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Original Article

A Phase II Study of Preoperative Chemoradiotherapy with Capecitabine Plus Simvastatin in Patients with Locally Advanced Rectal Cancer

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Purpose The purpose of this phase II trial was to evaluate whether the addition of simvastatin, a synthetic 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, to preoperative chemoradiotherapy (CRT) with capecitabine confers a clinical benefit to patients with locally advanced rectal cancer (LARC).

Materials and Methods Patients with LARC (defined by clinical stage T3/4 and/or lymph node positivity) received preoperative radiation (45-50.4 Gy in 25-28 daily fractions) with concomitant capecitabine (825 mg/m^2 twice per day) and simvastatin (80 mg, daily). Curative surgery was planned 4-8 weeks after completion of the CRT regimen. The primary endpoint was pathologic complete response (pCR). The secondary endpoints included sphincter-sparing surgery, R0 resection, disease-free survival, overall survival, the pattern of failure, and toxicity.

Results Between October 2014 and July 2017, 61 patients were enrolled; 53 patients completed CRT regimen and underwent total mesorectal excision. The pCR rate was 18.9% (n=10) by per-protocol analysis. Sphincter-sparing surgery was performed in 51 patients (96.2%). R0 resection was achieved in 51 patients (96.2%). One patient experienced grade 3 liver enzyme elevation. No patient experienced additional toxicity caused by simvastatin.

Conclusion The combination of 80 mg simvastatin with CRT and capecitabine did not improve pCR in patients with LARC, although it did not increase toxicity.

Key words Rectal neoplasms, Simvastatin, Capecitabine, Preoperative chemoradiotherapy, Pathologic complete response

Introduction

Treatment of locally advanced rectal cancer (LARC) generally involves total mesorectal excision (TME), radiotherapy, and chemotherapy. The optimal combination and sequence of these treatments have been investigated in several randomized trials, and preoperative chemoradiotherapy (CRT) with 5-fluorouracil (5-FU) has been found to improve the pathologic complete response (pCR) rate, tumor downstaging, and locoregional control compared to preoperative radiotherapy alone or postoperative CRT [1-3]. In particular, infusional 5-FU is more effective than intermittent bolus 5-FU during radiotherapy [4]. Capecitabine, an oral fluoropyrimidine, was designed to mimic continuous 5-FU infusion and generate 5-FU preferentially in tumor tissues. Two studies demonstrated that capecitabine was non-inferior to 5-FU as a component of preoperative CRT in rectal cancer [5,6]. Accordingly, capecitabine-based preoperative CRT has become the standard treatment for LARC. The pathologic response to preoperative CRT is known to correlate with long-term clinical outcomes in patients receiving preoperative CRT for rectal cancer [7]. To improve pathologic tumor regression, the addition of other agents to CRT with 5-FU or capecitabine has been investigated; however, these did not improve pathologic response, but instead, increased toxicity [8,9].

Statins are commonly used as cholesterol-lowering agents to prevent and treat cardiovascular diseases with favorable safety profiles. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which catalyzes the conversion of HMG-CoA into mevalonate. This process is the rate-limiting step of the cholesterol biosynthetic pathway. In addition to cholesterol reduction, statins also prevent the production of mevalonate and downstream isoprenoids, including farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) [10]. FPP and GGPP, which are essential substrates for posttranscriptional modifications of Ras and Rho homolog gene family, member A (*RHOA*)

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genes. These genes play important roles in intracellular signal transduction involved in cell growth, proliferation, migration, and survival [10-12]. Based on the effect of statins on posttranscriptional modifications of *RAS* and *RHOA*, the antineoplastic effect of statins has been suggested for various cancers [13].

