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Original Article

Genetic variability of ERCC1 genes in NER pathway influences the treatment outcome of gastric cancer

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Abstract: We conducted a prospective study to analyze whether six SNPs in *ERCC1* gene could serve as potential biomarkers for prognosis of gastric cancer. Between January 2010 and December 2012, 270 patients with pathologically proven gastric cancer and receiving platinum-based chemotherapy were recruited in our study. Genotyping of the *ERCC1* rs11615, rs2298881, rs3212955, rs3212961, rs3212986 and rs735482 were carried out using the Sequenom MassARRAY platform. By logistic regression analysis, patients carrying the *GT* and *TT* genotypes of rs3212986 showed a significantly poorer response to chemotherapy than did those carrying the GG genotype, and the ORs (95% CI) were 0.47 (0.25-0.88) and 0.18 (0.08-0.41), respectively. By Cox proportional hazards models, the *GT* and *TT* genotypes of rs3212986 were correlated with increased risk of death when compared with the *GG* genotype, and the adjusted HRs (95% CIs) were 1.79 (1.01-3.16) and 2.57 (1.18-5.62), respectively. However, we did not find significant association between *ERCC1* rs11615, rs2298881, rs3212955, rs3212961 and rs735482 and response to chemotherapy and overall survival in patients with gastric cancer. In conclusion, the results of the present retrospective study indicate that there is a significant difference in biological behavior between *ERCC1* rs3212986 gene polymorphism and treatment outcome of gastric cancer.

Keywords: *ERCC1*, polymorphism, gastric cancer, treatment outcome

Introduction

Gastric cancer, which has aggressive behavior, is frequently encountered tumors worldwide. It is estimated that about one million new cases of gastric cancer are occurred in 2012 (952,000 cases, 6.8% of the total), making it the fifth most common malignancy in the world, after cancers of the lung, breast, colorectum and prostate. More than 70% of cases (677,000 cases) occur in developing countries, and half the world total occurs in China [1]. Despite improved protocols for diagnosis and treatment, gastric carcinoma still has a poor prognosis. Following curative surgical resection, 5-year survival is between 10-15% [2].

Various conventional prognostic parameters have been in use for predicting the prognosis in gastric cancers, such as stage of the tumor, histological grade and histopathological type of tumor. In addition to these parameters, additional prognostic predictors, which can be evaluated more objectively and can lead to development of new treatment strategies, are necessary. However, patients with gastric cancer usually show different treatment outcomes even when they have similar stage of the tumor, histological grade and histopathological type of tumor, which suggests that molecular factors play an important outcome of gastric cancer. Therefore, the identification of molecular markers that are predictive of gastric cancer aggressiveness and prognosis could provide important clinically relevant insights into disease treatment [3].

In normal cells, DNA is continually subjected to a variety of assaults, including ionizing radiation, ultraviolet rays and genotoxic agents. Thus, efficient DNA repair is required for prevention the propagation of errors and maintaining genomic stability [4]. The repair of this damage involves more than 130 genes and several molecular pathways, including nucleotide excision repair (NER), base-excision repair, homolo-

Table 1. Demographic and clinical characteristics characteristics of patients with gastric cancer

Characteristics	Patients with gastric cancer	%
Age, years	64.25±9.10	
>60	171	63.33
≤60	99	36.67
Gender		
Female	103	38.15
Male	167	61.85
Lauren's classification		
Intestinal	160	59.26
Diffuse	110	40.74
TNM stage		
I-II	155	57.41
III-IV	115	42.59
Lymphatic metastasis		
Negative	196	72.59
Positive	74	27.41
Alcohol drinking		
Non-drinkers	115	42.59
Drinkers	155	57.41
Tobacco smoking		
Non-smokers	143	52.96
Smokers	127	47.04
Response to chemotherapy		
Responsive	176	65.19
Non-responsive	94	34.81

gous recombination, and non-homologous end joining [5]. NER is the main mechanism involved in cisplatin-induced DNA damage, and alteration of NER capacity may play an important role in the individualized treatment outcome of patients with gastric cancer receiving platinum-based chemotherapy. Excision repair cross complementation group 1 (ERCC1) is an essential factor involved in the DNA damage incision, whose products are important in NER and lie on chromosome 19q13.3 [6-8]. In our study, we conducted a prospective study to analyze whether six SNPs in ERCC1 gene could serve as potential biomarkers for prognosis of gastric cancer.

