Acute toxicities of concurrent chemoradiation with 5-fluorouracil versus capecitabine in locally advanced rectal cancer:

The Preliminary results of multicenter randomized control trial

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Abstract

Purpose: To compare the acute toxicities of concurrent chemoradiation (CCRT) with infusion 5-fluorouracil (5-FU) versus capecitabine in patients with locally advanced rectal cancer.

Materials and Methods: Between January 2015 and October 2015, 48 locally advanced rectal cancer patients from 7 radiotherapy centers in Thailand were randomized into 2 groups. The first group received infusion 5-FU chemotherapy (1,000 mg/m^2 days 1-5 and 29-33) during the course of radiation treatment while the other group received oral capecitabine (825 mg/m^2, twice daily, 5 days/week). The dose of whole pelvic radiation was 45-50.4 Gy. The acute toxicities during the course of treatment were recorded and compared.

Result: Forty-eight locally advanced rectal cancer patients were enrolled in the study, 21 patients were in 5-FU arm and 27 were in capecitabine arm. 47.9% were male and 52.1% were female with a median age of 59 years. Twenty- four patients were treated with preoperative CCRT and 24 patients with postoperative CCRT. No grade 3 or 4 dermatitis and genitourinary toxicities were observed. There were 83.3% of all patients

developed diarrhea; 90.4% were in 5-FU arm and 77.8% were in capecitabine arm (p= 0.215). Two patients in 5-FU arm had grade 3 diarrhea but none in capecitabine arm. Grade 1 or 2 hand-foot syndrome developed in capecitabine arm more than 5-FU arm, 22.2% versus 9.6% (p= 0.359). The incidence of grade 1 or 2 anemia was 23.8% and 11.1% in 5-FU and capecitabine arm, respectively (p=0.463). No grade 3 or more anemia and thrombocytopenia were observed. Three patients in 5-FU arm had Grade 3 or 4 leucopenia (14.3%), all of these developed febrile neutropenia, whereas none was observed in capecitabine arm. No treatment related death occurred in this study.

Conclusion: This preliminary report showed that the acute toxicities of CCRT with capecitabine in locally advanced rectal cancer are comparable to the standard infusion 5-FU.

Keywords: capecitabine, concurrent chemoradiation, rectal cancer, toxicity, 5-FU

Introduction

Concurrent chemoradiation has been utilized as a cornerstone of locally advanced rectal cancer treatment. It provides better local control, reduce tumor size which permits the feasibility of resection and ultimately improve overall outcome of treatment. In the past, the role of whole pelvic radiation combined with fluorouracil chemotherapy in rectal cancer was limited as an adjuvant postoperative situation in patient who had high risk feature for locoregional recurrent (stage T3, T4 or positive pelvic lymph node). German study group reported the significant better outcomes of preoperative CCRT compered with postoperative CCRT in terms of local control rate and toxicities[1,2] Since 2004, the role of CCRT in locally advanced rectal cancer has been shifted to preoperative setting.

Fluorouracil is one of the antimetabolite chemotherapeutic agents which inhibits thymidylate synthase enzyme resulting in DNA damage. Intravenous fluorouracil base chemotherapy has been a standard agent for concurrent with radiation in rectal cancer. At present, 5-FU has a number of different administrative forms which are converted into active metabolite in human body. Capecitabine is one of the oral forms of 5-FU which has been used in concurrently with radiotherapy for locally advanced rectal cancer. National Surgical Adjuvant Breast and Bowel Project (NSABP) R-04 study has been recently reported preoperative radiotherapy combined with capecitabine versus 5-FU in locally advanced rectal cancer and it showed the similar efficacy in terms of pathologic complete response rate (pCR), down-staging and sphincter preservation rate.[3] Moreover, it demonstrated about 26.6% and 25.6% of the patients had grade 3 to 5 acute toxicities in capecitabine and 5 -FU arms, respectively. Hofheinz and colleagues[4] conducted a randomized non-inferiority trial comparing CCRT with oral capecitabine to infusion 5-FU either preoperative or adjuvant postoperative CCRT in stage II-III locally advanced rectal cancer. The results demonstrated that capecitabine was non-inferior to infusion 5-FU, achieved similar overall survival and well-tolerated.

