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ORIGINAL ARTICLE

TP53 codon 72 polymorphism associated with prognosis in patients with advanced gastric cancer treated with paclitaxel and cisplatin

Jong Gwang Kim · Sang Kyun Sohn · Yee Soo Chae · Hong Suk Song · Ki-Young Kwon · Young Rok Do · Min Kyoung Kim · Kyung Hee Lee · Myung Soo Hyun · Won Sik Lee · Chang-Hak Sohn · Joo Seop Jung · Gab Chul Kim · Ho Young Chung · Wansik Yu

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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 advanced gastric cancer.
Patients and methods Fifty-seven patients with advanced gastric cancer treated with paclitaxel and cisplatin combination chemotherapy were enrolled in the present study. The genomic DNA was extracted from paraffin-embedded tissue, and the single nucleotide polymorphisms (SNPs) of ten apoptosis-related genes [LTA, TP53, BCL2L11, BID, FASL, caspase 3, caspase 6, caspase 7, and caspase 9] determined using a polymerase chain reaction–restriction fragment length polymorphism assay.
Results The Arg/Pro and Pro/Pro genotypes of TP53 codon 72 were significantly correlated with a lower response rate to the combination chemotherapy when compared to the Arg/Arg genotype (35.7 vs. 66.7%, *P*-value 0.019) in a logistic regression analysis. A multivariate survival analysis also showed that the time to progression for the patients with the Arg/Pro and Pro/Pro genotypes of TP53 codon 72 was worse than for the patients with the Arg/Arg genotype (Hazard ratio = 3.056, *P*-value = 0.047), whereas the overall survival was not significantly different.
Conclusion The TP53 codon 72 SNP was found to be predictive of the response to chemotherapy and correlate with the time to progression in patients with advanced gastric cancer treated with paclitaxel and cisplatin chemotherapy.

Keywords Gastric cancer · Chemotherapy · TP53 · Polymorphism

J. G. Kim (✉) · S. K. Sohn · Y. S. Chae
Department of Oncology/Hematology,
Kyungpook National University Hospital,
Kyungpook National University School of Medicine,
Daegu, South Korea
e-mail: jkk21c@knu.ac.kr

H. S. Song · K.-Y. Kwon · Y. R. Do
Department of Hematooncology,
Dongsan Medical Center,
Keimyung University School of Medicine,
Daegu, South Korea

M. K. Kim · K. H. Lee · M. S. Hyun
Department of Oncology/Hematology,
Yeungnam University Hospital, Daegu, South Korea

W. S. Lee
Department of Oncology/Hematology,
Daegu Fatima Hospital, Daegu, South Korea

C.-H. Sohn
Department of Oncology/Hematology,
Inje University Hospital, Busan, South Korea

J. S. Jung
Department of Oncology/Hematology,
Pusan National University Hospital, Pusan, South Korea

G. C. Kim
Department of Radiology,
Kyungpook National University Hospital,
Kyungpook National University School of Medicine,
Daegu, South Korea

H. Y. Chung · W. Yu
Department of General Surgery,
Kyungpook National University Hospital,
Kyungpook National University School of Medicine,
Daegu, South Korea

Introduction

Although the prognosis for advanced gastric cancer remains poor, combination chemotherapy has been found to improve the quality of life and overall survival (OS) when compared with the best supportive care in several randomized studies [1–3]. Among the various active chemotherapeutic agents, cisplatin-based combination chemotherapy is most commonly used with a high response rate of 37–56% [4–7]. Meanwhile, several clinical studies have shown that paclitaxel, which effectively blocks cancer cells in the G2/M phase through the inhibition of microtubular depolymerization, is also active against advanced gastric cancer [8–12], where about 40% of patients exhibit a clinical response to such treatment, with the remainder displaying varying levels of resistance [8–10]. Despite numerous efforts to identify suitable predictive markers, there is still a lack of accurate biomarkers to discriminate between patients who are likely to respond to combination chemotherapy and those who are not.

