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Original Article

Genetic polymorphisms in nucleotide excision repair pathway influences response to chemotherapy and overall survival in osteosarcoma

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Abstract: We analyzed the role of genetic polymorphisms of six important NER pathway genes in response to chemotherapy and clinical outcome of osteosarcoma patients. A prospective study including 172 osteosarcoma patients was conducted between January 2009 and January 2011. The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used for ERCC1 rs11615 and rs2298881, ERCC2 rs13181 and rs1799793, ERCC4 rs1800067, ERCC5 rs1047768, XPA 1800975, and XPC rs2228000 and rs2228001 gene polymorphisms. By logistic regression analysis, TT genotype of ERCC1 rs11615 genetic polymorphism was significant correlated with poor response to chemotherapy when compared with wide-type genotype (OR=0.27, 95% CI=0.10-0.71). AC and CC genotype of ERCC1 rs2298881 were significantly associated with poor response to chemotherapy when compared with AA genotype (For AC genotype, OR=0.45, 95% CI=0.21-0.97; for CC genotype, OR=0.19, 95% CI=0.06-0.58). By Cox proportional hazards regression analysis, TT genotype of ERCC1 rs11615 and CC genotype of ERCC1 rs2298881 suffered a 3.16 and 3.57-fold increased hazards of death (For ERCC1 rs11615, HR=3.16, 95% CI=1.19-9.16; for ERCC1 rs2298881, HR=3.57, 95% CI=1.10-11.35). In conclusion, our findings suggest that ERCC1 rs11615 and ERCC1 rs2298881 genetic polymorphisms are significantly associated with poor response to chemotherapy and unfavourable survival of osteosarcoma.

Keywords: NER pathway, response to chemotherapy, overall survival, osteosarcoma

Introduction

Osteosarcoma is a rare bone cancer which derived from mesenchymal tissues, and this cancer has a highest incidence in adolescents around 16 years and older patients above 60 years [1]. It is estimated that the annual incidence of osteosarcoma is about 3/1,000,000 [2-4]. Previous studies have reported that half of the osteosarcoma patients have poor clinical outcome and about 30% of them develop metastases or local relapse [5, 6]. Despite advances in surgical treatment and chemotherapy, the survival rates of the osteosarcoma patients are still not satisfactory. Although osteosarcoma patients with same TNM stages received similar treatment, the treatment outcome shows interindividual differences between patients [7, 8]. Therefore, genetic variants may play an important role in response to chemotherapeutic agents and treatment outcome of osteosarcoma.

DNA repair systems are involved in maintaining the stability and integrity of the genome, such as nucleotide excision repair (NER), base excision repair (BER) and mismatch repair (MMR) as well as double-strand break repair (DSBR) [9, 10]. Nucleotide excision repair (NER) is mainly involved in monitoring and repairing DNA damage caused by endogenous and exogenous factors as well as therapeutic agents [11]. Genetic variations could influence the response to chemotherapy and clinical outcomes in cancer patients. Several functional proteins influence the DNA repairing function of NER pro-

