Cancer Chemother Pharmacol (2009) 64:953–960
DOI 10.1007/s00280-009-0947-3

ORIGINAL ARTICLE

Prostaglandin synthase 2/cyclooxygenase 2 (PTGS2/COX2) 8473T>C polymorphism associated with prognosis for patients with colorectal cancer treated with capecitabine and oxaliplatin

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Received: 2 November 2008 / Accepted: 23 January 2009 / Published online: 15 February 2009

Abstract
Purpose The present study analyzed the polymorphisms of apoptosis-related genes and their impact on the response to chemotherapy and survival of patients with colorectal cancer.
Patients and methods A total of 76 patients with recurrent or metastatic colorectal cancer treated with capecitabine and oxaliplatin (XELOX) combination chemotherapy were enrolled in the present study. The single nucleotide polymorphisms of 15 apoptosis-related genes (TP53, BCL2L, TNFRSF10B, AKT1, PTGS2/COX2, BID, RIPK1, FAS, FASL, caspase 3, and caspase 6-10) were determined using a PCR-RFLP assay.
Results No significant association between the polymorphisms and the response was found for any of the genes analyzed. However, the T/T genotype of PTGS2 8473T>C (rs5275) was significantly correlated with a better progression-free survival (PFS) and overall survival (OS) when compared to the combined T/C and C/C genotype (Hazard ratio [HR] = 0.47; P value = 0.046 and HR = 0.16; P = 0.013, respectively) in a multivariate analysis adjusted for age, sex, performance status, disease status and curative resection. No association was noted between the other polymorphisms and survival.
Conclusion The PTGS2 8473T>C polymorphism was found to be correlated with PFS and OS in patients with advanced colorectal cancer treated with XELOX chemotherapy.

Keywords Colorectal cancer · Chemotherapy · Biomarker · PTGS2 · Polymorphism

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Introduction

Infused 5-fluorouracil/leucovorin (FU/LV) in combination with oxaliplatin, a third generation platinum analog, has proven to be more effective than FU/LV alone in the treatment of metastatic colorectal cancer (MCRC) [1–3]. Capecitabine is an oral fluoropyrimidine that generates FU preferentially in tumor tissue by exploiting the increased expression of the enzyme thymidine phosphorylase in tumors [4, 5], and previous phase III studies have already shown that capecitabine can replace bolus FU/LV as a first-line therapy for MCRC [6–8] and in the adjuvant

setting [9], with the added benefits of improved safety and convenience. Capecitabine has also been combined successfully with oxaliplatin (XELOX) to produce an effective first-line regimen for MCRC, as demonstrated in phase II and III studies [10–12]. However, about 40–50% of patients exhibit an objective response to such treatment, with the remainder displaying varying levels of resistance [11, 12]. Yet, despite numerous efforts to identify suitable predictive markers, there is still a lack of accurate biomarkers to distinguish between patients likely to respond favorably and unfavorably to combination chemotherapy.

Apoptosis is a distinct mode of cell death that is responsible for the deletion of cells in normal tissues, and it also occurs in specific pathologic contexts. Apoptosis occurs spontaneously in malignant tumors, often markedly retarding their growth, and it is also increased in tumors responding to irradiation, cytotoxic chemotherapy, heating and hormone ablation [13]. Most anticancer agents, regardless of their distinct mechanisms of action, ultimately kill cancer cells by inducing apoptosis [13, 14]. Several studies have suggested that functional differences between polymorphic variants of apoptosis-related genes may alter their ability to bind components of the transcriptional machinery, activate transcription, induce apoptosis and repress the transformation of primary cells [15–17]. Furthermore, recent studies have demonstrated that polymorphisms of apoptosis-related genes, such as TP53 codon 72 and the GNAS1, are associated with the susceptibility or prognosis of solid tumors [18–21]. For example, Xu et al. [19] found the TP53 codon 72 polymorphism to be a strong predictor of the pathologic response to neoadjuvant chemotherapy in 110 patients with breast cancer, while Frey et al. [20] reported that the overall survival for stage I–II colorectal cancer was significantly higher with the GNAS1 T/T genotype than with the T/C and C/C genotypes, whereas the GNAS1 T393C polymorphism (C/C) was an independent marker of poor overall survival in the case of colorectal cancer. However, few studies have investigated the predictive or prognostic value of these important polymorphisms for palliative chemotherapy in patients with advanced colorectal cancer.

