ERCC1 and XPD/ERCC2 Polymorphisms' Predictive Value of Oxaliplatin-Based Chemotherapies in Advanced Colorectal Cancer has an Ethnic Discrepancy: A Meta-analysis

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Our purpose is to evaluate the predictive value of the genetic polymorphisms of Excision repair cross-complementing group 1 (ERCC1) and xeroderma pigmentosum group D/excision repair cross-complementing group 2 (XPD/ERCC2) in patients with advanced colorectal cancer receiving oxaliplatin-based chemotherapy, and we performed a meta-analysis in order to obtain a more precise estimation for a more optimizing individual chemotherapy. The relevant cohort studies were identified by searching the electronic databases of MEDLINE, EMBASE, and CNKI. We used "colorectal," "cancer," "carcinoma," "ERCC1," "XPD or ERCC2," "polymorphism," "oxaliplatin," "treatment," or "chemotherapy" as key words. Inclusion criteria were patients with advanced colorectal cancer receiving oxaliplatin-based chemotherapy, evaluation of polymorphism of ERCC1 and XPD/ERCC2, and overall response rate (ORR). In this meta-analysis, a total of seven studies were selected according to the inclusion criteria. Five studies investigated ERCC1 codon

118 polymorphisms and three studies evaluated XPD/ERCC2 codon 751 polymorphisms. For ERCC1 codon C118T polymorphism, the ORR to oxaliplatin-based chemotherapy in patients with C/C wild genotype was 77.27% and it was 69.30% for C/T and T/T variant genotype. The pooled odds ratio (OR) for C/C wild-type vs. C/T and T/T genotype was 1.11 (95% CI, 0.86–1.42; $P = 0.42$). For XPD/ERCC2 Lys751Gln polymorphism, the response rate was 86.58 and 67.57% in patients with the A/A and either one or two C alleles (A/C or C/C) respectively, and the pooled OR was 1.15 (95% CI, 1.01–1.30; $P = 0.03$). Furthermore, we chose subgroup analysis in order to find the difference between the Caucasian and Asian ethnicity. The results indicated that Oxaliplatin sensitivity was significantly associated with ERCC1 C118T polymorphism in Asian people. XPD/ERCC2 Lys751Gln polymorphism had the predictive value especially for the patients from the America and Europe. *J. Clin. Lab. Anal.* 26:10–15, 2012. © 2012 Wiley Periodicals, Inc.

Key words: ERCC1 XPD/ERCC2; polymorphism; oxaliplatin-based chemotherapy; colorectal cancer; Meta-analysis.

INTRODUCTION

Platinum-based chemotherapeutic regimens have been widely used in the treatment of a variety of tumors, such as nasopharyngeal, esophageal, mammary, lung, gastric,

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and ovarian cancer. Oxaliplatin is a relatively new platinum analog, which has been approved to be used in the clinic in the European Union and the United States since 1999 and 2002. Compared with the earlier platinum analog cisplatin and carboplatin, Oxaliplatin has a different spectrum of toxicity, whose renal toxicity, peripheral neuritis, hematotoxicity, and gastrointestinal toxicity showed an obvious decrease (1). Interestingly, Oxaliplatin also showed a different spectrum of anti-tumor activity, which can especially be used for the treatment of metastatic colorectal cancer (CSC), a disease known to be insensitive to platinum (2–5). However, large data in clinical studies have showed that Oxaliplatin has drug resistance (6). Although many factors have been known to correlate with the resistance to Oxaliplatin-based chemotherapy, DNA repair capacity plays a key role in the Oxaliplatin sensitivity to colorectal carcinomas.

