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ORIGINAL ARTICLE

Simvastatin plus irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) as first-line chemotherapy in metastatic colorectal patients: a multicenter phase II study

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Abstract
Background Simvastatin has demonstrated anti-tumor activity in preclinical studies via tumor cell senescence, anti-angiogenesis, and apoptosis. This phase II trial evaluated the efficacy and toxicity profile of conventional FOLFIRI chemotherapy plus simvastatin in metastatic colorectal cancer patients.
Methods Patients received irinotecan 180 mg/m^2 as a 90-min infusion followed by leucovorin 200 mg/m^2 in a 2-h infusion, and then 5-FU 400 mg/m^2 bolus injection followed by 2,400 mg/m^2 as a 46-h continuous infusion. Treatment cycles were repeated every 2 weeks until documented disease progression, unacceptable toxicity, or patient's refusal. Simvastatin 40 mg tablet was given once daily per oral everyday during the period of chemotherapy without a rest.
Results From October 2005 to June 2006, 49 patients were enrolled. The overall response rate (ORR) was 46.9% (95% CI, 31.0–58.8) by intent-to-treat analysis and 45.8% (95% CI, 33.3–62.8) by per-protocol analysis. There were one complete response (CR) and 22 partial responses (PRs). Both CR and PRs were confirmed at least 4 weeks later. The disease-control rate was 83.7% (95% CI, 73.4–94.0). The median follow-up duration was 25.6 months (range, 20.9–28.8 months). The median survival of all patients was 21.8 months (95% CI, 14.4, 29.2). The median TTP was 9.9 months (95% CI, 6.4, 13.3). No patients experienced additional adverse effect that was definitely caused by simvastatin drug therapy in this trial.
Conclusion The combination of simvastatin plus FOLFIRI was a feasible regimen with promising antitumor activity.

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Introduction

Statins are synthetic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors which are commonly used drugs for the treatment of hypercholesterolemia. Statins inhibit the rate-limiting step of the mevalonate pathway in which mevalonic acid is the precursor in the biosynthesis of isoprenoid molecules such as cholesterol, dolichol, and ubiquinone. Mevalonate-derived prenyl groups, farnesyl pyrophosphate (FPP), and geranylgeranyl pyrophosphate (GGPP), facilitate essential intracellular functions of various proteins such as Ras and Rho [6, 11, 25]. Notably, Ras protein is important in the regulation of cell differentiation and proliferation. Given that approximately 30% of the human tumors have a mutation of *k-Ras* oncogene, expression of this oncogene is thought to be related to aberrant cellular growth [4, 12]. Several studies demonstrated the role of geranylgeranylated Rho proteins in statin-induced anti-tumor effects, while the results on farnesylated Ras have been controversial [13, 34]. Lovastatin augmented 5-fluorouracil (5-FU)/cisplatin-induced apoptosis in four different colon cancer cell lines and decreased expression of the anti-apoptotic protein bcl-2 and increased expression of the pro-apoptotic protein bax [1]. Hence, statins may be a novel molecular targeted agent for cancer treatment with known safety owing to long-term experience as a lipid-lowering agent in cardiovascular disease.

Recently, its potential beneficial effect beyond lipid-lowering effect has been highlighted in several epidemiology studies. One of the landmark studies, the MECC (The Molecular Epidemiology of Colorectal Cancer) study, demonstrated that the use of statins for more than 5 years was associated with a 47% relative reduction in the risk of colorectal cancer after adjustment for other known risk factors such as age, sex, ethnic group, hypercholesterolemia, history of colorectal cancer in a first-degree relative and level of vegetable consumption [23]. Another population-based case control study showed a risk reduction of cancer by 20% [adjusted odds ratio (OR), 0.80; 95% CI, 0.66–0.96] in statin users when used longer than 4 years [12]. Although the results from these studies support the hypothesis that statins may reduce the risk of cancer, overall results from observational studies still remain inconclusive. There were no protective effects of statin use against lung, breast or colorectal cancer in two recently published large studies [27, 33].

Based on the observation that high-dose statins inhibit cellular proliferation and induce apoptosis of cancer cells, few clinical trials have investigated the antitumor activity of high-dose monotherapy, including ours, in solid tumors [17, 19, 31]. The monotherapy was precluded from further clinical use as an anti-cancer agent due to high toxicity profile and low response rate. However, our group has recently shown that a low dose lovastatin induced senescence and G1 cell cycle arrest in human prostate cancer cells [20].