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 the polymorphic variants in apoptosis-related genes may alter the 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 MDM2 promoter, are associated with the susceptibility or prognosis of solid tumors [18–21]. For example, Xu et al. [18] reported that the TP52 codon 72 polymorphism was a strong predictor of the pathologic response to neoadjuvant chemotherapy in 110 patients with breast cancer, while Ohmiya et al. [19] reported that the overall risk of gastric carcinoma with the MDM2 single nucleotide polymorphism (SNP) 309 (G/G) was significantly increased when compared with T carriers, and that SNP309 (G/G) was an independent marker of poor OS in the case of advanced gastric carcinoma. However, few studies have investigated the predictive or prognostic value of these important polymorphisms for palliative chemotherapy in patients with advanced gastric 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 advanced gastric cancer.

Patients and methods

Study population

All the tissues investigated in this study were obtained from gastric cancer patients who had enrolled in two clinical studies using paclitaxel and cisplatin chemotherapy [11, 12]. 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 (Daegu, Korea). The tumor responses were classified according to the response evaluation criteria in solid tumors (RECIST) guidelines [22].

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 SNPs of ten apoptosis-related genes [LTA (lymphotoxin alpha, rs1041981), TP53 (rs1042522), BCL2L11 (rs724710), BID (rs8190315), FASL (FAS ligand, rs763110), caspase 3 (rs12108427), caspase 6 (rs1042891, rs2301717), caspase 7 (rs2227310), and caspase 9 (rs4645978)] were then determined using a polymerase chain reaction (PCR)–restriction fragment length polymorphism 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 OS or progression-free survival (PFS) according to the apoptosis-related gene polymorphisms were compared using log-rank tests. In 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 years vs. ≥60 years), sex (male vs. female), performance status (ECOG 0 vs. 1 or 2), and disease status (metastatic vs. recurrent). 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

Among 91 patients from two clinical studies, 57 patients with available specimens were enrolled in the present study. The median age of the patients was 55 (range 24–75) years, and 43 (75.4%) patients were male. Forty-four (77.2%) patients had a metastatic disease, while the others had a recurrent disease. Most of the patients (96.5%) had a good performance status (EGOG 0 or 1). The responses to the combination chemotherapy were as follows: complete response ($n = 2$, 3.5%), partial response ($n = 22$, 38.6%), stable disease ($n = 19$, 33.3%), and progressive disease ($n = 14$, 24.6%). At the median follow-up duration of 8.6 (range 1.8–13.8) months, the median time to progression and OS for all the patients was 4.9 (range 2.2–7.5) months and 10.8 (range 6.9–14.7) months, respectively, plus the estimated 1-year OS rate was 18.4 ± 7.7%.

Genotype frequency and effects on response to chemotherapy

The frequencies of each genotype, as shown in Table 1, were conformed to a Hardy–Weinberg equilibrium ($P > 0.05$). Since the genotypes for caspase 3 were all C/C, caspase 3 was excluded from the analysis. The logistic regression analysis showed that the TP53 codon 72 and caspase 6 polymorphisms were independent predictive factors for the response to chemotherapy. For the TP53 codon 72 polymorphisms, the Arg/Pro and Pro/Pro genotypes were significantly correlated with a lower response rate to the combination chemotherapy when compared to the Arg/Arg genotype (35.7% for Arg/Pro and Pro/Pro genotypes vs. 66.7% for Arg/Arg genotype, *P*-value 0.019). Meanwhile, the caspase + 14543C/C genotype was associated with a higher response rate when compared to the T/T genotype (54.5% for C/C genotype vs. 26.9% for T/T genotype, *P*-value 0.044).

