Cancer Chemother Pharmacol (2010) 66:493–500
DOI 10.1007/s00280-009-1186-3

ORIGINAL ARTICLE

The combination of ERCC1 and XRCC1 gene polymorphisms better predicts clinical outcome to oxaliplatin-based chemotherapy in metastatic colorectal cancer

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Received: 7 September 2009 / Accepted: 11 November 2009 / Published online: 4 December 2009

Abstract
Purpose To evaluate the effect of excision repair cross-complementing group 1 (ERCC1) and X-ray cross-complementing group 1 (XRCC1) gene polymorphisms on treatment outcome in patients receiving oxaliplatin-based regimens for metastatic colorectal cancer.
Methods Hundred and thirteen patients with a diagnosis of metastatic colorectal cancer were treated with oxaliplatin-based chemotherapy. ERCC1 codon 118C/T and XRCC1 codon 399A/G polymorphisms were tested by real-time polymerase chain reaction (RT-PCR) method in peripheral blood lymphocytes of these patients. Disease control rates and survivals were compared by types of genotypes.
Results Analyses of the patterns of the polymorphism located at ERCC1 codon 118 showed that 55 (48.67%) patients were homozygous for C/C genotype, 15 (13.27%) were homozygous for the T/T genotype, and 43 (38.06%) were heterozygous for C/T genotype. Analyses of the polymorphism located at XRCC1 codon 399 showed that 61 (53.98%) patients were homozygous for A/A genotype, 13 (11.50%) were homozygous for the G/G genotype, and 39 (34.52%) were heterozygous for A/G genotype. After two cycles of chemotherapy, there was complete response (CR) in 1 patient, partial response (PR) in 24 patients, and stable disease (SD) in 56 patients. Altogether in 81 (71.68%) patients the disease was controlled after chemotherapy. Thirty-two (28.32%) patients showed disease progression. After adjusting for some clinical factors, both the ERCC1 polymorphism and the XRCC1 polymorphism lost their roles in predicting DCR ($P = 0.662$, $P = 0.631$) and MST ($P = 0.692$, $P = 0.572$). But the combination of ERCC1 and XRCC1 polymorphisms was significantly associated with DCR ($P = 0.01$) and MST ($P = 0.000$) independently.
Conclusions This is the first study which showed that polymorphisms of ERCC1 and XRCC1, in combination not individually, were independent predictors for DCR and OS. This may contribute to the selection of patients who would benefit from oxaliplatin-based chemotherapy for metastatic colorectal cancer.

Keywords Metastatic colorectal cancer · XRCC1 · ERCC1 · Polymorphism · Oxaliplatin

Introduction

Colorectal cancer (CRC) is the third most common cancer and the fourth most frequent cause of cancer death worldwide [1]. The majority of patients diagnosed with CRC are no longer confined to the primary site: up to 30% of patients present with metastatic disease and 50–60% ultimately develop metastatic or advanced disease [2]. Although the outcome of patients with metastatic colorectal cancer has improved significantly and median overall survival (OS) of up to 20 months has been achieved [3], owning to the availability of new drugs such as oxaliplatin, irinotecan and targeted drugs. The 5-year survival rate is, at best, just 10.3% for them [4], which cannot satisfy the patients and the oncologists. Very recently, oxaliplatin has been approved as first- and second-line therapy in combination with 5-FU for the treatment of metastatic colorectal

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cancer [5, 6]. While chemotherapy has been clearly shown to improve survival, the objective responses of the various drugs range between 10 and 50% either as single agent or in combination. It is almost only those who respond to the drug that can benefit from the chemotherapy and their survival prolonged; the nonresponders had only toxicity and side effects. Thus, screening patients that are likely to respond seems to be very important. Predictive markers may help to identify prospectively those patients who are more likely to benefit from the treatment.

