RESEARCH ARTICLE

GSTP1, ERCC1 and ERCC2 Polymorphisms, Expression and Clinical Outcome of Oxaliplatin-based Adjuvant Chemotherapy in Colorectal Cancer in Chinese Population

Hui-Yan Li[1]*, Xin Ge[2], Guang-Ming Huang[2], Kai-Yu Li[2], Jing-Quan Zhao[2], Xi-Miao Yu[2], Wen-Si Bi[2], Yu-Lin Wang[3]

Abstract

Aim: Platinum agents have shown to be effective in the treatment of colorectal cancer. We assessed whether single nucleotide polymorphisms (SNPs) in GSTP1, ERCC1 Asn118Asn and ERCC2 Lys751Gln might predict the overall survival in patients receiving oxaliplatin-based chemotherapy in a Chinese population. Methods: SNPs of GSTP1, ERCC1 Asn118Asn and ERCC2 Lys751Gln in 335 colorectal cancer patients were assessed using TaqMan nuclease assays. Results: At the time of final analysis on Nov. 2011, the median follow-up period was 37.7 months (range from 1 to 60 months). A total of 229 patients died during follow-up. Our study showed GSTP1 Val/Val (HR=0.44, 95% CI=0.18-0.98), ERCC1 C/C (HR=0.20, 95% CI=0.10-0.79) and ERCC2 G/G (HR=0.48, 95% CI=0.19-0.97) to be significantly associated with better survival of colorectal cancer. GSTP1 Val/Val, ERCC1 C/C and ERCC2 G/G were also related to longer survival among patients with colon cancer, with HRs (95% CIs) of 0.41 (0.16-0.91), 0.16 (0.09-0.74) and 0.34 (0.16-0.91), respectively. Conclusion: GSTP1, GSTP1, ERCC1 Asn118Asn and ERCC2 Lys751Gln genotyping might facilitate tailored oxaliplatin-based chemotherapy for colorectal cancer patients.

Keywords: GSTP1 - ERCC1 Asn118Asn - ERCC2 Lys751Gln - colorectal cancer - chemotherapy

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Introduction

Colorectal cancer is the third most common cancer in men (663 000 cases, 10.0% of the total) and the second in women (571 000 cases, 9.4% of the total) worldwide (IARC, 2008). Despite improved screening methods, a significant proportion of cases are diagnosed in the advanced stages. For the advanced colorectal cancer, the chemotherapy either in the adjuvant or palliative setting is necessary. However, the objective responses of the various drugs range between 10 and 50%, either as single agents or in combination. Cisplatin or oxalipatin is commonly used with 5-fluorouracil (5-FU) as chemotherapy doublets in the treatment of colorectal cancer. Despite the efficacy of combined chemotherapies, a large proportion of patients display varying levels of resistance, indicating that the therapeutic efficacy has a remarkable interindividual variability. Since DNA kinking is the major feature of oxaliplatin-DNA adducts that block DNA replication and lead to cancer cell death (Faivre et al., 2003; Reed, 2005), which is recognized and repaired by the nucleotide excision repair (NER) pathways. It is reported the interindividual difference in the NER capacity may influence the efficacy of oxaliplain-based chemotherapy and clinical outcomes of the cancer patients. ERCC1 Asn118Asn and ERCC2 Lys751Gln are two important proteins in NER pathway. Several polymorphisms of the two genes have been reported to play important role in the response to oxaliplatin-based chemotherapy (Ishibashi et al., 2011; Noda et al., 2012).

Resistance to platinum agents may also depend on altered detoxification pathways. Growing evidence indicates that glutathione S-transferase (GST), a superfamily of dimeric phase II metabolic enzymes, determine cytotoxicity of a variety of chemotherapeutic agents including platinum drugs (Townsend and Tew, 2003). Previous study showed the polymorphisms of GSTP1 increase the efficacy of chemotherapeutic agents (Stoehlmacher et al., 2003; Stoehlmacher et al., 2004). The isoenzyme GSTP1 is highly expressed in human colorectal cancer issues, and participates in the detoxification of platinum drugs that may mediate the resistance to platinum-based chemotherapy. A single nucleotide polymorphism in exon 5 of the GSTP1 gene causing isoleucine to valine substitution in the 105th amino acid (Il105V) significantly decrease GSTP1 activity, and has a profound impact on chemotherapy for colorectal cancer patients (Stoehlmacher et al., 2003; Stoehlmacher et al., 2004).