Genotype and survival analysis

The multivariate survival analysis also showed that the TP53 codon 72 polymorphism was significantly associated with the time to progression. In the referent model, the time to progression for the patients with the Pro/Pro genotype was worse than for the patients with the Arg/Arg genotype (HR = 6.26, 95% CI 1.52–25.87, *P*-value = 0.011, Fig. 1). In the dominant mode for Pro allele, the estimated 1-year PFS rate for the patients with the Arg/Pro and Pro/Pro genotypes was 17.5 ± 8.7%, which was significantly lower than the rate for the patients with the Arg/Arg genotype (HR = 3.06, 95% CI 1.02–9.19; *P*-value = 0.047, Fig. 2), However, the OS was not significantly different. Meanwhile, no association was noted between the other polymorphisms and survival. For the clinical parameters, the performance status was also a significant prognostic factor in the Cox model for the time to progression and OS ($P < 0.001$).

Discussion

The prognostic impact of ten apoptosis-related gene polymorphisms was investigated in patients with advanced gastric adenocarcinoma treated with paclitaxel and cisplatin chemotherapy. As a result, the TP53 codon 72 polymorphism was found to have a predictive effect on the response to chemotherapy or time to progression in these patients.

Several studies have already suggested that the TP53 codon 72 polymorphism significantly modulates the p53-dependent apoptotic capacity [16, 22, 24]. The Arg72 form of wild-type p53 is at least five times more efficient in apoptosis induction than the Pro72 form, which is presumed to be related to the increased localization of the Arg72 form of p53 in the mitochondria when compared with the Pro72 form [16]. Given these results, recent studies have also demonstrated that the TP53 codon 72 polymorphism is associated with the risk or prognosis of several solid tumors, such as breast [18, 25], gastric [20], lung [21], and ovarian cancer [26]. However, data on the relationship between the TP53 codon 72 polymorphism and the clinical outcomes of advanced gastric cancer treated with chemotherapy have not yet been published.

In the present study, the time to progression for the patients with the Arg/Pro and Pro/Pro genotypes of TP53 codon 72 was significantly worse than for the patients with the Arg/Arg genotype (HR = 3.056, *P*-value = 0.047). Although the OS curves according to the TP53 codon 72 polymorphism showed a similar trend to the time to progression curves, it was statistically not significant. This may have been due to different kinds of second-line chemotherapy or the relatively small sample size in the current study. Nonetheless, the present results were in accordance with a recent finding for advanced head and neck carcinoma, where patients carrying the Pro/Pro genotype of wild-type TP53 were found to be less sensitive to cisplatin-based chemotherapy and displayed a poorer clinical outcome than patients with either the Arg/Arg or Arg/Pro genotype [24]. In another study by Xu et al. [18] that evaluated the effect of

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

Genotype	Frequency (%)	Response to chemotherapy (P-value[a])	Time to progression		Overall survival	
			HR	P-value[b]	HR	P-value[b]
LTA (+264C > A)	$n = 51$	NS		NS		NS
C/C	8 (15.7)		1		1	
C/A	40 (78.4)		0.884		8.096	
A/A	3 (5.9)		0.312		2.424	
TP53 (+11445Arg > Pro)	$n = 52$	0.036		0.040		
Arg/Arg	9 (17.3)		1		1	
Arg/Pro	33 (63.5)		2.580	0.099	1.394	
Pro/Pro	10 (19.2)		6.264	0.011	2.429	
Dominant model for Pro alleles		0.019		0.047		0.379
Arg/Arg	9 (17.3)		1		1	
Arg/Pro-Pro/Pro	43 (82.7)		3.056		1.666	
BCL2L11 (+26381C > T)	$n = 57$	NS		NS		NS
C/C	39 (68.4)		1		1	
C/T	8 (14.0)		0.631		0.928	
T/T	10 (17.5)		0.656		1.021	
BID (+30494A > G)	$n = 53$	NS		NS		NS
A/A	45 (84.9)		1		1	
A/G	7 (13.2)		0.492		0.388	
G/G	1 (1.9)		11.871		10.774	
FASL (−687C > T)	$n = 53$	0.060		NS		NS
C/C	41 (77.4)		1		1	
C/T	7 (13.2)		0.365		0.900	
T/T	5 (9.4)		3.038		0.491	
Caspase 6 (+14543C > T)	$n = 51$	0.044		NS		NS
C/C	11 (21.6)		1		1	
C/T	13 (25.5)		0.508		0.337	
T/T	27 (52.9)		0.953		0.316	
Caspase 6 (+5095G > T)	$n = 49$	NS		NS		NS
G/G	21 (42.9)		1		1	
G/T	23 (46.9)		1.332		0.535	
T/T	5 (10.2)		0.335		0.416	
Caspase 7 (+49726C > G)	$n = 55$	NS		NS		NS
C/C	8 (14.6)		1		1	
C/G	35 (63.6)		0.652		1.170	
G/G	12 (21.8)		1.049		0.663	
Caspase 9 (−693C > T)	$n = 49$	NS		NS		NS
C/C	7 (14.3)		1		1	
C/T	25 (51.0)		1.530		0.977	
T/T	17 (34.7)		1.655		0.932	