Oxaliplatin carrying a 1,2-diamino-cyclohexane ligand (DACH) has shown to exert its antitumor effects by Pt-DACH-DNA adducts formation, interfering with DNA replication, transcription and RNA synthesis. If the Pt-DACH-DNA adducts are not removed from DNA, they are lethal (7). Nucleotide excision repair (NER) as an important DNA repair pathway is thought to repair DNA damage caused by Oxaliplatin (8). Excision repair cross-complementing group 1 (ERCC1) xeroderma pigmentosum group D/excision repair cross-complementing group 2 (XPD/ERCC2) and other repair factors participate in the key steps of NER such as the damage recognition and removal of the lesion (9). ERCC1, an excision nuclease, forms a heterodimer with Xeroderma Pigmentosum F (XPF) and executes a 5' incision into the damaged DNA strand (10). XPD/ERCC2 recognizes and repairs many structurally unrelated lesions, and its protein has a role in the initiation of RNA transcription by RNA polymerase II (11). Single nucleotide polymorphisms (SNP) in ERCC1 and XPD/ERCC2 that alter the efficiency of DNA repair capacity could be used as valuable predictive factors for oxaliplatin-based chemotherapy.

Recently, several analyses have shown that the polymorphisms of ERCC1 and XPD/ERCC2 correlate with the sensitivity of platinum-based chemotherapies in nonsmall cell lung cancer (NSCLC) (12). However, whether the polymorphisms of ERCC1 and XPD/ERCC2 can be effective predictive markers of colorectal cancer treated with Oxaliplatin-based chemotherapy has not been systematically addressed. Therefore, a meta-analysis of published studies was performed in order to further explore the relationship between polymorphisms of ERCC1, XPD/ERCC2 and the sensitivity to Oxaliplatin-based chemotherapy in advanced colorectal cancer.

MATERIALS AND METHODS

Literature Search Strategy

We searched for relevant publications before December 31, 2010 in English or in Chinese literature by using three electronic databases (MEDLINE, EMBASE, and CNKI) with the following key words “colorectal,” “cancer,” “carcinoma,” “ERCC1,” “XPD or ERCC2,” “polymorphism,” “oxaliplatin,” “treatment or chemotherapy.” The inclusion criteria as the following were identified. (1) Patients with advanced colorectal cancer receiving oxaliplatin-based chemotherapy; (2) Eligible Cohort studies; (3) ERCC1 and XPD/ERCC2 polymorphisms' assessment. We excluded studies with the same data or overlapping data by the same authors.

Data Extraction

Research data were manually extracted from each published article by two different investigators. The following information were collected from each study: first author, publication date, country (ethnicity), a total number of patients included in the study, chemotherapy protocols, genotype of ERCC1 codon 118 and XPD/ERCC2 codon 751 polymorphism and the overall response rate (ORR).

Response Criteria

The endpoints in our meta-analysis were response rate (RR) to chemotherapy, which evaluated according to WHO criteria. Objective responses to chemotherapy were divided into the following categories: complete responders (CR, disappearance of the disease); partial responders (PR, at least 50 reduction in tumor load); stable disease (SD $\leq$ 25 progression, $<$ 50 shrinkage). Progressive disease was classified as nonresponders (size enlargement $>$ 25 or appearance of new lesions).

Therefore, $RR = CR + PR + SD$.

Statistical Analysis

We calculated the ORR, the pooled odds ratio (OR), and 95% confidence interval (CI); meanwhile, the results were weighted by trial size in our meta-analysis. Both the fixed effect model (the inverse variance-weighted method) and the random effect model (DerSimonian and Laird method) were used to evaluate the pooled OR according to Mantel-Haenszel. The Cochran Q statistics test was used for the assessment of heterogeneity. The pooled OR estimation was calculated by the fixed effect model if the effects were assumed to be homogenous, otherwise if the effects were heterogeneous the random effects model were used. The significance of the pooled OR was determined by the Z-test. Subgroup analysis was conducted

according to ethnicity difference between Asian and Caucasian people in order to estimate ethnic-specific OR. Publication bias was analyzed by funnel plot. An asymmetric plot suggested possible publication bias. Funnel plot asymmetry was assessed by Egger's linear regression test, a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of the OR. The statistical tests used in meta-analysis were performed with RevMan 4.2 and STATA 9.0 software. *P* value <0.05 was considered significant in our analysis.

