Preoperative Capecitabine with Pelvic Radiotherapy for Locally Advanced Rectal Cancer (Phase I Trial)

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Objective: *Phase I multicenter study defined the maximal tolerated dose (MTD), dose-limiting toxicity (DLT) and safety profile of capecitabine in combination with preoperative radiation for patients with locally advanced rectal cancer (LARC).*
Material and Method: *Patients were treated with oral capecitabine (700, 800, 900, 1000, 1100 and 1200 mg/m2 twice daily continuously) plus preoperative whole pelvic irradiation (45-46 Gy in 23-25 fractions over 5–6 weeks). Surgery was performed at the median of 42 days after chemoradiation treatment.*
Results: *Twenty-seven patients were in this trial. Eighteen patients (3 per dose level) had received capecitabine from 700 mg/m2 twice daily to the highest dose level of 1200 mg/m2 twice daily. There were no grade 3/4 DLTs during dose escalation, a further nine patients were included at the highest capecitabine dose. Two of the twelve patients (16%) receiving capecitabine 1200 mg/m2 twice daily developed grade 3 diarrhea and discontinued treatment. There were no other grade 3/4 adverse events. After capecitabine chemoradiation, 24 of 27 patients (89%) received definite surgery. Primary and lymph node down staging occurred in ten patients (42%). Sphincter-sparing surgery was performed in seven patients (26%) and abdominal-perineal resection was performed in 17 patients (63%).*
Conclusion: *Preoperative capecitabine chemoradiation based on continuous daily capecitabine is very well tolerated in patients with LARC. The authors did not reach the MTD in the present study.*

Keywords: *Rectal cancer, Chemoradiation, Capecitabine, Radiotherapy*

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Rectal cancer is relatively common in Thailand, representing about 4% of all Thai cancer patients. Over 1144 new cases are diagnosed annually[1]. Local recurrence with and without distant metastasis is a significant problem following curative surgery[2-4]. While adjuvant 5-FU-based chemoradiation has been the most effective treatment to date, it is associated with slight increases in severe complications such as diarrhea and myelosuppression compared with adjuvant radiotherapy alone[5,6].

For locally advanced rectal cancer (LARC), preoperative chemoradiation has been used to downstage tumors and is followed by radical surgery in 26-

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62% of patients[7,8]. There are also reports of radical surgery with sphincter preservation in 49-67% of patients[9-11]. Preoperative chemoradiation can also decrease locoregional recurrence and a reduction of the small bowel complications compared with post-operative chemoradiation[12-14]. For inoperable tumors, preoperative chemoradiation has shown an increase in the resectable rate and provides an improvement of locoregional control[15]. The disadvantage of pre-operative chemoradiation is the difficulty in selecting appropriate patients and loss of pathological staging information.

Various attempts have been made to improve the efficacy of 5-FU-based chemoradiation, including the addition of other agents or modification of the means of 5-FU delivery, but most attempts have failed. However, continuous infusional delivery of 5-FU throughout the period of radiotherapy has shown significantly improved overall and disease-free survival compared with bolus administration of 5-FU[16]. Nevertheless, infusional delivery of 5-FU necessitates central venous line access with its ensuing inconvenience and increased risk of adverse venous events such as infection or thrombosis. Furthermore, most cancer patients prefer oral chemotherapy to intravenous infusional chemotherapy[17].