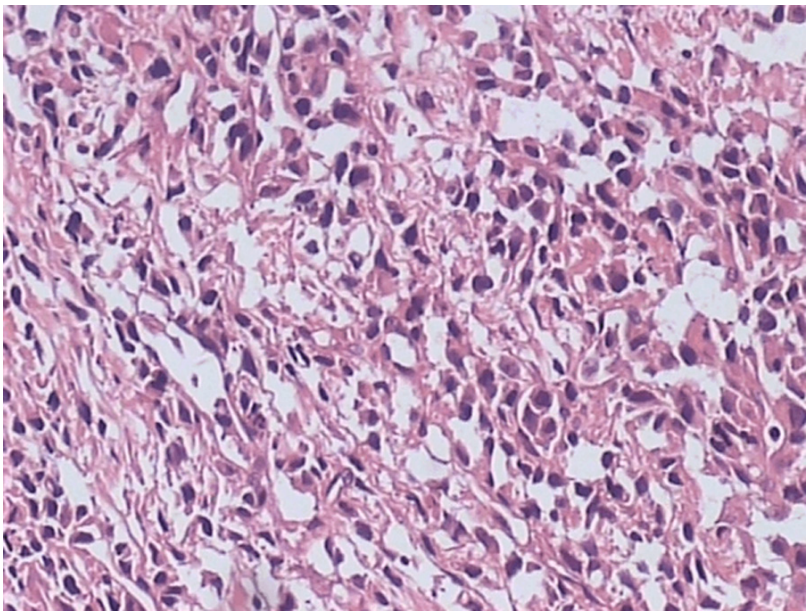

Figure 1. Chondroblastic osteosarcoma.

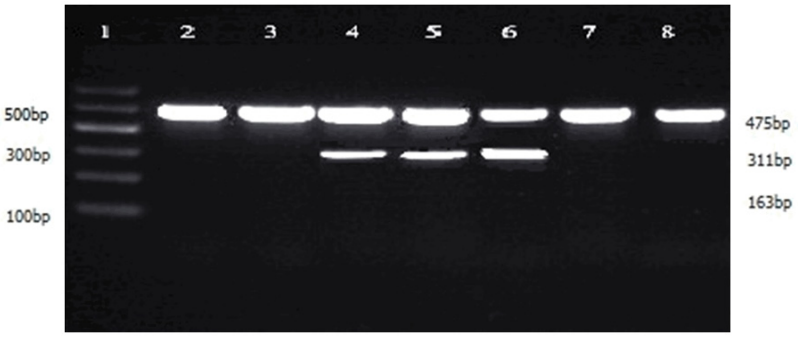

Figure 2. Genotype of ERCC1 rs11615 polymorphism, 2 and 8 were C/C genotype (474 bp); 4, 5 and 6 were C/T genotype (474 bp, 311 bp and 163 bp); 3 and 7 were TT genotype (311 bp and 163 bp).

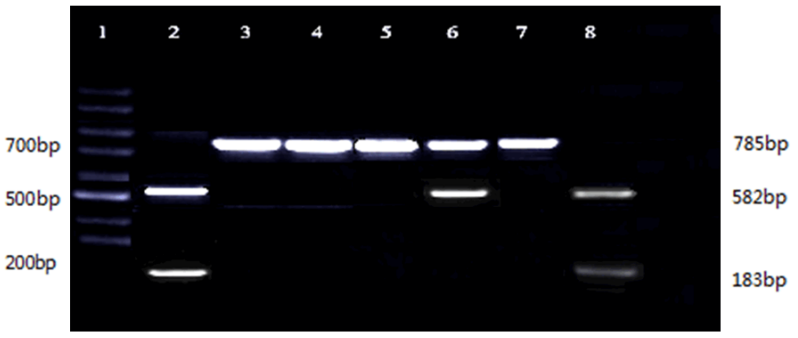

Figure 3. Kaplan-Meier survival curves by ERCC1 rs11615 polymorphisms in osteosarcoma patients.

cess, and thus alter treatment outcomes of cancer patients.

Currently, there are several previous studies investigate the role of polymorphisms in the NER pathway in the treatment outcome of osteosarcoma, but the results are inconsistent [12-15]. In this present study, we analyzed the role of genetic polymorphism of six important NER pathway genes in response to chemotherapy and clinical outcome of osteosarcoma patients.

Materials and methods

Study subjects

A total of 172 osteosarcoma patients were enrolled between January 2009 and January 2011. Osteosarcoma patients were newly diagnosed and histopathologically confirmed independently by two pathologists (**Figure 1**). The exclusion criteria were patients who were suffered from other malignant tumors or distant metastasis preoperatively, and received radiotherapy or chemotherapy before enrolling into our study.