RESULTS

Study Characteristics

According to the searching criteria related to ERCC1, XPD/ERCC2 SNPs and the sensitivity of Oxaliplatin-based chemotherapy in advanced colorectal cancer, we searched the online Medline database and retrieved a total of 16 references by browsing titles and abstracts. There were no additional references provided by EMBASE database. Seven studies finally included in the meta-analysis after exclusion. Except one study (13), the studies are all reported excluded patients. Table 1 lists these studies identified and their main characteristics.

Nine studies were excluded: these included three articles written by the Jun Liang's group due to overlap of study data (14–16); two studies compare only ERCC1 expression levels (17, 18); one is only about ERCC1 codon 259 (19); one reported only the survival time (20); and two articles did not include the related data (21, 22). Hence, a total 7 studies met our inclusion criteria, of which five investigated the SNPs of ERCC1 codon 118 (13, 23–26) and three studies report the SNPs of XPD/ERCC1 codon 751 (26–28). In each article, gene polymorphisms were detected by “real-time” quantitative polymerase chain reaction (qPCR) or TaqMan technique. All studies used peripheral blood to assess the germ line genotype.

Meta-analysis Statistic Results

A total of 527 patients were investigated for ERCC1 codon C118 T (the patients with C/C genotype was 198), and 379 patients were evaluated for XPD/ERCC2 codon 751 (the patients with A/A genotype was 200).

For ERCC1 codon C118 T SNPs, five articles reported the ORR; the results indicated that the ORR of patients with C/C to Oxaliplatin-based chemotherapy was 77.27 (Table 2). Significant homogeneity existed in these five studies when the C/C genotype was compared with C/T or T/T; therefore, the fixed effects model was used to calibrate the results. There was no significant evidence that C/C genotype associated with the clinical outcome of advanced colorectal cancer treated with oxaliplatin.

TABLE 1. Characteristics of Researches Included in the Meta-Analysis and the Genotype Frequencies of ERCC1 Codon 118 and XPD/ERCC2 Codon 751

First author (reference)	Country	Number of pts	Clinical stage	Chemotherapy	Methods	Gene	Chemotherapy cycle
Peter Mu-Hsin Chang (13)	China (Asian)	168	Unresectable metastatic colorectal cancer	FOLFOX-4	PCR-RFLP	ERCC1 codon 118	NS
Jun Liang	China (Asian)	113	Metastatic colorectal cancer	FOLFOX-4	TaqMan PCR	ERCC1 codon 118	≤2 cycles
K.-L.G.Spindler (24)	Danmark (Caucasian)	66	Advanced colorectal cancer	XELOX	PCR	ERCC1 codon 118	6 cycles
Jun Liang* (25)	China (Asian)	62	IV colorectal cancer	FOLFOX or XELOX	TaqMan PCR	ERCC1 codon 118	2–3 cycles
L Pare (26)	Spain (Caucasian)	118	Metastatic CRC	OX combined with 5-FU	TaqMan PCR	ERCC1 118 XPD ⁷⁵¹	9 cycles
David J. Park (27)	America (Caucasian)	70	Refractory advanced colorectal cancer	5-FU/oxaliplatin	PCR-RFLP	XPD codon 751	NS
Jiun-I. Lai (28)	China (Asian)	188	Unresectable metastatic CRC	FOLFOX-4	PCR-RFLP	XPD 751	NS

PCR, polymerase chain reaction restriction, RFLP, fragment length polymorphism, NS, not stated.

TABLE 2. Meta-analysis for ERCC1 Codon 118 SNP and Oxaliplatin Treatment of Advanced Colorectal Cancer

Study	C/C		C/T or T/T		RR	95% CI	Weigh
	Responder	N	Responder	N			
Peter Mu-Hsin Chang (13)	74	80	68	88	1.20	1.05,1.36	30.60
Jun Liang (23)	44	55	37	58	1.25	0.99,1.59	25.78
K.-L.G.Spindler (24)	5	6	55	60	0.91	0.63,1.31	19.47
Jun Liang* (25)	23	33	11	29	1.84	1.10,3.08	13.76
L Pare (26)	7	24	57	94	0.48	0.25,0.92	10.39
Sum	153	198	228	329	1.11	0.86,1.42	100.00