HR hazard ratio, *NS* not significant

[a] P-values correspond to multivariate logistic regression adjusted for age, sex, performance status, and status of disease

[b] P-values correspond to Cox model adjusted for age, sex, performance status, and status of disease

the TP codon 72 polymorphism on the response to neoadjuvant chemotherapy in 110 primary breast cancer patients, the response to anthracycline-based chemotherapy was lower among patients with the Pro/Pro genotype and higher among patients with the Pro/Arg or Arg/Arg genotype. Although the frequency of TP53 mutation was higher in tumors with the Arg/Arg variant [27], they suggested that the resistance to chemotherapy in the Pro/Pro tumors was

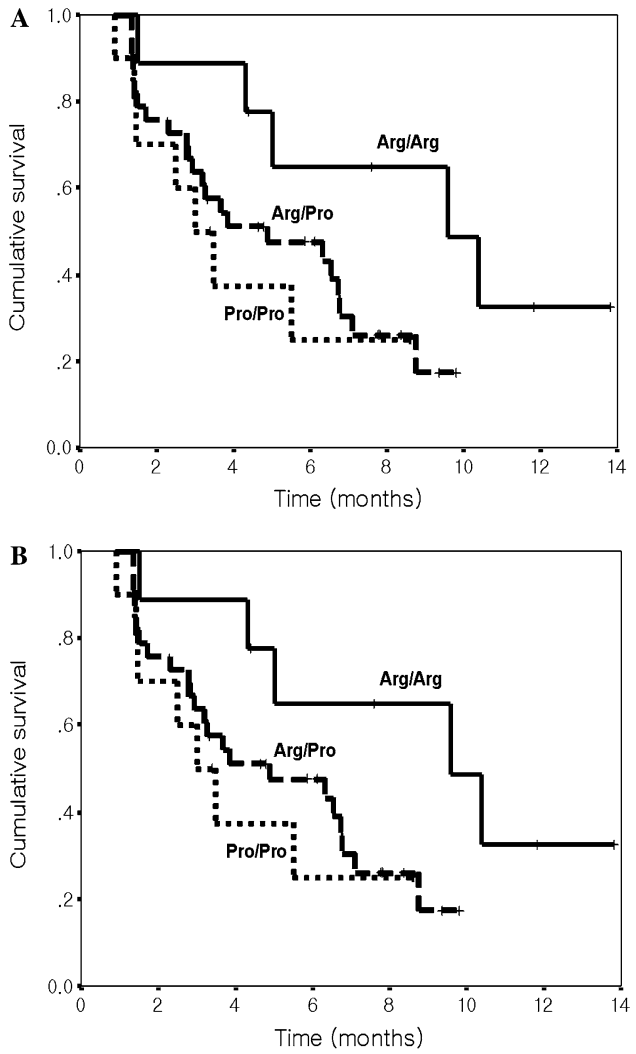

Fig. 1 Time to progression (**a**) and overall survival (**b**) curves according to the referent model of TP53 codon 72 polymorphism in patients with advanced gastric cancer (**a** $P = 0.011$, **b** $P = 0.345$). *P*-values correspond to multivariate Cox model adjusted for age, sex, performance status, and status of disease