Capecitabine (Xeloda®, F. Hoffmann-La Roche Ltd.) is an oral, tumor-activated fluoropyrimidine that preferentially delivers 5-FU to tumor cells via a three-step *in-vivo* enzymatic conversion. The final step is mediated by the enzyme thymidine phosphorylase (TP), which is significantly up regulated in tumor tissue compared with adjacent healthy tissue[18,19]. TP expression is also enhanced by radiotherapy and the *in-vivo* anti-tumor activity of radiotherapy and capecitabine in human xenograft models is consequently more than an additive compared with either agent alone due to the TP up regulation[20]. Oral administration of capecitabine mimics continuous infusions of 5-FU and has proven activity as first-line treatment for advanced colorectal cancer[21] and is at least equivalent to 5-FU as adjuvant treatment for early-stage colon cancer[22]. Furthermore, capecitabine offers a clinically significant advantage over 5-FU/LV in terms of medical resource use[23] and safety[24-25]. The improved safety profile of capecitabine versus 5-FU-based therapy is apparent in patients receiving capecitabine for either metastatic or early-stage disease. Therefore, the use of capecitabine with radiotherapy as a radiosensitiser offers a promising, rational combination option for preoperative therapy in patients with LARC.

The objectives of the present study were to define the maximal tolerated dose (MTD), dose-limiting toxicity (DLT) and safety profile of capecitabine administered concurrently with preoperative radiation in patients with LARC.

Material and Method

This was an open-label, single-arm, multi-center (5 centers) study of increasing dose levels of capecitabine given concurrently with preoperative standard (anterior-posterior or multiple-field technique) whole pelvic irradiation (45 Gy in 25 fractions, given 5 days a week for 5-6 weeks). For radiation treatment, most of the treatment centers still used a cobalt-60 machine and the AP/PA opposed fields were used to give a more homogeneous dose distribution through the whole pelvis. A 3- or 4-field technique was used for patients who had anterior-posterior separation more than 10 cm. The authors used the prone position with a full bladder during irradiation to reduce the volume of the small bowel in the treatment area.

Capecitabine was administered continuously, every day for 5 weeks on an outpatient basis using escalating dose schedule from 700, 800, 900, 1000, 1100 to 1200 mg/m^2, oral twice daily. Three patients were planned at each dose level. Subsequent dose levels were not administered until all three patients reached the 2-week point beyond the completion of concurrent chemoradiation. If DLT was observed in one patient of a 3-patient cohort, three additional patients were then recruited into that cohort. If DLT was seen in two or more of a 6-patient cohort, the DLT was defined at that dose level. The dose level below that would then be expanded to six patients, to ensure that this dose was tolerable before being classified as the MTD. The MTD was defined as the dose below that causing DLT in at least two patients in the cohort of six patients. When the MTD was reached, twelve patients were required to confirm the safety at that dose level.

The present study was performed according to the principles of Declaration of Helsinki and its subsequent amendments and to good clinical practice guidelines. Institutional review board approval was obtained and each patient gave written informed consent.

Eligibility criteria were LARC with histological proof of adenocarcinoma. Tumors were required to extend through the bowel wall based on clinical, endorectal ultrasonography and/or radiographic evaluation, without associated distant metastasis. All patients had an ECOG performance status score of 0-1 and adequate bone marrow, liver and kidney function.

Baseline evaluations and all adverse events encountered during treatment were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0. Complete blood counts, urinalysis and safety evaluations were performed at weeks 0, 2, 3, 4, 5, end of chemoradiation (day 40) and before surgery (day 61). Blood chemistry analysis was performed at weeks 0 and 3, and days 40 and 61. If patients experienced any grade 2 adverse events, capecitabine was withheld until the event resolved to grade 0 or 1, and then restarted at the same dose with prophylactic treatment if necessary. If the patient experienced any grade 3 or 4 adverse events, treatment was discontinued until the event resolved to grade 0 or 1; radiotherapy was then restarted along with a reduced dose of capecitabine or without the drug.

After completion of capecitabine chemo radiation, patients underwent either abdomino-perineal resection (APR) or low anterior resection (LAR) within 4-6 weeks. Additional postoperative radiation (10-20 Gy in 1-2 weeks) was given in patients with positive tumor cells at the surgical margin, gross residual tumor, or tumor invasion of other organs or structures in the pelvis.