Demographic and clinical characteristics of osteosarcoma patients were collected by self-designed questionnaire and medical records. The clinical and pathological characteristics included sex, gender, Enneking stage (I, II and III), histological type (osteoblastic, chondroblastic, fibroblastic and mixed), tumor location (long tubular bones and axial skeleton), type of therapy (amputation and limb salvage) and tumor metastasis.

Table 1. Clinicopathological characteristics of included osteosarcoma

Characteristics		Frequencies of osteosarcoma patients	%
Age, years			
	< 20	62.21	107
	≥ 20	37.79	65
Gender			
	Male	66.28	114
	Female	33.72	58
Enneking stage			
	I-II	56.40	97
	III	43.60	75
histological type			
	Osteoblastic	27.33	47
	Chondroblastic	44.19	76
	Fibroblastic	12.79	22
	Mixed	15.70	27
Type of therapy			
	Amputation	33.14	57
	Limb salvage	66.86	115
Tumor location			
	Long tubular bones	62.21	107
	Axial skeleton	37.79	65
Metastasis			
	Yes	35.47	61
	No	64.53	111

After enrolling into our study, all the osteosarcoma patients received preoperatively chemotherapy and adjuvant chemotherapy after treatment. The response to chemotherapy was assessed using the response evaluation criteria from European Organization for Research and Treatment of Cancer. Poor response to chemotherapy was defined as patients who manifested less than 90% of tumor necrosis, and good response to chemotherapy was defined as those who presented more than 90% of tumor necrosis. The overall survival was used as the end point of study. The overall survival was defined as the date of beginning of treatment to the date of death or last clinical follow-up. All the patients were followed up until the date of January 2014, and patients without an event or death until the end of follow-up were censored at the date of January 2014.

Written informed consents were obtained from participants. The study protocol was approved by the Ethical Committee of our hospital, and all participants gave written informed consent according to the Declaration of Helsinki.

DNA extraction and genotyping

Venous blood samples were collected from each participant, and then placed in EDTA anticoagulant and centrifuged at 2700 rpm for ten min at room temperature. The collected blood samples were kept in a refrigerator maintained until further usage. The genomic DNA was extracted by DNA Extraction Kit (Qiagen Inc., Valencia, CA, USA). The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used for ERCC1 rs11615 and rs2298881, ERCC2 rs13181 and rs1799793, ERCC4 rs1800067, ERCC5 rs1047768, XPA 1800975, and XPC rs2228000 and rs2228001 gene polymorphisms (**Figures 2** and **3**). PCR reactions were carried out with an initial denaturation at 95°C for 5 min, 35 cycles of amplification with denaturation at 95°C for 30 sec, annealing at 56°C for 30 sec, and extension at 72°C for 30 sec, followed by a final extension step of 7 min at 72°C. Each PCR product was analyzed by 3% agarose gel electrophoresis to identify the purity and integrity, observed under ultraviolet lamp and recorded by photography.

Statistical analysis

The continuous variables were expressed by mean and standard deviation (SD), while the categorical variables were evaluated using frequencies and percentage. The differences between continuous variables were calculated by student t test, while those between categorical variables were performed by chi-square test. Association between genotype polymorphisms of the ERCC1 rs11615 and rs2298881, ERCC2 rs13181 and rs1799793, ERCC4 rs1800067, ERCC5 rs1047768, XPA 1800975, and XPC rs2228000 and rs2228001 and response to chemotherapy were estimated using unconditional logistic regression, and the results were expressed as odds ratios (ORs) with associated 95% intervals (CIs). Multivariate Cox proportional hazards models were used to estimate the effect of the ERCC1 rs11615 and

Table 2. Polymorphisms of NER pathway genes and response to chemotherapy inpatients with osteosarcoma

