Genetics and Molecular Research

ERCC1 C118T polymorphism has predictive value for platinum-based chemotherapy in patients with late-stage bladder cancer

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Genet. Mol. Res. 15 (2): gmr.15027801
Received October 8, 2015
Accepted December 23, 2015
Published May 23, 2016
DOI http://dx.doi.org/10.4238/gmr.15027801

ABSTRACT. This study aims to investigate the association between *ERCC1* codon C118T polymorphism and the response rate of platinum-based chemotherapy in patients with late-stage bladder cancer. A total of 41 eligible patients histologically confirmed as having stage IV muscle-invasive transitional cell carcinoma of the bladder were treated with platinum-based chemotherapy for 2-6 cycles. The genotypes of patients were determined by PCR amplification of genomic DNA followed by restriction enzyme digestion. Positive responses were categorized as complete and partial responses. In addition, progression-free survival (PFS) and overall survival (OS) were also determined as indicators of long-term outcomes. The genotype frequencies of C/C, C/T and T/T genotypes were 56.1, 34.1, and 9.8%, respectively. Positive response was observed in 14 patients (34.1%), while 27 patients (65.9%) were

negative responders. As compared with individuals carrying the C/T and T/T genotypes, those with the C/C genotype had significantly improved short-term treatment responses (P = 0.018). The median PFS of patients carrying the C/C genotype was 6.3 months, while that of patients with C/T and T/T genotypes was 4.2 months (P = 0.023). Moreover, the median OS for patients carrying the C/C genotype was also longer as compared with that of patients carrying C/T and T/T (11.7 months *vs* 8.5 months, P = 0.040). Our results indicated that the *ERCC1* codon 118 polymorphism may have predictive potential for chemotherapy treatment responses in late-stage bladder cancer patients.

Key words: *ERCC1*; Polymorphism; Bladder cancer; Chemotherapy

INTRODUCTION

Bladder cancer (BC) is the most common malignancy of the urinary tract, and is the 7th and 17th most common cancer in men and women, respectively (Jemal et al., 2011). Approximately 356,000 new cases and approximately 145,000 deaths are attributed to this disease each year (Ploeg et al., 2009). During the initial diagnosis of BC, approximately 30% of the cases are diagnosed as muscle-invasive BC, 15% of which are already metastatic (Rosenberg et al., 2005). For patients with late-stage BC, treatments remain a clinical challenge. Cisplatin-containing combination chemotherapy has been the standard treatment for BC since the late 1980s. Gemcitabine combined with cisplatin (GC) have been used as the standard first-line regime, and has been shown to improve the overall survival and quality of life of BC patients. However, less than 50% patients were found to be responsive to chemotherapy (von der Maase et al., 2000). Therefore, it is important to find new biomarkers to accurately predict disease prognosis and patient responses to therapies.

Differential chemotherapy responses and survival rates may be related to an individual's genomic variations, which may influence the expression and/or function of enzymes associated with drug metabolism (Kalikaki et al., 2009). Platinum compounds including cisplatin are heavy metal complexes that form adducts and covalent cross-links between the two DNA strands, thus effectively blocking DNA replication and transcription. Excision repair cross-complementation group 1 (ERCC1), a crucial complex in the nucleotide excision repair (NER) pathways, plays a pivotal role in DNA damage recognition and removal of damaged nucleotides (van Duin et al., 1987). Altered expression of the *ERCC1* gene can influence DNA repair (Furuta et al., 2002), and its protein level correlates with sensitivity to platinum and its associated compounds (Scheil-Bertram et al., 2010). It has also been reported that *ERCC1* single nucleotide polymorphisms (SNPs) may have an effect on *ERCC1* mRNA expression (Yu et al., 2000; Ma et al., 2007).