TABLE 3. Meta-analysis for XPD/ERCC2 Codon 751 SNP and Oxaliplatin Treatment of Advanced Colorectal Cancer

Study	A/A		A/C or C/C		RR	95% CI	Weigh
	Responder	N	Responder	N			
L Pare (26)	35	52	32	69	1.45	1.06,1.99	28.21
David J.Park (27)	18	21	41	49	1.02	0.83,1.27	25.23
Jiun-I. Lai (28)	147	158	27	30	1.03	0.91,1.17	46.55
Sum	200	231	100	148	1.15	1.01,1.30	100.00

Forest plot of ERCC1 codon C118 T SNPs showed that the pooled OR was 1.11, 95% CI (0.86–1.42) by fixed effects ($P = 0.42$) with $P_{\text{heterogeneity}} = 0.01$.

For ERCC2/XPD codon 751, three articles reported the pool RR, in which RR of A/A genotype to Oxaliplatin-based chemotherapy was 86.58 (Table 3). No significant heterogeneity existed in these studies when A/A genotype was compared with A/C or C/C. The fixed effects model was used to pool the result. The summary OR was 1.15, 95% CI (1.01–1.30) by random effects ($P = 0.03$) with $P_{\text{heterogeneity}} = 0.05$.

Egger's test provided no evidence for funnel plot asymmetry in the comparison of C/C gene type vs. C/T or T/T gene type in the RR analysis in advanced colorectal cancer. (Begg's funnel plot have not shown.)

Subgroup Analysis

To examine the effect of ethnicity, the studied population in our analysis was divided into two groups, one from Asia (mainly from China), and the other from Europe and America. We performed subgroup analysis in order to find the characteristics of ethnicity. Subgroup analysis indicated that the association can be found between the ERCC1 codon C118T polymorphism and the clinical outcome of advanced colorectal cancer treated with oxaliplatin in Asian people. On the other hand, for the patients from Europe and America, no statistical significance can be found between different genotypes and the sensitivity of Oxaliplatin (Table 4). For the ERCC2/XPD codon 751 polymorphism, subgroup analysis indicated that if the patients were from Europe and America, the predictive value

TABLE 4. Subgroup Analysis of Correlation Between Polymorphism of ERCC1 Codon 118 and Oxaliplatin Treatment of Advanced Colorectal Cancer

Region	Genotype	RR	95% CI	Z	P
Europe and America	C/C	0.68	0.30–1.57	0.90	0.37
China	C/C	1.26	1.07–1.49	2.79	0.005

TABLE 5. Subgroup Analysis of Correlation Between Polymorphism of XPD/ERCC2 Codon 751 and Oxaliplatin Treatment of Advanced Colorectal Cancer

Region	Genotype	RR	95% CI	Z	P
Europe and America	A/A	1.25	1.02–1.53	2.16	0.03
China	A/A	1.03	0.91–1.17	0.51	0.61

of ERCC2/XPD codon 751 polymorphism to Oxaliplatin sensitivity was much more important (Table 5).

DISCUSSION

On a worldwide scale especially in the western countries, an estimated increasing new cases of colorectal cancer have been diagnosed in recent decades. Although improved screening conditions, as well as modest gains in screening rates allowed more cases to be detected at an earlier stage, a significant proportion of colorectal cancer is diagnosed at advanced stages. Therefore, the effectively managed chemotherapy should be applied to treat advanced colorectal cancer. Oxaliplatin-based chemotherapy are widely used either in the adjuvant or palliative

setting, but its objective responses has been found to change between 10 and 50% (29). In order to improve its efficacy and safety, individuating drug therapy should be considered. As pharmacokinetics sheds new light on the classical pharmacological question and understanding why individuals respond differently to various drug treatments, it was considered into applying to the antitumor individual chemotherapy.