Gene	Genotypes	MAF		Good responder	%	Non-responder	%	Adjusted OR (95% CI)[1]	*P* values
		In database	Patients						
ERCC1 rs11615	CC	0.243	0.235	81	75.70	35	53.85	1.0	-
	CT			16	14.95	15	23.08	0.46 (0.19-1.13)	0.06
	TT			10	9.35	15	23.08	0.27 (0.10-0.71)	< 0.05
ERCC1 rs2298881	AA	0.444	0.378	50	46.73	16	24.62	1.0	-
	AC			48	44.86	34	52.31	0.45 (0.21-0.97)	< 0.05
	CC			9	8.41	15	23.08	0.19 (0.06-0.58)	< 0.05
ERCC2 rs13181	AA	0.095	0.116	92	85.98	51	78.46	1.0	-
	AC			10	9.35	8	12.31	0.69 (0.23-2.16)	0.47
	CC			5	4.67	6	9.23	0.46 (0.11-1.93)	0.21
ERCC2 rs1799793	GG	0.1945	0.209	79	73.83	42	64.62	1.0	-
	GA			17	15.89	13	20.00	0.70 (0.29-1.72)	0.38
	AA			11	10.28	10	15.38	0.58 (0.21-1.68)	0.26
ERCC4 rs1800067	GG	0.0286	0.378	103	96.26	59	90.77	1.0	-
	GA			3	2.80	4	6.15	0.43 (0.06-2.65)	0.27
	AA			1	0.93	2	3.08	0.29 (0.005-5.65)	0.28
ERCC5 rs1047768	TT	0.4930	0.410	44	41.12	21	32.31	1.0	-
	TC			43	40.19	30	46.15	0.68 (0.32-1.45)	0.29
	CC			19	18.69	15	23.08	0.60 (0.24-1.56)	0.25
XPA rs1800975	GG	0.3536	0.363	49	45.79	22	33.85		-
	GA			45	42.06	32	49.23	0.63 (0.30-1.31)	0.18
	AA			13	12.15	11	16.92	0.53 (0.19-1.54)	0.19
XPC rs2228000	CC	0.325	0.323	53	49.53	28	43.08	1.0	-
	CT			42	39.25	29	44.62	0.77 (0.38-1.56)	0.43
	TT			12	11.21	8	12.31	0.79 (0.26-2.52)	0.65
XPC rs2228001	AA	0.372	0.375	47	43.93	20	30.77	1.0	-
	AC			46	42.99	35	53.85	0.56 (0.27-1.17)	0.09
	CC			14	13.08	10	15.38	0.60 (0.21-1.78)	0.29

[1]Adjusted for age, gender, tumor stage and histological type, tumor location and metastasis.

rs2298881, ERCC2 rs13181 and rs1799793, ERCC4 rs1800067 and ERCC5 rs1047768, XPA 1800975, and XPC rs2228000 and rs2228001 polymorphisms on the overall survival of osteosarcoma patients, and the results were assessed by hazards ratios (HRs) and 95% confidence intervals (CIs). The wide-type genotype was used as reference. Two-tailed *P* values < 0.05 were considered statistically significant. All the statistical analyses were performed using Statistical Analyses System (SAS) package (version 10.0; SAS Institute, Cary, NC).

Results

The distributions of clinicopathological characteristics of the osteosarcoma patients are presented in **Table 1**. The mean age of the included subjects at the time of enrolling into our study was 17.8 ± 9.7 years. Of the 172 included subjects, 114 (66.28%) patients were males, 75 (43.6%) were at III Enneking stage, 47 (27.33%) were osteoblastic type, 76 (44.19%) were chondroblastic type, 22 (12.79%) were fibroblastic type, 27 (15.70%) were mixed type, 115 (66.86%) received limb salvage, 107 (62.21%) had tumor at long tubular bones, and 61 (35.47%) showed metastasis.