Oxaliplatin is a platinum-based therapeutic agent that has shown in vitro and in vivo antitumor activities in colorectal cancer [7]. It carries a 1,2-diamino-cyclohexane ring leading to DNA damage by forming DNA–platinum monoadducts with guanines that are converted into diadducts overtime. In contrast to cisplatin, oxaliplatin-induced adducts are apparently not recognized or processed by mismatch repair, but predominantly repaired by the nucleotide excision repair pathway and base excision repair pathway [8]. Nucleotide excision repair is responsible for the removal of a DNA segment with its associated bulky adduct, followed by the restoration of that DNA segment [9]. Excision repair cross-complementing group 1 (ERCC1) is an excision nuclease within the nucleotide excision repair (NER) pathway and is involved in the oxaliplatin metabolism [10]. Base excision repair (BER) pathway plays a key role in repairing DNA damage due to cellular metabolism and consists of multiple enzyme systems [11], the X-ray repair cross-complementing group 1 (XRCC1) is one of rate-limiting members of BER and interacts with other proteins involved in several stages of the BER pathways, including repairing specific base damage caused by oxaliplatin [12].

It is widely recognized that apart from confounding environmental and physiologic factors, inherited variability in drug-metabolizing enzymes, drug transporters, and drug targets plays an important role in the variability of treatment outcomes. Single nucleotide polymorphism (SNP) is a type of genetic diversity within a population's gene pool; it arises through mutation, but been observed in more than 1% of general population compared with mutation. Within a population, SNP can be assigned a minor allele frequency. It can also be inherited like any other DNA sequence, allowing its inheritance to be tracked from parent to child. SNP falling within coding sequences of genes may influence mRNA transcription, stability, protein expression or enzyme function and structure [13–15]. Thus, the SNP in host genes involved in the drug metabolism may lead to various responses to the same drugs and determine the different outcomes of the same chemotherapy.

In this study, we tested the hypothesis whether the SNP in ERCC1-118 and XRCC1-399, alone or in combination, have the potential to predict clinical disease control, overall survival in metastatic colorectal patients treated with oxaliplatin-based chemotherapy. Yet, the possibility of individualizing DNA repair profiles is becoming a central issue to improve chemotherapy strategies.

Patients and methods

Subjects

From 1 Sep 2005 through 31 Aug 2008, 126 patients with histologically confirmed metastatic colorectal cancer were enrolled in the oxaliplatin-based chemotherapy study at Cancer Treatment Center in the Affiliated Hospital of Medical College, Qingdao University (China). Among all the 126 patients, 113 were eligible for the analysis. All patients signed an informed consent form before entering the study. They also signed an informed consent form for blood sample collection to establish the clinical significance of genetic polymorphisms. All specimens (blood samples) were obtained at the time of treatment protocol entry. The clinical data and specimens were evaluated retrospectively. Patients' performance status was classified according to Eastern Cooperative Oncology Group (ECOG) criteria. Patients with an ECOG status greater than 2 were not eligible for this study.

Chemotherapy regimens

For this study, all participants received the following combination therapy regimen: modified FOLFOX4 regimen once every 3 weeks: oxaliplatin; (Jiang su Heng-rui Express, China; H20040817) 130 mg/m^2, day 1; CF (calciumfolinate; Jiangsu Heng-rui Express, China; H20040817) 130 mg/m^2, day 1–5;5-Fu (5-fluorouracil; Tian jin Ji-yao Express, China; H12020959) 300 mg/m^2, day 1–5. Xelox regimen once every 3 weeks: oxaliplatin; (Jiang su Heng-rui Express, China; H20040817) 130 mg/m^2, day 1; Xeloda (capecitabine; Roche, Switzerland; H20030383) 1,250 mg/m^2, day 1–14. The treatment was given until disease progression, unacceptable toxicity, or patient's refusal to continue treatment.