In our previous *in vitro* study, the addition of simvastatin to CRT with 5-FU showed a synergistic antineoplastic effect in various colon cancer cells [14]. Several preclinical studies reported that statin had a radiosensitizing effect on lung and breast cancer cells [15,16]. In addition, a retrospective clinical study suggested that statin use was associated with improved pathologic response to preoperative CRT in rectal cancer [17]. Moreover, our group has conducted clinical trials investigating the effects of chemotherapy plus simvastatin in colorectal cancer and showed that there was no additive toxicity [18,19]. Therefore, the purpose of this study was to investigate the synergistic effects and feasibility of simvastatin combined with capecitabine and preoperative radiotherapy in patients with LARC.

Materials and Methods

1. Study design and patients

This open-label, single-arm, prospective phase II trial was approved by the Institutional Review Board of the Samsung Medical Center (No. 2014-03-056). The trial was conducted in accordance with the principles of the Declaration of Helsinki. The patients provided written informed consent before enrollment in the study.

Eligible patients were histologically confirmed to have adenocarcinoma of the rectum and clinically diagnosed with T3 or T4 lesions, or regional lymph node involvement. Clinical staging was performed using rectal magnetic resonance imaging and chest and abdominopelvic computed tomography. Eligible patients were 20 years or older and presented with an Eastern Collaborative Oncology Group performance status of 0 to 1. All patients presented with no clinical evidence of distant metastasis and required adequate bone marrow function (absolute neutrophil count ≥ 1,500/mm^3 and platelet count ≥ 100,000/mm^3), liver function (total bilirubin levels < 1.5 times the upper limit of normal [ULN], transaminase levels < 2.5 times the ULN), and kidney function (creatinine clearance ≥ 50 mL/min or serum creatinine levels < 1.5 times the ULN).

Patients were excluded from the study if they had undergone prior statin therapy within 1 year from the date of study entry or creatine phosphokinase (CPK) levels more than five times the ULN at baseline. Patients with a history of other malignancies within the past 5 years, and previous chemotherapy or radiotherapy were also ineligible. Other exclusion criteria were severe comorbid disease, uncontrolled infection, and women who were pregnant or nursing.

2. Treatment

Capecitabine (825 mg/m^2) was administered orally twice a day, and simvastatin (80 mg) was administered orally once a day on days of irradiation concurrently with the radiotherapy. Radiotherapy was administered once a day at 1.8 Gy/fraction per day, 5 days per week (from Monday to Friday) for a total dose of 45-50.4 Gy in 25-28 fractions. Capecitabine was interrupted if grade 3 or 4 toxicity occurred (except for anemia) and restarted at a reduced dose of 75% when toxicity had resolved to grade 0 or 1. Simvastatin was discontinued if CPK levels increased to more than 5 times the ULN and restarted when CPK levels decreased to less than three times the ULN.

Curative surgery (especially TME, which was considered the first choice of surgery procedure) was performed 4-8 weeks after the completion of preoperative CRT. Postoperative chemotherapy was performed with four cycles of 5-FU and leucovorin, six cycles of capecitabine, or eight cycles of FOLFOX (5-FU, leucovorin, and oxaliplatin).

3. Efficacy assessment

Tumor staging of resected specimens was based on the TNM classification of the American Joint Committee on Cancer (7th edition). The pathological response to preoperative CRT was evaluated according to the Dworak tumor response grading system as follows: grade 0 (no response), grade 1 (minimal response: dominant tumor mass with obvious fibrosis, vasculopathy), grade 2 (moderate response: dominant fibrotic changes with a few easy-to-find tumor cells or groups), grade 3 (near-complete response: few microscopically difficult-to-find tumor cells in fibrotic tissue with or without mucous substance), and grade 4 (complete response: no tumor cells, only fibrotic mass or acellular mucin pools) [20].

pCR was prospectively defined as grade 4 according to the Dworak grading system. The secondary objectives were the rate of sphincter-sparing surgical procedure, rate of R0 resection, disease-free survival (DFS), overall survival (OS), pattern of failure, safety, and toxicity. R0 resection was defined as no evidence of tumor at the surgical margin macroscopically or microscopically. DFS was calculated from the day of study enrollment to the date of disease recurrence or death. OS was calculated from the day of study enrollment to the date of death or the last follow-up. Failure was defined as locoregional recurrence or distant metastasis. Safety was assessed by documenting adverse events graded using the National Cancer Institute Common Terminology Criteria for

