A phase II trial of celecoxib in addition to neoadjuvant concurrent chemoradiation for patients diagnosed with locally advanced rectal adenocarcinoma

Original Article

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ABSTRACT

Background: Neoadjuvant chemoradiotherapy followed by total mesorectal excision is the standard therapy for localized rectal adenocarcinoma. Neoadjuvant chemoradiation has been shown to increase local control and facilitate surgery. In this trial, we aimed to assess the impact of celecoxib in addition to neoadjuvant chemoradiation on pathologic response rates and treatment-related toxicity in locally advanced rectal adenocarcinoma.

Patients and Methods: Total 30 patients were enrolled in this phase 2 study. Patients underwent full colonoscopy + baseline scans and then received neoadjuvant therapy (capecitabine 825 mg/m^2 bid in combination with celecoxib 200 mg bid and radiotherapy (50–50.4 Gy/25–28 fraction, 5 fractions/week). Surgery was done 8–12 weeks after chemoradiation. Acute complications were scored by common toxicity criteria 5.0.

Results: Of 30 patients, total mesorectal excision was done in 22 patients. Tumor regression grade was reported as: seven (31.8%) patients had grade 0 or complete response, seven (31.8%) patients had grade 1 or moderate response, six (27%) patients had grade 2 or minimal response and two (9%) patients had grade 3 or poor response. No patients had acute hematologic or cardio-vascular toxicity.

Conclusion: Results indicate that adding celecoxib to neoadjuvant therapy for rectal adenocarcinoma can promote pathologic complete response and decrease acute therapy toxicity.

Key Words: Celecoxib, neoadjuvant chemoradiation, rectal adenocarcinoma.

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INTRODUCTION

In recent years, the prevalence of colorectal cancer (CRC) has been dramatically growing at an alarming rate worldwide. There are estimated 1.93 million new CRC cases diagnosed, and 0.94 million CRC caused deaths in 2020 globally. CRC is the third most frequently diagnosed cancer, representing 10% of the global cancer incidence (total 19.29 million new cases) and 9.4% of all cancer deaths (total 9.96 million). CRC is the third leading cause of cancer deaths in both genders worldwide, with an estimated 515 637 deaths among males and 419 536 deaths among females in 2020. Today, more than 5.25 million (5-year prevalence) people worldwide are living with CRC. According to estimates from (GLOBOCAN 2020), there are 1.15 million new cases of colon cancer and 0.7 million new cases of rectal cancers in 2020 globally[1].

In Egypt, according to results of the national population-based cancer registry program; it was estimated that 4942 cases were newly diagnosed with CRC in 2020, of which 1512 cases were rectal cancers[2].

Standard treatment for locally advanced rectal adenocarcinoma (stage II and III) is surgery and chemoradiotion (before or after surgery)[3]. Neoadjuvant chemoradiation is associated with easier resection, lower risk of small bowel toxicity, better functional outcome, and better tolerability as compared with adjuvant chemoradiation[4].

Cycloxygenase-2 (COX II) enzyme which is an effective enzyme in prostaglandin synthesis, has an important role in both inflammation and tumor growth. COX II gene over expression is detected in 40% of colon adenoma and 90% of colorectal adenocarcinoma[5].

The COX-2-derived prostaglandin-E2 (PGE2) is over expressed in CRC and has been shown to promote tumor proliferation and angiogenesis by binding to trans-

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membrane G-protein-coupled receptors, this ultimately activates downstream signaling pathways that can increase tumor cell survival and migration. Patients with colorectal adenocarcinomas that have an increased COX-2 expression, have been found to have reduced 5-year survival and higher rates of developing local recurrence and/or metastatic disease as compared with those without elevated COX-2[6,7].

The COX-2/PGE2 pathway has been also shown to stimulate the function and survival of the CRC stem cells which have been found to be the driving force behind carcinogenesis; maintaining tumor growth and ultimately nourishing resistance to chemoradiation. Based on the above mentioned data, celecoxib may have a good clinical potential for prevention and treatment of colon cancer and other gastrointestinal tumors[8–10].