Clinical evaluation

To evaluate response to therapy, a patient was required to have completed two cycles of therapy or to have progressed before completing two cycles. Chemotherapy response criteria: each patient had a bidimensionally measurable CT scan lesion at the time of the treatment initiation. One end point was the tumor response to chemotherapy evaluated according to the WHO criteria. Disease control from the treatment corresponded to a complete

(disappearance of the tumor) or partial (at least 50% reduction in tumor load of the lesions) response or stable disease (<25% progression, <50% shrinkage). Patients with tumor progression (size enlargement >25% or appearance of new lesions) was classified as disease uncontrollers. All results were confirmed at least 4 weeks after initial assessment. Disease uncontrollers underwent salvage chemotherapy (28 patients) or best support care (4 patients) based on their conditions and their willingness. Among those (28) who on palliative chemotherapy, all of them received irinotecan-based chemotherapy, and no patient got molecular targeted treatment. In either case, metastasectomy was never performed. The major end point overall survival (OS) was calculated as the time from the start of oxaliplatin treatment until death from any cause or until last contact if the patient was known to be alive.

Genotyping

Three milliliters of whole blood in heparinized tube were sampled at the time of treatment protocol entry and stored at −70°C until the analysis for this study. DNA was extracted from these samples using the Blood Genomic DNA Isolation Kit (Watson Biotechnologies, China). The genotyping was analyzed by single base primer extension assay using SNP Shot assay kit according to manufacturer's recommendation (ABI, Foster City, CA, USA). Briefly, the genomic DNA region containing one of the two SNPs was amplified with PCR reaction separately. Each PCR reaction contained: DNA 20.0 ng, TaqMan® Universal PCR Master Mix 12.5 μl (including: AmpliTaq Gold® DNA Polymerase, AmpErase® UNG, dNTPs with dUTP, Passive Reference 1, and optimized buffer, etc.), 20*TaqMan® SNP Genotyping Assay Mix 1.25 μl (including sequence-specific forward and reverse primers and two TaqMan® MGB probes: one probe labeled with VIC® dye detects the Allele 1 sequence, one probe labeled with FAM™ dye detects the Allele 2 sequence), and ultrapure water 9.25 μl in 25-μl reaction volume. Reactions were incubated at 95°C for 10 min, then denatured at 92°C for 30 s, annealed and extended at 60°C for 1 min. The last two procedures were cycled 40 times. The final products were analyzed on an ABI 7500 automated sequence analyzer.

Statistical methods

Before assessing clinical associations, genotype frequencies were checked for agreement with those expected under Hardy–Weinberg equilibrium. Contingency tables and Fisher's exact test were used for the categorical variables to evaluate the association of each polymorphism with the response to chemotherapy. The association between the genetic polymorphisms and overall survival was estimated using the method of Kaplan and Meier and assessed using the log-rank test. For the analysis of the combination of ERCC1 and XRCC1 polymorphisms, individuals were placed into categories indicating the number of variant alleles present from both polymorphisms. Logistic regression test and Cox multivariate analysis were also applied to adjust for age, gender, performance status, histology, number of metastatic sites, location of the tumor, and chemotherapy regimen, with number of variant alleles represented by indicator variables. All statistical analyses were carried out by SPSS15.0 with a significance level of $P = 0.05$ that is 2-sided.

Result

Patient characteristics and treatment outcomes

Among the 126 patients enrolled in this study, 113 patients were eligible for the data analyses and genotype analysis (Table 1). This group of 113 patients included 54 (47.79%) women and 59 (52.21%) men. The response of the patients was as follows: in 81 (71.68%) disease was controlled by

Table 1 Patient characteristics

Patients characteristics	Number of patients (%)
Gender	
Male	59 (52.21)
Female	54 (47.79)
Median age	57 (33–75)
≤50	33 (19.67)
51–69	61 (55.72)
≥70	9 (24.51)
Original tumor site	
Colon	49 (43.36)
Rectum	64 (56.64)
Differentiation	
Well-differentiated	19 (16.81)
Moderately differentiated	35 (30.97)
Poorly differentiated	59 (52.22)
PS score	
0–1	85 (75.22)
2	28 (24.78)
Chemotherapy regimens	
Modified FOLFOX4	57 (50.44)
Xelox	56 (49.56)
Number of organs involved	
1	64 (39.34)
2	38 (25.41)
>3	9 (32.79)

chemotherapy [1 complete response (CR), 24 partial response (PR), 56 stable disease (SD)], and 32 (28.32%) showed disease progression (PD). The median age was 57 years (range 33–75 years). The median overall survival time was 16 months (95% CI; 15.4–16.6 months) with a median follow-up period of 20 months (range 5–28 months). The patient characteristics are presented in Table 1.