At the end of follow-up, 107 (62.21%) patients showed good response to chemotherapy, while 65 (37.79%) presented poor response to chemotherapy. By unconditional logistic regression analysis, we found that the TT genotype of ERCC1 rs11615 genetic polymorphisms was significant correlated with poor response to

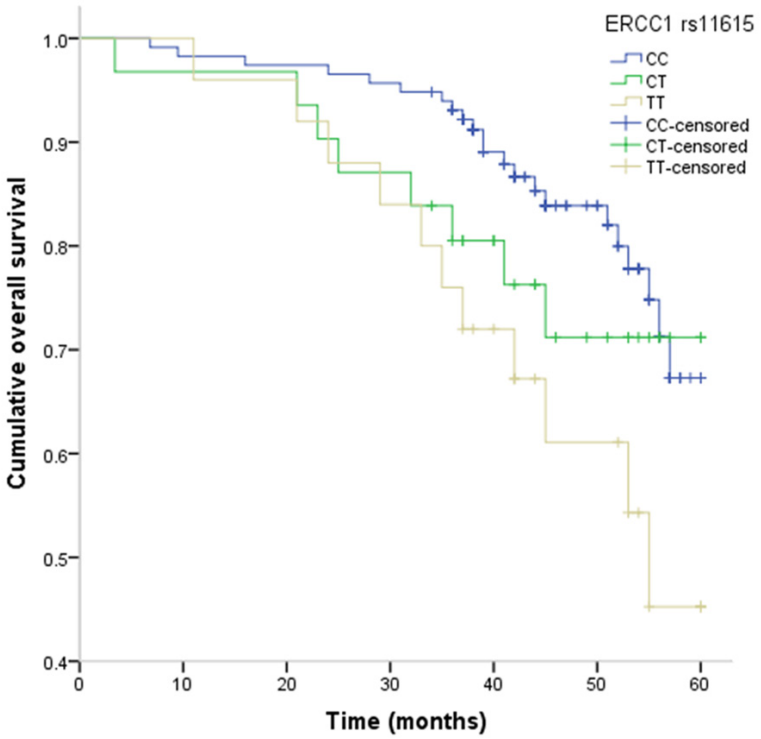

Figure 4. Kaplan-Meier survival curves by ERCC1 rs2298881 polymorphisms in osteosarcoma patients.

chemotherapy when compared with the wide-type genotype (OR=0.27, 95% CI=0.10-0.71) (**Table 2**). Similarly, we found that the AC and CC genotypes of ERCC1 rs2298881 were significantly associated with poor response to chemotherapy when compared with the AA genotype (For the AC genotype, OR=0.45, 95% CI=0.21-0.97; for the CC genotype, OR=0.19, 95% CI=0.06-0.58). However, ERCC2 rs13181, ERCC2 rs1799793, ERCC4 rs1800067, ERCC5 rs1047768, XPA rs1800975, XPC rs2228000 and XPC rs2228001 did not significantly influence the response to chemotherapy in patients with osteosarcoma.

At the end of January 2014, 41 (23.84%) patients died from all causes during the follow-up period. The five-year survival rate of osteosarcoma patients was 76.16%. By Cox proportional hazards regression analysis, the TT genotype of ERCC1 rs11615 was significantly associated with a shorter survival time when compared with the CC genotype (**Figure 4**), and this genotype was correlated with an elevated increased risk of death in osteosarcoma patients compared to the wide-type genotype (HR=3.36, 95% CI=1.19-9.16) (**Table 3**). Furthermore, the CC genotype of ERCC1 rs2298881 had a significantly worse survival than the AA genotype (**Figure 5**), and this genotype of ERCC1 rs2298881 suffered a 3.57-fold increased hazards of death (HR=3.57, 95% CI=1.10-11.35). However, other seven SNPs were not associated with the overall survival of osteosarcoma patients.

Discussion

It is well known that identifying biomarkers correlated with osteosarcoma survival could play an important role in influencing the individualized therapy and post-operational treatment for different patients. Although several studies have revealed that polymorphisms in NER gene could alter the overall survival of osteosarcoma, the results are inconsistent [12-15]. In our study, we found that the ERCC1 rs11615 and ERCC1 rs2298881 genetic polymorphisms could influence the response to chemotherapy, and could effectively predict the prognosis of osteosarcoma.