Statistical analysis

Frequency distribution table with descriptive statistics; number and percent, median and range were described the result. Non-parametric statistics i.e. Fisher's Exact test was used to compare grade and adverse events at different does levels as well abnormal renal function as mild renal impairment. A p-value less than 0.05 (2-sided) was considered significant difference.

Results

Between October 1999 and January 2003, the authors enrolled 27 patients with newly diagnosed LARC. Pretreatment staging was determined from whole abdomen or pelvic CT scanning in 25 patients (93%) and by endoscopic rectal ultrasonography in 16 patients (59%). Chest x-ray and upper abdomen ultrasonography were performed to exclude disease other than pelvic disease. Pretreatment staging was unknown in two patients, as whole abdomen CT scanning had not been performed. Baseline patient characteristics are shown in Table 1.

Table 1. Patient baseline characteristics (n = 27)

	No. of patients	%
Median age (range), years	54 (30-69)	
Gender		
Male	15	56
Female	12	44
ECOG score		
0	13	48
1	14	52
Pre-treatment tumour stage		
I	4	15
II	12	44
III	9	33
Unknown	2	7
Tumour histology		
Well differentiated	10	37
Moderately differentiated	15	56
Poorly differentiated	2	7
Distance from anal verge		
<5 cm	16	59
5-7 cm	10	37
>7 cm	1	4
Radiation treatment technique		
2-Fields (AP/PA)	20	74
3-Fields (PA + 2 Lat)	5	19
4-Fields (AP/PA + 2 Lat)	2	7
Dose/fraction		
1.8 Gy	93	7
2.0 Gy	2	7
Median treatment time (range), days	37 (30-49)	

Safety

Between October 1999 and May 2002, 3 patients were treated at each dose level of capecitabine: 700, 800, 900, 1000, 1100, and 1200 mg/m^2 twice daily. Eighteen patients received treatment without dose interruption.

Two patients on capecitabine 700 and 1000 mg/m^2 twice daily had grade 2 anemia and required blood transfusion during the treatment. One patient on capecitabine 900 mg/m^2 twice daily had grade 2 leukopenia at week 4 (whole pelvic irradiation 36 Gy in 20 fractions) and had to interrupt capecitabine for 4 days: she recovered to grade 1 before surgery. No patients developed neutropenia or thrombocytopenia.

Three patients had grade 2 diarrhea. One patient on capecitabine 900 mg/m^2 twice daily had grade 2 diarrhea during the rest period before surgery.

Two patients had grade 2 diarrhea at weeks 4 and 5, respectively, while receiving capecitabine 1100 mg/m^2 twice daily. They all recovered to grade 0 or 1 before surgery. Two patients had grade 2 dysuria: one on capecitabine 900 mg/m^2 twice daily at week 3 and another on capecitabine 1000 mg/m^2 twice daily at week 4. Both these patients had normal urinalysis. One patient had grade 2 hand-foot syndrome (HFS) on capecitabine 900 mg/m^2 twice daily at week 5: she received treatment with pyridoxine (vitamin B_6) and recovered to grade 1 before surgery.

As the authors did not find any severe adverse events during dose escalation, it was decided not to increase the dose of capecitabine but to enroll additional patients (3 patients at a time, to a total of 12) at the highest capecitabine dose level (1200 mg/m^2 twice daily) to be certain of the results. DLT should be observed in four or more patients in a 12-patient cohort to define the MTD.

