Original Article

A randomized comparative study between neoadjuvant 5-fluorouracil and leukovorin versus 5-fluorouracil and cisplatin along with concurrent radiation in locally advanced carcinoma rectum

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ABSTRACT

Context: Concurrent chemoradiotherapy (CCRT) with cisplatin-5-fluorouracil (CDDP-5FU) in rectal cancer is based on the concept of biochemical modulation. **Aims:** The study was designed to evaluate whether CCRT with CDDP and 5-FU is noninferior to CCRT with leukovorin (LV) and 5FU in downstaging locally advanced rectal adenocarcinoma and to compare the toxicities between the two arms. **Settings and Design**: Single institutional, noninferiority, prospective, randomized study. **Subjects and Methods**: In control arm ($N = 24$) patients received chemotherapy. With bolus 5FU 350 mg/m^2/day and LV 20 mg/m^2/day for days 1-5 and 29-33. In study arm ($N = 25$), patients received chemotherapy with bolus 5 FU 350 mg/m^2/day for days 1-5 and 29-33 and CDDP 100 mg/m^2/day at days 1 and 29. Patients in both the arm received concurrent radiation (50.4 Gy in 28#, in conventional fractionation of 1.8 Gy per fraction). Six to eight weeks after concurrent chemoradiation patients underwent assessment and surgery. Postoperatively, adjuvant chemotherapy with m-FOLFO $\times$ 6 of 4 months was given to all patients. **Statistical Analysis**: The Chi-square test was used to compare categorical variables between the groups. **Results:** Response rate as assessed by Response Evaluation Criteria in Solid Tumors (RECIST criteria) was comparable between the two treatment arms ($P = 0.9541$). Pathological complete response rate of study arm was comparable to control arm (20 vs 20.83%, $P = 0.7778$ was not significant). Surgery with R0 resection was possible in 72% cases of study arm compared to 62.5% cases of control arm; $P = 0.6861$, not significant. Grade III toxicities were quite comparable between two treatment arms. **Conclusions**: In terms of pathologic complete response (pCR), R0 resection and toxicity profile of both the arms were comparable.

Key words: Biochemical modulation, cisplatin-5FU, concurrent chemoradiation, rectal cancer

INTRODUCTION

Globally, colorectal cancer (CRC) is the fourth most common cancer in males and third leading cause of cancer in females with mortality paralleling incidence.[1] Unlike the high incidence of rectal cancer in western world, CRC does not figure amongst the 10 most common malignancies in India. The age-standardized rates of CRC in India have been estimated to be 4.2 and 3.2/100,000 for males and females, respectively.[2] The 5-year survival is 90% when CRC is diagnosed at an early stage, however, less than 40% cases are diagnosed when the cancer is still localized.[3] Surgical resection is the only curative treatment. Curative surgery includes total mesorectal excision (TME) as standard procedure (abdominoperineal resection (APR), low anterior resection, and local excision). However, following potentially curative resection, local recurrence

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rate varies between 5 and 40%.[4,5] This high recurrence rate is largely due to presentation of rectal cancer in locally advanced stages. Downstaging of rectal carcinoma before TME can contribute to reduction of recurrence rate as well as improve sphincter preservation and survival. Downstaging can be achieved by use of 5-fluorouracil (5FU) or 5FU-leukovorin (LV) or capecitabine (Cape) based neoadjuvant concurrent chemoradiation. The patients are followed-up postoperatively with total of 6 months of perioperative treatment with adjuvant chemotherapy of capecitabone-oxaliplatin or FOLFOX regimens. Cisplatin (CDDP)-5FU therapy is based on the concept of biochemical modulation and is widely used for gastric and esophageal carcinomas.[6-12] In contrast, as for colorectal carcinoma, many authors have reported that LV-5FU therapy is effective in clinical studies.[13-17] However, there are only three reports that CDDP-5FU therapy is also effective for advanced colorectal carcinoma.[18-20] The study was designed to evaluate whether concurrent chemoradiotherapy (CCRT) with CDDP and 5-FU is noninferior to CCRT with LV and 5-FU in down staging locally advanced rectal adenocarcinoma to complete pathological response and surgery with R0 resection and to compare the toxicities between the two arms.