Materials and methods

Study population

Between March 2010 and March 2013, 270 patients with pathologically proven gastric cancer and receiving platinum-based chemotherapy were recruited in our study. Patients who had primary tumors other than gastric cancer, tumors of an unknown origin or any histopathological diagnosis other than gastric cancer were excluded from this study. The exclusion criteria were patients who underwent preoperative radiotherapy or chemotherapy and had distant metastasis found preoperatively.

Demographic and clinical characteristics of patients with gastric cancer were investigated by trained nurses through self-designed questionnaire and medical record, including gender, age, histological classification, TNM stage, lymphatic metastasis and etc. Lauren's classification was used to classify the histological classification, and all gastric cancer patients were histopathologically confirmed by two pathologists independently. The TNM stage was defined according to the 7th edition of the TNM staging system of the International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC). All patients with gastric cancer signed the written informed consents before enrolling into this study. The protocol of this study was approved by the ethics committee of our hospital.

Assessment of clinical outcome

All patients received platinum-based chemotherapy. The chemotherapy was repeated at three-weekly intervals for up to six cycles unless unacceptable toxicity, disease progression or patients' refusal to continue treatment. The objective tumor response was assessed locally by the attending physician using Response Evaluation Criteria in Solid Tumors (RECIST) [9]. Patients presenting complete remission (CR) and partial remission (PR) were considered to be responsive, and those showing stable disease (SD) and progressive disease (PD) were considered as non-responsive. Overall survival (OS) was used to be the endpoint index, and the OS was defined between the date of chemotherapy and the data of confirmed death from any cause or the end of follow-up. All the patients were followed-up until March 2015.

Genotyping

5 ml peripheral blood sample was drawn from patients with gastric cancer, and the blood samples were kept in -20°C. 0.5 mg/ml Ethy-

Table 2. Association between ERCC1 gene polymorphisms and response to chemotherapy

SNPs	Patients	%	Responsive	%	Non-responsive	%	OR (95% CI)[1]	*P* value
rs11615								
TT	108	48.21	72	50.70	36	43.90	1.0 (Ref.)	-
TC	94	41.96	58	40.85	36	43.90	0.81 (0.43-1.49)	0.46
CC	22	9.82	12	8.45	10	12.20	0.60 (0.21-1.72)	0.28
rs2298881								
CC	106	39.26	75	42.61	31	32.98	1.0 (Ref.)	-
AC	130	48.15	83	47.16	47	50.00	0.73 (0.40-1.31)	0.26
AA	33	12.22	18	10.23	15	15.96	0.50 (0.21-1.21)	0.08
rs3212955								
AA	161	59.63	111	63.07	50	53.19	1.0 (Ref.)	-
AG	85	31.48	52	29.55	33	35.11	0.71 (0.40-1.28)	0.22
GG	24	8.89	13	7.39	11	11.70	0.53 (0.20-1.42)	0.15
rs3212961								
CC	99	36.67	67	38.07	32	34.04	1.0 (Ref.)	-
AC	125	46.30	79	44.89	46	48.94	0.82 (0.45-1.48)	0.48
AA	46	17.04	30	17.05	16	17.02	0.90 (0.40-2.03)	0.77
rs3212986								
GG	120	44.44	93	52.84	27	28.72	1.0 (Ref.)	-
GT	108	40.00	67	38.07	41	43.62	0.47 (0.25-0.88)	0.01
TT	42	15.56	16	9.09	26	27.66	0.18 (0.08-0.41)	<0.01
rs735482								
AA	127	47.04	86	48.86	41	43.62	1.0 (Ref.)	-
AC	119	44.07	77	43.75	42	44.68	0.87 (0.50-1.54)	0.62
CC	24	8.89	13	7.39	11	11.70	0.56 (0.21-1.52)	0.20

[1]Adjusted for age, gender, Lauren's classification, TNM stage, lymphatic metastasis, alcohol drinking and tobacco smoking.

lenediaminetetra-acetic acid was used as the anticoagulant.