Allele frequencies

The analysis of the polymorphism located at ERCC1 codon 118 in the blood showed that 55 (48.67%) were homozygous for C/C genotype, 15 (13.27%) were homozygous for the T/T genotype, and 43 (38.06%) were heterozygous (C/T genotype). The frequencies of the C and T alleles at codon 118 were 67.7 and 32.3%, respectively. The analysis of the polymorphism located at XRCC1 codon 399 in the blood showed that 61 (53.98%) were homozygous for A/A genotype, 13 (11.50%) were homozygous for the G/G genotype, and 39 (34.52%) were heterozygous (A/G genotype). The frequencies of the A and G alleles at codon 118 were 71.2 and 28.8%, respectively. Allelic distribution of both genes was in agreement with the Hardy–Weinberg equilibrium. (ERCC1: $\chi^2 = 1.90$, $P = 0.167$; XRCC1: $\chi^2 = 2.81$, $P = 0.094$). No clear patterns for significant associations between any of these polymorphisms and any of the other demographic (gender), clinical (performance status, location of the tumor, and number of metastases), or pathological (tumor differentiation) characteristics were observed (data not shown).

ERCC1 C118T polymorphism and treatment outcome

By contingency tables, the difference of DCR in three ERCC1 genotypes showed a trend towards statistical difference ($P = 0.093$). When adjusted for age, sex, tumor histological grade, location of the tumor, PS score, chemotherapy regimen and number of metastases by logistic regression test, the difference was quite poor ($P = 0.662$). The relationship between disease control rate (DCR) and ERCC1 genotypes was significant ($P = 0.027$) by Fisher's exact test, while the relationship disappeared ($P = 0.631$) after adjusting by logistic regression test. Individuals with the wild-type genotype (C/C) had an MST of 17 months, those with the heterozygous genotype (C/T) and variant genotype (T/T) had an MST of 16 months, The log-rank test was significant ($P = 0.001$). Kaplan–Meier curves of the three polymorphisms are shown in Fig. 1. The Cox multivariate analysis adjusted for above demographic, clinical and pathological characteristics, showed that no difference among the three genotypes (Tables 2, 3).

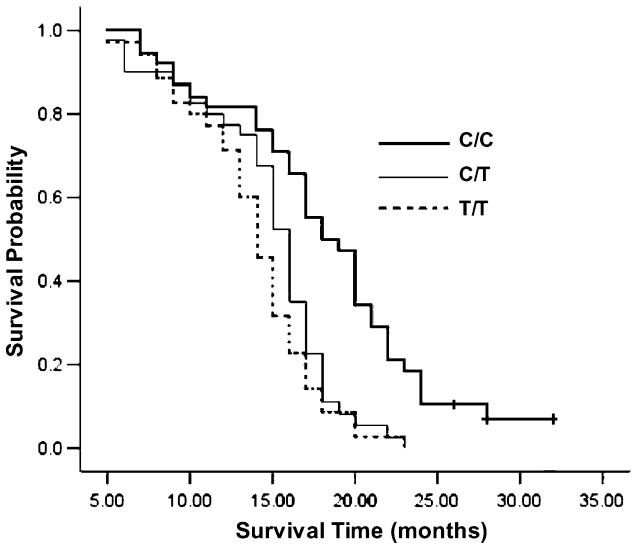

Fig. 1 Kaplan–Meier curves of ERCC1 C118T polymorphism

XRCC1 A399G polymorphism and treatment outcome

The relationship between DCR and ERCC1 genotypes reached borderline significance ($P = 0.068$) by crosstab, while the relationship disappeared ($P = 0.631$) after adjusting for those characters by logistic regression test. Individuals with the wild-type genotype (Arg/Arg) had an MST of 17 months, those with the heterozygous genotype (Arg/Gln) and variant genotype (Gln/Gln) both had an MST of 15 months. Similar to the analysis result of ERCC1, the log-rank test was significant ($P = 0.000$). Kaplan–Meier curves of the three polymorphisms are shown in Fig. 2. The Cox multivariate analysis adjusted for the above mentioned factors showed no difference of MST among the three genotypes (Tables 4, 5)