SUBJECTS AND METHODS

It was a single institutional, noninferiority, prospective, randomized study taken place from January 2011 to March 2013. Inclusion criterias were: Histologically confirmed primary adenocarcinoma of the rectum, primary growth restricted to within 15 cm from the anal verge, stage T3, T4, and/or N+, and M0 (7th edition TNM staging); absence of complete obstruction; no prior chemotherapy for study cancer, no prior pelvic radiotherapy/surgery, or major comorbidities; age 18-70 years; Eastern Cooperative Oncology Group (ECOG) performance status 0-2; adequate hematological, renal, hepatic and cardiac function, and patient must provide informed consent before trial entry. Patients were randomized by computer generated randomization procedure. Pretreatment assessment included history taking, clinical examination (including per rectal (P/R) finding), biopsy from the primary site, contrast-enhanced computed tomography (CECT) of abdomen, routine investigation—complete hemogram and biochemistry (urea/creatinine/liver function test (LFT)). In control arm (N = 24), patients received chemotherapy with bolus 5-FU 350 mg/m^2/day and LV 20 mg/m^2/day for days 1-5 and 29-33. In study arm (N = 25), patients received chemotherapy with bolus 5-FU 350 mg/m^2/day for days 1-5 and 29-33 and CDDP 100 mg/m^2/day at days 1 and 29.

External beam radiation was given with telecobalt-60 machine. Dose prescription of 50.4 Gy in 28 fractions, in conventional fractionation of single fraction of 1.8 Gy per day was given. The patients were treated in prone position with a full bladder. Conventional treatment planning with anteroposterior/posteroanterior (AP/PA) portals was used. The superior port edge was placed at the L4/L5 vertebral body. The distal port edge should be 5 cm below distal margin of the tumor. Most low lying rectal tumors were treated at least to the level of dentate line. Anterior and posterior portals will have at least a 1.5 cm margin on the pelvic brim. Irradiation was delivered 5 days per week at a dose of 1.8 Gy/day to a total dose of 39.6 Gy with AP/PA portals followed by three field (one PA and two lateral portal) techniques delivering six fractions of 1.8 Gy to a total of 50.4 Gy. Upper and lower border of lateral field was identical to AP/PA fields, Anterior margin: Just anterior to symphysis pubis; and posterior margin: To cover the whole sacrum so that whole of presacral space is irradiated. During treatment, the patients had blood reports of complete blood count (CBC), renal function test (RFT), LFT, and electrolytes. Clinical assessment for grading of treatment induced toxicities was done using Common Terminology Criteria for Adverse Events (CTCAE) version 4. Six to eight weeks after concurrent chemoradiation patients underwent assessment with CECT scan of whole abdomen and responses were assessed using Response Evaluation Criteria in Solid Tumors (RECIST) criteria. After surgical assessment, all operable patients underwent surgery with total mesorectal resection with intention of achieving R0 resection. Postoperatively, adjuvant chemotherapy with m-FOLFOX 6 of 4 months was given to all patients irrespective of pathological response. Primary endpoint was response rate as assessed by RECIST criteria. Secondary endpoints were surgery with R0 resection, pathologic complete response (pCR), and acute and late toxicities. After completion of treatment, patients were followed-up every month for the first 6 months, then every 2 months for the next 6 months, then 3 monthly till the end of the study. Posttreatment evaluation included detailed clinical examination, radiological assessment (including CECT scan of abdomen) every 6 monthly, or earlier if there are signs and symptoms suggestive of recurrence, assessment of toxicity using CTCAE version 4. MEDCALC version 11 software was used for data analysis. The Chi-square test or Fisher's exact test test was utilized to compare categorical variables between the groups. Statistical significance was assumed at $P < 0.05$, with all tests being two-tailed.

RESULTS

Between January 2011 and March 2013, 53 patients were selected of which four patients (two patients remained inoperable, one found to have progressive disease with liver metastases after chemoradiation and treated outside this study protocol, and one patient was lost to follow-up)