Accordingly, the present study analyzed the polymorphisms of apoptosis-related genes and their impact on the response to chemotherapy and survival of patients with MCRC treated with XELOX chemotherapy.

Patients and methods

Study population

All the tissues investigated in this study were obtained from consecutive patients with MCRC treated with XELOX chemotherapy as the first-line treatment at two medical centers in Daegu, Korea (Kyungpook National University Hospital and Daegu Catholic University Medical Center). The XELOX chemotherapy consisted of capecitabine (1,000 mg/m^2 b.i.d on days 1–14, followed by a 7-day rest period) and oxaliplatin (130 mg/m^2 i.v on day 1) based on a 3-week cycle. The chemotherapy continued until disease progression, patient refusal or an unacceptable toxicity. Written informed consent for gene expression analyses was received from the patients before enrollment, and the study was approved by the Institutional Research Board at Kyungpook National University Hospital. Tumors were measured every three cycles by computed tomography scan until the tumor progressed. The tumor responses were classified according to the response evaluation criteria in solid tumors (RECIST) guidelines [22]. Patients with a complete

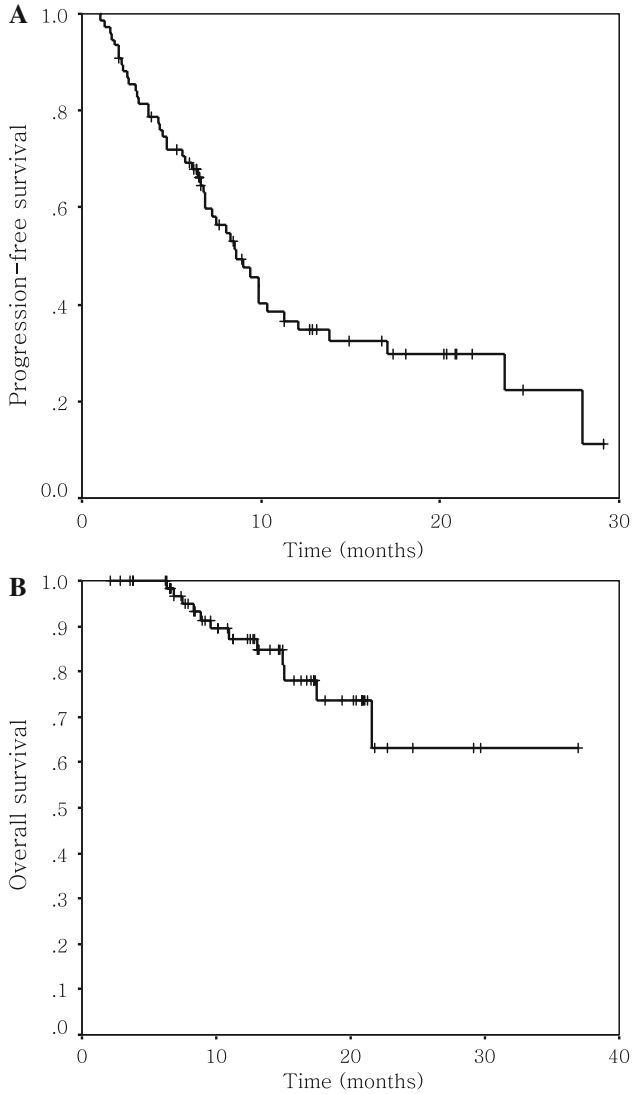

Fig. 1 Progression-free (**a**) and overall survival (**b**) curves for all patients

Table 1 Multivariate analysis of chemotherapy response and survival according to polymorphisms of apoptosis-related genes