Between June 2002 and January 2003, the authors enrolled an additional nine patients to receive capecitabine 1200 mg/m^2 twice daily with pelvic radiation. Three patients had grade 2 diarrhea on the last week of treatment and recovered to grade 0 before surgery. Two patients had grade 3 diarrhea. The first one had grade 3 diarrhea on day 31 (whole pelvic irradiation 41.4 Gy in 23 fractions) and discontinued treatment. She received supportive treatment until recovery within 1 month; however, the patient developed brain metastasis and did not undergo surgery. The second patient had grade 2 diarrhea on day 27 and discontinued capecitabine but continued radiotherapy. On day 29, her diarrhea progressed to grade 3 and treatment had to be discontinued (whole pelvic irradiation 37.8 Gy in 21 fractions). She received supportive treatment and recovered to grade 1 diarrhea within 13 days. She received further external beam irradiation to complete preoperative radiation (total dose of 45.6 Gy in 26 fractions); the total treatment time was 50 days. One patient had grade 2 dysuria with normal urinalysis at the end of treatment. One patient had grade 2 leukopenia at the end of treatment. Two patients had grade 2 leukopenia at week 5 and recovered to grade 0 before surgery. Two patients had grade 2 neutropenia at the end of treatment and recovered to grade 0 before surgery. Except for grade 3 diarrhea, there were no other grade 3/4 clinical or hematological/laboratory adverse events.

With respect to liver function evaluation, three patients had grade 1 (< 1.5 times the upper limit of normal [ULN]) and grade 2 (1.5-3x ULN) hyperbilirubinaemia. Neither of them had any symptoms nor other abnormal liver function tests. Two patients on capecitabine 1100 mg/m^2 twice daily had grade 1 and grade 2 hyperbilirubinaemia at week 4 and day 40, respectively, while one patient on capecitabine 1200 mg/m^2 twice daily had grade 1 hyperbilirubinaemia before surgery.

The maximum toxicity for all 27 patients is summarized in Table 2. Treatment-related grade 2-3 adverse events at each capecitabine dose level are summarized in Table 3.

The authors did not reach the MTD or find the DLT. To provide more information of the safety on the dose level of capecitabine 1200 mg/m^2 twice daily, the authors compared grade 2 adverse events at this capecitabine dose with those occurring at all lower capecitabine dose levels (Table 4). There was no statistically significant or apparent difference in adverse events comparing capecitabine doses < 1200 and 1200 mg/m^2 twice daily. In a similar manner, the authors compared grade 2 adverse events in patients with normal renal function (creatinine clearance > 80 ml/min, n = 11) and mild renal impairment (creatinine clearance

Table 2. Maximum toxicity per patient at each capecitabine dose level (n = 27)

Adverse event	No. of patients (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	14 (52)	6 (22)	2 (7)	0
Dysuria	17 (63)	3 (11)	0	0
Hand-foot syndrome	2 (8)	1 (4)	0	-
Radiation dermatitis	22 (81)	2 (7)	0	0
Anaemia	7 (26)	2 (7)	0	0
Leukocytopenia	12 (44)	3 (11)	0	0
Neutropenia	7 (26)	2 (7)	0	0

Table 3. Treatment-related grade 2/3 adverse events at each capecitabine dose level

Grade 2/3 adverse event*	Capecitabine dose level					
	700 mg/m^2 bid (n = 3)	800 mg/m^2 bid (n = 3)	900 mg/m^2 bid (n = 3)	1000 mg/m^2 bid (n = 3)	1100 mg/m^2 bid (n = 3)	1200 mg/m^2 bid (n = 12)
Diarrhoea	0	0	1	0	2	3 + 2*
Dysuria	0	0	1	1	0	1
Hand-foot syndrome	0	0	1	0	0	0
Radiation dermatitis	1	0	0	1	0	0
Anaemia	1	0	0	1	0	0
Leukocytopenia	0	0	1	0	0	2
Neutropenia	0	0	0	0	0	2

* All adverse haematological and non-haematological adverse events were grade 2 except for 2 patients with grade 3 diarrhoea

Table 4. Comparison of grade 2 adverse events at different capecitabine dose levels

Adverse event	Capecitabine dose level		p-value[1]
	< 1200 mg/m^2 bid (n = 15)	1200 mg/m^2 bid (n = 12)	
Clinical			
Diarrhoea[2]	3 (20%)	5 (42%)	0.3981
Dysuria	2 (13%)	1 (8%)	1.0000
Hand-foot syndrome	1 (7%)	0	1.0000
Radiation dermatitis	2 (13%)	0	0.4872

[1] Fisher's exact test (2-sided)
[2] Grade 2/3

51-80 ml/min, n = 12) (Table 5). Again, there was no apparent difference in the rate of adverse events comparing these subgroups of patients.