were discarded. So there were 49 evaluable patients who were randomly assigned to one of the treatment arm. The accrual in both the arms was comparable. The characteristics of the patients enrolled are listed in Table 1. In our study, 55.1% of the patients had pretreatment carcinoembryonic antigen (CEA) >5 ng/ml, which is considered as a poor prognostic marker. Response rate as assessed by RECIST criteria (control arm vs study arm: Complete response 16.66 vs 20%, partial response 50 vs 52%, stable disease 20.83 vs 20%, and progressive disease 12.5 vs 8%) [Table 2] was comparable between the two treatment arms (P = 0.9541). Pathological complete response rate [Table 3] of study arm was comparable to study arm (20 vs 20.83%, P = 0.7778 was not significant). Surgery with R0 resection [Table 3] was possible in 72% cases of study arm compared to 62.5% cases of control arm, P = 0.6861 not significant. Grade III hematological (control arm vs study arm = 8.33 vs 12%), gastrointestinal (12.5 vs 12%), genitourinary (8.33 vs 8%), and skin toxicity (20.83 vs 12%) were quite comparable between two treatment arms [Table 4].

Table 1: Patients characteristics

	Treatment				*P* value
	Control arm (*n*=24) (%)		Study arm (*n*=25) (%)		
Age group (years)					
20 to ≤30	2	8.33	2	8	0.7923
>30 to ≤40	7	29.1	8	32	
>40 to ≤50	9	37.5	8	32	
>50 to ≤60	4	16.6	7	28	
>60 to ≤70	2	8.33	0	0	
Sex					
Males	18	75	18	72	0.9316
Females	6	25	7	28	
Religion					
Hindu	19	79.16	17	68	0.5745
Muslim	5	20.84	8	32	
Residence					
Rural	7	29.1	9	36	0.8374
Urban	17	70.9	16	64	
Socioeconomic status					
Lower	15	62.5	14	56	0.8690
Middle	7	29.1	8	32	
Upper	2	8.33	3	12	
Diet					
Nonvegetarian	3	12.5	3	12	0.7021
Vegetarian	21	87.5	22	88	
Family history					
Absent	22	91.67	23	92	0.6318
Present	2	8.33	2	8	
ECOG performance status					
0	2	8.33	2	8	0.9951
I	16	66.66	17	68	
II	6	25	6	24	
Mode at presentation					
With colostomy	7	29.1	7	28	0.8213
Without colostomy	17	70.9	18	72	
Grade					
I	7	29.1	8	32	0.9727
II	12	50	13	52	
III	4	16.66	3	12	
IV	1	4.16	1	4	
Stage					
T3	7	29.1	8	32	0.9244
T4	17	70.9	17	68	
Pretreatment CEA (ng/ml)					
0 to ≤2.5	4	16.66	6	24	0.6872
>2.5 to ≤5	7	29.1	5	20	
>5	13	54.16	14	56	

ECOG: Eastern Cooperative Oncology Group, CEA: carcinoembryonic antigen

DISCUSSION

Combined modality therapy consisting of surgery, radiotherapy, and chemotherapy is the recommended management strategy for patients with stage II and III rectal cancer. The 5-year survival is 90% when CRC is diagnosed at an early stage, however, less than 40% cases are diagnosed when the cancer is still localized.[3] TME is now the standard technique for primary resectable rectal cancer and has significantly improved local control.[21,22] Adam showed in 1994 that the incidence of local recurrence 5 years after resection will rise from 10 to 78% in case of circumferential margin (CRM) involvement.[23] This concept holds good specially for locally advanced rectal cancer of

Table 2: Treatment response according to RECIST criteria

Response	Control arm (*n*=24) (%)		Study arm (*n*=25) (%)		*P* value
Complete response	4	16.66	5	20	0.9541
Partial response	12	50	13	52	
Stable disease	5	20.83	5	20	
Progressive disease	3	12.5	2	8	

RECIST: Response evaluation criteria in solid tumor

Table 3: Comparison of pathological complete response rate and surgery with R0 resection between the two treatment arms

	Control arm (*n*=24) (%)		Study arm (*n*=25) (%)		*P* value
Pathological CR rate	5	20.83	5	20	0.7778
R0 resection	15	62.5	18	72	0.6861

CR: Complete response

Table 4: Treatment toxicity

Toxicity	RTOG grading	Control arm (*n*=24) (%)		Study arm (*n*=25) (%)		*P* value
Hematological toxicity	I	10	41.66	9	36	0.8890
	II	3	12.5	2	8	
	III	2	8.33	3	12	
Gastrointestinal toxicity	I	10	41.66	8	32	0.8789
	II	3	12.5	3	12	
	III	3	12.5	3	12	
Genitourinary toxicity	I	10	41.66	6	24	0.4435
	II	3	12.5	2	8	
	III	2	8.33	2	8	
Skin toxicity	I	16	66.66	16	64	0.4771
	II	3	12.5	6	24	
	III	5	20.83	3	12	