Genotype	Frequency (%)	Response to chemotherapy *P value	Progression-free survival			Overall survival		
			HR	95% CI	**P value	HR	95% CI	**P value
TP53 (rs1042522)		0.215			0.425			0.940
G/G	19 (28.4)		1			1		
G/C	36 (53.7)		0.62	0.29–1.31	0.209	1.03	0.25–4.30	0.965
C/C	12 (17.6)		0.59	0.20–1.73	0.589	1.36	0.21–9.08	0.749
CASP6 (rs1042891)		0.673			0.370			0.832
C/C	13 (21.0)		1			1		
C/T	16 (25.8)		1.74	0.63–4.84	0.287	2.14	0.18–25.40	0.546
T/T	33 (53.2)		1.06	0.40–2.82	0.905	1.73	0.20–15.37	0.623
TNFRSF10B (rs1047266)		0.909			0.386			0.878
C/C	41 (63.1)		1			1		
C/T	22 (33.8)		0.75	0.37–1.52	0.430	0.72	0.21–2.53	0.609
T/T	2 (3.1)		2.21	0.44–11.13	0.338	–	–	0.989
CASP9 (rs1052571)		0.990			0.702			0.577
C/C	15 (20.8)		1			1		
C/T	36 (50.0)		0.91	0.40–2.05	0.818	0.83	0.16–4.50	0.833
T/T	21 (29.2)		1.24	0.51–3.05	0.634	1.76	0.31–10.09	0.524
AKT1 (rs1130233)		0.498			0.433			0.781
G/G	19 (28.4)		1			1		
G/A	37 (55.2)		0.86	0.45–2.05	0.907	1.23	0.24–6.16	0.804
A/A	11 (16.4)		1.71	0.63–4.67	0.293	2.08	0.24–17.90	0.505
FAS (rs1800682)		0.958			0.290			0.459
T/T	18 (25.7)		1			1		
T/C	42 (60.0)		1.51	0.68–3.37	0.311	0.82	0.18–3.62	0.790
C/C	10 (14.3)		2.36	0.81–6.90	0.116	2.48	0.41–14.86	0.320
BCL2 (rs1801018)		0.678			0.871			0.975
A/A	53 (82.8)		1			1		
A/G	10 (13.2)		10.77	0.26–2.29	0.632	1.23	0.20–7.58	0.822
G/G	1 (1.6)		1.19	0.15–9.59	0.871	–		0.990
CASP7 (rs2227310)		0.958			0.878			0.822
C/C	18 (27.7)		1			1		
C/G	35 (53.8)		1.18	0.55–2.53	0.670	1.66	0.33–8.52	0.541
G/G	12 (18.5)		0.96	0.38–2.58	0.975	1.28	0.18–9.41	0.806
RIPK1 (rs2272990)		0.201			0.621			
G/G	50 (70.4)		1			1		
G/A	20 (28.2)		0.70	0.34–1.43	0.329	1.62	0.48–5.51	0.441
A/A	1 (1.4)		–		0.980	–		
CASP6 (rs2301717)		0.496			0.344			0.290
G/G	30 (43.5)		1			1		
G/T	31 (44.9)		0.72	0.38–1.38	0.320	0.38	0.11–0.140	0.146
T/T	8 (11.6)		0.44	0.12–1.58	0.205	0.32	0.03–3.15	0.328
CASP3 (rs2705897)		0.255			0.441			0.752
G/G	1 (1.3)		–		0.980	–		
G/T	35 (55.6)		1.60	0.78–3.27	0.201	0.63	0.19–2.10	0.450
T/T	27 (42.9)		1			1		
CASP8 (rs3769818)		0.337			0.539			0.146
T/T	1 (1.3)		–		0.975	–		
T/C	37 (52.1)		0.71	0.38–1.30	0.266	0.25	0.06–1.00	0.052