Genomic DNA was extracted from peripheral blood leukocytes using a DNA extraction kit (Beijing Bioteke Co. Ltd. Beijing, China). Genotyping of *ERCC1* rs11615, rs2298881, rs3212955, rs3212961, rs3212986 and rs735482 was carried out using the Sequenom MassARRAY platform (San Diego, CA, USA). Multiplex PCR mixture contained 1× HotStar Taq buffer, 2.8 mM $MgCl_2$, 0.1 U of HotStar Taq polymerase, 2 ng of genomic DNA, 0.5 pmol of each primer, and 0.5 mmol of dNTPs. Reaction was performed at 94°C for 15 min, followed by 45 cycles at 94°C for 20 s, 56°C for 30 s, and 72°C for 1 min, with a final incubation at 72°C for 3 min. Unincorporated dNTPs were deactivated using 0.3 U of shrimp alkaline phosphatase (SAP) followed by primer extension using 5.4 pmol of each extension probe, 50 mmol of iPlex Termination Mix, and 0.5 U of iPLEX enzyme (Sequenom; San Diego, CA). The extension reactions were carried out with an initial denaturation step of 8 min at 94°C, followed by 30 cycles at 94°C for 30 s, annealing at 60°C for 30 s, and extension at 72°C for 1 min. Purified extension reaction products with cation exchange resin were spotted onto SpectroCHIPs and measured by MALDI-TOF mass spectrometry. Additionally, approximately 10% of the samples were randomly selected and retested, and the results were 100% concordant.

Statistical analysis

Frequencies were used to describe the distribution of categorical variables and median and interquartile range was used for continuous variables. ORs and their corresponding 95% CIs were used to assess the associations between gene polymorphisms of *ERCC*1 rs11615, rs2298881, rs3212955, rs3212961, rs3212986 and rs735482 and response to chemotherapy in patients with gastric cancer. The associ-

Table 3. Association between ERCC1 gene polymorphisms and overall survival of gastric cancer

SNPs	Patients	%	Death	%	Alive	%	HR (95% CI)[1]	*P* value
rs11615								
TT	125	46.30	52	44.44	73	39.89	1.0 (Ref.)	-
TC	115	42.59	51	43.59	64	34.97	1.12 (0.65-1.93)	0.67
CC	30	11.11	14	11.97	16	8.74	1.22 (0.51-2.05)	0.61
rs2298881								
CC	106	39.26	44	37.61	62	33.88	1.0 (Ref.)	-
AC	130	48.15	57	48.72	73	39.89	1.10 (0.63-1.91)	0.72
AA	33	12.22	16	13.68	17	9.29	1.33 (0.56-3.13)	0.48
rs3212955								
AA	161	59.63	67	57.26	94	51.37	1.0 (Ref.)	-
AG	85	31.48	39	33.33	46	25.14	1.19 (0.68-2.08)	0.52
GG	24	8.89	12	10.26	12	6.56	1.40 (0.54-3.64)	0.44
rs3212961								
CC	99	36.67	39	33.33	60	32.79	1.0 (Ref.)	-
AC	125	46.30	56	47.86	69	37.70	1.25 (0.71-2.21)	0.42
AA	46	17.04	22	18.80	24	13.11	1.41 (0.65-3.03)	0.34
rs3212986								
GG	120	44.44	44	37.61	76	41.53	1.0 (Ref.)	-
GT	108	40.00	51	43.59	57	31.15	1.79 (1.01-3.16)	0.02
TT	42	15.56	22	18.80	20	10.93	2.57 (1.18-5.62)	0.01
rs735482								
AA	127	47.04	52	44.44	75	40.98	1.0 (Ref.)	-
AC	119	44.07	54	46.15	65	35.52	1.20 (0.70-2.05)	0.48
CC	24	8.89	10	8.55	14	7.65	1.03 (0.38-2.71)	0.95

[1]Adjusted for age, gender, Lauren's classification, TNM stage, lymphatic metastasis, alcohol drinking and tobacco smoking.

ations between the *ERCC1* rs11615, rs2298881, rs3212955, rs3212961, rs3212986 and rs735482 polymorphisms and the OS of patients with gastric cancer were assessed by a Cox proportional hazards model, and the results were expressed by hazard ratios (HRs) their 95% CIs. Survival distributions were estimated using the Kaplan-Meier method and assessed using the log-rank test. The wide-type genotype was used as reference. Kaplan-Meier method was taken to plot the OS curves. A *p*-value less than 0.05 were considered statistically significant. Statistical analysis was done using statistical package SPSS 16.0 software (version 16.0, SPSS Inc., Chicago, IL, USA).