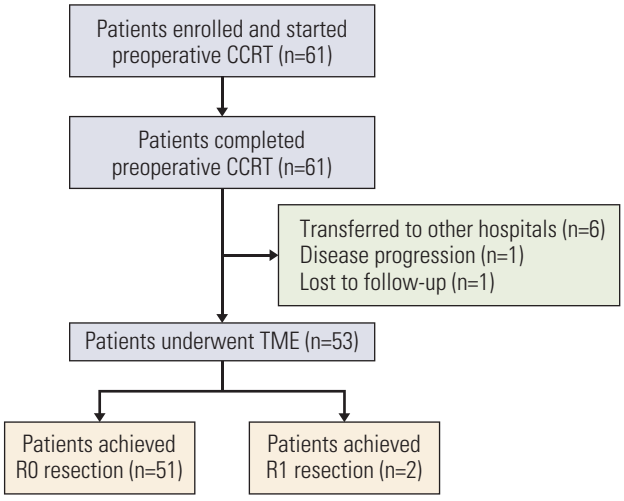

Fig. 1. CONSORT diagram. CCRT, concurrent chemoradiotherapy; TME, total mesorectal excision.

Adverse Events (ver. 4.0).

4. Statistical analysis

For this phase II study, a sample size of 55 was calculated as sufficient to accept the hypothesis that the pCR rate was greater than 30% and to reject the hypothesis that the pCR rate was less than 15% with a one-sided significance level of 0.1 and a power of 90% using Simon's two-stage phase II optimal design. The first stage required at least four out of 23 patients to have pCR before proceeding to the second stage. An additional 32 patients were to be enrolled; if 12 or more

Table 1. Basic characteristics

Characteristic	No. (%) (n=53)
Age, median (range, yr)	55 (31-76)
Sex	
Male	34 (64.2)
Female	19 (35.8)
ECOG PS (%)	
0	39 (73.6)
1	14 (26.4)
Clinical T category	
cT2	3 (5.7)
cT3	44 (83.0)
cT4	6 (11.3)
Clinical N category	
cN0	5 (9.4)
cN1-2	48 (90.6)
Distance from anal verge (cm)	
0-5	30 (56.6)
6-9	19 (35.8)
≥ 10	4 (7.5)
CEA, median (range, ng/mL)	1.94 (0.5-129.06)
CA 19-9, median (range, U/mL)	10.69 (1.2-152.91)
Tumor histology	
Well differentiated	22 (41.5)
Moderately differentiated	27 (50.9)
Poorly differentiated	2 (3.8)
Undifferentiated	2 (3.8)

CA, carbohydrate antigen; CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Acute adverse events in preoperative chemoradiotherapy by intent-to-treat analysis

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic toxicity				
Neutropenia	-	-	-	-
Anemia	-	-	-	-
Thrombocytopenia	3 (4.9)	-	-	-
Febrile neutropenia	-	-	-	-
Nonhematologic toxicity				
Nausea	13 (21.3)	-	-	-
Anorexia	8 (13.1)	-	-	-
Diarrhea	4 (6.6)	1 (1.6)	-	-
Constipation	2 (3.3)	-	-	-
Abdominal pain	2 (3.3)	3 (4.9)	-	-
Anal pain	1 (1.6)	-	-	-
Palmar-plantar erythrodysesthesia syndrome	7 (11.5)	-	-	-
Fatigue	3 (4.9)	-	-	-
Liver enzymes elevation	1 (1.6)	-	1 (1.6)	-

Values are presented as number (%).

of the 55 assessable patients experienced pCR, the treatment would be considered sufficiently active. Considering a drop-out rate of 10%, a total of 61 patients were needed. The analyses of baseline characteristics and efficacy were based on the per-protocol population. Demographic and baseline characteristics and adverse event data were summarized using descriptive statistics. DFS and OS were estimated using Kaplan-Meier survival curve. All statistical analyses were performed using SPSS for Windows ver. 27.0 (IBM Corp., Armonk, NY).