Table 1 continued

Genotype	Frequency (%)	Response to chemotherapy *P value	Progression-free survival			Overall survival		
			HR	95% CI	**P value	HR	95% CI	**P value
C/C	33 (46.5)		1			1		
PTGS2 (rs5275)		0.472			0.038			0.040
T/T	55 (82.1)		1			1		
T/C	11 (16.4)		2.19	1.05–4.61	0.038	4.49	1.07–18.79	
C/C	1 (1.5)							
Dominant model for C alleles		0.472			0.046			0.013
T/T	55 (82.1)		1			1		
T/C + C/C	12 (17.9)		2.13	1.01–4.48		6.12	1.54–22.38	
FASLG (rs763110)		0.914			0.875			0.675
T/T	6 (7.9)		1			1		
T/C	26 (34.2)		0.76	0.25–2.37	0.638	1.05	0.10–11.42	0.968
C/C	41 (53.9)		0.86	0.29–2.60	0.791	0.60	0.06–6.13	0.665
BID (rs8190315)		0.544			0.297			
G/G	1 (1.4)		3.26	0.40–26.58	0.270	–	–	0.990
G/A	13 (18.1)		1.56	0.72–3.38	0.264	1.07	0.22–5.23	0.931
A/A	58 (80.6)		1			1		

HR hazard ratio, *CI* confidence interval

P values correspond to multivariate logistic regression (*) and Cox model (**) adjusted for age, sex, performance status, disease status and curative resection

response (CR) or partial response (PR) required a confirmatory disease assessment at least 4 weeks later.

Genotyping of apoptosis-related gene polymorphisms

The genomic DNA was extracted from paraffin-embedded tumor-bearing tissue using a Wizard genomic DNA purification kit (Promega, Madison, WI, USA). The single nucleotide polymorphisms (SNPs) of 15 apoptosis-related genes [TP53 (rs1042522), BCL2L (BCL2 ligand, rs1801018), TNFRSF10B (rs1047266), AKT1 (rs1130233), PTGS2/COX2 (rs5275), BID (rs8190315), RIPK1 (rs2272990), FAS (rs1800682), FASL (FAS ligand, rs763110), caspase 3 (rs2705897), caspase 6 (rs1042891, rs2301717), caspase 7 (rs2227310), caspase 8 (rs3769818), caspase 9 (rs1052571), and caspase 10 (rs13006529)] were then determined using a polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) assay. For quality control, the genotyping analysis was performed blind as regards the subjects. The selected PCR-amplified DNA samples ($n = 2$, for each genotype) were also examined by DNA sequencing to confirm the genotyping results.

Statistical analysis

The genotypes for each SNP were analyzed as a three-group categoric variable (referent model) and grouped according to the dominant and recessive model. The survival estimates were calculated using the Kaplan–Meier method. The differences in overall survival (OS) or progression-free survival (PFS) according to the apoptosis-related gene polymorphisms were compared using log-rank tests. For the multivariate analysis, a logistic regression model was applied to identify independent predictors associated with the response to chemotherapy, and Cox's proportional hazard regression model was used for the survival analyses. The analyses were always adjusted for age (<60 versus ≥60 years), sex (male versus female), performance status (ECOG 0 versus 1 or 2), disease status (metastatic versus recurrent), and curative resection (R0 versus R1/R2 or no resection). The hazard ratio (HR) and 95% confidence interval (CI) were also estimated. A cut-off *P* value of 0.05 was adopted for all the statistical analyses. The statistical data were obtained using an SPSS software package (SPSS 11.5 Inc. Chicago, IL, USA).

Results

Patient characteristics

From March 2005 to December 2007, a total of 76 patients were enrolled in the current study. The median age of the patients was 59.5 (range, 37–79) years, and 48 (63.2%)

patients were male. As much as 50 (65.8%) patients had a metastatic disease, while the others had a recurrent disease. Most of the patients (96.1%) had a good performance status (EGOG 0 or 1). The liver and lungs were the most common sites of the metastases. The median number of chemotherapy cycles was 8 (range, 2–12). Since 25 of the 76 patients had undergone a complete surgical resection before the chemotherapy, 51 patients were assessable for response. The responses to the chemotherapy were as follows: complete response ($n = 6$, 11.8%), partial response ($n = 20$, 39.2%), stable disease ($n = 12$, 23.5%), and progressive disease ($n = 13$, 25.5%). A total of 61 patients (80.3%) received irinotecan-containing second-line chemotherapy after disease progression. At the median follow-up duration of 13.1 (range, 2.1–36.19) months, the median PFS for all the patients was 8.6 (range, 6.3–10.9) months, while the median OS was not reached. The estimated 2-year PFS and OS rate was 22.3 ± 7.9 and 63.1 ± 11.7%, respectively (Fig. 1).