Recently, *ERCC1* polymorphisms were found to be associated with colorectal cancer risk (Yang et al., 2015). In addition, expression of *ERCC1* could predict the clinical outcomes of non-small cell lung cancer patients receiving platinum-based chemotherapy (Wang et al., 2014). Furthermore, several SNPs of *ERCC1*, especially *ERCC1* codon C118T, have been suggested to be important for predicting the efficacy of platinum-based chemotherapy in cancers. It has been shown that high expression of the *ERCC1* gene is associated with poor clinical outcome following cisplatin-based adjuvant chemotherapy for locally advanced BC. However, there has

been no report on the association between the *ERCC1* codon C118T polymorphism and the response rate in BC patients treated with platinum-based chemotherapy. Therefore, we performed this retrospective study in order to determine whether *ERCC1* codon C118T polymorphism can be used as a novel biomarker to predict BC prognosis and treatment responses.

MATERIAL AND METHODS

Study subjects

All patients for the study were recruited from the affiliated Cancer Hospital of Jiangsu Province in China between January 2010 and September 2012. A total of 41 eligible patients were histologically diagnosed with stage IV muscle-invasive transitional cell carcinoma. The disease stages were classified based on the American Joint Committee on Cancer tumor-node-metastasis (TNM) classification. Tumor sizes were measured using computed tomography or magnetic resonance imaging. All patients had a Karnofsky Performance Score of not less than 70, and showed normal electrocardiograms. In addition, all patients had normal blood chemistries and hepatic and renal function at the beginning of the treatment. Written informed consent was given by all the subjects prior to the blood collection (5 mL). The study was approved by the Institutional Review Board of the Nanjing Medical University, Nanjing, China.

Chemotherapy regime and evaluation of therapeutic effect

All patients were treated with gemcitabine + cisplatin (GC). Patients were administered gemcitabine (1000 mg/m^2) on days 1 and 8, and GC (70 mg/m^2) was given on day 2 in the 3-week treatment cycle. All chemotherapeutic drugs were administered intravenously, and all patients received 2-6 cycles. Patient responses to treatment were determined after 2 cycles. Therapeutic effects were evaluated according to the Response Evaluation Criteria in Solid Tumors recommended by the National Cancer Institute (Therasse et al., 2000). The short-term responses were classified into 4 groups: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CR was defined as the complete disappearance of all measurable tumors with no observed relapse for 4 weeks. PR required at least 30% reduction in measurable lesions. Patients with SD showed less than a 30% decrease in tumors or no more than a 20% increase in the size of measurable lesions. PD was assigned to patients when measurable lesions increased by more than 20% or new tumor foci were found. CR and PR were considered positive responses, while both SD and PD were considered as negative responses. Patient follow-up was performed every 3 months following chemotherapy as well as by routine phone calls. Progression-free survival (PFS) was calculated from the date when chemotherapy was started until the date of confirmed relapse, and overall survival (OS) was defined as the time between start of chemotherapy and death or date of last follow-up.

DNA collection and genotyping

Venous blood was collected from all patients, and genomic DNA was extracted according to the manufacturer protocol using the Qiagen blood Mini kit (Qiagen, Hilden, Germany). For genotyping of *ERCC1* codon C118T polymorphisms, PCR amplification of genomic DNA was followed by restriction enzyme digestion (PCR-RFLP). The primers

used were as follows: *ERCC1*-F, 5'-GCAGAGCTCACCTGAGGAAC-3'; *ERCC1*-R, 5'-GAGGTGCAAGAAGAGGTGGA-3'. The PCR was performed in a 25-μL reaction volume containing 100 ng template DNA, 1 μM each primer, 2.5 mM each dNTP, 2.0 mM $MgCl_2$, and 1.0 IU Taq polymerase with 10X buffer (TaKaRa, Japan). PCR was carried out in a T Profession thermocycler (Biometra, Göttingen, Germany) with the following cycling parameters: initial denaturation at 95°C for 5 min; 35 cycles of 45 s at 95°C, 45 s at 65°C, and 45 s at 72°C; and final extension at 72°C for 7 min. PCR products were digested overnight with 5 IU *Bsr*DI enzyme (TaKaRa, Japan). DNA fragments were run on a 2% agarose gel stained with ethidium bromide. For the *ERCC1* gene, the three possible genotypes were defined by distinct banding patterns: homozygous CC genotype corresponded to a 208 bp band, heterozygous CT genotype corresponded to 2 bands at 208 and 128 bp, and homozygous TT genotype corresponded to a 218 bp band.