Published literature suggests the use of aspirin or non-steroidal anti-inflammatory drugs to decrease the risk for CRC. In fact, the US Preventative and Screening Task Force recommends that adults aged 50 to 59 years with a 10-year cardiovascular disease risk greater than or equal to 10% and a life expectancy of greater than or equal to 10 years and without an increased bleeding risk should take low-dose aspirin daily for at least 10 years for the primary prevention of both cardiovascular disease and CRC[11].

With standard neo-adjuvant therapy, around 15–20% of rectal adenocarcinomas can achieve a pathological complete response, which is associated with a reduction in local recurrence and improved disease-free and overall survival. Neoadjuvant chemoradiation with single agent capecitabine or 5-fluorouracil has been used for years as the standard treatment of locally advanced rectal adenocarcinoma after trials of other effective chemotherapeutics in the metastatic setting (irinotecan and oxaliplatinum) failed to add clinically meaningful benefits to concurrent chemoradiation with single agent fluoropyrimidine in the localized setting[12,13].

Despite current advances in the delivery of radiotherapy, the rates of pathologic complete responses remain low. Since other chemotherapeutics failed to establish a real benefit when added to fluoropyrimidine in that context, the use of nonchemotherapeutic adjuncts to standard chemoradiation like statins, metformin, aspirin, and celecoxib has been investigated in many trials and showed promising results in terms of enhancing pathologic response to neoadjuvant therapy with no added major toxicities[5].

In patients with familial adenomatous polyposis, treatment with celecoxib significantly reduced the number of colorectal polyps[14]. Celecoxib was also reported to have a synergistic effect on radiotherapy for other tumors in basic studies[15], as well as favorable responses recorded when celecoxib was added to 5-Fluorouracil[16] or Uracil/Tegafur[17,18] or capecitabine[19] in chemoradiation trials for rectal adenocarcinoma patients. Celecoxib was designed to have minimal harmful effects on gastric mucosa, yet the two major concerns for its use still are the development of peptic ulcer disease as well as the increased risk of serious cardiovascular thrombotic events that can be fatal, this particular risk is proportional to the duration of use and presence of pre-existing cardiovascular disease[20].

PATIENTS AND METHODS:

Our study was a Phase 2 prospective unblinded single arm trial conducted on newly diagnosed patients with locally advanced rectal adenocarcinoma, presented to the department of Clinical Oncology, Ain Shams University Hospitals during the period from January 2020 to December 2021. Primary endpoint was to determine the pathological complete response (pCR) rate when combining standard preoperative long course concurrent chemoradiation with celecoxib. Secondary endpoints included assessing the acute toxicity profile of the study protocol, negative resection margins rates, primary tumor and nodal downstaging rates, and sphincteric preservation rate.

Patients

Our study included adult patients (age greater than 18 years), ECOG performance status less than or equal to 2. Patients with pathologically proven adenocarcinoma of the rectum, AJCC T3-4 and/or N1-2 M0 were included. Superior margin of the tumor below the L5-S1 spine junction or within 15 cm from anal verge by colonoscopy. Patient were excluded if there were any of the following; distant metastasis, Prior pelvic irradiation, inflammatory bowel disease or any medical conditions which preclude radical therapy, history of synchronous or double malignancies within 5 years, pregnancy, hypersensitivity to celecoxib, or capecitabine, history of peptic ulcer disease or NSAID-related gastrointestinal bleeding, cardiovascular diseases like congestive heart failure, symptomatic coronary artery disease, or recent myocardial infarction. Patients with controlled coronary artery disease with acceptable baseline ECG and adequate left ventricular ejection fraction were possibly included and closely monitored by weekly ECG and essential investigations whenever indicated. (Table 1) shows the epidemiologic characteristics of our patients.

