Correlation analysis between polymorphism of *GSTP1*, *XPD* and *XRCC1* gene in esophageal carcinoma patients and treatment efficiency of cisplatin chemo-therapy.

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Abstract

Objective: As a common malignant tumor, esophageal carcinoma lacked specific clinical symptoms, leading to distal metastasis at terminal stage. Cisplatin is the first-line chemotherapy drug for the treatment of esophageal cancer. Identification of sensitive molecular marker is thus of critical importance for individualized treatment of cancer. This study analysed polymorphism of *GSTP1*, *XPD* and *XRCC1* genes, aiming to illustrate its correlation with treatment efficacy of cisplatin on esophageal cancer, in order to provide evidences for individualized treatment effect.

Methods: A total of 104 esophageal carcinoma patients were recruited for follow-ups. Using Response Evaluation Criteria in Solid Tumor (RECIST), treatment efficacy was evaluated. PCR-RFLP was employed for detecting gene polymorphism.

Results: Frequency distribution of *XRCC1* Arg399Gln, *XPD* Lys751Gln and *GSTP1* Ile105Val all fitted Hardy-Weinberg equilibrium (p>0.05). Both one-factor and multi-factor analysis showed higher effective rate and survival time of patients with *XRCC1* Arg399Gln GA+AA genotype after receiving cisplatin treatment compared to those patients with GG genotype (p<0.05). Patients with GSTA1 Ile105Val AG+GG had higher effective rate and survival time than individuals with AA genotype (p<0.05). No significant difference was observed among patients with different genotypes at *XPD* Lys751Gln locus (p>0.05).

Conclusions: Esophageal carcinoma patients with *XRCC1* Arg399Gln GA+AA genotype and *GSTP1* Il3105Val AG+GG genotype are more sensitive to cisplatin treatment.

Keywords: *XRCC1*, *GSTP1*, *XPD*, Esophageal carcinoma, Cisplatin, Gene polymorphism.

Introduction

Esophageal Cancer (EC) is a common malignant tumor ranked as the sixth cause of morality worldwide. Recent survey showed that EC had the fourth high incidence and mortality among all malignant tumors in China [1]. In certain areas of China such as Henan Province, the incidence and mortality of EC are even higher than liver cancer, and ranked as the third deadly cancer [2], thus severely affecting public health.

Surgery is the major approach for treating EC. However, due to the infiltrative growth toward peripheral tissues/organs, the post-op survival rate maintains at a relatively low level. Meanwhile due to the lack of specific clinical manifestation, EC patients are usually at terminal stage or with metastasis at the time of confirmed diagnosis, making radical surgery impossible. Chemotherapy thus has become the major treatment way for EC. Combined drug chemotherapy mainly using platinum-based drug is the primary plan for EC treatment [3]. Cisplatin combined with 5-fluorouracil has become the classical plan for treating EC patients [4]. Individual difference

in treatment efficacy is a common phenomenon in clinic, as mainly caused by unique genetic characteristics of patients [5]. Therefore, searching for molecular index in predicting drug sensitivity is of critical importance for treating EC.

Platinum-based drug can bind to tumor cell DNA to form complex, thus impeding DNA replication and blocking cancer progression. The self-repair mechanism of DNA by tumor cells, however, can weaken treatment efficiency of platinum-based drugs. Therefore, DNA repair potency is correlated with treatment efficacy [6]. Repair function related with platinum drug resistance is mainly consisted of nucleotide incision and base removal/repairmen [7-9]. Current findings revealed that the repair potency of human X-ray Repair Cross-Complementing gene 1 (*XRCC1*) was correlated with Single Nucleotide Polymorphism (SNP) at 399th locus, thus affecting chemotherapy efficiency of platinum based drugs [10-14]. Xeroderma pigmentosum group D (*XPD*) gene facilitates DNA repair by denaturing damaged site. Previous findings showed the close relationship between SNP of *XPD* gene at 751st locus

and the sensitivity to platinum based drugs [15-17]. Moreover, study has found that Glutathione S-Transferase P1 (*GSTP1*) activity can be down-regulated by SNP of *GSTP1* gene at 105th locus, thus weakening platinum drug sensitivity [18,19]. Currently few studies have been performed regarding the molecular markers guiding treatment efficiency of platinum based drugs in EC patients. This study thus examined gene polymorphism at these three SNP loci, in order to elucidate their correlations with EC treatment efficacy using platinum drugs, thus paving grounds for individualized treatment of EC.