DNA damage caused by several exogenous or endogenous factors could be significantly influenced by efficient DNA repair to restore genomic integrity, and DNA repair pathway involves a number of DNA repair genes [16, 17], and these genes are responsible for different functions of DNA repairing [18]. ERCC1 gene polymorphisms are involved in transcription-coupled NER. In our study, we found that the rs11615 and ERCC1 rs2298881 genetic polymorphisms were related with poorer response to chemotherapy and shorter survival of osteosarcoma. Previous studies have reported the association between ERCC1 polymorphisms and response to chemotherapy and overall survival of osteosarcoma in several kinds of cancers, such as non-small cell lung cancer, pancreatic cancer, ovarian cancer, colorectal cancer and gastric cancer [19-23]. Kamikozuru et al. conducted a study with 67 pancreatic cancer patients, and

Table 3. Association between gene polymorphisms on overall survival of osteosarcoma patients

Gene		Patients	%	Deaths	%	Adjusted HR (95% CI)[1]	*P* values
ERCC1 rs11615	CC	116	67.44	22	53.66	1.0	-
	CT	31	18.02	8	19.51	1.49 (0.50-4.03)	0.4
	TT	25	14.53	11	26.83	3.36 (1.19-9.16)	0.07
ERCC1 rs2298881	AA	66	38.37	11	26.83	1.0	-
	AC	82	47.67	20	48.78	1.61 (0.66-4.07)	0.25
	CC	24	13.95	10	24.39	3.57 (1.10-11.35)	0.01
ERCC2 rs13181	AA	143	83.14	33	80.49	1.0	-
	AC	18	10.47	5	12.20	1.28 (0.33-4.19)	0.66
	CC	11	6.40	3	7.32	1.25 (0.20-5.60)	0.75
ERCC2 rs1799793	GG	121	70.35	27	65.85	1.0	-
	GA	30	17.44	8	19.51	1.27 (0.44-3.38)	0.61
	AA	21	12.21	6	14.63	1.39 (0.40-4.26)	0.53
ERCC4 rs1800067	GG	162	94.19	38	92.68	1.0	-
	GA	7	4.07	2	4.88	1.31 (0.12-8.36)	0.76
	AA	3	1.74	1	2.44	1.63 (0.03-32.04)	0.69
ERCC5 rs1047768	TT	65	37.79	14	34.15	1.0	-
	TC	73	42.44	18	43.90	1.19 (0.50-2.88)	0.67
	CC	34	19.77	9	21.95	1.31 (0.44-3.79)	0.58
XPA rs1800975	GG	71	41.28	16	39.02	1.0	-
	GA	77	44.77	19	46.34	1.13 (0.49-2.60)	0.76
	AA	24	13.95	6	14.63	1.15 (0.32-3.70)	0.8
XPC rs2228000	CC	81	47.09	18	43.90	1.0	-
	CT	71	41.28	18	43.90	1.19 (0.52-2.69)	0.65
	TT	20	11.63	5	12.20	1.17 (0.29-4.00)	0.79
XPC rs2228001	AA	67	38.95	15	36.59	1.0	-
	AC	81	47.09	20	48.78	1.14 (0.50-2.65)	0.74
	CC	24	13.95	7	17.07	1.43 (0.42-4.51)	0.51

[1]Adjusted for age, gender, tumor stage, type of therapy, tumor location and metastasis.