Methods

Informed consent was obtained from all participants, we reviewed all patients' files to collect clinical and pathological data. Complete history taking and physical examination of each participant was done at first visit. Clinical staging was performed by means of Magnetic Resonance Image (MRI) rectal protocol, total colonoscopy, contrast computed tomography chest and abdomen. Nuclear medicine study (whole body bone scan or PET scan) were performed if clinically indicated. Acceptable

basic blood counts: white blood cell greater than 4 $\times 10^9$/L, neutrophil count greater than 1.5×10^9/L, platelet count greater than 100×10^9/L, serum bilirubin less than 1.5×ULN (upper limit of normal), AST/ALT (Aspartate transaminase/Alanine transaminase) less than 3×ULN, serum creatinine less than 1.5×ULN. Eligible participants received neoadjuvant chemoradiotherapy with capecitabine (825 mg/m^2 bid)+celecoxib (200 mg bid), both on radiation days + radiotherapy (50–50.4 Gy in 25–28 daily fractions; 5 fractions/week), we prescribed what we believed to be the lowest effective dose of celecoxib in order to minimize the chances of occurrence of any cardiac or gastrointestinal toxicities. Treatment tolerance was evaluated on weekly basis by clinical examination and blood counts. Toxicities were reported on the basis of Common Terminology Criteria (CTCAE version 5.0), published by the US National Cancer Institute on November 27, 2017. Baseline ECG was obtained for all patients before initiation of therapy, follow up ECG was also obtained at 4 and 8 weeks from initiation of therapy. Planned total mesorectal excision was done within 8–12 weeks from completion of neoadjuvant therapy. Grading of pathological response in surgical specimens was done according to AJCC and CAP guidelines modified from (Ryan *et al*.) as follows[21]:

0- Complete response: no remaining viable carcinoma cells

1- Moderate response: only small clusters or isolated cells remaining.

2- Minimal response: residual tumor with predominant fibrosis.

3- Poor response: extensive viable residual tumor.

Table 1: Epidemiologic characteristics of study population

Age	Range	(35–75 years)
	Mean age	55 years
Sex	Female	9
	Male	21
Family history of colorectal or other LYNCH-related malignancies	Positive 26%	Negative 74%
Active Smoking	Smokers 50%	Non-smokers 50%
DM	Positive 17%	Negative 83%
HTN	Positive 26%	Negative 74%
Controlled IHD	Positive 6%	Negative 94%
Treatment center	ASUH: 83%	EHI: 17%
Treatment interruption	< 1 week	53%
	>1–2 weeks	17%
	>2–3 weeks	13%
	>3 weeks	17%

ASUH, Ainshams University Hospitals; EHI, Egyptian health insurance facility.

RESULTS:

Twenty-two patients successfully underwent total mesorectal excision while eight patients have not been operated; two of them achieved complete clinical response after treatment but they refused surgery with Abdomino-perineal resection (for the poor quality of life associated with permanent stoma) and instead, they opted for 6 months of XELOX protocol followed by maintenance xeloda and intense follow-up by means of regular clinical examination, MRI rectal protocol every 3 months and interval colonoscopies. Those patients who opted for intense follow-up after clinical complete response were meticulously counselled that on the earliest signs of disease progression, they should be scheduled for radical surgery otherwise they will miss their chances of cure. Two other patients developed peritoneal metastases after treatment and one patient developed liver metastases (all were switched to systemic therapy with XELOX as first line therapy for metastatic disease), three patients remained nonmetastatic after therapy without significant downstaging (CRM was involved) so they continued on systemic therapy with 4 cycles of XELOX as part of total neoadjuvant protocol to improve their surgical chances, two of them were successfully downstaged and underwent surgery (were excluded from our analysis for total neoadjuvant approach) and the last one developed severe neutropenic sepsis after second cycle of XELOX then refused to continue further treatment at this stage. Clinical staging and pathological aspects are shown in (Table 2).