The combination of ERCC1 C118T and XRCC1 A399G polymorphisms and treatment outcome

In order to evaluate the effect of the combination of ERCC1 and XRCC1 polymorphisms, we divided the patients into three groups. Based on the above analysis result of these two genes, we defined ERCC1 C/C genotype and XRCC1 A/A genotype as favorable genotypes, and other genotypes as risk genotypes. In 33.6% of patients (38) there were two favorable genotypes (group 1); 35.4% of patients (40) had one favorable genotype (group 2), and 31% of patients (35) had no favorable genotypes (group 3). The χ^2 test showed that the DCR was significantly different among the three groups, which were 80.38% in group 1, 61.54% in group 2 and 71.68% in group 3 ($P = 0.002$). The logistic regression test also confirmed the difference after adjusting for the above factors ($P = 0.01$). Median survival times in group 1 patients, group 2 patients, and

Table 2 ERCC1 C118T polymorphism and DCR

ERCC1 118 genotypes	Cases [*n* (%)]		Chi-square test		Binary logistic regression analysis	
	Disease controllers	Disease uncontrollers	χ^2	*P*	χ^2	*P*
C/C	44 (80.0)	11 (20.0)	4.743	0.093	0.191	0.662
C/T	29 (67.44)	14 (33.56)				
T/T	8 (53.33)	7 (46.67)				
Total	81 (71.68)	32 (28.32)				

Table 3 ERCC1 C118T polymorphism and MST

ERCC1 118 genotypes	MST (months) (95% CI)	Log-rank test		Cox regression analysis		
		χ^2	*P*	HR	95% CI	*P*
C/C	17 (15.740, 18.260)	11.671	0.001	1		0.136
C/T	16 (15.398, 16.602)			1.457	0.935, 2.268	0.096
T/T	16 (14.224, 17.776)			1.654	0.910, 3.006	0.099
Total	16 (15.370, 16.630)					

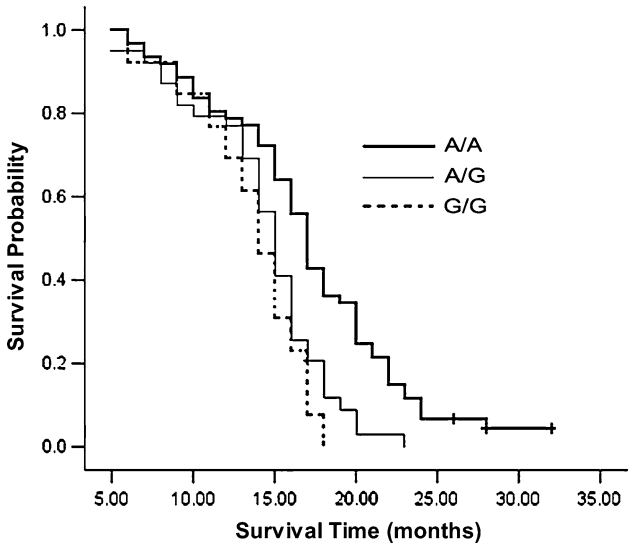

Fig. 2 Kaplan–Meier curves of XRCC1 A399G polymorphism

group 3 patients were 18, 16, and 15 months, respectively. Kaplan–Meier curves of the three groups are shown in Fig. 3. The adverse effect with shorter MST in groups 2 and 3 was also observed in the multivariate analysis (Tables 6, 7).

In addition, patients with a performance status ECOG = 2 showed an increased risk of dying of 1.41 (95% CI 1.099–1.809; $P = 0.007$) when compared with patients who showed a superior performance status (ECOG, 0–1). Age, sex, tumor histological grade, chemotherapy regimen, location of the tumor and number of metastases were not associated with MST in this series of patients.