This was a preliminary result of multicenter randomized study evaluated and compared the acute

toxicities during course of CCRT either preoperative or adjuvant postoperative treatment in locally advanced rectal cancer using oral capecitabine versus infusion 5-FU.

Material and methods

This was a multicenter randomized study. It was approved by institutional ethic committee. All patients gave written informed consent before enrolling into the study. Between January 2015 and October 2015, 48 patients from 7 radiotherapy cancers treated with concurrent chemoradiation were enrolled into the study. Twenty-one patients were randomized into intravenous 5-FU arm and 27 patients into oral capecitabine arm.

Eligibility criteria

Locally advanced, non-distant metastatic rectal cancer patients with pathologically proven adenocarcinoma of rectum were included. Either preoperative or postoperative CCRT was allowed. For preoperative CCRT, clinical tumor stage of T3-4, N positive, M0 was recruited, these were investigated by abdominal CT scan, transrectal ultrasound or abdominal MRI. Postoperative CCRT, included patients who underwent low anterior resection (LAR) or abdominoperineal resection (APR), and pathologic T3- 4 or N1-2 stage were elibible. The age of patient was over 18 years with good performance status (ECOG 0-2) and adequate hematologic, renal and liver functions. No serious uncontrolled underlying disease such as cardiovascular, neurologic disease including human immunodeficiency disease.

Chemotherapy

Patients in capecitabine arm received oral capecitabine (INTACAPE, INTAS Pharmaceuticals Ltd.) dose of 825 mg/m^2 twice a day on the days of radiotherapy, 5 days per week during course of radiation and 5 doses of adjuvant single capecitabine 2500 mg/m2 days 1-14, repeated every 3 weeks after underwent radical resection. For postoperative situation, patients received 2 cycles of capecitabine dose 2,500 mg/m^2 before radiation and additional 3 cycles after CCRT. For intravenous infusion 5-FU arm, the dose of 1,000 mg/m^2 was given on days 1-5 and 29-33 during radiotherapy and received 4 cycles of bolus 5-FU 500 mg/m^2 (days1-5) every 4 weeks after surgery. For postoperative setting, patient received bolus 5-FU for 2 cycles before and after course of CCRT. Patient was admitted during the period of infusion 5-FU.

Whole pelvic radiotherapy (WPRT)

All techniques of standard WPRT for rectal cancer were allowed. For conventional technique, could be deliver by using two-field (anteroposterior field, AP-PA), three-field (posterior and 2-lateral fields) or four-field technique (AP-PA/2-lateral fields). The superior border was at the junction of L4-L5 spine, inferior border was below obturator foramen or cover 2-3 cm margin below lower end of primary tumor and the lateral border was 1.5 cm lateral to pelvic rim. The lateral pelvic field, anterior border was at posterior border of pubic symphysis for T3 stage or at anterior border of symphysis for T4 stage, the posterior border covered entire the sacral bone. For advanced three-dimensional conformal technique, the target volume included gross primary tumor and involved pelvic lymph node, entire mesorectum, internal iliac lymph node and presacral lymph node group (include external iliac lymph node group when patient had T4 stage, include inguinal lymph node when the primary tumor involved anal canal). The pelvic radiotherapy total dose of 45-50.4 Gy was delivered in conventional fractionation, five fractions per week over 5-6 weeks. Consider a boost dose of radiation if the resection margin was involved by cancer cells.

Toxicity

Physical examination and laboratory tests were assessed every 1 week during course of CCRT by radiation oncologists. The acute treatment related toxicities were scored and recorded based on Radiation Therapy Oncology Group (RTOG) criteria and the National Cancer Institute Common Toxicity Criteria (CTCAE) version 4.0.