From a genetic viewpoint, in a multi-factorial disease,

*[1]Department of Radiology, the Third Affiliated Hospital of Harbin Medical University, [2]Department of General Surgery, Heilongjiang Province's Hospital, Harbin, [3]Department of Hepatopancreatobiliary and Splenic Medicine, Affiliated Hospital of Medical College of Chinese People's Armed Police Force, Tianjin, China *For correspondence: liuyixia1997@126.com*

analysis of single polymorphism is difficult to explain its role in altering the extent of a physiologic or pathologic phenotype. Therefore, combined analysis of the DNA repaired gene in the NER pathways and GSTP1 gene may actually identify patients with maximal benefit, or toxicity, from oxaliplatin-based adjuvant chemotherapy. Therefore, in the current study, we clarify the impact of three genetic polymorphisms within genes involved in the detoxification of oxalipatin (GSTP1) and DNA repair genes (ERCC1 Asn118Asn and ERCC2 Lys751Gln) on the clinical outcome of colorectal cancer patients receiving adjuvant chemotherapy.

Materials and Methods

Patients

335 cases were firstly diagnosed as primary advanced colorectal carcinoma (including 182 colon and 153 rectal cancer patients) between Jan. 2006 and Nov. 2007. All the patients were treated with 5-FU/oxaliplatin regimen (FOLFOX6) as the initial treatment. Individuals who had not primary cancer, died for blood sampling, were lost to follow-up, or were unwilling to participate were excluded. The treatment regimen consisted of intravenous leucovorin (400 mg/m^2) on the first day, intravenous 5-FU (400 mg/m^2) on the first day followed by an intravenous dose of 2,400 mg/m^2 over 46 h, and intravenous oxaliplatin (85 mg/m^2) on the first day. The disease were assessed by computed tomography every 4 cycles. If patients had hematologic toxic effects of grade 3 or grade 4 or nonhematologic toxic effects of grades 2 to 4, their daily dose was reduced properly.

Data collection

A uniform questionnaire was used for all subjects regarding sociodemographic characteristics, alcohol consumption, smoking and other potential confounding factors by face to face interviewers. Information was collected on known or potential risk factors including BMI, alcohol consumption, cigarette use, physical activity and family history of colorectal cancer.

Alcohol consumption were divided into never and moderate and heavy drinkers. Individuals who drank 100 -250 g alcohol (400 ml beers, 250 wine ml and 100 ml white spirit) per month and continued for 6 months were regarded as moderate drinkers, and those who drank more than 250 g alcohol per month were as heavy drinkers. Tobacco smoking was categorized into never and current drinking. Individuals who smoked 20-50 packets of cigarettes per year, or smoked more than one cigarette per day and continued for 6 months were regarded as moderate smokers, and those who smoked more than 50 packets of cigarettes per years were as heavy smokers. Height, current body weight and body weight 10 years before the study were recorded to analyze the body mass index (BMI, kg/m^2).

DNA extraction and genotyping

All participants provided 5ml blood, and the blood were stored at -20 °C. Genomic DNA was extracted using a Qiagen Blood Kit (Qiagen, Chastworth, CA) according to the manufacturer's protocol.

The GSTP1, ERCC1 Asn118Asn and ERCC2 Lys751Gln genotyping was conducted with TaqMan Gene Expression assays using the ABI PRISM®7900HT Sequence Detection System (Applied Biosystems, Poster City, CA). Primer, probes, and reaction conditions are available upon request. We also performed genotyping of internal positive control samples, use of no template controls, and use of replicates for 20% of samples for quality control.