Discussion

Interindividual variations in DNA repair ability have been recognized to modulate tumor responses to DNA damage inducing drugs; nucleotide excision repair activity and base excision repair activity have been shown to influence platinum-based chemotherapy [16, 17]. The objective of this study was to evaluate whether common germline polymorphisms in ERCC1 and XRCC1 predict OS and DCR in patients with metastatic colorectal cancer receiving oxaliplatin-based chemotherapy. We also sought to investigate the combined effect of these two factors. Different from the previous study, this is the first study which showed that the polymorphisms of ERCC1 and XRCC1, in combination not individually, were significantly associated with DCR and OS, and the combination of these two gene polymorphisms could be used as an independent predictive marker.

ERCC1 is the primary enzyme in the NER pathway, and important for the removal of DNA adducts caused by oxaliplatin compounds [18]. High ERCC1 levels are associated with increased platinum resistance. The in vitro studies suggest a C to T transition at codon 118 of the ERCC1 gene, which results in the same amino acid asparagine, is associated with higher ERCC1 mRNA levels resulting in resistance to platinum drugs [19]. However, the clinical data regarding the assumed relationship between ERCC1 codon 118 polymorphism and platinum sensitivity is controversial [20–22], even in the treatment of colorectal cancer [23–25]. In this study, patients with ERCC1 118C/C genotype tended to have higher DCR and longer OS than patients with the other polymorphisms, but the advantage was not significant. Thus, the predictive role of the ERCC1

Table 4 XRCC1 A399G polymorphism and response rate

XRCC1 399 genotypes	Case [*n* (%)]		Chi-square test		Binary logistic regression analysis	
	Disease controllers	Disease uncontrollers	χ^2	*P*	χ^2	*P*
A/A	49 (80.38)	12 (19.62)	5.387	0.068	0.230	0.631
A/G	25 (64.1)	14 (35.9)				
G/G	7 (53.85)	6 (46.15)				
Total	81 (71.68)	32 (28.32)				

Table 5 XRCC1 A399G polymorphism and MST

XRCC1 399 genotypes	MST (months) (95% CI)	Log-rank test		Cox regression analysis		
		χ^2	*P*	HR	95% CI	*P*
A/A	17 (16.085, 17.915)	14.902	0.000	1		0.834
A/G	15 (14.322, 15.678)			1.089	0.571, 2.078	0.796
G/G	15 (13.826, 16.174)			1.307	0.525, 3.252	0.565
Total	16 (15.370, 16.630)					

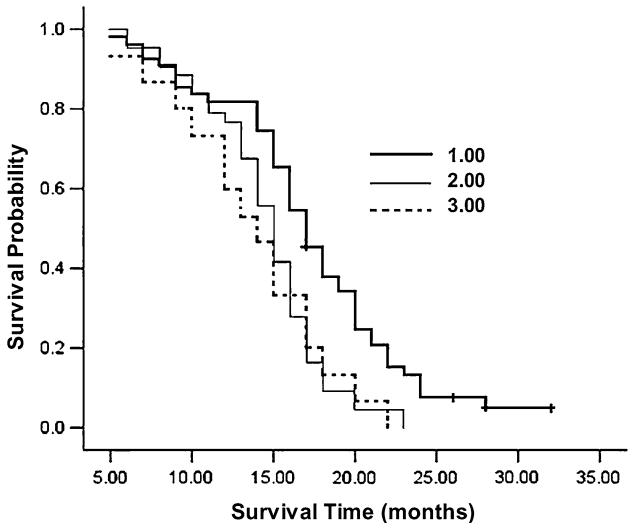

Fig. 3 Kaplan–Meier curves of the combination of ERCC1 and XRCC1 polymorphisms

codon 118 polymorphism in oxaliplatin-treated patients may need additional study.