Results

The mean age of the subjects with gastric cancer was 64.25±9.10 years (ranging from 34 to 78 years). A total of 103 (38.15%) females and 167 (61.85%) males were collected in our study. Of 270 patients with gastric cancer, 160 (59.26%) patients were intestinal type of Lauren's classification, 110 (40.74%) were diffuse type, 155 (57.41%) were (TNM) stage I-II, 115 (42.59%) were (TNM) stage III-IV, 74 (27.41%) exhibited positive lymphatic metastasis, 155 (57.41%) had a habit of smoking, 127 (47.04%) had a habit of drinking, and 176 (65.19%) showed responsive (**Table 1**).

At the end of the follow-up, 176 patients with gastric cancer showed responsive to chemotherapy, with a response rate of 65.19%. By logistic regression analysis, patients carrying the *GT* and *TT* genotypes of rs3212986 showed a significantly poorer response to chemotherapy than did those carrying the *GG* genotype, and the ORs (95% CI) were 0.47 (0.25-0.88) and 0.18 (0.08-0.41), respectively (**Table 2**). However, we did not find significant association between *ERCC1* rs11615, rs2298881, rs3212955, rs3212961 and rs735482 and response to chemotherapy in patients with gastric cancer.

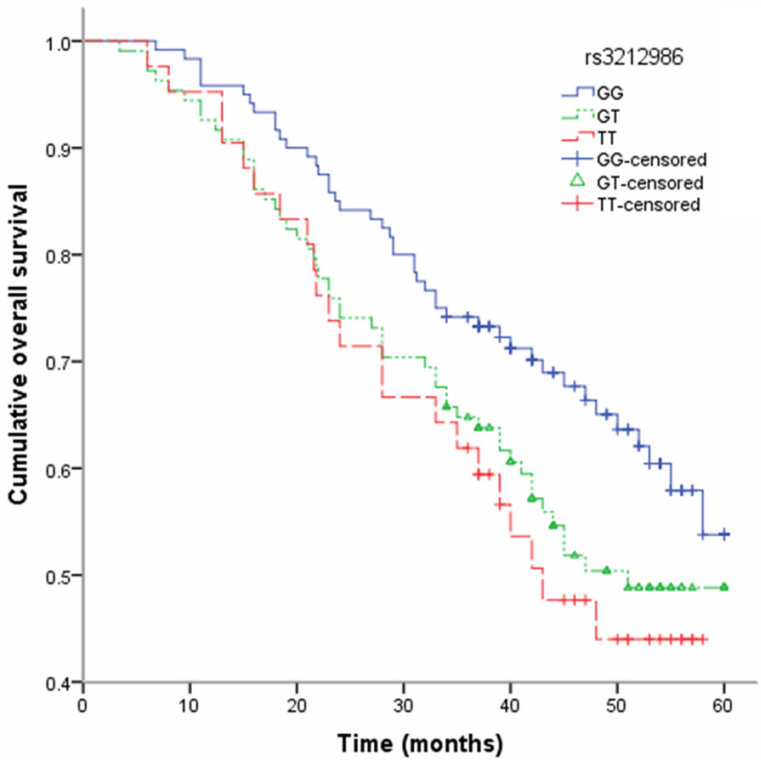

Figure 1. Kaplan-Meier survival curves by ERCC1 rs3212986 polymorphism in patients with gastric cancer.