Table 2: Clinical staging and pathological aspects

Grade of carcinoma	G-1: 0%	G-2: 90%	G-3: 10%
Clinical Stage: AJCC 8th edition	T3N0	2 A	7%
	T4N0	2B–C	4%
	T2N1	3A	7%
	T3N1	3B	23%
	T4N1		6%
	T3N2	3C	30%
	T4N2		23%
Tumor location	Upper (>10–15 cm from AV)		20%
	Mid (>5–10 cm from AV)		40%
	Low (1–5 cm from AV)		40%
Pretreatment CRM status by MRI	Involved: 54%		Not involved: 46%
Presence of EMVI	Present: 24%		Absent or no comment in MRI: 76%
Type of surgery	LAR	57%	
	APR	17%	
	No surgery	**Patient refusal of permanent colostomy: 6%**	**Tumor Progression and/or no downstaging: 20%**

APR, abdomino-perineal resection; CRM, circumferential resection margin; EMVI, extramural vascular invasion; LAR, low anterior resection.

Response evaluation

Response was evaluated by pathological examination of the surgical specimen after surgery. Tumor regression grade was reported according to the degree of fibrosis and tumor regressive changes; seven of 22 (31.8%) patients had pathologic complete response (pCR), seven (31.8%) patients attained partial response to therapy, the rate of favorable response (partial or complete) was 63.6% (14/22 patients), six (27%) patients developed minimal response to therapy and two (9%) patients had no response at all. Primary tumor downstaging was observed in 19 (63%) patients, nodal downstaging was found in 22 (73%), the rate of sphincteric preservation was 77% whilst negative resection margins (including CRM) were achievable in all operated patients 100%.

Toxicity evaluation

The most common toxicities reported by our participants were; grade I radiation dermatitis (19 of 30, 63%) which was frequently managed by topical moisturizers and anti-inflammatory creams, grade I diarrhea (17 of 30, 56%), grade I cystitis (17 of 30, 56%), both were managed by instructing high fluid intake and reassuring the patient about their nature, also grade I fatigue reported in (17 of 30, 56%), grade I nausea was reported by (15/30, 50%) while therapy related grade I abdominal or pelvic pain was encountered in (14/30, 46%) of cohort (usually managed with paracetamol when needed) and less frequently the above-mentioned toxicities were reported as grade II. There were no grade III or IV toxicities at all. Hand and foot syndrome of any grade was not reported by any of our participants and more importantly there were no hematologic toxicities or cardiovascular events as shown in (Table 3).

Table 3: Analysis of toxicity

Toxicity (CTCAE-5)	No change	G-1	G-2	All
Nausea	12	15	3	60%
Fatigue	5	17	8	83%
Therapy related abdominal or pelvic pain	11	14	5	63%
Diarrhea	4	17	9	87%
Dermatitis	3	19	8	90%
Cystitis	6	17	7	80%

Hand and foot syndrome	30			
Chest pain	30	0	0	0
ECG changes	30	0	0	0
CBC changes	Anemia of any grade: 0	Neutropenia of any grade: 0	Thrombocytopenia of any grade: 0	0

DISCUSSION

The management of localized rectal adenocarcinoma requires a multidisciplinary effort of medical, radiation, and surgical oncologists to provide the best care. The landmark German Rectal Cancer study group CAO/ARO/AIO-94 identified improved local control with preoperative versus postoperative chemoradiation[22]. Updated results from this study showed that both the degree of tumor regression and the rate of pCR were associated with improved disease-free survival as well as better local control. Therefore, pCR is considered an acceptable endpoint for phase II studies[23]. The 5-year probability of death from locally advanced rectal adenocarcinoma is 44%, and local recurrences occur in almost 40% of cases. Therefore, it is imperative to seek new treatment strategies that potentially improve survival and tolerability[24].