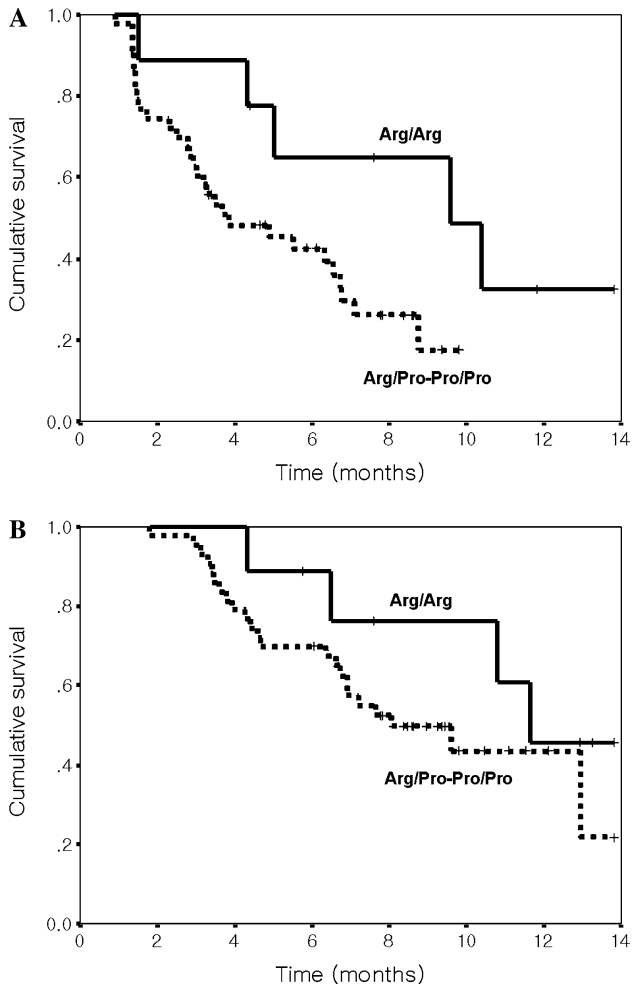

Fig. 2 Time to progression (**a**) and overall survival (**b**) curves according to the dominant model for Pro allele of TP53 codon 72 polymorphism in patients with advanced gastric cancer (**a** $P = 0.379$, **b** $P = 0.047$). *P*-values correspond to multivariate Cox model adjusted for age, sex, performance status, and status of disease

largely due to the Pro form of wild-type TP53 per se rather than the mutation. Furthermore, the TP53 Pro allele was also associated with a poorer prognosis in ovarian cancer patients who received adjuvant cisplatin plus paclitaxel chemotherapy [27]. These results are also consistent with an in vitro study, which showed that anticancer agents, such as doxorubicin, 5-fluorouracil, and cisplatin, induced a higher level of apoptosis in human H1299 cells expressing the Arg/Arg genotype of TP53 codon 72 than in cells expressing the Pro/Pro genotype [24]. In addition, in a colony-survival assay, doxorubicin and cisplatin were more cytotoxic to cells expressing the Arg variant than to cells expressing the Pro variant [24]. However, in a study of gastric adenocarcinoma, Zhang et al. [20] reported that the frequency of the Arg homozygous allele was positively correlated to the patient's age at the baseline, yet the age-related increase in the percentage of codon 72 Arg TP53 was not correlated to the prognosis for 102 gastric cancer patients who underwent gastroscopy or gastrectomy.

In conclusion, the TP53 codon 72 SNP was found to be predictive of the response to chemotherapy and correlate with the time to progression in patients with advanced gastric cancer treated with paclitaxel and cisplatin chemotherapy. However, further study is warranted to clarify the role of apoptosis-related gene polymorphisms as a predictive or prognostic biomarker in patients treated with chemotherapy.

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