Preoperative Chemoradiation for Locally Advanced Rectal Cancer with Capecitabine 2,000 mg/m^2/Day

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Objective: *Evaluate the efficacy and the tolerability of preoperative chemoradiation with high dose Capecitabine.*
Material and Method: *Fifteen patients with locally advanced resectable rectal cancer were treated with Capecitabine 2,000 mg/m2/day, orally 7 days/week concurrent with whole pelvic irradiation 45 Gy in 25 fractions/5 weeks. Patients underwent surgery in the following 4-6 weeks.*
Results: *After complete treatment, 11 patients (73%) underwent surgery. Ten patients (66%) had sphincter preservative surgery; three of them had primary tumors located in the lower rectum. Five patients had grade 2 and one patient had grade 3 diarrhea. No grade 4 toxicity was reported.*
Conclusion: *Preoperative Capecitabine 2,000 mg/m2/day concurrent with whole pelvic irradiation were effective and well tolerated. The potential dose limiting toxicity effect was the diarrhea.*

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

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Rectal cancer is one of ten most common cancers in Thailand, representing about 4% of all Thai cancer patients, and over 1,144 new cases are diagnosed annually[1]. The pre-operative chemoradiation treatment by using 5FU based regimen is the standard treatment for locally advanced resectable rectal cancer (LARC). The continuous infusion of 5FU throughout the period of radiotherapy has indicated a significantly improved overall and disease-free survival rate as compared with bolus administration of 5FU[2]. Therefore, the use of Capecitabine with radiotherapy as a radiosensitiser offers a promising, rational combination option for preoperative treatment in LARC.

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There were three published phase I trials of Capecitabine concurrent with whole pelvic irradiation. Two of them used the Capecitabine orally in two divided doses per day, 7 days a week, during the whole course of pelvic irradiation 50.4 Gy in 28 fractions. The first one was from Germany[3], and the maximum tolerance dose (MTD) of Capecitabine was 1,650 mg/m^2/day and the dose limiting toxicities (DLT) was hand-foot syndrome (HFS). The second trial was from Greece[4], and found the MTD of Capecitabine was 1,600 mg/m2/day and the DLT were HFS and diarrhea. The third study was from Australia[5], and they used Capecitabine only 5 days a week, Monday to Friday (On radiation treatment dates). They reported the MTD of Capecitabine was 1,800 mg/m2/day with the DLT were diarrhea and skin dermatitis.

These trials compared to phase I study[6] which did not reach the MTD by using Capecitabine dose up to 2,400 mg/m2/day, orally 7 day/week concurrent with

whole pelvic irradiation 45 Gy in 25 fractions. There were less severe adverse events, possible due to the shorter radiation schedule. Most of the grade 2 toxicities occurred in the last week or at the end of treatment. The results suggest that diarrhea might be the DLT since the authors found grade 2-3 diarrhea increase followed the Capecitabine dose higher than 2,000 mg/m^2/day compared to the dose less than or equal to 2,000 mg/m^2/day.

The summary of phase I trials of Capecitabine chemoradiation regimens in patients with LARC are shown in Table 1.

The objective of the presented was to evaluate the efficacy and the tolerable levels of the preoperative chemoradiation by using Capecitabine 2,000 mg/m^2/day concurrent with whole pelvic irradiation of 45 Gy in 25 fractions.

Material and Method

This was a phase II study of preoperative concurrent chemoradiation for LARC patients. The authors used Linear accelerator machine (10 MV) and the standard (3-field technique) whole pelvic irradiation 45 Gy in 25 fractions, given 5 days a week for 5-6 weeks with patients in the prone position with a full bladder to reduce volume of the small bowel in the treated area. This was done concurrently with Capecitabine 2,000 mg/m^2/day, oral in two divided doses, 7 days a week on an outpatient basis.

Eligibility criteria were LARC with histological proof of adenocarcinoma. Tumors were required to extend through the bowel wall and/or regional lymph nodes enlargement based on clinical, endoscopic rectal ultrasonography and/or radiographic evaluation. All patients had an Eastern Cooperative Oncology Group (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 and safety evaluations were performed at weeks 0, 2, 3, 4, 5, and at the end of chemoradiation and before surgery. Blood chemistry analysis was performed at weeks 0, at the end of chemoradiation and before surgery. 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 or low anterior resection 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.