Statistical analysis

All statistical analyzes were performed using the SPSS software (version 16.0; SPSS Inc., USA). The correlations between genotype frequencies, clinicopathological features, and therapeutic responses were assessed by χ^2 tests. PFS and OS survival curves were plotted using the Kaplan-Meier method and were verified using the log-rank test. Cox proportional hazards regression analysis was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) in order to evaluate the overall relative risk of relapse and death associated with clinicopathological features and *ERCC1* genotype. All statistics were two-sided, and $P < 0.05$ was considered to be statistically significant.

RESULTS

Patient characteristics

We studied 41 pathologically verified BC patients (median age = 65 year). All cases were confirmed as muscle-invasive urothelial carcinoma by pathologists; 47.5% of the cases were low-grade, and the rest were high-grade. All the patients were at stage IV of the disease, 26.8% of which were locally advanced (regional lymph node metastasis without distant metastasis), while the remaining 73.2% were metastatic. We administered 2 cycles of GC chemotherapy to 28 patients, and the remaining 13 patients received at least 2 cycles of chemotherapy (but no more than 6 cycles). Of the 41 patients enrolled in this study with BC, the genotype frequencies for the *ERCC1* codon 118 polymorphisms C/C, C/T, and T/T, were 56.1% (23/41), 34.1% (14/41), and 9.8% (4/41), respectively. The clinical characteristics of BC patients are presented in Table 1.

Relationship between short-term treatment responses and patient characteristics

In our study, positive responses to treatment were observed in 14 patients (34.1%), while negative responses occurred in 27 patients (65.9%). The distribution of distinct clinicopathologic features such as gender, age, pathology, stage, and cycles of chemotherapy to short-term treatment responses was evaluated. As shown in Table 1, locally advanced cases (any T, N1-3, M0) were found to be more responsive to chemotherapy as compared with

metastatic cases (any T, any N, M1) (P = 0.018). In addition, we found that patients carrying the *ERCC1* codon 118 C/C have significantly better short-term treatment responses to platinum-based chemotherapy as compared to those carrying the C/T and T/T polymorphisms (P = 0.016).

Influence of clinicopathological features and *ERCC1* C118T polymorphisms on PFS and OS

As shown in Table 1, patients with low-grade urothelial carcinoma have longer median PFS and OS as compared with those with high-grade carcinoma (P < 0.05). Consistent with results for the association of *ERCC1* C118T polymorphism with short-term treatment responses to platinum-based chemotherapy, the C/C genotype was also correlated with improved long-term survival. The median PFS for patients carrying the C/C genotype was 6.3 months, while that for patients with C/T and T/T genotypes was 4.2 months (P = 0.023) (Figure 1). Moreover, the median OS for patients carrying the C/C genotype was also longer as compared with those carrying C/T and T/T (11.7 months *vs* 8.5 months, P = 0.040) (Figure 2).

Table 1. Distribution of selected variables in the cases.

Variables	Cases [N (%)]	Response		P value	PFS[a]	P value	OS[a]	P value
		Positive	Negative					
Age (means ± SD)	63.6 ± 7.3							
<64	21 (51.2)	5	16	0.271	69.1	0.146	12.9	0.638
≥64	20 (48.8)	9	11		68.5		13.1	
Gender								
Male	34 (82.9)	12	22	0.924	7.4	0.302	11.8	0.978
Female	7 (17.1)	2	5		9.1		12.7	
Clinical stage								
IV (any T, N1-3, M0)	10 (26.8)	7	3	**0.018**				
IV (any T, any N, M1)	31 (73.2)	7	24					
Chemotherapy cycles								
2	28 (31.7)	12	16	0.170				
≥2	13 (68.3)	2	11					
Pathology								
Low-grade	19 (47.5)	8	11	0.504	12.3	< 0.001	17.4	< 0.001
High-grade	22 (52.5)	6	16		4.8		8.3	
ERCC1 codon 118 genotype								
T/T	4 (9.8)	0	4	**0.020**				
C/T	14 (34.1)	2	12					
C/C	23 (56.1)	12	11					
T/T+ C/T	18 (43.9)	2	16	**0.016**	4	**0.023**	8	**0.040**
C/C	23 (56.1)	12	11		6		11	
Surgical treatment								
Yes	13 (31.7)							
No	28 (68.3)							
Radiotherapy								
Yes	7 (17.1)							
No	34 (82.9)							