Statistical analysis

Follow-up began on the first day of participating. The overall survival was the time from study entry until death regardless of cause. All statistical tests are two sided. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) software 13.0 for windows. The main statistical methods used are Kaplan-Meier method, and the Cox Hazard regression model. Two of the censored times in the Kaplan-Meier plots presented are caused by patients being disease recurrence, development of lung or bone metastases, death from any cause or lost to follow-up. The main outcome variable analyzed is the presence of polymorphisms of GSTP1, ERCC1 Asn118Asn and ERCC2 Lys751Gln in the prognosis of osteosarcoma. The active genotype of GSTP1, ERCC1 Asn118Asn and ERCC2 Lys751Gln was taken as reference group. Therefore, in the Cox regression model, we divided patients into different groups according to a specific gene polymorphism. Similarly, in the Kaplan-Meier analysis, gene-by-gene comparisons can be made.

Results

The characteristics of the study subjects were summarized in Table 1. The mean age at diagnosis is

Table 1. Characteristics of Included Cases in our Studies

Variables	Cases (%) N=335	Patient deaths N=217	Five-year survival rate (%)	P value
Age (mean±SD, years)	61.5±6.9			
<45	28 (8.3)	22 (10.3)	19.60%	0.59
45-55	55 (16.5)	43 (19.7)	22.70%	
55-65	112 (33.5)	65 (30)	42.00%	
>65	140 (41.7)	87 (40)	37.90%	
Gender				
Male	232 (69.4)	149 (68.5)	36.10%	
Female	103 (30.6)	68 (31.5)	33.30%	
TNM stage				
I	19 (5.7)	3 (1.3)	85.20%	<0.05
II	55 (16.4)	20 (9.2)	63.70%	
III	136 (40.5)	14 (6.3)	25.90%	
IV	125 (37.4)	94 (43.2)	25.20%	
Grade				
In situ or well differentiated	98 (29.3)	72 (33.4)	26.20%	0.13
Moderately differentiated	148 (44.3)	105 (48.5)	29.10%	
Poorly/undifferentiated	45 (13.5)	17 (7.9)	62.10%	
Unknown	43 (12.9)	22 (10.2)	48.80%	
Histological subtype				
Adenocarcinoma	192 (57.3)	130 (59.8)	32.40%	0.54
Other	143 (42.7)	87 (40.2)	39.00%	
Location				
colon	182 (54.3)	106 (48.8)	41.80%	0.21
rectal	153 (46.7)	111 (51.2)	27.50%	

Table 2. Associations of GSTP1, ERCC1 Asn118Asn and ERCC2 Lys751Gln Gene Polymorphisms with Colorectal Cancer

Genotype	No. of patients (%) N=335	Patient deaths N=229	Median overall survival (months)	HR (95% CI)	HR (95% CI)[1]	P
GSTP1						
IIe/IIe	185 (55.2)	131 (60.3)	32.5	1.0 (Ref.)	1.0 (Ref.)	-
IIe /Val	120 (35.7)	76 (35.1)	37.8	0.89 (0.61-1.31)	0.85(0.58-1.28)	0.44
Val/Val	30 (9.1)	10 (4.6)	42.4	0.47 (0.20-1.03)	0.44(0.18-0.98)	<0.05
ERCC1 Asn118Asn						
T/T	166 (49.5)	121 (55.8)	33.1	1.0 (Ref.)	1.0 (Ref.)	-
C/T	140 (41.9)	89 (40.8)	37.2	0.87 (0.60-1.26)	0.81(0.52-1.14)	0.16
C/C	29 (8.6)	7 (3.4)	43.2	0.22 (0.12-0.81)	0.20(0.10-0.79)	<0.05
ERCC2 Lys751Gln						
T/T	153 (45.7)	110 (50.9)	31.8	1.0 (Ref.)	1.0 (Ref.)	-
T/G	150 (44.8)	95 (43.7)	36.8	0.88 (0.61-1.28)	0.86(0.56-1.20)	0.48
G/G	32 (9.5)	12 (5.4)	41.4	0.52 (0.23-1.09)	0.48(0.19-0.97)	<0.05

[1]Adjusted for age, gender, TNM stage, tumor grade, and histological subtype and location