The adjuvant chemotherapy was Leucovorin (LV) 20 mg/m^2/day, followed by 5-Fluorouracil (5FU) 425 mg/m^2/day, intravenous venous injection on day 1-5, and every 4 weeks for 4-6 cycles.

Results

From January 2001 to April 2003, 15 patients with newly diagnosed LARC were given pre-treatment staging by CT whole abdomen (n = 14, 93%), CT pelvis & abdominal ultrasonography (n = 1, 7%), endoscopic rectal ultrasonography (n = 9, 60%) and chest-x ray (n = 15, 100%). Baseline patient characteristics are shown in Table 2.

Table 1. Phase I studies of Capecitabine chemoradiation regimens in patients with locally advance rectal cancer

Study (phase I)	n	RT (Gy)	Capecitabine MTD (mg/m^2/d)	DLT	SP	DS	pCR
Dunst[3] 2002	36	50.4	1650 7 d/wk	HF-syndrome	-	90% (9/10)	11% (1/9)
Souglakos[4] 2003	31	50.4	1600 7 d/wk	Diarrhoea	-	-	-
Ngan[5] 2004	28	50.4	1800 M-F	HF-syndrome Diarrhoea	44%	54%	19%
Veerasarn[6] 2006	27	45.0	2400 7 d/wk	Skin dermatitis Diarrhoea	26%	42%	4%

RT = radiation dose, MTD = maximum tolerance dose, DLT = dose limiting toxicity, SP = sphincter preservation, DS = down staging, pCR = pathological complete response, HF-syndrome = hand-foot syndrome

Table 2. Patient characteristics

Patient characteristic	n (%)
Gender	
Male	6 (40)
Female	9 (60)
Age	
Median age (years)	56 (range 32-69)
Tumor histology: adenocarcinoma	
Well differentiated	2 (13%)
Moderately well differentiated	10 (67%)
Poorly differentiated	2 (13%)
Unknown	1 (7%)
Pre-treatment staging	
Stage IIA T3N0M0	11 (73%)
Stage IIIA T2N1M0	1 (7%)
Stage IIIB T3N1M0	2 (13%)
Stage IV T3N1M1*	1 (7%)

* Lung metastasis

For the preoperative chemoradiation, the mean total treatment time was 38 days (SD $\pm$ 5.3). Twelve patients completed treatment as planned. The treatment was modified in three patients. The first one discontinued the drug in the last week due to grade 2 leucocytopenia. The treatment of the second one was stopped temporality (both radiation and the drug) at week 4 due to grade 2 diarrhea for 7 days. The diarrhea was resolved to grade 1 and then the treatment restarted again. The treatment of the third one was stopped due to grade 3 diarrhea during the last week. He received a total radiation dose of 41.4 Gy in 23 fractions. The summarized results of the maximum treatment toxicities per person are shown in Table 3, in some cases more than one kind of toxicity occurred in a single patient.

After preoperative chemoradiation, four patients (27%) who had lesions located at lower rectum refused radical surgery because of unwanted permanent colostomy and 11 patients (73%) underwent surgery; sphincter preservative surgery (SP), n = 10 and abdomino-perineal resection (APR), n = 1. The mean time from end of chemoradiation to surgery was 54 days (SD $\pm$ 14.4). There were R0 resections. The pathological tumors were down staged in five patients (45%). Three patients had pathological primary tumor down staged, one patient had regional lymph nodes down staged, and one patient had both primary tumor & regional lymph nodes down staged.

One patient had the primary lesion located at the lower rectum, 5 cm from the anal verge. After preoperative chemoradiation, the lesion was a clinically complete response and the transanal biopsy was negative for malignancy. The patients refused the radical surgery. The surgeon did the wide excision and then the patient received the postoperative radiation.

One patient had peri-operative partial gut obstruction and required temporary ileostomy for 8 months.

The comparison of disease staging, the location of the tumor and the type of surgery is shown in Table 4. The clinical outcome is summarized in Table 5.