Results

1. Patient characteristics

Sixty-one patients were enrolled between October 2014 and July 2017 at the Samsung Medical Center. Among these 61 patients, 53 were assessable; eight patients who did not undergo surgery were excluded from the final analysis. Six patients were transferred to other hospitals for surgery. One patient was lost to follow-up, and pulmonary metastasis was occurred in one patient after preoperative CRT (Fig. 1). Baseline demographic and clinical characteristics of the per-protocol population are presented in Table 1. The median age was 55 years (range, 31 to 76 years), and 34 patients (64.2%) were men. Twenty-seven patients (50.9%) presented a moderately differentiated grade. Forty-four patients (83.0%) presented with clinical T3 tumors, and the majority of the patients (90.6%) presented with clinically regional nodal metastasis.

2. Preoperative CRT

All patients completed both chemotherapy and radiotherapy per protocol and received simvastatin without dose reduction. Grade 3 liver enzyme elevation occurred in one patient (1.6%) after the completion of preoperative CRT. There were no treatment-related deaths or grade 4 adverse events. Finally, none of the patients presented with simvastatin-induced myotoxicity or muscle enzyme elevation (Table 2).

3. Surgical outcomes

All 53 assessable patients underwent TME; 51 of which underwent sphincter-preserving surgery (96.2%) (Table 3). Temporary diversion ostomy was performed in 27 patients (50.9%). Combined resection of the adjacent organ (vagina) was performed in one patient (1.9%) who was pathologically confirmed with vaginal invasion and achieved R0 resection. Postoperative complications occurred in two patients (3.8%): wound discharge and ileostomy dehiscence.

Table 3. Pathologic characteristics

Characteristic	No. (%) (n=53)
Operative mode	
Low anterior resection	47 (88.7)
Abdominoperineal resection	2 (3.8)
Intersphincteric resection	4 (7.5)
Completeness of local tumor resection	
R0	51 (96.2)
R1	2 (3.8)
R2	0
Pathologic T category	
ypT0	10 (18.9)
ypT1	7 (13.2)
ypT2	12 (22.6)
ypT3	23 (43.4)
ypT4	1 (1.9)
Lymphatic invasion	
Yes	6 (11.3)
No	47 (88.7)
Vascular invasion	
Yes	2 (3.8)
No	51 (96.2)
No. of sampled lymph nodes, median (range)	12 (1-32)
Pathologic N category	
ypN0	40 (75.5)
ypN1	7 (13.2)
ypN2	6 (11.3)
Dworak grade	
G1	7 (13.2)
G2	25 (47.2)
G3	11 (20.8)
G4 (pCR)	10 (18.9)
Microsatellite instability status[a]	
MSI-high	0
MSI-low	2 (4.7)
MSI-stable	41 (95.3)

MSI, microsatellite instability; pCR, pathologic complete response. [a]Data are from 43 patients excluding 10 patients who achieved pCR.

Table 4. T category comparison at study entry and after surgery

Pretreatment	After surgery				
	ypT0	ypT1	ypT2	ypT3	ypT4
cT2	-	2	1	-	-
cT3	9	5	11	19	-
cT4	1	-	-	4	1
Downstaging	32 of 53 (60.4%)				