Genotype frequency and effects on response to chemotherapy

The frequencies of each genotype, as shown in Table 1, conformed to Hardy–Weinberg equilibrium ($P > 0.05$). In the logistic regression analysis, no significant association between the polymorphisms and the responses was found for any genes analyzed for the 51 patients assessable for response.

Genotype and survival analysis

The multivariate survival analysis showed that the PTGS2 8473T>C polymorphism was significantly associated with the PFS and OS. In the referent model, the estimated 2-year OS rate for the patients with the T/C genotype was 22.5 ± 8.5%, which was significantly lower than the rate for the patients with the T/T genotype (HR = 4.49; 95% CI, 1.07–18.79; P value = 0.038). In the dominant model for C allele, the PFS and OS were better for the patients with the T/T genotype than for the patients with the combined T/C and C/C genotype (PFS, HR = 0.47; 95% CI = 0.22–0.99; P value = 0.046, OS, HR = 0.16; 95% CI = 0.04–0.65; $P = 0.013$, Fig. 2). Meanwhile, no association was noted between the other polymorphisms and survival. For the clinical parameters, curative resection was also a significant prognostic factor in the Cox model for the PFS and OS ($P < 0.001$; Table 2).

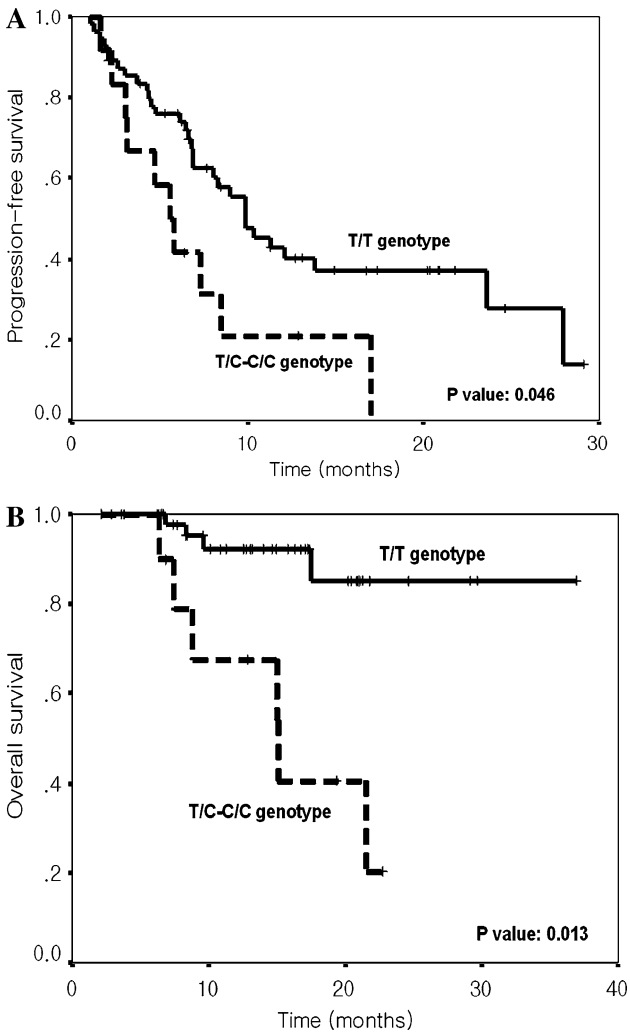

Fig. 2 Progression-free (**a**) and overall survival (**b**) curves according to PTGS2 8473T>C polymorphism in patients with advanced colorectal cancer. *P* values correspond to multivariate Cox model adjusted for age, sex, performance status, disease status and curative resection

Discussion

The prognostic impact of 15 apoptosis-related gene polymorphisms was investigated in patients with advanced colorectal adenocarcinoma treated with capecitabine and oxaliplatin chemotherapy. As a result, the PTGS2 8473T>C (rs5275) polymorphism was found to have a predictive effect on the survival of these patients.