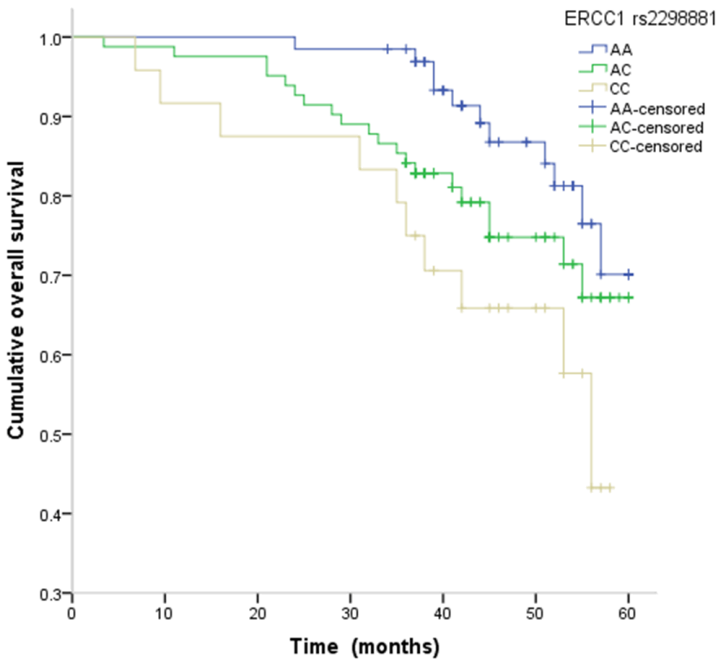

Figure 5. Genotype of ERCC1 rs2298881 polymorphism, 5 and 7 were AA genotype (765 bp); 3, 4 and 6 were AC genotype (765 bp, 582 bp and 183 bp); 2 and 8 were AA genotype (582 bp and 183 bp).

found that the ERCC1 rs11615 polymorphism was correlated with the prognosis of patients with pancreatic cancer treated with platinum-based chemotherapy [19]. Li et al. conducted a meta-analysis with 10 studies to investigate the association between ERCC1 rs11615 and rs3212986 polymorphisms and response to platinum-based chemotherapy in epithelial ovarian cancer, and they only found that the ERCC1 rs3212986 polymorphism could influence the overall survival of

epithelial ovarian cancer [20]. Qian et al. reported that the TT genotype of ERCC1 rs11615 gene polymorphism was associated with a poor prognosis of colorectal cancer in a meta-analysis [21]. Kalikaki et al. reported that the ERCC1 rs11615 polymorphism was associated with progression-free survival [22]. The divergences in results from different studies on ERCC1 gene polymorphisms may be related to variation in ethnic origin of population, sample size, type of tumor, genotyping method and also by chance.

For the association between ERCC1 rs11615 and ERCC1 rs2298881 genetic polymorphisms and overall survival of osteosarcoma, several studies have reported their association, but the results are inconsistent [12, 24-27]. Ji et al. conducted a study with 214 osteosarcoma patients and reported that the TT genotype of ERCC1 rs11615 was associated with an elevated risk of death from osteosarcoma [25]. Hao et al. reported that the ERCC1 rs11615 polymorphism could influence the death from osteosarcoma [27]. However, some studies did not find the association between ERCC1 rs11615 and ERCC1 rs2298881 polymorphisms and prognosis of osteosarcoma. Yang et al. conducted a study in a Chinese population, and suggested that the ERCC1 gene polymorphisms were not associated with response to chemotherapy [24]. Li et al. also reported that there was no evidence of association between ERCC1 gene polymorphisms and prognosis in osteosarcoma [12]. Similarly, Goričar et al. conducted a study with 66 osteosarcoma patients, and they did not find significant association of ERCC1 rs11615 and ERCC1 rs2298881 polymorphisms with overall survival of osteosarcoma and cisplatin-based chemotherapy in osteosarcoma patients [26]. The results of above-mentioned studies are inconsistent. Therefore, further large sample studies are greatly needed to confirm the association between ERCC1 gene polymorphisms and overall survival of osteosarcoma.

In summary, our findings suggest that ERCC1 rs11615 and ERCC1 rs2298881 polymorphisms are significantly associated with poor response to chemotherapy and unfavourable survival of osteosarcoma. Our study demonstrates that genetic polymorphisms of NER pathway could be applied in the prediction of the prognosis of osteosarcoma. Further validation studies based on various ethnicities and molecular investigations are greatly required.

Disclosure of conflict of interest

None.

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