The overexpression of prostaglandin E2 (derived by COX-2) in CRC has been shown to promote tumor cell proliferation and angiogenesis by binding to trans-membrane G-protein-coupled receptors, this ultimately activates downstream signaling pathways that can increase tumor cell survival and migration. COX-2 overexpression in CRC has been found to reduce 5-year survival and induce higher rates of developing local recurrence and metastatic disease as compared with those without elevated COX-2. The COX-2/PGE2 pathway has been also shown to stimulate the function and survival of the CRC stem cells which have been found to be the driving force behind carcinogenesis; maintaining tumor growth and ultimately nourishing resistance to chemoradiation. Preclinical evidence showed improved radiation responses, inhibition of angiogenesis and metastasis with COX-2 inhibition in COX-2 overexpressing rectal adenocarcinomas, that's why we designed this trial to potentially improve pCR rates and assess tolerability of the combo of celecoxib and standard chemoradiation in Egyptian patients.

Historically, standard chemoradiation (with no adjuncts) has been associated with a pCR rate of 15–20%, sphincter-sparing surgery rate of 39–44%, surgical downstaging rate of 40–80%, incidence of grade 3 or more radiation dermatitis of 43–78%, and an incidence of radiation proctitis of 2–39%[25,26]. Our study noted a pCR rate of 31.8%. Primary tumor downstaging was observed in 63% of the operated cohort while nodal downstaging was accomplished in 73%. Rate of sphincter preservation was 77% and negative resection margins were achievable in all operated patients 100%.

Our results are comparable to the published literature regarding the use of celecoxib as an adjunct to neoadjuvant chemoradiation for localized rectal adenocarcinoma; we could achieve a pCR rate of 31.8% which is our primary endpoint. Data from Debucquoy *et al*.[16] reported a pCR rate of 11% after combining celecoxib 400 mg bid with radiation (50 Gy/25 F)+Infusional 5-FU. Wang *et al*.[18] reported a pCR rate of 13% by means of radiotherapy 44 Gy in 22 fractions + concurrent chemotherapy (tegafur-uracil and folinate) on days 1–30 and 38–65+Celecoxib (400 mg/day) given from days 1 to 65 followed by surgery on day 70. Aghili *et al*.[27] also reported a pCR rate of 26.7% by using (celecoxib 100 mg qid + neoadjuvant therapy; capecitabine 825 mg/m2 bid and radiotherapy 50–50.4 Gy in 25–28 fraction). Finally, Emelio *et al*.[28] reported a pCR rate of 31% after adding celecoxib 200 mg bid to a long course CCRT consisted of capecitabine 850 mg/m2 bid for 5 weeks, weekly oxaliplatin 50 mg/m^2 intravenous, along with concurrent 45 gray radiation therapy in 25 fractions, which we could achieve without the significant cost and potential toxicity from adding oxaliplatin to neoadjuvant therapy. The use of capecitabine instead of infusional FFU was very convenient to our patients as no need for hospital admission or day-case intravenous administration, together with the help of celecoxib in minimizing radiation toxicity both attained higher rates of patient adherence to study protocol and yielded relatively higher rates of pCR compared with older trials which used celecoxib in this regard.

As regard Primary tumor and nodal downstaging; we were able to achieve a Primary tumor (T) downstaging in 63% of operated cohort while nodal (N) downstaging was accomplished in 73% as compared with Debucquoy *et al*. who were able to attain a 72% rate of T and N downstaging in the celecoxib group, while Wang *et al*. reported T or N downstaging in 81% of their study participants. Aghili *et al*. also reported a primary tumor down staging rate of 43.3% and nodal downstaging of 30.8%. Finally, Emelio *et al*. reported a combined primary tumor and nodal downstaging rate of 75%. It is worth mentioning that three (10%) patients of our cohort developed metastatic disease after neoadjuvant therapy which may be higher than what is

reported in the literature; a possible explanation for that is the frequent interruptions of radiotherapy machines as well as the relatively younger age of presentation in many of our cases which is frequently associated and advanced tumor stage and extensive nodal involvement at presentation with a high probability of developing distant metastases when systemic therapy is delayed, we believe this could be a relative indication to start with neoadjuvant/induction chemotherapy followed by chemoradiation in such cases.