RTOG: Radiation therapy oncology group

T3 and T4 lesions with nodal involvement. Preoperative and postoperative radiation treatment strategies have been extensively studied with intention for better disease control. Randomized trials have demonstrated that the addition of chemotherapy to preoperative radiotherapy significantly enhances tumor downstaging, pathologic response, and local control over radiation alone. So downstaging before the TME procedure may decrease the incidence of CRM involvement and local recurrence. The recently published 5-year results of the randomized German CAO/ARO/AIO 94 trial of preoperative versus postoperative chemoradiotherapy support a standard preoperative treatment approach.[24] However, in the Dutch Total Mesorectal Excision (TME) trial, no tumor downstaging was detected in the week after 5 × 5 Gy.[25] A recent Polish trial demonstrated that a radiotherapy schedule of 50.4 Gy combined with chemotherapy (5-FU/LV) followed after 4-6 weeks by surgery resulted in a significant higher percentage of downstaging compared with short-term preoperative radiotherapy of 5 × 5 Gy followed by surgery within 7 days.[26] So downstaging is dependent on both the total radiotherapy dose and the interval between the end of the radiotherapy and the surgery. With chemoradiation firmly established as the standardized treatment both pre- and postoperatively, the choice of chemotherapy in chemoradiation became a controversial issue. 5FU and its modulation drugs became the choice of concurrent chemotherapy with potent radiosensitizer effects for gastrointestinal cancer. The EORTC 22921 study and the French FFCD 9203 study employed 5FU bolus injection modulated with LV.[27,28] However, 5FU administered by continuous infusion or orally (Cape/tegafur-uracil (UFT)) may be more effective and less toxic than 5 FU administered by bolus injection.[29-31] Neoadjuvant 5FU-LV chemoradiation results in average of 18% complete pathological response with downstaging possible in 59%.[32]

Cape is an oral prodrug of 5FU with three-step *in vivo* enzymatic conversion to tumor-activated fluoropyrimidine carbamate. The final step is mediated by the enzyme thymidine phosphorylase (TP), which is upregulated in tumor tissue compared with adjacent healthy tissue. This theoretically allows a selective activation of the drug and low systemic toxicity.[33] Cape has proven activity as both adjuvant and first-line treatment for CRC. There is a potential therapeutic advantage to the use of Cape in combination with radiation. Exposure of normal tissues to 5FU within the radiation field is likely to be lower with oral Cape compared with intravenous 5FU. This was demonstrated in a study conducted in 19 CRC patients that compared 5FU concentrations in primary tumor and adjacent normal tissue, liver metastasis and adjacent normal tissue, and plasma following administration of Cape; there was a potential therapeutic advantage to the use of Cape in combination with radiation, but with limited toxicities of normal tissues.[33] The results from two large, randomized phase III trials including over 1,200 patients showed that oral Cape was more active than bolus 5FU/LV in terms of tumor response (26 versus 17%); and produced at least equivalent time to disease progression (TTP) and overall survival, with an improved safety profile.[34] Efficacy and safety are mirrored in the adjuvant setting, with recently published data from a large phase III trial of 1,987 patients with Dukes' C colon carcinoma showing a significant improvement in relapse-free survival and trends towards superior disease-free and overall survival.[35] Reviewed by Punt *et al*., oxaliplatin or irinotecan were used in conjugation with 5FU and/or LV as an effective chemotherapy with improved survival in advanced CRC.[36] Both *in vivo* and *in vitro*, oxaliplatin has been shown to have at least an additive interaction with radiotherapy in the management of digestive tract tumors.[37,38]