Statistical analysis

The primary endpoint of this study was to compare the acute toxicities between 2 groups. The secondary endpoint was cost-effectiveness between the two regimens, which will be reported in the near future. The proportion of patients in each arm reporting each type of adverse toxicity experience was calculated. Differences in the severity of toxicities between groups were described as percentage and were compared using the Chi-square test or Fisher' exact test. A two-tailed p-value of less than 0.05 was defined as having statistical significance. Statistical analyses were performed using SPSS statistical software version 20.

Results

Between January 2015 and October 2015, forty-eight locally advanced rectal cancer patients from 7 radiotherapy centers in Thailand were enrolled. Twenty-one and 27 patients were randomly assigned to infusion 5-FU group and capecitabine groups, respectively. The median age of the patients was 59 years (26-86 years). The baseline patient characteristics were well balanced between 2 groups (Table 1). Numbers of patient treated with preoperative CCRT (N=24) and postoperative CCRT (N=24) were equal. All patients completed course of CCRT.

Regarding overall acute non-hematologic toxicities, diarrhea (83.3%) was the most frequent side effect, followed by skin reaction (45.8%), genitourinary (22.9%) and hand foot syndrome (1.7%).

There was no statistically difference in the incidence of all grade non-hematologic adverse events between the two groups (Table 2). Grade 1-2 diarrhea occurred more in 5-FU arm (80.9% versus 77.8%). Two patients in 5-FU arm (9.5%) had grade 3 diarrhea but none in capecitabine arm. Similarly,

Table 1 Baseline patient characteristics

	5- fluoriuracil arm (N=21)	Capecitebine arm (N=27)	p-value
Age (years)			0.387
- Median	57	59	
- Range	26-71	44-86	
Gender:			0.971
- Male	10	13	
- Female	11	14	
Treatment:			0.383
- Preoperative	9	15	
- Postoperative	12	12	
Tumor stage			
Preoperative			

	5- fluoriuracil arm (N=21)	Capecitebine arm (N=27)	p-value
- T3	8	14	0.656
- T4	1	1	
Postoperative			
- T1-2	0	1	
- T3	11	9	
- T4	1	2	
Nodal stage			0.844
Preoperative			
- N negative	3	5	
- N positive	6	10	
Postoperative			
- N0	7	4	
- N1	2	3	
- N2-3	3	4	
- NA	-	1	

patients in 5-FU arm had more incidence of mild grade dermatitis than in capecitabine arm (47.6% versus 44.4%). On the other hand, Grade 1 or 2 hand-foot syndrome developed more in capecitabine arm than 5-FU arm, 22.2% versus 9.6% (p= 0.359). Grade 1 or 2 of genitourinary adverse effect was also occurred in capecitabine arm more than in 5-FU arm, 25.9% versus 19.1%, p = 0.345 (Figure 1). No grade 3 or 4 dermatitis and genitourinary toxicities were observed in this study.

The acute hematologic toxicities during CCRT are shown in Table 3, 12 of 48 patients in this study (25%) experienced the acute hematologic toxicities. The incidence of grade 1- 2 anemia was 23.8% and 11.1% in 5-FU and capecitabine arm, respectively (p=0.463). No grade 3 or more anemia were observed in both group. Severe leucopenia occurred in 3 patients (14.3%) treated in 5-FU arm, two had grade 4 and the other had grade 3, whereas none occurred in capecitabine arm. Moreover, all patients in 5-FU arm who experienced severe leucopenia also developed febrile neutropenia. No thrombocytopenia occurred in our series. There was no treatment related death.