Clinical outcome

After concurrent chemoradiation, 24 of 27 patients (89%) underwent definite surgery (abdominoperineal resection, n = 17; low anterior resection, n = 7). Bypass surgery was performed in a patient with an unresectable tumor, who then received additional radiation (20 Gy in 10 fractions) to the primary tumor; this patient died 4 months later as a result of locoregional disease progression. One patient was unsuitable for surgery due to the development of liver and brain metastasis: he had palliative treatment and died 22 months later. Another patient refused surgery because of unwanted permanent colostomy and remained alive with disease for 20 months.

Capecitabine chemoradiation resulted in pathological tumor downstaging in 10 patients (42%) compared to pretreatment staging. Pathological complete response (pCR) occurred in one patient (4%) with partial response in nine patients (38%). Two patients had incomplete surgery with positive surgical margins and received additional postoperative radiation (16.2 Gy in 9 fractions and 20 Gy in 3 fractions, respectively). Two patients were found to have intra-abdominal metastasis during surgery: one had liver metastasis and the other had ovarian and omental metastasis. Two patients had peri-operative complications. One patient had perineal wound necrosis and had debridement with flap reposition. The other patient had perineal wound infection and a small bowel obstruction, which recovered with supportive treatment. One patient was found to have a rectovaginal fistula when the abdominoperineal resection was performed. A summary of treatment and response rates in patients who underwent surgery is given in Table 6.

For a median follow-up of 30 months (range 4-56 months), there were 16 patients (59%) alive without disease progression. Eleven patients had disease progression and eight of them died from their disease.

Table 5. Comparison of grade 2 adverse events in patients with normal renal function and mild renal impairment

Adverse event	Normal renal function[1] (n = 11)	Mild renal impairment[2] (n = 12)	p-value[3]
Clinical			
Diarrhoea[4]	2 (18%)	4 (33%)	0.6404
Dysuria	1 (9%)	1 (8%)	1.0000
Hand-foot syndrome	1 (9%)	0	0.4783
Radiation dermatitis	1 (9%)	0	0.4783

[1] Normal renal function = creatinine clearance >80 ml/min
[2] Mild renal impairment = creatinine clearance 51 80 ml/min
[3] Fisher's exact test (2-sided)
[4] Grade 2/3

Table 6. Treatment and response rate in patients undergoing definite surgery (n = 24)

	No. of patients	%
Median time from radiation to surgery (range), days	42 (34-62)	
Surgical procedure, no.		
Sphincter preserving surgery	7	26
Abdominoperineal resection	17	63
Median hospital stay (range), days	14 (9-50)	
Post-treatment tumour pathological staging		
0	1	4
I	6	22
II	8	30
III	7	26
IV	2	8
Pathologic response rate		
Complete response	1	4
Partial response	9	38

Table 7. Patient status at a median follow-up duration of 30 months

Patient status	Capecitabine dose level						
	700 mg/m^2 bid	800 mg/m^2 bid	900 mg/m^2 bid	1000 mg/m^2 bid	1100 mg/m^2 bid	1200 mg/m^2 bid	Total, n (%)
A-NED	3	3	1	1	1	7	16 (59)
AWD	0	0	0	1	0	2	3 (11)
DWD	0	0	2	1	2	3	8 (30)

A-NED = alive with no evidence of disease; AWD = alive with disease; DWD = dead with disease

One patient had a pathologically complete response and developed a late complication (vesicovaginal fistula at 11 months). The fistula was healed by supportive treatment. A summary of patient status is given in Table 7.