After radical surgery, the adjuvant chemotherapy by using 5FU/LV was given in seven patients. Four patients did not receive adjuvant chemotherapy. One patient developed brain metastasis shortly after surgery. Three patients refused adjuvant chemotherapy. The first one was the patient who had initial lung metastasis, and who refused the adjuvant chemotherapy because the lesion in the lung was stable after completing the preoperative treatment. The other two

Table 3. Summary of maximal treatment toxicity per person

Treatment toxicity	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Hematologic				
Hemoglobinemia	1 (7)	1 (7)	0	0
Leucocytopenia	4 (27)	3 (20)	0	0
Thrombocytopenia	0	0	0	0
Non-hematologic				
Diarrhea	9 (60)	5 (33)	1 (7)	0
Nausea/vomiting	0	1 (7)	1 (7)	0
Dysurea	1 (7)	1 (7)	0	0
Hand-foot syndrome	2 (13)	1 (7)	0	0
Skin (radiation port)	13 (87)	2 (13)	0	0

Table 4. Comparison of the pre-treatment staging, pathological staging, distance from anal verge and the type of surgery

No.	Pre-treatment staging	Pathlogical staging	Distance from anal verge (cm)	Type of surgery
1	T3N0M0*	-	3	-
2	T3N1M0	T2N0M0	3	Coloanal Anastomosis
3	T3N0M1	T2N1M1	10	LAR
4	T3N0M0	T3N0M0	7	LAR
5	T2N1M0	T3N0M0	5	LAR
6	T3N0M0*	-	3	-
7	T3N0M0	T3N0M0	10	LAR
8	T3N0M0	T3N0M0	4	APR
9	T3N0M0	T3N1M0	7	LAR
10	T3N0M0*	-	0	-
11	T3N0M0	T2N0M0	6	LAR
12	T3N0M0	T3N0M0	10	LAR
13	T3N1M0*	-	5	-
14	T3N0M0	T2N0M0	8	LAR
15	T3N0M0	T0NxM0	5	Wide Excision

* Refuse surgery, LAR = low anterior resection, APR = abdomino-perineal resection

Table 5. Summary of clinical outcome

Tumor location (distance from anal verge)	n	Type of surgery	
		SP	APR
Lower rectum (≤ 5 cm)	4	3	1
Mid rectum (6-8 cm)	3	3	-
Upper rectum (≥ 9 cm)	4	4	-

SP = sphincter preservative surgery, APR = abdomino-perineal resection

had pathological down staged of the disease to T2N0M0 and T0N0M0.

The median time to follow up was 36.9 months (range 3.2-59.3 months). Four patients (27%) remained alive without disease progression, 12 patients had disease progression and three of them died from the disease. Most of the disease relapses were distant metastasis without loco-regional recurrence. Five patients had lung metastasis, one had liver and lung metastasis, two had intraabdominal metastasis, one had brain metastasis, and the other one had bone metastasis.

Discussion

Preoperative chemoradiation using 5FU base regimen has the potential advantage of increasing resectability and improving local control in patients with LARC[7]. German phase II trials[8] used the MTD of Capecitabine 1,650 mg/m2/day, everyday during the whole pelvic irradiation 50.4 Gy in 28 fractions, which showed a high response and down-staging rate with only infrequent grade 3-4 adverse events. The study from Korea[9] and the one from Italy[10] showed the same treatment results. Compared to the presented study, the radiation dose was lower and the down-staging and the sphincter preservation rate were less frequent. The authors further plan to increase the radiation dose in order to compare the response rate and the grade 3-4 toxicity.

There was also the retrospective study from Korea[11] comparing the efficacy of bolus 5FU/LV with the Capecitabine. In 1993 -1999, they used two cycles of 5FU/LV for 5 days each, on the 1st and 5th week of whole pelvic irradiation. In addition, since 1999-2002, the chemotherapy regimen had changed to two cycles of Capecitabine 1,650 mg/m^2/day and LV 20 mg/m^2/day, for two weeks and was followed by one week rest period. The down-staging, sphincter preservation, and the pathological complete response rate were significantly higher in the Capecitabine group. The grade 3-4 toxicities were statistically more prevalent in the 5FU group. There was no phase III randomized trial comparing these two regimens and the authors need to wait for results from the prospective NSABP R-04 trial.

Comparing Capecitabine and bolus 5FU/LV (Mayo Clinic Regimen) in advanced colorectal cancer, Capecitabine demonstrated safety profiles superior to that of 5FU/LV, with a significant lower incidence of stomatitis and myelosuppression, but it slightly increased the rate of diarrhea. The hand-foot syndrome was the common toxicity of Capecitabine[12].