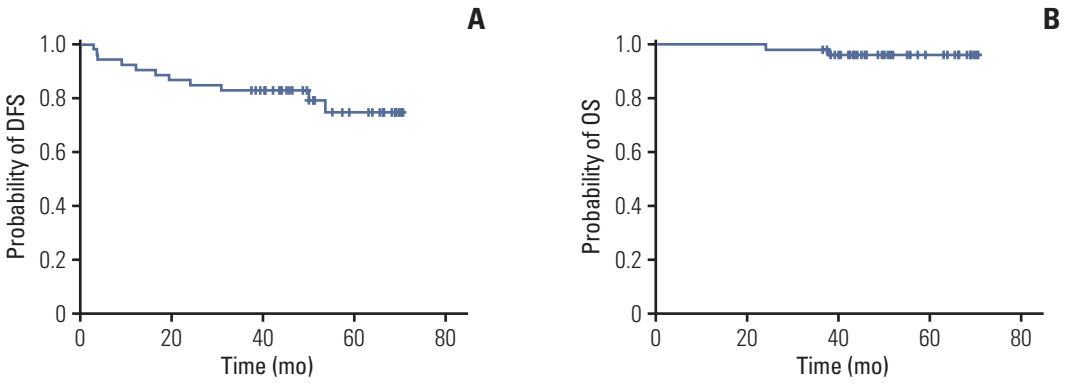

Fig. 2. Kaplan-Meier survival curve of disease-free survival (DFS) (A) and overall survival (OS) (B).

4. Pathologic responses

A total of 10 patients (18.9%) achieved pCR (Dworak grade 4), and 11 patients (20.8%) showed near-complete response (Dworak grade 3), whereas 25 (47.2%) and seven patients (13.2%) showed moderate (Dworak grade 2) and minimal (Dworak grade 1) responses to preoperative CRT, respectively, by per-protocol analysis. pCR rate by intent-to-treat analysis was 16.4%. The overall tumor downstaging rate was 60.4% (32 of 53) (Table 4). The median number of lymph nodes sampled was 12 (range, 1 to 32). R0 resection was achieved in 51 patients (96.2%).

5. Pattern of failure and survival analysis

The median follow-up duration was 46.3 months (range, 24.2 to 70.6 months). Ten of 53 patients (18.9%) experienced treatment failure: locoregional recurrence occurred in three patients (5.7%) and distant metastasis occurred in seven (13.2%). The distant metastatic sites included the lung (n=3), liver (n=2), abdominal lymph nodes (n=1), and peritoneal seeding (n=1). The median DFS and OS were not reached at the end of follow-up (Fig. 2).

Discussion

This is the first study to evaluate the efficacy and safety of simvastatin with preoperative CRT for LARC. This study showed that radiotherapy concurrent with capecitabine and simvastatin followed by TME for LARC resulted in a pCR in close to 20% of the treated patients. In addition, with the exception of two patients, all patients who received CRT underwent sphincter-sparing surgical procedures. In summary, the addition of simvastatin at a dose of 80 mg/day, which was within therapeutic dose range of hypercholesterolemia, did not increase the toxicity of preoperative CRT with capecitabine.

In LARC, pCR is a reliable surrogate marker for tumor response to preoperative CRT and reflects favorable clinical outcomes in terms of local control, distant metastasis, DFS, and OS [21]. In the current study, the primary endpoint was the pCR rate, and 18.9% (10/53) of the population treated according to the protocol achieved a pCR. However, several studies have also analyzed the prognostic significance of near-complete tumor responses. Consequently, near-complete tumor response is associated with a good prognosis [22,23]. In the present trial, a near-complete response (Dworak grade 3) was observed in 20.8% of patients (11/53); thus, a total of 39.5% of patients (21/53) showed a favorable pathologic response. Although this study did not satisfy the requirements for statistical significance, the pathologic response of this study showed promising results.

The anticancer effects of statins were found to depend on their blood concentration. To reach this serum concentration, simvastatin has to be administered at a dose of at least 1-2 mg/kg/day. Although our group used 40 mg/day of simvastatin in previous studies, this dose might be insufficient to achieve the concentration range with the anticancer effects. The safety of high doses of simvastatin should also be considered. The starting dose of simvastatin as a cardiovascular dose is 40 mg/day; however, 80 mg/day of simvastatin is permitted in patients at high risk for cardiovascular events. In addition, our previous clinical study in which 80 mg/day of simvastatin was combined with cetuximab and irinotecan in metastatic colorectal cancer showed the dose of simvastatin was well tolerated [24]. Therefore, 80 mg/day of simvastatin was used in this study.