Discussion

Preoperative (neoadjuvant) chemoradiation has the potential advantage of increasing resectability and improving local control and survival in patients with LARC[14]. Explanations favoring preoperative

treatment are as follows: limiting the potential spread of cancer cells released during resection; increased resectability rate by reducing the size of the primary tumor and regional lymph nodes; and potential reduction in radiation enteritis because the small bowel is not fixed in the pelvis, and the well oxygenated cancer cells are more sensitive to radiation compared with those being left postoperatively. In addition, preoperative chemoradiation often allows patients to undergo more conservative sphincter-sparing surgery.

5-FU has been the most frequently used radiosensitiser for many years. The rationale for using infusional 5-FU instead of bolus administration is based on its short half-life (8-14 minutes in the blood), which suggested that the once-traditional schedule of bolus administration might not provide optimal tumor exposure to the drug[26]. In the postoperative setting, continuous infusion of 5-FU during pelvic radiation has proven to be an effective adjuvant therapy for LARC patients to prevent local recurrence[16]. However, protracted infusions of 5-FU are inconvenient for patients and are labor intensive for medical staff. Continuous administration of oral capecitabine mimics protracted infusion of 5-FU. Therefore, the present phase I study was performed to determine the DLT and the MTD of oral capecitabine in combination with preoperative radiotherapy.

The optimum dose of preoperative radiation has not been defined. Preoperative radiotherapy (25 Gy in 5 fractions in 1 week), as reported by the Swedish Rectal Cancer Trial (1997)[27], shows improved 5-year local control and survival compared with surgery alone. A short-term, high-dose regimen is suitable for tumors located higher than 8-9 cm from the anal verge, where anterior resection is the treatment of choice. For more distal lesions, a total dose of 45-50.8 Gy in 5-6 weeks is recommended to enhance the options for sphincter preservation. A study from the University of Kentucky used a preoperative radiation dose of 40-45 Gy in 4.5 weeks and demonstrated good results with 5-year survival and recurrence rates of 82% and 13%, respectively[28]. A study from MD Anderson Cancer Center used preoperative chemoradiation with a whole pelvic irradiation dose of 45 Gy in 25 fractions, which showed tumor downstaging in 62% and sphincter-preservation surgery in 59% of patients[10]. Following those studies, the authors used a conventional preoperative radiation dose of 45 Gy in 25 fractions in 5-6 weeks with concurrent chemotherapy to achieve local control and to improve the chances of sphincter preservation.

With escalated doses of oral capecitabine, ranging from 700 to 1200 mg/m^2 twice daily the authors did not reach the MTD. The main adverse event was grade 2 (22%) and grade 3 (8%) diarrhea, which is a recognized, acute side effect of whole pelvic irradiation and is related to treatment with 5-FU and capecitabine. This potential DLT appeared at a slightly higher incidence compared with other studies[29,30]. Most of the patients with grade 2 diarrhea had received the AP/PA opposing field technique, while the two patients with grade 3 diarrhea received capecitabine 1200 mg/m^2 twice daily were treated with a 3-field radiation technique. A few patients experienced grade 1/2 HFS, which is a well-known side effect of capecitabine that is rarely serious and never life-threatening[24]. One patient had serum bilirubin concentrations > 1.5x ULN but hyperbilirubinaemia is a known side effect of capecitabine and is rarely associated with clinical abnormalities. Other concurrent liver function test abnormalities are uncommon, suggesting that hyperbilirubinaemia is not associated with hepatobiliary dysfunction[24,25]. All other adverse events were mild.