Based on the observation of statin-induced cell senescence as well as synergism with 5-FU in preclinical studies, we designed a phase II study of conventional FOLFIRI chemotherapy plus a low-dose simvastatin that is equivalent to cardiovascular dose in metastatic colorectal cancer patients.

Patients and methods

Patient eligibility

Eligible patients were required to have histologically confirmed metastatic adenocarcinoma of the colon or rectum, at least one unidimensionally measurable lesion according to RECIST criteria, no previous chemotherapy or radiotherapy, age $\geq$ 18, an Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 2, a life expectancy of at least 3 months, adequate hematologic parameters (absolute neutrophil count $\geq$ 1,500/μl; platelet count $\geq$ 100,000/μl), renal function (creatinine clearance by Cockroft formula $\geq$ 50 ml/min or creatinine $\leq$ 1.5 mg/dl), and liver parameters [aspartate aminotransferase (AST), alanine aminotransferase (ALT) $\leq$3× the upper limits of normal (ULN), total bilirubin <2× ULN]. Patients, who received adjuvant chemotherapy more than 12 months from the date of study entry, were eligible for the study. Patients who were on statin therapy at the time of study entry were excluded. Patients with metastasis to the central nervous system, prior history of another malignancy within 5 years of study entry except for basal cell carcinoma of the skin or carcinoma in situ of the uterine cervix, were excluded from the study. All participants provided written informed consent before they entered the study, which was approved by the institutional review board.

Treatment

Patients received irinotecan 180 mg/m^2 diluted in 500 ml 5% dextrose as a 90-min infusion followed by leucovorin 200 mg/m^2 in a 2-h infusion, and then 5-FU 400 mg/m^2 bolus injection followed by 2,400 mg/m^2 as a 46-h continuous infusion. Treatment cycles were repeated every 2 weeks until evidence of disease progression, unacceptable toxicity, or patient's refusal. If continuation of chemotherapy was considered as the best interest of patient by the physician, maximum of up to 18 cycles was allowed. For emesis prophylaxis, 5-HT3 antagonists were given before chemotherapy. Atropine 0.25 mg subcutaneous was administered for prophylaxis of cholinergic syndrome. No prophylactic granulocyte colony-stimulating factors were recommended for neutropenia. Simvastatin 40 mg tablet

was given once daily per oral everyday during the period of chemotherapy without a rest. Simvastatin was stopped upon termination of FOLFIRI chemotherapy.

Administration of irinotecan or 5-FU was delayed as long as there was diarrhea or mucositis of CTC grade 1 or greater, neutropenia less than 1,500/μl, or thrombocytopenia less than 100,000/μl. The dose of irinotecan was reduced by 25% of the previous dose in case of CTC grade 3 or greater diarrhea. The doses of irinotecan 5-FU and were reduced by 25% of the previous dose in case of grade 3 or greater non-hematologic toxicity. If ANC was greater than 1,000/μl and platelet greater than 75,000/μl after a week delay, chemotherapy was administered without dose reductions. If ANC was less than 1,000/μl or platelet less than 75,000/μl after a week delay, chemotherapy was delayed for one additional week. If ANC was greater than 1,000/μl and platelet count greater than ≥75,000/μl following a 2-week delay from the planned date of chemotherapy, doses of irinotecan and 5-FU were reduced by 25%. If patients required a delay of longer than 2 weeks for recovery, patients went off the study protocol.

Efficacy assessment

The primary objective of the study was response rate and secondary objectives were toxicity, overall survival, and time-to progression (TTP). Pretreatment evaluation included history and physical examination, complete blood cell count with differentials, chemistry, CK, LDH, lipid profile, chest X-ray, computed tomography (CT) scan of abdomen and pelvis, and any other diagnostic procedures as clinically indicated. During treatment, a history taking, physical examination including toxicity assessment, complete blood cell count, and chemistry were performed every 2 weeks before each cycle. Appropriate imaging studies including abdominal and pelvis CT scan were performed every 6 weeks to evaluate treatment response, or sooner if needed for documentation of disease progression. Responses were to be confirmed by subsequent CT scans for 4–6 weeks after the initial response documentation. Patients were assessed for every 2–3 months for disease progression following the completion of the chemotherapy. Responses were classified according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria [30].