Toxicity from the combination of simvastatin and capecitabine during radiotherapy was tolerable in this study, and there were no treatment-related mortalities. Moreover, there were no significant statin-associated side effects, such as elevation of CPK levels or myositis. Meanwhile, previous studies have shown that adding oxaliplatin to preoperative CRT

with 5-FU or capecitabine did not improve clinical outcomes but added significant toxicity [8,9].

The potential antineoplastic effects of statins have been investigated in preclinical and clinical settings. Numerous preclinical studies have suggested that statins exhibit antineoplastic effects in a variety of tumors by inhibiting tumor cell growth and angiogenesis, inducing apoptosis, and suppressing tumor metastasis [13]. However, clinical studies have provided conflicting data regarding whether statins specifically reduce the risk of cancer [25]. A phase III randomized controlled trial evaluated whether the addition of simvastatin to XELIRI (capecitabine plus irinotecan)/FOLFIRI chemotherapy confers a clinical benefit to patients with metastatic colorectal cancer in a second-line setting. This study showed that progression-free survival (PFS) was not improved by adding simvastatin to XELIRI/FOLFIRI compared with XELIRI/FOLFIRI alone in patients with previously treated metastatic colorectal cancer (median PFS, 5.9 months vs. 7.0 months; p=0.937) [19].

As not all patients benefit equally from statins as antineoplastic therapy, the development of predictive biomarkers of statins efficacy as anticancer agents has recently been researched. It has been reported that p53 loss and certain p53 mutations induce the expression of mevalonate pathway genes in cancer cells [26,27], and tumors harboring certain p53 mutations are vulnerable to statin therapy [27,28]. Our previous experimental study suggested that simvastatin might overcome cetuximab resistance in colorectal cancer cells harboring *KRAS* mutations [29]. In addition, the study postulated that simvastatin might potentiate the antitumor effects of radiation through induction of apoptosis, which could be associated with the downregulation of *BIRC5* and *CTGF* [14]. A recent study showed that statin could elicit effective antitumor immune responses by inducing immunogenic cell death as well as enhancing dendritic cell-mediated CD8+ T-cell immunity against *KRAS* mutant tumors [30]. Promising evidence suggests that certain molecular subtypes of cancers can potentially predict the efficacy of statins; however, further research is needed before these biomarkers can be used clinically.

In conclusion, this study did not demonstrate the effect of simvastatin in the patient with rectal cancer with preoperative CRT. However, simvastatin had many scientific backgrounds of anticancer effect and did not show additional toxicities. Moreover, statin could have beneficial effects on radiation-induced normal tissue damage [31]. Therefore, statin seems to be a drug of considerable merit. To investigate the optimal dose and schedule of statin, as well as efficient combination strategies in the treatment of rectal cancer patients a large-scale clinical study is needed in the future.

Ethical Statement

The protocol was approved by the Institutional Review Board of the Samsung Medical Center (No. 2014-03-056). The trial was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients. This trial was registered at clinicaltrials.gov (NCT02161822).

Author Contributions

Conceived and designed the analysis: Kang WK, Kim ST, Lee J, Park SH, Park JO, Park YS, Lim HY.
Collected the data: Jo H, Kang WK, Kim ST, Lee J, Park SH, Park JO, Park YS, Lim HY, Yu JI, Park HC, Choi DH, Park Y, Cho YB, Huh JW, Yun SH, Kim HC, Lee WY.
Contributed data or analysis tools: Kang WK, Kim ST, Lee J, Park SH, Park JO, Park YS, Lim HY, Yu JI, Park HC, Choi DH, Park Y, Cho YB, Huh JW, Yun SH, Kim HC, Lee WY.
Performed the analysis: Jo H, Kang WK.
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Conflicts of Interest

Simvastatin and capecitabine were provided by CJ Corp. and Roche, respectively. Neither company was involved in the collection or analysis of the data or in the preparation of the manuscript.

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