Other phase I/II studies of preoperative capecitabine chemoradiation have been performed in patients with LARC. A phase I study by Dunst et al[29] from Germany recommended oral capecitabine 825 mg/m^2 twice daily with whole pelvic radiotherapy (50.4 Gy in 28 fractions in 6-7 weeks) as neoadjuvant treatment for LARC. The majority of patients in the present study received postoperative treatment. The DLT was HFS, occurring at a dose of capecitabine 1000 mg/m^2 twice daily. Another phase I trial from Australia[30] recommended oral capecitabine 900 mg/m^2 twice daily given 5 days (weekdays) every week through the period of radiotherapy (50.4 Gy in 28 fractions in 5.5 weeks). DLT (cystitis, skin reaction, diarrhea, and dehydration) was reached at a capecitabine dose level of 1000 mg/m^2 twice daily. Although the safety profile of capecitabine was similar in our study, the authors found less severe adverse events, possibly due to our radiation treatment schedule being shorter with a total whole pelvic radiation dose of 45 Gy in 25 fractions in 5 weeks without a 5.4-9 Gy boost at the primary tumor as in others studies and the total accumulated capecitabine dose being less. In the present study, most of the grade 2 adverse events occurred in the final week or at the end of treatment, so that it may have been possible to complete the treatment schedule before grade 3 adverse events developed. In addition, the fact that the presented patients were younger and only included those in the

preoperative setting could have rendered therapy more tolerable.

Another dose schedule of capecitabine chemoradiation has been investigated in a Korean study[31]. The authors used oral capecitabine 825 mg/m^2 plus LV 10 mg/m^2 twice daily orally for 14 days for 2 cycles with an intervening 7-day rest period in combination with whole pelvic irradiation (45 Gy in 25 fractions followed by a boost dose of 5.4 Gy in 3 fractions). Sphincter preservation was possible in 72% of patients with distal rectal cancer without delays in postoperative wound healing. Since LV does not appear to increase the efficacy of capecitabine and is associated with increased adverse effects[32], there has been little further interest in using the combination of capecitabine plus LV in preoperative chemoradiation therapy.

Preliminary results have recently become available from several phase II trials of preoperative capecitabine chemoradiation in LARC. In one phase II study, Dunst et al[33] used their recommended phase I regimen (capecitabine 825 mg/m^2 twice daily with whole pelvic radiotherapy). Interim analysis of 58 patients showed clinical complete or partial response in 61% of patients and downstaging in 74%. Interim results using the same dose of capecitabine (825 mg/m^2 twice daily) on a continuous daily outpatient basis as part of preoperative chemoradiation have also shown similarly high response and downstaging rates with only infrequent grade 3/4 adverse events during ongoing studies in the USA[34,35], China[36], France[37], Italy[38,39], and the Czech Republic[40]. The downstaging rate of 42% and pathologic overall response rate of 42% the authors achieved are promising, although it is important to note that the effectiveness of therapy in allowing sphincter-preserving surgery is dependent on many factors such as the size, depth of penetration, and distance of the tumor from the anal verge. In the present study, the rate of sphincter preservation is lower than the other studies. Forty-one percent of patients had tumor located $\geq$ 5 cm from the anal verge but only 26% underwent sphincter-sparing surgery. This might be because the limitation of the surgical procedure. Most of the study centers use the manual technique for the end-to-end anastomosis that made it difficult to have a distal margin < 3-5 cm. The other reason came from the lower total radiation dose to the primary tumor, since there was no radiation boost to the primary area after the whole pelvic irradiation.

There is currently no comparative trial data on capecitabine chemoradiation compared with continuous infusional 5-FU/LV-based regimens and a longer duration of follow up are required to confirm the benefits of capecitabine chemoradiation in terms of organ preservation and overall survival. However, in view of the promising results obtained thus far, the National Surgical Adjuvant Breast and Bowel Project (NSABP) is conducting a prospective randomized trial to compare oral capecitabine 825 mg/m^2 twice daily with infusional 5-FU/LV in patients receiving preoperative radiation for resectable stage II/III rectal cancer (45 Gy in 25 fractions plus 5.4 Gy boost for unfixed tumors or 10.8 Gy boost for fixed tumors). Results of this trial will define the future role of preoperative chemoradiation in patients with potentially operable LARC.