Patients who received at least one cycle of treatment were considered assessable for response and toxicity. TTP was calculated from the first day of treatment to the date on which disease progression was first documented or of the last follow-up. Overall survival was calculated from the first day of treatment to the date of death or last follow-up. Toxicity was monitored according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) scale version 3.0.

Statistical considerations

According to a Simon's two-stage phase II optimal design [28], a sample size of 44 was required to accept the hypothesis that the true response rate is greater than 35% with 90% power, and to reject the hypothesis that the response rate is less than 15% with 5% significance. At the first stage, if there were fewer than three responses out of the initial 19 patients, an early termination of the study was required. Assuming that 10% of patients were inassessable, a total of 49 patients were planned to be accrued for this study.

Descriptive statistics were reported as proportions and medians. Kaplan–Meier estimates were used in the analysis of time-to-event variable and the 95% confidence interval (CI) for the median time to event was computed. The dose intensity (DI) was calculated as the ratio of the total dose in milligrams per square meter of the patient, divided by the total treatment duration expressed in days. The relative DI was calculated as the ratio of the DI actually delivered to the DI planned by the protocol.

Results

Patient characteristics

From October 2005 to June 2006, 49 patients were enrolled. The baseline characteristics are summarized in Table 1. The median age was 55 years (range 24–72 years). Approximately two-thirds of the patient had recurrent disease after curative resection. All patients had adenocarcinoma and 65% had moderate differentiation in grade. Thirty-six (74%) had liver metastases, 18 lymph node metastases (37%) and 26 (53%) had 2 or more sites of metastases.

Treatment and drug delivery

In total, 461 cycles were administered with a median of 9 cycles per patient (range 1–18 cycles). The delivered relative dose intensities were 80.4% for irinotecan, 87.9% for 5-FU and 100% for simvastatin.

Response

Forty-eight (98.0%) of 49 patients were assessable for response. The overall response rate (ORR) was 46.9% (95% CI, 31.0–58.8) by intent-to-treat analysis and 45.8% (95% CI, 33.3–62.8) by per-protocol analysis. There were one complete response (CR) and 22 partial responses (PRs). All CRs and PRs were confirmed at least 4 weeks later. The

Table 1 Patient characteristics

	No. of patients	%
Patients	49	100
Age (years)		
Median	55	
Range	24–72	
Sex		
Male	40	81.6
Female	9	18.4
Performance		
ECOG, 0–1	48	98.0
ECOG, 2	1	2.0
Primary site		
Colon	32	65.3
Rectum	17	34.7
Prior surgery		
Curative resection	34	69.4
Palliative surgery	5	10.2
No surgery	10	20.4
Prior adjuvant chemotherapy or chemoradiation therapy	8	16.3
Histology of adenocarcinoma		
Well differentiated	3	6.1
Moderately differentiated	32	65.3
Poorly differentiated	6	12.2
Grade undetermined	8	16.3
Metastatic sites		
Liver	36	73.5
Lymph node	18	36.7
Lung	15	30.6
Other organs	3	6.1
No. of organs		
1	23	46.9
2	19	38.8
>2	7	14.3

ECOG Eastern Cooperative Oncology Group

disease-control rate was 83.7% (95% CI, 73.4–94.0). A total of 40 patients (82%) received a second-line treatment, including oxaliplatin-based chemotherapy ($n = 31$) and cetuximab/irinotecan chemotherapy ($n = 6$).

Survival

All patients were included in the survival analysis. The median follow-up duration was 25.6 months (range 20.9–28.8 months). The median survival of all patients was 21.8 months (95% CI, 14.4, 29.2) (Fig. 1) and the median TTP was 9.9 months (95% CI, 6.4, 13.3) (Fig. 2).