Table 3. HR (95% CI) for Prognosis of Colorectal Cancer by Tumor Site

Gene	Colon		Rectum	
	Cases n=182	HR(95% CI)[1]	Cases n=153	HR (95% CI)[1]
GSTP1				
IIe/IIe	99 (54.4)	1.0 (Ref.)	86 (56.2)	1.0 (Ref.)
IIe /Val	67 (36.7)	0.80(0.51-1.02)	53 (34.5)	0.91(0.62-1.34)
Val/Val	16 (8.9)	0.41(0.16-0.91)	14 (9.3)	0.56(0.35-1.07)
ERCC1 Asn118Asn				
T/T	82 (45.3)	1.0 (Ref.)	83 (54.5)	1.0 (Ref.)
C/T	77 (42.4)	0.73(0.44-1.01)	63 (41.3)	0.93(0.61-1.33)
C/C	22 (12.3)	0.16(0.09-0.74)	6 (4.2)	0.35(0.17-0.93)
ERCC2 Lys751Gln				
T/T	81 (44.6)	1.0 (Ref.)	72 (47.0)	1.0 (Ref.)
T/G	83 (45.6)	0.70(0.49-1.13)	67 (43.8)	0.93(0.59-1.26)
G/G	18 (9.8)	0.34(0.16-0.91)	14 (9.1)	0.56(0.31-1.14)

[1]Adjusted for age, gender, TNM stage, tumor grade, and histological subtype and location

61.5±6.9 years. About 57.3% of the patients are males. Majority of the patients were TNM III and IV, and most of the patients were adenocarcinoma. At the time of diagnosis, 7.4% of the patients presented metastasis, while 32.3% developed metastasis during follow-up. At the time of final analysis on Nov. 2011, the median follow-up period was 37.7 months (ranged from 1 month to 60 months). A total of 229 patients died during follow-up.

Table 2 showed the overall survival data according to SNPs of GSTP1, ERCC1 Asn118Asn and ERCC2 Lys751Gln polymorphisms. Individuals with GSTP1 Val/Val genotype had a longer survival time and significantly lower the death of colorectal cancer compared with the wide-type genotype (GSTP1 IIe/IIe). Compared with patients with ERCC1 T/T genotype, patients with a homozygous ERCC1 C/C genotype had an increased survival time, with a median survival time of 43.2 months (HR=0.20, 95% CI=0.10-0.79). Meanwhile, the ERCC2 G/G genotype had a lower risk of death than those with T/T genotype, with HR (95% CI) of 0.48 (0.19-0.97).

Patients with colon cancer had a lower risk of death from colorectal cancer (Table 3). In comparision to the homozygotes of GSTP1, ERCC1 and ERCC2, colon patients with GSTP1 Val/Val, ERCC1 C/C or ERCC2 G/G showed a significantly and heavy association with decreased risk of death from colorectal cancer (HR=0.41, 95% CI=0.16-0.91 for GSTP1 Val/Val; HR=0.16, 95% CI=0.09-0.74 for ERCC1 C/C; and HR=0.34, 95% CI=0.16-0.91 for ERCC2 G/G).

Discussion

Interindividual variations in DNA repair ability have been recognized to modulate tumor responses to DNA damage inducing drugs. The nucleotide excision repair activity have been shown to influence platinum-based chemotherapy (Sharma et al., 2007; Martin et al., 2008). The objective of our study was to evaluate the polymorphisms in GSTP1, ERCC1 Asn118Asn and ERCC2 Lys751Gln predict the survival of colorectal cancer patients receiving 5-FU/oxaliplatin chemotherapy. Our pervious study explore the association of two DNA repaired genes, XRCC1 and XRCC3, with the survival of colorectal cancer (Zhao et al., 2012), and this is the first study which showed the GSTP1 Val/Val, ERCC1 C/C and ERCC2 G/G were significantly associated with better survival of colorectal cancer, and these three gene polymorphisms could be used as predictive markers for the prognosis of colorectal cancer.

