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Association of DNA repair gene polymorphisms with response to cisplatin-based concurrent chemoradiotherapy in patients with cervical carcinoma

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ABSTRACT

Purpose: The aim of this study was to investigate polymorphisms in DNA repair genes as potential predictive factors among Chinese cervical cancer patients.
Methods: A total of 72 patients with cervical carcinoma, who received cisplatin-based chemoradiotherapy and whose responses were evaluated by Response Evaluation Criteria in Solid Tumors, were included. The association between response to chemoradiotherapy and the genotypes for 29 single-nucleotide polymorphisms (SNPs) in 25 DNA repair genes were analyzed.
Results: A minor allele of SNP rs9350 in the exonuclease 1 gene was associated with a better response rate, regardless of age and tumor stage (odds ratio, 8.316; $p = 0.002$).
Conclusion: SNP rs9350 in the exonuclease 1 gene is involved in inter-individual differences in the response to cisplatin-based chemoradiotherapy, in patients with cervical carcinoma.
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1. Introduction

Cervical cancer is the second most common cause of cancer-related deaths among female individuals worldwide, resulting in 275,000 deaths annually [1]. Cisplatin-based concurrent chemoradiotherapy (CCRT) has become the standard treatment for patients with locally advanced cervical cancer [2]. When compared to radiotherapy alone, this combined approach was shown to improve the local control rate as well as overall survival [3,4]. However, a subset of patients showed no response to this therapy [5].

For decades, there has been worldwide effort to improve the clinical response of cancer patients, and there has been increasing interest in the molecular profiling of cancer patients and application of targeted therapeutics [6]. Extensive scientific and clinical studies in these areas have been performed in patients with lung cancer or colorectal cancer [7–9], but few predictive molecular factors have been identified in cervical cancer patients [10].

Because the combination of cisplatin and radiation induce various DNA damage and chromosomal integrity disturbances, activities involved in the process of DNA or chromosome damage repair may influence the response of patients with cervical carcinoma after chemoradiotherapy [11]. In fact, a single-nucleotide polymorphism (SNP) in *ERCC1*, rs11615, was demonstrated to be associated with the response of patients with advanced non-small cell lung cancer to platinum-based chemotherapy [12]. Given that SNPs can be identified by using blood samples, they are promising biomarkers in the clinical decision-making process for cancer patients. A recent study of the association between 30 SNPs in 27 DNA repair genes and the response to platinum-based chemotherapy in non-small cell lung cancer patients further suggested their predictive role in cancer therapy [13]. However, the clinical significance of these SNPs remains unclear in cervical carcinoma.

Thus, in this study, we carried out a single hospital-based retrospective analysis of 72 patients with cervical carcinoma to determine the associations between 29 SNPs in 25 DNA repair genes and the patient response to cisplatin-based chemoradiotherapy. We chose the response evaluated by the Response Evaluation Criteria in Solid Tumors [14] as the primary endpoint to search for predictive factors for the primary effect of chemoradiotherapy.

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Table 1
29 SNPs in 25 DNA repair genes.

Pathway	Gene	SNP	Base change	AA change	MAF
Base excision repair	*PARP1*	rs1136410	T2285C	Val762Ala	0.45
	APE1	rs1130409	T444G	Asp148Glu	0.46
	MBD4	rs140693	G1036A	Glu346Lys	0.28
	OGG1	rs1052133	C977G	Ser326Cys	0.49
	XRCC1	rs1799782	C580T	Arg194Trp	0.24
		rs25489	G839A	Arg280His	0.10
		rs25487	G1196A	Arg399Gln	0.24
DNA damage response	*TP53*	rs1042522	G215C	Arg72Pro	0.49
Nucleotide excision repair	*XPG* (*ERCC5*)	rs17655	C3310G	His1104Asp	0.44
	CSB (*ERCC6*)	rs2228528	G1196A	Gly399Asp	0.46
	XPC	rs2228001	A2815C	Lys939Gln	0.38
	XPD (*ERCC2*)	rs13181	A2251C	Lys751Gln	0.10
	ERCC1	rs11615	C354T	Asn118Asn	0.27
Mismatch repair	*MLH3*	rs175080	C2531T	Pro844Leu	0.12
	MSH3	rs26279	G3133A	Thr1045Ala	0.35
Exonuclease	*EXO1*	rs9350	C2270T	Pro757Leu	0.41
		rs4149963	C1316T	Thr439Met	0.10
		rs735943	A1061G	His354Arg	0.15
DNA double-strand break repair	*BRCA2*	rs144848	A1114C	Asn372His	0.23
	SNM1	rs3750898	C949G	His317Asp	0.10
	NBS1	rs1805794	C553G	Gln185Glu	0.45
	XRCC3	rs861539	C722T	Thr241Met	0.07
	BRCA1	rs16942	G3548A	Lys1183Arg	0.34
DNA polymerase	*POLD1*	rs1726801	G356A	Arg119His	0.19
	POLI	rs8305	A2191G	Thr731Ala	0.27
	REV1	rs3087386	T770C	Phe257Ser	0.36
	POLZ	rs462779	C3671T	Thr1224Ile	0.48
Other pathways	*FANCA*	rs2239359	G1501A	Ser501Gly	0.20
	WRN	rs1346044	T4099C	Cys1367Arg	0.09

Table 2
Clinicopathological characteristics of the patients according to tumor response.

Variable	Nonresponders (n = 20)		Responders (n = 52)		
	N	%	*N*	%	*p*-Value
Age, years					
≤55	13	65	22	42	0.604
>55	7	35	30	58	
Tumor size, cm					
≤4	16	80	39	75	0.764
>4	4	20	13	25	
Histology					
Adenocarcinoma	2	10	2	4	0.307
Squamous cell	18	90	50	96	
Histologic grade					
Well and moderately differentiated	16	80	49	94	0.088
Poorly differentiated	4	20	3	6	
Node status					
N0	5	25	24	46	0.117
N1	15	75	28	54	
FIGO stage					
II	9	45	26	50	0.742
III	11	55	25	48	
IV	0	0	1	2	
HPV status					
Positive	18	90	48	92	0.667
Negative	2	10	4	8	

2. Materials and methods

2.1. Selected population

A total of 72 patients with cervical cancer who had not received prior treatment were given cisplatin-based chemoradiotherapy at The First Affiliated Hospital of Xi'an Jiaotong University between September 2013 and July 2015. Staging was performed according to International Federation of Gynecology and Obstetrics staging system classification. All patients were Chinese and were histologically diagnosed with squamous cell carcinoma or adenocarcinoma.

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