[a]Measured in a month. Significant values are in bold.

In the Cox regression model, the PFS and OS for patients with the C/C genotype at *ERCC1* codon 118 C/T were approximately 1.83- and 1.94-fold higher than those with C/T and T/T genotypes (P = 0.016, HR = 1.83, 95%CI = 1.12-2.99; P = 0.010, HR = 1.94, 95%CI = 1.17-3.27). Low-grade pathology (P = 0.002, HR = 8.36, 95%CI = 2.19-31,87; P = 0.038, HR = 3.24, 95%CI = 1.07-9.83), localized tumors (P = 0.002, HR = 5.37, 95%CI = 1.82-15.81;

P = 0.001, HR = 6.417, 95%CI = 2.21-18.60), and surgery after adjuvant chemotherapy (P = 0.001, HR = 0.124, 95%CI = 0.04-0.43; P < 0.001, HR = 0.04, 95%CI = 0.01-0.18) were also associated with prolonged patients survival, as indicated by PFS and OS.

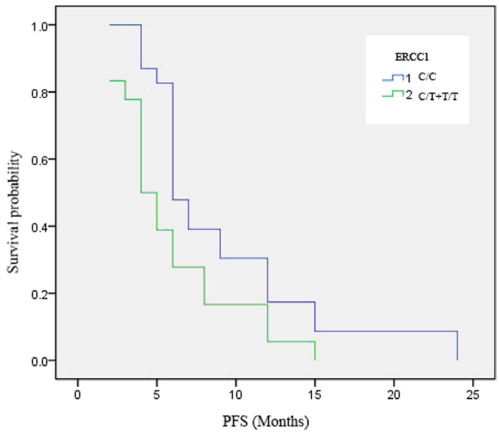

Figure 1. Kaplan-Meier curves of PFS in late-stage BC patients with the genotypes C/C (blue line) or C/T + T/T (green line) and receiving platinum-based chemotherapy (P < 0.05).

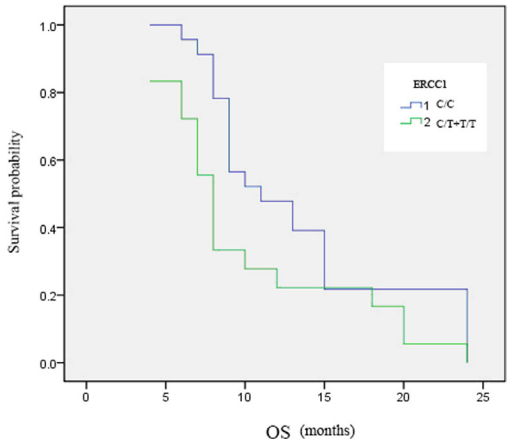

Figure 2. Kaplan-Meier curves of OS in late-stage BC patients with the genotypes C/C (blue line) or C/T + T/T (green line) and receiving platinum-based chemotherapy (P < 0.05).

DISCUSSION

Late-stage BC is a lethal disease with limited therapeutic options. The 5-year survival rate for patients with metastatic BC is only 5% (Siegel et al., 2014). GC regime have been used as the standard first-line chemotherapy for this disease. However, the response rate is only 49%, and the death rate due to drug toxicity is high (von der Maase et al., 2000). It is therefore important to predict whether a regimen is effective in each patient with BC before initiation of chemotherapy. Cytostatic drugs including cisplatin and gemcitabin destroy the integrity of genetic information in DNA. Platinum compounds form DNA-platinum adducts, which may

alter the structure of DNA, leading to apoptosis of cancer cells. However, such changes in the DNA helix can be easily identified and repaired by NER systems, which may play important roles in the ability of tumor cells to resist platinum compounds.