Preoperative capecitabine chemoradiation is well tolerated in patients with potentially resectable LARC. The authors did not reach the MTD using capecitabine doses up to 1200 mg/m^2 twice daily on a continuous daily basis in combination with whole pelvic irradiation (45 Gy in 25 fractions in 5-6 week). The results suggest that the diarrhea might be the DLT, although this could not be confirmed.

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การรักษาโรคมะเร็งไส้ตรง โดยการฉายรังสีรักษาก่อนการผ่าตัดร่วมกับการให้ยาเคมี ชนิด capecitabine (Phase I Trial)

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วัตถุประสงค์: *การศึกษาแบบ Phase I เพื่อรักษาโรคมะเร็งไส้ตรง โดยการฉายรังสีรักษาก่อนการผ่าตัดร่วมกับการให้ยาเคมีบำบัดชนิด capecitabine เพื่อศึกษาว่าขนาดยา capecitabine มีข้อจำกัดใด ๆ มีโอกาสเกิดผลแทรกซ้อนอย่างไร และให้ผลการรักษาเป็นอย่างไรบ้าง*

วัสดุและวิธีการ: *ผู้ป่วยโรคมะเร็งไส้ตรงจะได้รับการฉายรังสีรักษาที่บริเวณช่องเชิงกราน (ปริมาณรังสีรวม 45 Gy แบ่งให้ 25 ครั้ง ในเวลา 5-6 สัปดาห์) ร่วมกับยาเคมีบำบัดชนิด capecitabine (700, 800, 900, 1000, 1100 และ 1200 mg/m^2 โดยวิธีรับประทานวันละ 2 ครั้ง) โดยเริ่มจากผู้ป่วยกลุ่มละ 3 รายที่จะได้รับยา capecitabine ในระดับเดียวกัน ถ้าไม่เกิดผลแทรกซ้อนรุนแรง ก็จะเริ่มให้ยาในระดับที่สูงขึ้นต่อไป และเมื่อการรักษาเสร็จสิ้นแล้ว ผู้ป่วยจะได้รับการผ่าตัดหลังจากนั้นภายใน 6 สัปดาห์*

ผลการศึกษา: *มีผู้ป่วยโรคมะเร็งไส้ตรงจำนวน 27 ราย ได้รับการรักษาในการศึกษาครั้งนี้ ผู้ป่วย 18 รายแรก (ผู้ป่วยได้รับยา capecitabine ระดับละ 3 ราย) ไม่เกิดผลแทรกซ้อนรุนแรง จึงเพิ่มจำนวนผู้ป่วยอีก 9 ราย ซึ่งรวมมีผู้ป่วย 12 ราย ที่ได้รับยา capecitabine 1200 mg/m^2 โดยวิธีรับประทานวันละ 2 ครั้ง ซึ่งเป็นระดับยาที่สูงที่สุด พบว่ามีผู้ป่วย 2 ราย (ร้อยละ 16) ที่เกิดอาการท้องเสียรุนแรงจนต้องพักการรักษา เมื่อเสร็จสิ้นการรักษามีผู้ป่วย 24 ราย (ร้อยละ 89) ได้รับการผ่าตัด และผลการผ่าตัดพบมี 10 ราย (ร้อยละ 42) ที่โรคมีขนาดเล็กลง สามารถผ่าตัดโดยเก็บทวารหนักไว้ได้จำนวน 7 ราย (ร้อยละ 26) และผ่าตัดแบบ APR จำนวน 17 ราย (ร้อยละ 63)*

สรุป: *การรักษาโรคมะเร็งไส้ตรงโดยการฉายรังสีรักษาก่อนการผ่าตัด ร่วมกับการให้ยาเคมีบำบัดชนิด capecitabine จนถึงระดับสูงสุด (1200 mg/m^2 โดยวิธีรับประทานวันละ 2 ครั้ง) สามารถทำให้ก้อนมะเร็งยุบลงได้ และไม่พบผลแทรกซ้อนรุนแรงจากการรักษา*