ERCC1 C118T (rs11615) and C8092A (rs3212986) are two common SNPs related to colorectal cancer patients treated with oxaliplatin-based chemotherapy (30). In our meta-analysis, we assessed the role of ERCC1 C118T polymorphisms in relation to their response to oxaliplatin-based chemotherapeutic agents in patients with advanced colorectal cancer. We found that the Asian/Chinese patients with the C/C genotypes in the ERCC1 C118T polymorphism exhibited a higher response to oxaliplatin-based chemotherapy than those with the C/T or T/T genotype. For the C118T polymorphism, the common AAC coding for asparagines (Asn) is transformed into AAT, which is rarely used (20). The consequences of this synonymous substitution are not yet clear, but there is some evidence that the 118T allele is associated with higher ERCC1 expression and shorter overall survival in colorectal cancer patients treated with oxaliplatin-based regimens (31). One of the theories is that these effects might be caused by differences in the translational efficiency of the 118T codon. The level of intratumoral ERCC1 mRNA has been studied for its usefulness as a predictive marker of chemotherapeutic response and survival in patients with NSCLC treated with cisplatin combination chemotherapy (32). However, the molecular mechanisms mediating SNP-induced ERCC1 mRNA changes remain largely unknown.

The prevalence in Caucasians and Asian of the 118C alleles of ERCC1 according to NCBI website is 0.35 and 0.41, respectively. In order to distinguish the difference between the Caucasians and Asians ethnicity, we performed a subgroup analysis. The results indicated that the association between ERCC1 codon 118 polymorphism and the clinical outcome of advanced colorectal cancer treated with oxaliplatin can only be found in Asian. Our conclusions remind the predictive value of ERCC1 C118T polymorphism is valid in Asian people.

The XPD/ERCC2 gene has three common SNPs that have been intensively studied in the context of genetic susceptibility to various types of cancer, which are polymorphisms in exon 6 (Arg156Arg, C → A), exon 10 (Asp312Asn, G → A), and exon 23 (Lys751Gln, A → C). Some studies reported that Polymorphisms of XPD codon 751 and 312 did not reveal statistically different responses to chemotherapy among the wild type, homozygous, or heterozygous genotypes in patients with NSCLC treated with cisplatin combination chemother-

apy, therefore XPD Lys751Gln as a predictive maker for chemotherapy response has been questioned. Although there were only three articles reported the relationship between XPD Lys751Gln polymorphism and the sensitivity of Oxaliplatin-based chemotherapy in our analysis, we concluded a positive trend of XPD Lys751Gln. According to the further subgroup analysis, we found that the summary frequency of the Lys751 allele among Caucasians was significantly lower than that among Asians. Therefore, the predictive value of XPD Lys751Gln polymorphism among Caucasians is confirmed in our analysis.

Despite our efforts in performing a comprehensive analysis, for example, we used the funnel plot to evaluate the publication bias and it reflects good funnel plot symmetry. Limitations of our meta-analysis need to be addressed. First, heterogeneity in our meta-analysis is required to be solved because most of the included studies were retrospective and differed significantly in their study design, such as patient selection, chemotherapeutic protocol and follow-up time. In addition, at most times we used the unadjusted estimates and the potential biases cannot be totally avoided in our meta analysis. Because of the limited articles available, we were not able to compare the different Oxaliplatin-based regimen such as 5-Fu and Capecitabine. In most recent days, there was a systemic review to evaluate the prognostic factors of ERCC1 and ERCC2 polymorphisms and platinum-based chemotherapies in Gastrointestinal cancer (33). Compare with it, we choose articles fully published in English and Chinese. Our meta analysis emphasize the ethnic discrepancy of the predict value between Asians and Caucasians. Since Oxaliplatin showed a different spectrum of antitumor, which can especially be used for the treatment of metastatic colorectal cancer, a disease known to be insensitive to platinum, we focused on colorectal cancer in the meta-analysis.

In summary, our meta-analysis suggests that ERCC1 codon 118 polymorphisms have predictive value in Oxaliplatin-based chemotherapy to the Asian/Chinese patients with advanced colorectal cancer. Meanwhile for the patients from the America and Europe, the XPD/ERCC2 codon 751 polymorphisms' predictive value was also confirmed in our subgroup meta-analysis. Therefore, it is necessary to conduct large trials using standardized unbiased methods and instruct the individual antitumor chemotherapy in clinic practice.

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