At the end of March 2015, 117 patients had died from all causes, and the five-year survival rate was 43.33%. We found that the GT and TT genotypes of rs3212986 were associated with short overall survival time when compared with the *GG* genotype (for *GT* vs. *GG* genotype: 43.14 months vs. 48.16 months; for *TT* vs. *GG* genotype: 40.75 months vs. 48.16 months; **Figure 1**). By Cox proportional hazards models, the *GT* and *TT* genotypes of rs3212986 were correlated with increased risk of death when compared with the *GG* genotype, and the adjusted HRs (95% CIs) were 1.79 (1.01-3.16) and 2.57 (1.18-5.62), respectively (**Table 3**). Moreover, we did not find significant association between *ERCC1* rs11615, rs2298881, rs3212955, rs3212961 and rs735482 and overall survival in patients with gastric cancer.

Discussion

Patients with gastric cancer always show individualized response to platinum-based chemotherapy. Previous studies have indicated that genetic factors may contribute to the individual response to platinum-based chemotherapy. It is reported that chemotherapy response results from hereditary factors by increased the cell activity of biotransformation, accumulation of intracellular and the weakened capacity of DNA repairing [10]. In the present study, we investigated the association between six SNPs in *ERCC1* gene and treatment outcome of gastric cancer treated by platinum-based chemotherapy. Our analysis indicated that patients with the *GT* and *TT* genotypes of *ERCC1* rs3212986 were significantly associated with poorer response to chemotherapy and shorter overall survival time when compared with GG genotype.

The excision repair cross complementation group 1 (*ERCC1*) enzyme belongs to nucleotide excision repair (NER) system, and this gene has a role in repairing DNA adducts and other DNA helix-distorting lesions [11], including platinum intra-strand DNA adducts. Moreover, it is reported that *ERCC1* is associated with resistance to platinum-based chemotherapy through reducing platinum-induced DNA damage [12, 13]. Platinum plays an important role in binding to DNA and forming bulky DNA adducts, and it caused inter-strand and intra-strand cross-link generation, as well as DNA-protein cross-links, and thus causes inhibition of cell growth and apoptosis of targeted cells unless repaired. It is reported that *ERCC1* enzyme involved in recognizing and removing platinum-induced intra-strand adducts in DNA, and contributes to resistance to platinum-based chemotherapy in several kinds of cancers, such as non-small cell lung cancer, ovarian cancer, bone tumor and colorectal cancer [14-18].

For the correlation between *ERCC1* rs3212986 polymorphism and treatment outcome of gastric cancer, six previous studies have reported their association [19-24]. Li et al. reported that the *TT* genotype of *ERCC1* rs3212986 had statistically significant hazards of poor prognosis

when compared with those carrying unfavorable genotypes [23]. In our study, we suggested that the *AA* genotype of *ERCC1* rs3212986 could influence the response to platinum-based chemotherapy and overall survival of gastric cancer patients, which is in line with the results of our study. However, some studies reported inconsistent results with ours. Xue et al. performed a study in a Chinese population, and they reported that the *TT* genotype of *ERCC1* rs3212986 was associated with better response to chemotherapy and longer overall survival than those with the *AA* genotype [19]. Yu et al. conducted a study in a Chinese population, and they reported that no association was found between *ERCC1* rs3212986 polymorphism and treatment outcome of gastric cancer [20]. Liu et al. performed a study in 231 subjects with gastric cancer, and they found that *ERCC1* rs3212986 polymorphism did not influence the treatment outcome of gastric cancer [21]. Li et al. and Park et al. also did not find significant association between *ERCC1* rs32-12986 polymorphism and prognosis of gastric cancer [22, 24]. The inconsistency results might be caused by differences in ethnicities, source of patients, sample size, and by chance.

There were two limitations in our study. First, Patients with gastric cancer were selected from one hospital, and selection bias cannot be avoided in this study. Second, other genetic polymorphisms of the DNA repair genes may be involved in the prognosis of gastric cancer, and they may have interaction with *ERCC1* gene polymorphisms in the treatment outcome of gastric cancer. Third, the sample size of patients with gastric cancer is relative small, which may reduce the statistical power to find differences between groups. Further large sample and multicenter studies are greatly needed to confirm the finding of our study.

Our study suggests that *ERCC1* rs3212986 might affect the clinical outcome of patients with gastric cancer receiving platinum-based chemotherapy. Our finding could be helpful in designing personalized chemotherapy strategies to promote the response to chemotherapy and prolong the survival time, and also provides incentive to explore the predictive value of other genes.

Disclosure of conflict of interest

None.

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