ERCC1 is one of the multifunctional enzymes that belong to the NER complex in cooperation with the xeroderma pigmentosum complementation group F. It is an endonuclease that plays crucial roles in recognition, stabilization, and incision of cisplatin-induced DNA adducts (Simon et al., 2007). The predictive value of *ERCC1* expression in platinum-based chemotherapy responses has been reported in various cancers such as non-small cell cancer, ovarian cancer, and cervical cancer, as well as BC (Dabholkar et al., 1994; Kong et al., 2006; Bellmunt et al., 2007; Chen et al., 2010; Hoffmann et al., 2010; Okuda et al., 2011; Park et al., 2011; Cheng et al., 2012; Lv et al., 2014). A systemic review published in 2012 further confirmed the predictive value of *ERCC* codon C118T polymorphism in advanced colorectal patients treated with platinum-based chemotherapy in the Asian population. This recent meta-analysis involving 356 advanced BC patients has provided evidence that low/negative expression of *ERCC1* is associated with higher objective responses, median progression-free survival, and median OS during platinum-based chemotherapy. Therefore, we proposed that ERCC1 may be a suitable marker of prognosis and sensitivity to platinum-based chemotherapy in patients with advanced BC (Lu et al., 2012).

Genetic polymorphism may affect structure, function, stability, and folding of proteins. Polymorphism in the *ERCC1* genes could also affect its expression, which may influence the chemotherapy responses in various cancers. A study by Cheng et al. (2012) reported that the C118T polymorphism of *ERCC1* is associated with patient responses to cisplatin-based chemotherapy in late-stage non-small cell lung cancer. The response rate of patients carrying an *ERCC1* codon 118 C/C allele was more than two-fold higher as compared with that of patients with either the C/T or T/T genotype. In contrast, Moxley et al. (2013) found that polymorphisms of *ERCC1* codon 118 were not associated with clinical responses or survival to platinum-based chemotherapy in advanced epithelial ovarian cancer. To date, no relevant report regarding the association between *ERCC1* codon 118 polymorphism and treatment responses in BC patients has been generated. Results from our current study revealed that patients with the C/C genotype at *ERCC1* codon 118 have significantly better short-term treatment responses to platinum-based chemotherapy and prolonged PFS and OS as compared with other genotypes. However, there was a lack of statistical significance in short-term responses between patients carrying the C/C genotype and those carrying the C/T genotype. This may be due to the limited sample size in our study groups. Using multivariate analysis, *ERCC* codon 118 C/T polymorphism was identified as an independent predictor of PFS and OS in late-stage BC patients receiving platinum-based chemotherapy. Furthermore, we demonstrated that tumor stage, pathology, surgery, and *ERCC* codon were also independent predictors of PFS and OS in late-stage BC patients receiving platinum-based chemotherapy.

However, the following limitations of our study must be acknowledged. First, this study included only 41 subjects. Second, the study was only conducted in the Asian population. Race may influence the therapeutic significance of the study due to genotype frequencies. Moreover, various factors including stage, pathological differentiation, surgery, and radiology after chemotherapy, as well as supportive care before death may also play important roles in determining the PFS or OS. Thus, more precise and large-scale studies need to be performed in order to verify our results.

In conclusion, we evaluated the effect of the *ERCC1* C118T polymorphism on treatment response to platinum-based chemotherapy in 41 late-stage BC patients. The

ERCC1 codon118 C/C genotype may be of predictive value in individualized chemotherapy for BC patients.

Conflicts of interest

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Research supported by the Affiliated Cancer Hospital of Jiangsu Province of Nanjing Medical University, Nanjing, China (#ZQ 201301 and #ZQ 201302) and the Nanjing Science and Technology Plan Project (#201201087).

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