Capecitabine can be administered in the out-patient setting. The common dose of 1,650 mg/m^2 is given in two divided doses per day, every day for six weeks. When compared to the single agent regimen of 2,500 mg/m^2/day for two weeks followed by one week rest for two cycles, it is equivalent to the accumulative dose of 2,000 mg/m^2/day, everyday for five weeks as in the current study. The cumulative dose was equal to 70 gm/m^2. The common toxicities were diarrhea, hand-foot syndrome and skin dermatitis in radiation treatment area. As in current study, the potential DLT was diarrhea, since there were five patients who had grade 2 and one patient who had grade 3 toxicity. The

Table 6. Phase II studies of Capecitabine chemoradiation regimens in patients with locally advance rectal cancer

Study (phase II)	n	RT (Gy)	Chemotherapymg/m^2/day	Toxicity (Grade 3)	SP	DS	pCR
Dunst[8] 2004	63	50.4	Capecitabine1650, 7 d/wk	Diarrhoea 4% Leucocytopenia10%	-	73%	4%
Kim JC[9] 2005	95	50.0	Capecitabine1650, 7 d/wk	Diarrhoea 3% Leucocytopenia 1%	74%	76%	12%
De Paoli[10] 2006	53	50.4	Capecitabine1650, 7 d/wk	Diarrhoea 2% HF-syndrome 4% Leucocytopenia 4%	59%	57%	24%
Current study	15	45.0	Capecitabine2000, 7 d/wk	Diarrhoea 7%	67%	33%	7%
Kim JS[11] 2006	127	50.4	5FU 500/LV 20, wk 1 & 5	Diarrhoea 23% Leucocytopenia 8%	42%	70%	11%
	97	50.4	Capecitabine1650/LV 20, 14 D x 2	Diarrhoea 11% HF-syndrome 6%	67%	87%	22%

SP = sphincter preservation, DS = down staged, pCR = pathological complete response

incidence of hand-foot syndrome in the present study was very low. The authors could not explain the exact reason, but compared to the previously mentioned studies, the toxicities were not severe, because the radiation dose was lower than any of these other studies. The treatment was stopped before the severe grade 3-4 toxicity occurred.

The summary of phase II trials of Capecitabine chemoradiation regimens in patients with LARC are shown in Table 6.

Conclusion

Preoperative Capecitabine 2,000 mg/m^2/day concurrent with whole pelvic radiation 45 Gy in 25 fractions is well tolerated in patients with potentially resectable LARC. The treatment benefits were the down staged effect and the possibility of sphincter preservation for distal lesions. Both hematologic and non-hematologic toxicities were not increased. The results suggest that diarrhea might be the DLT. Finally, increasing the radiation dose to 50.4 Gy in 28 fractions to the primary lesion was recommended.

Acknowledgement

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References

1. Deerasamee S, Martin N, Sontipong S, Sriamporn S, Sriplung H. Cancer in Thailand. Vol. II, 1992-1994. IARC Technical Report No. 34. Lyon, France: International Agency for Research on Cancer; 1999.
2. O'Connell MJ, Martenson JA, Wieand HS, Krook JE, Macdonald JS, Haller DG, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 1994; 331: 502-7.
3. Dunst J, Reese T, Sutter T, Zuhlke H, Hinke A, Kolling-Schlebusch K, et al. Phase I trial evaluating the concurrent combination of radiotherapy and capecitabine in rectal cancer. J Clin Oncol 2002; 20: 3983-91.
4. Souglakos J, Androulakis N, Mavroudis D, Kourousis C, Kakolyris S, Vardakis N, et al. Multicenter dose-finding study of concurrent capecitabine and radiotherapy as adjuvant treatment for operable rectal cancer. Int J Radiat Oncol Biol Phys 2003; 56: 1284-7.
5. Ngan SY, Michael M, Mackay J, McKendrick J, Leong T, Lim JD, et al. A phase I trial of preoperative radiotherapy and capecitabine for locally advanced, potentially resectable rectal cancer. Br J Cancer 2004; 91: 1019-24.
6. Veerasarn V, Phromratanapongse P, Lorvidhaya V, Lertsanguansinchai P, Lertbutsayanukul C, Panichevaluk A, et al. Preoperative capecitabine with pelvic radiotherapy for locally advanced rectal cancer (phase I trial). J Med Assoc Thai 2006; 89: 1874-84.
7. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004; 351: 1731-40.
8. Dunst J, Reese T, Debus J, Hoelscher T, Budach W, Rudat V, et al. Phase-II-study of preoperative