The NER system is a major DNA repair system in mammalian cells for the removal of bulky, helix distorting DNA adducts produced by platinum agents. ERCC1 and ERCC2 is primary enzyme in the NER pathway, and seem to be mainly involved in repair of oxaliplatin-induced DNA damage (Kweekel et al., 2005). High ERCC1 and ERCC2 levels are related to increased removal of oxaliplatin-induced DNA adducts and oxaliplatin resistance. The in vitro studies indicated the ERCC1 T allele and ERCC2 T allele are associated with higher mRNA levels and DNA single-strand break repair than the ERCC1 C allele and ERCC2 T allele genotypes, and thus to induce the resistance to oxaliplatin based chemotherapy which used to damage the DNA of cancer cells. Previous studies showed the ERCC1 118 C allele and ERCC2 G allele are associated with decreased risk of death from non-small-cell lung cancer, colorectal cancer, gastric cancer, nasopharyngeal cancer, bladder cancer, and breast cancer (Baek et al., 2006; Rajaraman et al., 2008; Cao et al., 2011; Ishibashi et al., 2011; Sun et al., 2011;

Rouissi et al., 2011). Moreover, reports show an improved survival rate for colorectal cancer patients with ERCC1 118 C allele and ERCC2 G allele receiving 5-FU/oxaplatin chemotherapy (Ishibashi et al., 2011; Noda et al., 2012). Similar results were found for esophageal cancer and gastric cancer (Keam et al., 2008; Leichman et al., 2011). The results of our study are in line with previous studies, and proved the predictive role of ERCC1 codon 118 and ERCC2 codon 751 polymorphism in cancer patients receiving 5-FU/oxaplatin chemotherapy.

Increasing evidence has suggested an important role for drug-metabolizing enzymes in determining interindividual variations in therapeutic response. The GSTP1 is one of the multifunctional enzymes that detoxify a varety of electrophilic compounds. Previous studies suggested that genetic polymorphism in GSTP1 influence the efficacy of detoxifying cytotoxins generated by chemotherapeutics (Kim et al., 2011). The impairment of the GSTP1 Val/Val capacity caused by the A to G substitution could decrease the the enzyme function of detoxifying oxaliplatin-based chemotherapy. Previous study showed the GSTP1 Val allele could have a favorable overall survival in regarding to gastric cancer, breast cancer and prostate cancer (Kwee et al., 2012; Woolston et al., 2012; Zha et al., 2012). A previous study showed the individuals with GSTP1 Val allele had 0.3 fold risk of death from colorectal cancer compared with GSPT IIe/IIe genotype (Jun et al., 2009). Our study showed individuals with GSTP1 Val/Val have lower risk of colorectal cancer than the wide-type genotype, which is in agreement with previous reports in this cancer (Jun et al., 2009). However, there still some contradicting reports. A study conducted in Netherlands showed GSTP1 codon 105 polymorphism is not associated with oxaliplatin efficacy in advanced colorectal cancer patients (Kweekel et al., 2009; Kim et al., 2011). The lack of a predictive role for the GSTP1 polymorphism may be due to the difference in tissue-specificity and drug-specificity of GSTP1 isoenzymes, and the variation in ethnicities and study design.

Our previous study showed the tumor located in rectum had higher cancer risk than colon (Han et al., 2012). Therefore, the risk of death from rectum cancer might be higher than risk in colon, and our study showed a significantly lower risk of death from colon. This showed a gradually decreased risk of death from proximal colon to distal colon and to rectum. Previous study also found the difference risk between colon and rectum (Storm et al., 2010; Lascorz et al., 2012). A study conducted in Denmark also observed differences between colon and rectal cancer, with rectal cancer having better survival compared to colon cancer (Storm et al., 2010).

Limitations of this work included its retrospective single-center design and lack of other DNA repair genes. Until being confirmed by multi-center prospective studies, results from this study should not be over-interpreted. The limited numbers of cases would decrease the power the find the difference. Further study with large sample size is warranted.

In conclusion, the present study based on the analysis of GSTP1, ERCC1 Asn118Asn and ERCC2 Lys751Gln gene polymorphisms shows GSTP1 Val/Val, ERCC1 C/C and ERCC2 G/G genotypes might be association with better survival of colorectal cancer. Further studies are needed to validate the results of our study in Chinese population.

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