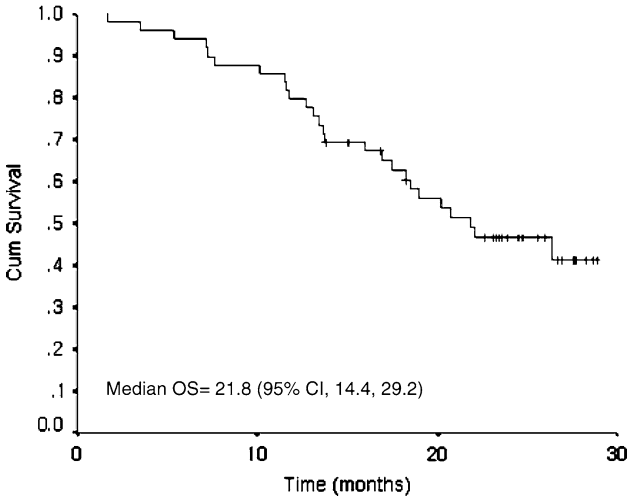

Fig. 1 Overall survival

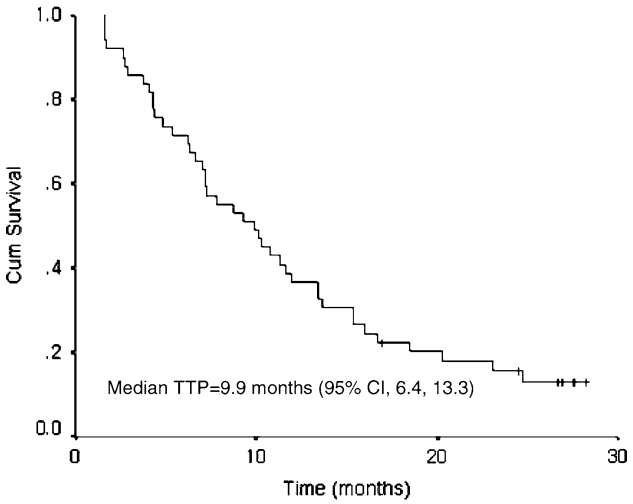

Fig. 2 Time to progression

Toxicity

All patients were assessable for safety. Toxicities observed during the study are listed in Table 2. The most common toxic effects were neutropenia and nausea. Approximately half of the patients experienced at least one episode of grade 1–4 neutropenia during their course of therapy with 8.2% ($n = 4$) grade 3 and 4.1% ($n = 2$) grade 4. Grade 3 or 4 neutropenia was 2.2% of all cycles administered ($n = 461$) with only 3 episodes of febrile neutropenia. There was no treatment related death or life-threatening neutropenic fever. Non-hematologic toxicities of grade 3 to 4 occurred in less than 1% of cycles. Grade 3 nausea occurred in 6.1% ($n = 3$) of patients and only one patient (2.0%) experienced grade 3 diarrhea. No patients had severe peripheral neuropathy requiring treatment interruptions. Mild liver enzyme

Table 2 Drug delivery

Drug delivery	
Total number of cycles administered	461
Number of cycles per patient	
Median	9
Range	1–18
Relative dose-intensity per patient	
Irinotecan (%, median)	80.4
5-Fluorouracil (%, median)	87.9

elevations were observed in only two patients (grade 1 or 2), which were eventually normalized. No patients were discontinued from the study due to toxicities. No patients seemed to experience additional adverse effect from simvastatin drug therapy such as myotoxicity or elevations in serum creatine phosphokinase (Table 3).

Discussion

The present study represents the first clinical trial to evaluate anti-tumor activity and safety profile of HMG CoA inhibitor in combination with conventional cytotoxic chemotherapy in solid tumor. The addition of low-dose simvastatin did not significantly increase the toxicity of conventional cytotoxic chemotherapy, FOLFIRI in colorectal cancer patients. Notably, a low-dose simvastatin seems to prolong TTP when combined with FOLFIRI chemotherapy.

The overall response rate of 46.9% (95% CI, 31.0–58.8) and median survival time of 21.9 months were comparable to other studies on FOLFIRI alone [8, 9, 32]. Given the fact that TTP is often considered as clinical index reflective of anti-tumor activity of cytostatic drug, it was of particular interest to observe modestly prolonged TTP [9.9 months (95% CI, 6.4–13.3)] in simvastatin/FOLFIRI combination when compared with FOLFIRI alone in other studies (range 6.7–8.5 months) [8, 9, 32]. The interpretation is clearly limited due to non-randomized nature of this study. The addition of low dose simvastatin did not significantly increase the toxicity of the FOLFIRI combination chemotherapy. The most common toxic effects were neutropenia and nausea, which were probably due to FOLFIRI regimen. Myotoxicity or elevation in serum creatine phosphokinase due to statin was not observed in this cohort of patients. Therefore, this combination regimen was very tolerable as anticipated.