A Phase I-II Multicenter Study of the Dutch Colorectal Cancer Group, the maximum tolerated dose (MTD) and efficacy of oxaliplatin added to Cape and radiotherapy (Capox-RT) as neoadjuvant therapy were evaluated in 21 patients with T3-4 rectal cancer patients. The patients received escalating doses of oxaliplatin (day 1 and 29) with a fixed dose of Cape of 1,000 mg/m^2 twice daily (days 1-14 and 25-38) added to RT with 50.4 Gy and surgery after 6-8 weeks. The MTD, determined during phase I, was used in the subsequent phase II, in which R0 resection rate (a negative circumferential resection margin) was the primary end point. In the phase I part, oxaliplatin at 85 mg/m^2 was established as MTD. In phase II, the main toxicity was grade III diarrhea (18%). All patients underwent surgery, and 20 patients had a resectable tumor. An R0 was achieved in 17/21 patients, downstaging to T0-2 in 7/21 and a pCR in 2/21. It was combination of Capox-RT that has an acceptable acute toxicity profile and a high R0 resection rate of 81% in locally advanced rectal cancer. However, the pCR rate was low.[39]

Carlomagno *et al*., reported 43 patients treated with preoperative RT: 45 Gy/25 fractions with concurrent Cape: 825 mg/m^2 per day twice daily on days 1-14 every 3 weeks/2 cycles and oxaliplatin 50 mg/m^2 days 1 and 8 every 3 weeks; and pCR rate was 20.9%.[40] Fakih *et al*., reported 25 patients treated with RT: 50.4 Gy/1.8 Gy day with concurrent Cape: 725 mg/m^2/day twice daily Monday to Friday and oxaliplatin 50 mg/m^2 weekly for 5 weeks. pCR rate was 24%, effective downstaging was possible in 52% of patients and 20% of patients had Grade 3 diarrhea.[41]

Reference of CCRT with CDDP and 5-FU is limited. Only few trials used CDDP in part of CCRT in rectal carcinoma. CDDP-5FU chemotherapy is based on the concept of

biochemical modulation. The concept of biochemical modulation has recently been the focus of considerable attention in cancer chemotherapy. The purpose of biochemical modulation is to increase the effect of an anticancer drug, that is, to increase antitumor effects and reduce side effects by changing the pharmacokinetics of the effector (anticancer drug) with a modulator. As the mechanism of modulation, CDDP promotes methionine synthesis in cells by suppressing the intake of extracellular methionine. This promotion of methionine synthesis accelerates the folic acid metabolic circuit and increases 5,10-methylenetetrahydrofolic acid (5,10-CH2FH4), which forms a ternary complex with fluorodeoxyuridine monophosphate (FdUMP, metabolic product of 5FU) and thymidylate synthase (TS). The reaction lowers TS activity and inhibits deoxyribonucleic acid (DNA) synthesis.[12,42,43] As for colorectal carcinoma, LV-5FU therapy is commonly used in Western countries.[13-17,44,45] Moreover, several authors have reported that there are no advantages with CDDP-5FU therapy for colorectal carcinoma.[43-45] In contrast, in Japan LV-5FU is not yet established from the viewpoint of protocol, side effects, and cost performance. CDDP-5FU therapy has the same mechanism as LV-5FU therapy from the point of increasing TS inhibition.[16] It is usually applied to gastric and esophageal carcinoma and many authors have reported its efficacy.[6,7,9-12,46] In addition, one paper reported that CDDP-5FU therapy is effective for colorectal carcinoma.[18] Recently, several authors have reported that the combination of continuous administration of 5FU with a low-dose daily infusion of CDDP is more effective and side effects due to the protocol are milder than the combination with bolus injection of CDDP.[12,19,20]

In our study response rate (control arm vs study arm: Complete response 16.66 vs 20%, partial response 50 vs 52%, stable disease 20.83 vs 20%, and progressive disease 12.5 vs 8%) [Table 2] was comparable between the two treatment arms (P = 0.9541). Pathological complete response rate [Table 3] of study arm was comparable to study arm (20 vs 20.83%, P = 0.7778 was not significant). Surgery with R0 resection [Table 3] was possible in 72% cases of study arm compared to 62.5% cases of control arm, P = 0.6861 not significant. Grade III hematological (control arm vs study arm = 8.33 vs 12%), gastrointestinal (12.5 vs 12%), genitourinary (8.33 vs 8%), and skin toxicity (20.83 vs 12%) were quite comparable between two treatment arms [Table 4]. In conclusion, CCRT with CDDP-5FU is noninferior to 5FU-LV in downstaging locally advanced adenocarcinoma rectum with comparable toxicity profile. Accural in this study was limited. More accrual of patients in this study and longer median follow-up will give us a clearer picture in terms of response, toxicity, disease free survival, and overall survival.

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