)
	cT4	6 (2.6)	3 (1.3)	7 (3.1)	17 (7.4)	6 (2.6)	39 (17.0)
Total		53 (23.1)	15 (6.6)	52 (22.7)	95 (41.5)	14 (6.1)	229 (100)

Abbreviations: c, clinical; p, pathologic; T, tumor; y, postneoadjuvant.

been demonstrated by Chau et al,[15] wherein 12% of the patients progressed on induction chemotherapy. Therefore, clinical response assessment was performed with the help of MRI and radiologic response was documented at the completion of CAPRT. One potential concern of using beforehand chemotherapy would be the possibility of excessive toxicity, which could make pelvic radiotherapy even more difficult for the patient to tolerate. Although it was expected, all patients managed to complete planned doses of CAPRT.

This treatment strategy has shown several potential benefits. With the use of modern surgical techniques along with improvements in preoperative chemoradiation through advancements in radiation treatment delivery technology, the risk of local failure has substantially decreased. Therefore, now, the main concern for the patients with LARC is micrometastasis and one of the possible ways for the eradication of this micrometastasis would be the start of early treatment with systemic therapy.

Although it is not specifically quantified in this retrospective analysis, most of the patients reported remarkable remission of symptoms, like rectal bleeding or pain, commonly after the first cycle of receiving neoadjuvant chemotherapy. This initial chemotherapy was found to be quicker in alleviating tumor-related symptoms than conventional chemoradiation.[17] Theoretically, the delivery of systemic therapy before any surgical intervention or radiotherapy has proven to be more effective because the blood supply to the tumor bed has not been altered, which facilitates the optimal delivery of drug to the primary disease.

One of the mainly observed shortfalls of adjuvant chemotherapy in various clinical trials is that approximately 17%-28% of eligible patients do not start postoperative chemotherapy or nearly 37%-52% begin their treatment after a significant delay.[17-19] One of the basic reasons of delay observed in the initiation of adjuvant chemotherapy is temporary diverting ileostomy or colostomy. Therefore, with the chemotherapy-first approach, this delay because of temporary ileostomy can be avoided. Furthermore, using this approach, time to temporary stoma reversal could be substantially reduced (3 v 9 months), resulting in improved quality of life. Another tangible benefit of giving neoadjuvant chemotherapy is that patients would be able to receive complete chemotherapy cycles, as compared with adjuvant chemotherapy where poor tolerance and high toxicities are observed after concurrent chemoradiation and surgery.[8,17-19] In this study, almost all patients were able to complete cycles of induction CAPOX, without any disruption or major toxicities.

Moreover, many studies have reported that final pathologic stage is more predictive of long-term survival outcomes than preclinical stage and patients with pCR have shown the overall survival rates ranging from 83% to 96%.[20-25]

There are certain shortcomings of our study. First, better outcome to pCR because of presurgical chemotherapy and chemoradiation can be an association rather than cause effect. Second, even a much larger number of patients analyzed retrospectively cannot remove the desirability of a randomized controlled clinical trial to support this analysis.

TABLE 5. Pathologic Nodal Response

		Post-Treatment N Staging				
		ypNx[a]	ypN0	ypN1	ypN2	Total
Pretreatment N staging, No. (%)	cN0	0 (0)	14 (6.1)	2 (0.9)	0 (0)	16.(7.0)
	cN1	0 (0)	35 (15.3)	6 (2.6)	4 (1.7)	45 (19.7)
	cN2	4 (1.7)	95 (41.5)	32 (14)	37 (16.2)	168 (73.4)
Total		4 (1.7)	144 (62.9)	40 (17.5)	41 (17.9)	229 (100)

Abbreviations: c, clinical; N, nodal; p, pathologic; y, postneoadjuvant.
[a]Lymph nodes were not identified in four patients.

It is the largest series to date of induction chemotherapy and complete delivery of all nonsurgical treatment before surgery in our experience and knowledge. We believe that it is a viable treatment option for LARC, and further studies depicting the role of induction chemotherapy with more effective systemic therapies are needed, so that increased pathologic response rates and long-term survival outcomes can be achieved.

In conclusion, our experience strongly indicates that chemotherapy upfront with CAPOX is manageable and well-tolerated with acceptable toxicity. The combination of CAPOX and CAPRT results in good tumor regression and substantial pCR rates. In the absence of large-scale, adequately powered, randomized data, we feel that the logic of this paradigm and our preliminary data support the continuous use of this approach, particularly in locally advanced patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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