One of the major obstacles in vigorous therapeutic application of statin as anti-tumor agent would be the requirement of very high concentrations of drugs to induce tumor cell apoptosis. In one study, 50 μM of statin was required to inhibit proliferation of MCF-7 breast cancer cells [26]. Other studies have also reported that 10–100 μM concentrations of statin were needed to effectively inhibit tumor cell growth in vitro [5]. A dose of 200 mg/kg/day would produce serum concentrations in the range of 2–20 μM, [7] whereas therapeutic dose for the treatment of hypercholesterolemia is 1 mg/kg/day with serum level of 0.1 μM [22]. There has been a report that levels of 20–25 μM were associated with progressive anorexia and death [18]. On other hand, several recent reports support the potential anti-tumor effect of low dose statin. Less than 1 μM lovastatin significantly attenuated colon cancer metastasis in vitro and

Table 3 Toxicity profile

Toxicity	Per cycle ($N = 461$)				Per patient ($N = 49$)			
	NCI-CTC grade (%)				NCI-CTC grade (%)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic toxicities								
Neutropenia	15 (3.3)	32 (6.9)	7 (1.5)	3 (0.7)	4 (8.2)	16 (32.7)	4 (8.2)	2 (4.1)
Febrile neutropenia	–	1 (0.2)	2 (0.4)	–	–	1(2.0)	1(2.0)	–
Thrombocytopenia	2 (0.2)	–	–	–	2 (4.1)	–	–	–
Non-hematologic toxicities								
Vomiting	85 (18.4)	31 (6.7)	3 (0.7)	–	25 (51.0)	17 (34.7)	3 (6.1)	–
Nausea	165 (35.8)	58 (12.6)	2 (0.4)	–	38 (77.6)	23 (46.9)	2 (4.1)	–
Diarrhea	36 (7.8)	10 (2.2)	2 (0.4)	–	19 (38.8)	7 (14.3)	1 (2.0)	–
Constipation	26 (5.6)	–	–	–	12 (24.5)	–	–	–
Stomatitis	53 (11.5)	9 (2.0)	–	–	16 (32.7)	5 (10.2)	–	–
Peripheral neuropathy	–				6 (12.2)	3 (6.1)	–	–
Elevated liver enzyme	1 (0.2)	1 (0.2)	–	–	1 (2.0)	1 (2.0)	–	–

NCI-CTC National Cancer Institute Common Toxicity Criteria

suggested a possible protective effect of statin against E-selectin mediated metastasis [21]. Our group along with others have demonstrated that nanomolar to 0.3 μM statin induced cell senescence or cytostatic effect of tumor cells [15, 20]. In addition, low concentrations of statins (i.e. therapeutic dose for hyperlipidemia) induced apoptosis of microvascular endothelial cells and lowered VEGF serum levels implicating a possible anti-angiogenic role in cancer treatment [2, 3, 10]. Hence, we hypothesized that the dose of statin administered in cardiovascular disease as lipid lowering agent may be combined with cytotoxic chemotherapy to render cytostatic effect via anti-angiogenesis or senescence of tumor cells.

The majority of irinotecan and its metabolites are excreted in the bile. The biliary excretion of SN-38, an active metabolite of irinotecan, is enhanced by the formation of SN-38 glucuronide (SN-38G), which is catalyzed primarily by the enzyme uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1) [14]. Of interest, simvastatin also undergoes lactonization via the glucuronidation pathway by UGT1A1 and 1A3 [24]. The pharmacokinetic parameters of the two drugs may be altered when administered concurrently which needs to be confirmed in future trials.

Recent biomarker analyses demonstrated that colorectal tumor bearing mutation K-ras did not benefit from cetuximab where as those with wild-type K-ras did benefit from cetuximab [16]. Thus, more effective therapy should be sought in subgroup of colorectal cancer patients with K-ras mutations which comprise of 42% of all tumors ($n = 394$) tested [16]. Lovastatin inhibited the growth of pancreatic cancer cells regardless of K-ras mutational status, suggesting that lovastatin inhibition of pancreatic cancer cell growth was not directly dependent on the presence of K-ras mutation [29]. Hence, the clinical benefit from simvastatin plus cytotoxic chemotherapy should be tested in colorectal cancer with K-ras mutation.

In summary, we report for the first time that the addition of simvastatin at the dose used in cardiovascular disease was feasible in terms of toxicity. Its effect on overall survival of metastatic colon cancer patients needs to be confirmed in phase III trial.

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