Discussion

Concurrent chemoradiotherapy plays an important role in rectal cancer treatment. Since the German CAO/ARO/AIO 94 trial[1] has reported the better locoregional control in preoperative compare

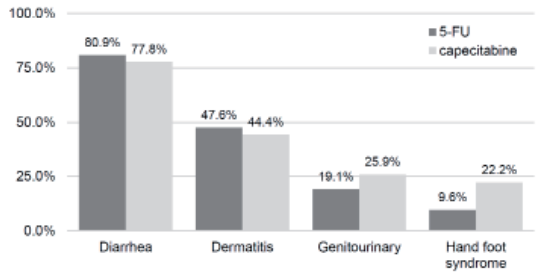

Figure 1 Grade 1-2 non-hematologic toxicities

Table 2 Acute non-hematologic toxicities

Toxicity	5- Fluorouracil arm (N=21)			Capecitabine arm (N=27)			p-value
	Grade 1	Grade 2	Grade 3-4	Grade 1	Grade 2	Grade 3-4	
Radiation dermatitis	7(33.3%)	3 (14.3%)	0	10 (37%)	2(7.4%)	0	0.739
Diarrhea	9 (42.8%)	8 (38.1%)	2 (9.5%)	14 (51.9%)	7 (25.9%)	0	0.215
Genitourinary symptoms	3 (14.3%)	1 (4.8%)	0	7 (25.9%)	0	0	0.345
Hand-foot syndrome	1 (4.8%)	1(4.8%)	0	5 (18.5%)	1 (3.7%)	0	0.359

Table 3 Acute hematologic toxiciies

Toxicity	5- Fluorouracil arm (N=21)			Capecitabine arm (N=27)			p-value
	Grade 1	Grade 2	Grade 3-4	Grade 1	Grade 2	Grade 3-4	
Hemoglobin	1	4	0	1	2	0	0.463
Leucopenia	0	1	3	0	0	0	0.132

with postoperative CCRT, the preoperative CCRT has become a preferable treatment. Fluorouracil chemotherapy is a standard agent using concurrently with radiotherapy in locally advanced rectal cancer treatment. Many retrospective and prospective studies used 5-FU either bolus or continuous infusion (CI) concurrently with radiotherapy in locally advanced rectal cancer.[5-9]. Treatment was well tolerated with severe grade 3 or more toxicities included diarrhea (5-20%), leucopenia or neutropenia (1.6-13%). Our study reported the incidences of severe grade 3 or 4 acute diarrhea 9.5% and leucopenia 14.3% in 5-FU CCRT arm. The results were difficult to compare due to many factors effected to the treatment related toxicity such as the radiation dose, dose of 5-FU or type of 5-FU administrated (infusion or bolus injection). A large number of phase II clinical trials of capecitabine CCRT as preoperative treatment for rectal cancer have been studied.[10-14] They found only 1-3% incidence of acute grade 3 or more hematologic toxicities and less than 10% of grade 3 to 4 acute non-hematologic toxicities

In this study, we used the same dosage of oral capecitabine is 825 mg/m^2 twice daily on the days of radiotherapy as in Ramani et al.[15], which had an excellence result. Their study reported low incidence of grade 3 acute toxicities included 4% for diarrhea and 1% for neutropenia, whereas the patients in capecitabine arm of our study had no grade 3 toxicity of diarrhea and neutropenia. As we know that the acute toxicities of patients who received postoperative radiotherapy would occur more frequently than preoperative radiotherapy, almost half of the patients in capecitabine arm in this series were treated with postoperative CCRT, the results of the acute toxicities either all grade or severe grade were comparable to other capecitabine with preoperative setting.

In this study, capecitabine arm shows comparable side effect to 5-FU arm. Severe diarrhea and

leucopenia occurred more often in 5-FU arm while hand foot reaction occurred more often in capecitabine arm. Nonetheless, all different results show no statistical significance. In contrast, the previous randomized non-inferiority study from German showed significant differences in acute toxicities in term of leucopenia which occurred more in 5-FU arm while capecitabine arm caused higher rates of hand foot reaction and fatigue[4]. A non statistically significant outcome in our study might result from a relatively small number of population.

In summary, based on the better safety profiles, this analysis shows that oral capecitabine can be a good alternative choice to infusion 5-FU in concurrent CCRT for patients with locally advanced rectal cancer.

Conclusion

This preliminary reported that the acute toxicities of concurrent chemoradiotherapy with capecitabine for locally advanced rectal cancer were comparable to the infusion 5-FU.

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