XRCC1 is one of the most important DNA repair genes. The XRCC1 protein physically interacts with ligase III and poly(ADP ribose) polymerase, playing an important role in the removal of DNA adducts through base excision repair (BER) and in the repair of double strand breaks which also induced by platinum [26]. The in vitro study shows cells having a 399 A to G SNP impair DNA repair activity by failing to recognize single-strand breaks. Theoretically, cells with a 399 A to G SNP, such as Arg/Glu and Glu/Glu, show larger amounts of damaged DNA and augment the effect of oxaliplatin [27]. However, the predictive value of the polymorphism was not always consistent with in vitro findings in the clinical studies [24, 25, 27, 28]. In the present study, patients with XRCC1 399 Arg/Arg seemed to have a better treatment outcome, but there was no significant association between them statistically after adjusting for other factors that may influence the chemotherapy efficacy.

Different from the analysis of SNP in one gene, the combination of two favorable genotypes was significantly associated with a good treatment outcome. One interpretation is that ERCC1 codon 118 polymorphism may be in linkage disequilibrium with XRCC1 codon 399 polymorphism, for both genes located on the same region of chromosome 19 (Table 8). The linkage disequilibrium between them can directly affect their expressions, or their functions, leading to decreasing or increasing DNA repair activity. Another reason maybe it is the bias caused by the small sample size and number of events.

In addition, in vitro tests may not accurately reflect the situation in vivo, and information on functional effects of polymorphisms from experimental investigations is not always conclusive. A number of additional factors can contribute to inconsistent findings among association studies. These factors include cancer type, stage or grade of the tumor, patient ethnicity, limited sample size, misclassification of phenotype, and population structure, etc. [29]. For example, the XRCC1 Arg399Gln genotypes frequencies in our study are in close agreement with those recently reported in oriental patients [30–32], but different from data from western countries [33]. So, interpretation of our results is complicated by controversies regarding which polymorphism confers increased or decreased DNA repair activity and which assay evaluates DNA repair activity most accruable, although various assays have been developed to quantify DNA repair activity. If gene mRNA levels or

Table 6 The combination of ERCC1 and XRCC1 Polymorphisms and response rate

XRCC1 combined with ERCC1 genotypes	Cases [*n* (%)]		Chi-Square Test		Binary logistic regression analysis	
	Disease controllers	Disease uncontrollers	χ^2	*P*	χ^2	*P*
Group 1	35 (80.38)	3 (19.62)	12.386	0.002	6.676	0.01
Group 2	23 (61.54)	17 (38.46)				
Group 3	23 (71.68)	12 (28.32)				
Total	81 (71.68)	32 (28.32)				

Table 7 The combination of ERCC1 and XRCC1 polymorphisms and MST

XRCC1 combined with ERCC1 genotypes	MST (months) (95% CI)	Log-rank test		Cox regression analysis		
		χ^2	*P*	HR	95% CI	*P*
Group 1	18 (15.986, 20.014)	20.965	0.000	1		0.000
Group 2	16 (15.489, 16.511)			2.247	1.375, 3.671	0.001
Group 3	15 (14.175, 15.825)			2.595	1.561, 4.313	0.000
Total	16 (15.370, 16.630)					

Table 8 Distribution of ERCC1 and XRCC1 polymorphisms

Polymorphisms	XRCC1 polymorphism		
	A/A	A/G_	G/G_
ERCC1 polymorphism			
C/C	39	15	2
C/T	17	16	9
T/T	5	7	3

Fisher's exact test, $P = 0.004$

protein levels were observed at the same time, the result could be more convincing.

To conclude, in our study the genotype of ERCC1 118C/C or XRCC1 399 Arg/Arg seem to indicate better treatment outcome, but its predictive role can be effected by some other clinical factors, especially the patient's performance status. A combined genotype analysis of ERCC1-118 and XRCC1-399 may contribute to the selection of patients who would benefit from oxaliplatin-based chemotherapy for metastatic colorectal cancer independently. In the current study, germline genotypes were determined from peripheral blood mononuclear cells, this offers better clinical accessibility and applicability, compared to tumor tissue DNA or mRNA, which making these tests potentially useful in the clinical setting. Our study is limited by its small sample size and different cycles of chemotherapy. Future studies, preferably within the context of large randomized prospective control trials, should attempt to determine how accurately these markers will predict outcome, and, if found to be a truly independent determinant of outcome, treatment should be assigned on the basis of marker status.

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