In terms of sphincteric preservation; 77% of our operated cohort were successfully managed with sphincter preserving surgery (low or ultra-low anterior resection) while 23% were operated with Abdominoperineal resection and had to accept a permanent stoma, all with negative resection margins. Our results are comparable with data from Wang *et al*. who could achieve a 75% rate of sphincteric preservation. Emelio *et al*. also reported a 56% rate of sphincter preserving surgery in the celecoxib group. Unfotunately 27% of our study participants could not proceed for surgery after neoadjuvant chemoradiation either due to tumor progression or concerns regarding quality of life after abdominoperineal resection, we believe this inversely affected the results and further investigation or maybe different treatment approaches are needed to improve outcomes in such cases.

In terms of tolerability, the majority of our patients completed their planned course of treatment without significant adverse events or major interruptions. The most common acute toxicities reported by our study participants were; grade I radiation dermatitis (63%), grade I diarrhea (56%), and grade I cycstitis (56%), all was easily manageable by first reassuring the patient about their nature and also by using topical emollients, topical anti-inflammatory creams and encouraging high fluid intake. There were no grade 3–4 toxicities at all. Historically, grade 3 or 4 diarrhea or proctitis has been reported at 43–78% and radiation dermatitis at 2–39%.

Major Issues concerning the toxicity of COX-2 inhibitors such as peptic ulcer disease and ischaemic heart disease were only observed with long-term administration[20]. There were no reported cases of either of these two potential complications in our study likely due to the relatively short period of exposure and the low dose of celecoxib. It is worth noting that none of our patients developed capecitabine-induced hand and foot syndrome which is consistent with data from Zhang and colleagues; it is possible that improved tolerance of capecitabine among our patients was related to the use of celecoxib[29]. It is worth mentioning that despite low rates of toxicities reported by our cohort, 30% of patients, unfortunately, had more than 2 weeks of interruption of therapy; this was essentially due to frequent breakdowns of our radiotherapy machine and its poor maintenance (especially during the coronavirus disease 2019 pandemic) rather than noncompliance to treatment protocol.

All things considered, our explanation of improved results in the celecoxib group across trials -including our study- as compared with historical controls is that on one hand, celecoxib as an anti-inflammatory drug offered since the very beginning of neoadjuvant therapy mitigates radiation irritative adverse events, encourages adherence to concurrent therapy schedule and potentially decreases interruptions, on the other hand, its well proven biological effects in terms of enhancing radiation sensitivity and targeting the COX-2/PGE2 pathway likely have an impact on the pattern of response.

Our study is the first and only study to test celecoxib with standard neo-adjuvant concurrent chemoradiation for rectal adenocarcinoma in Egyptian and African populations. Results are encouraging as we could almost double the pCR rates with a relatively cheap drug which also has an acceptable safety profile.

Unfortunately, there were many limitations to our study including the single-arm design without a control group which makes it challenging to attribute observed treatment effects solely to the addition of the celecoxib, the relatively short period of poor accrual that could be partly attributed to the confounding coronavirus disease 2019 pandemic which influenced patient recruitment, treatment adherence, and overall study dynamics. Most of our participants came from a single center. The sample size was limited to 30 patients (considering the cost of the drug as we were provided with very limited financial support) potentially weakening the statistical power and the generalizability of the findings. 27% of study participants were not operated according to study protocol due to different reasons, this may have a negative impact on results. Frequent treatment interruptions (more than half of study participants had > 1-week interruption with 30% of patients had > 2-weeks' interruption mainly due to poor radiotherapy machine maintenance and frequent breakdowns) could be a detrimental factor and may explain insignificant responses and even disease progression in some of patients. Larger randomized controlled study with longer follow-up would be needed to better determine the effectiveness of this combination and we would like to pursue this in the future.

CONCLUSION

We conclude that celecoxib (200 mg/bid) as an adjunct to neoadjuvant concurrent chemoradiation for rectal adenocarcinoma is safe and improves

compliance to neoadjuvant .therapy along with its well documented biological effects, it can promote pathologic complete response rates besides primary tumor and nodal downstaging as well as achieving a good quality total mesorectal excision with high rates of sphincter preservation.

CONFLICT OF INTEREST

There are no conflicts of interest.

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