chemoradiation with capecitabine in rectal cancer. ASCO Annual Meeting Proceedings (Post-Meeting Edition) J Clin Oncol 2004; 22(14 Suppl): 3559.
9. Kim JC, Kim TW, Kim JH, Yu CS, Kim HC, Chang HM, et al. Preoperative concurrent radiotherapy with capecitabine before total mesorectal excision in locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2005; 63: 346-53.
10. De Paoli A, Chiara S, Luppi G, Friso ML, Beretta GD, Del Prete S, et al. Capecitabine in combination with preoperative radiation therapy in locally advanced, resectable, rectal cancer: a multicentric phase II study. Ann Oncol 2006; 17: 246-51.
11. Kim JS, Kim JS, Cho MJ, Yoon WH, Song KS. Comparison of the efficacy of oral capecitabine versus bolus 5-FU in preoperative radiotherapy of locally advanced rectal cancer. J Korean Med Sci 2006; 21: 52-7.
12. Cassidy J, Twelves C, Van Cutsem E, Hoff P, Bajetta E, Boyer M, et al. First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. Ann Oncol 2002; 13: 566-75.

การรักษาโรคมะเร็งลำไส้ตรง โดยการฉายรังสีรักษาก่อนการผ่าตัดร่วมกับการให้ยาเคมีบำบัด ชนิด capecitabine 2,000 mg/m^2 ต่อวัน

วุฒิศิริ วีรสาร, วิรุณ บุญนุช, วิทูร ชินสว่างวัฒนกุล, ดรินทร์ โล่ห์สิริวัฒน์, ปราณี มหมัดซอและ

วัตถุประสงค์*: เพื่อศึกษาผลการรักษาและผลแทรกซ้อนของ การรักษาโรคมะเร็งลำไส้ตรงโดยวิธีการฉายรังสีรักษาก่อนการผ่าตัดร่วมกับการให้ยาเคมีบำบัดชนิด capecitabine ปริมาณยา 2,000 mg/m^2 ต่อวัน*

วัสดุและวิธีการ*: ผู้ป่วยโรคมะเร็งลำไส้ตรงจำนวน 15 ราย ได้รับการฉายรังสีรักษาบริเวณช่องเชิงกราน ปริมาณ รังสีรวม 45 Gy แบ่งให้ 25 ครั้ง ในเวลา 5 สัปดาห์ ร่วมกับการให้ยาเคมีบำบัดชนิด capecitabine ปริมาณยา 2,000 mg/m^2 ต่อวัน โดยแบ่งรับประทานวันละ 2 ครั้ง 7 วันต่อสัปดาห์ ตลอดระยะเวลาที่ได้รับรังสีรักษา เมื่อการรักษาเสร็จสิ้นแล้ว ผู้ป่วยจะได้รับการผ่าตัดภายในระยะเวลา 4-6 สัปดาห์*

ผลการศึกษา*: เมื่อการรักษาเสร็จสิ้นแล้ว ผู้ป่วย 11 ราย ได้รับการผ่าตัด ผู้ป่วย 10 ราย ได้รับการผ่าตัดแบบเก็บรักษากล้ามเนื้อหูรูดทวารหนักไว้ได้ ในจำนวนนี้ มีผู้ป่วย 3 ราย ที่มีโรคมะเร็งอยู่ที่บริเวณลำไส้ตรงส่วนปลาย มีผู้ป่วย 5 ราย ที่มีอาการท้องเสียระดับ 2 และมีผู้ป่วย 1 ราย ที่มีอาการท้องเสียระดับ 3 แต่ไม่มีผู้ใดมีอาการแทรกซ้อนใด ๆ รุนแรงถึงระดับ 4*

สรุป*: การรักษาโรคมะเร็งลำไส้ตรงโดยวิธีการฉายรังสีรักษาก่อนการผ่าตัดร่วมกับการให้ยาเคมีบำบัดชนิด capecitabine ปริมาณยา 2,000 mg/m^2 ต่อวัน เป็นวิธีการรักษาที่ได้ผล และผู้ป่วยสามารถทนการรักษาได้ อาการท้องเสียเป็นอาการแทรกซ้อนที่พบได้มากที่สุดจากการรักษาวิธีนี้*