In addition to its well-known role in inflammatory reactions, COX-2 plays a role in tumor progression, angiogenesis, metastasis and abrogation of the antitumor immune response [23–25]. COX-2 prevents apoptosis via the generation of antiapoptotic PGE_2 and PGI_2 and the removal of the proapoptotic substrate arachidonic acid [26–28]. The COX-2 gene, designated as PTGS2, carries a common T>C polymorphism at position 8473 in the 3′-untranslated region. Cok et al. [29] previously reported that the 3′-untranslated region of the murine COX-2 gene contains several regulatory elements altering mRNA stability and translational efficacy, suggesting that the polymorphism in the corresponding region of the human COX-2 gene could have a similar influence on COX-2 expression. Furthermore, Park

Table 2 Multivariate survival analysis including clinical parameters

Parameters	Frequency (%)	Progression-free survival			Overall survival		
		HR	95% CI	*P* value	HR	95% CI	*P* value
Age				0.459			0.938
≤60	42 (55.3)	1			1		
>60	34 (44.7)	0.79	0.39–1.59		0.95	0.24–3.78	
Disease status				0.957			0.391
Metastatic	50 (65.8)	1			1		
Recurrent	26(34.2)	1.02	0.54–2.06		0.49	0.10–2.50	
Curative (R0) resection				<0.001			0.385
No	45 (59.2)	1			1		
Yes	31 (40.8)	0.23	0.11–0.49		0.52	0.12–2.28	
PTGS2/COX2 (rs5275)	N = 67			0.046			0.013
T/T	55 (82.1)	0.47	0.22–0.99		0.16	0.04–0.65	
T/C + CC	12 (17.9)	1			1		

HR hazard ratio, *CI* confidence interval *P* values correspond to multivariate Cox model adjusted for age, sex, performance status, disease status and curative resection

et al. [30] also suggested that the 8473T>C polymorphism located within the functional region of 3′-UTR of the COX-2 gene may affect the message stability and/or translational efficiency, and so this results in differential COX-2 expression. Given these results, several studies have demonstrated that the PTGS2 gene polymorphism is associated with the risk of several solid tumors, such as breast [31], prostate [32], lung [33] and colorectal cancer [34]. However, no data has yet been published on the relationship between the PTGS2/COX2 gene polymorphism and the clinical outcomes of MCRC treated with chemotherapy.

In the present study, the PFS and OS were significantly better for patients with the T/T genotype of PTGS2 8473T>C than for patients with the combined T/C and C/C genotype (PFS; HR = 0.47, *P* value = 0.046, OS; HR = 0.16, *P* value = 0.013). In a previous study by Heer et al. [35], a high level of COX-2 expression after preoperative radiotherapy in resection specimens was associated with apoptosis resistance, high distant recurrence rates and a poor prognosis in 1,231 patients with rectal cancer, although COX-2 expression in colorectal cancer epithelial cells was not found to be related to the overall survival of patients with colorectal cancer who underwent surgical resection [36]. Smith et al. [37] also reported that COX-2 overexpression and reduced apoptosis in pretreatment biopsies were predictive of a poor response of rectal cancer to chemoradiotherapy. In a recent study by Langsenlehner et al. [31], which evaluated the role of the PTGS2 (COX-2) 8473T>C polymorphism on the risk of breast cancer, the homozygous PTGS2 8473 C/C genotype was found to be associated with an increased risk of breast cancer, and the expression of PTGS2 8473 C allele, associated with the increased risk of breast cancer, hypothesized to be higher than that of the "wild-type" 8473 T allele. Meanwhile, Cox et al. [34] reported that the polymorphisms in the PTGS2 gene may be associated with an increased risk of colorectal cancer. One possible explanation for these results is that the DNA sequence variations in the PTGS2 gene may alter COX-2 production and/or activity, thereby causing interindividual differences in carcinogenesis, apoptosis inhibition, angiogenesis and tumor cell metastasis.

In conclusion, the PTGS2 8473T>C polymorphism was found to be correlated with the PFS and OS in patients with advanced colorectal cancer treated with XELOX chemotherapy. However, further studies are warranted to clarify the role of apoptosis-related genes as a predictive or prognostic biomarker for colorectal cancer patients treated with chemotherapy.

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