Materials and Methods

Major equipment and reagent

Gel imaging analyzer (Alpha Innotech, Japan). Model 2720 PCR cycler (ABI, US). Model 22331 Hamburg protein/nucleic acid analyzer (Eppendorf, Germany). Electrophoresis apparatus, electrophoresis tank, model DYY-6C power (Liuyi Instrument, China). DNA extraction kit (TaKaRa, Japan). PCR amplification kit (TaKaRa, Japan). MspI, MboII and BsmAI restriction enzymes (TaKaRa, Japan).

Research objects

A total of 104 EC patients who were diagnosed in the Affiliated First Hospital of Quanzhou from January 1st 2011 to December 31st 2013 were recruited. The study was approved by the Ethic Committee of the Affiliated First Hospital of Quanzhou, Fujian Medical University, China. All participants had signed the informed consent form before enrolment.

Inclusive criteria: (1) EC diagnosis by pathology examination; (2) Not received platinum based drugs treatment previously; (3) Received EC treatment by combined chemotherapy mainly using platinum based drugs; (4) With complete clinical data; (5) Normal kidney and liver functions. After obtaining informed consent of patients, 5 ml fasted venous blood samples were collected before chemotherapy and were stored at -80°C fridge for further experiments.

Follow-up and treatment efficacy evaluation

Survival time was calculated since confirmation of the diagnosis. Follow-up was performed until December 31st, 2015 with 6~60 months length. No individual was lost during the follow-up. Basic information, treatment plan, treatment time period and efficacy were all collected. Treatment efficacy was evaluated based on Response Evaluation Criteria in Solid Tumor (RECIST) stipulated by European Cancer Research Institute and Treatment Society, National Cancer Institute, and Canadian National Cancer Research Institute. Treatment efficacy can be divided by complete response (CR): disappearance of all lesions and <10 mm dimension of all pathology lymph nodes; Partial Response (PR): ≥ 30% decrease of the summation of diameters of all lesions; Stable Disease (SD), no response or progression of disease; and Progression Disease (PD): ≥ 20% of lesion diameter summation, or >5 mm increase of absolute value of all

diameters, or development of new lesions. Overall effective rate was calculated as (CR+PR)/(CR+PR+SD+PD).

Genetic polymorphism assay

Whole genomic DNA was extracted from peripheral blood. DNA purity and content was measured by protein-nucleic acid analyzer. Those samples with A260/A280 values between 1.8 and 2.0 were used for further experiments. Gene polymorphism was examined by PCR and PCR-restriction fragment length polymorphism (RFLP). Primers were designed and synthesized by Jierui (China) and were shown in Table 1. After amplifying targeted fragments by PCR, 5 μL PCR product was used for agarose gel electrophoresis to determine the successful amplification of target genes. MspI, MboII, BsmAI enzymes were then used to digest PCR products at polymorphism loci including *XRCC1* Arg399Gln, *XPD* Lys751Gln and *GSTP1* Ile105Val. 2% agarose gel electrophoresis was used for genotyping after enzymatic digestion.

Statistical analysis

SPSS19.0 software was used for statistical analysis. Chi-square test was employed to test if allele frequency fitted Hardy-Weinberg equilibrium and to compare parameters between two groups. Enumeration data were analysed by Logistic regression by multi-variate analysis. Survival analysis was assessed by Kaplan-Meier method. The comparison between survival rates was performed by Log-rank test. A statistical significance was defined when $p < 0.05$. Test level $\alpha = 0.05$.

Results

Basic information of patients

The age of enrolled 104 patients age ranged from 35 to 73 y old with an average age of 58.89 ± 8.25 y old, including 72 cases older than 60 y (69.23%), and 32 patients (30.77%) younger than 60 y. There were 65 males (62.50%) and 39 females (37.50%). In an ECOG behavioral score, there were 17 cases (16.35%), 58 cases (55.77%) and 29 cases (27.88%) with 0, 1 and 2 scores. All patients belonged to squamous carcinoma, with 82 cases (78.85%) at moderate to high differentiation and 22 cases (21.15%) at low differentiation.

Genotype distribution

Table 2 showed genotyping analysis tested by PCR-RFLP. At *XRCC1* Arg399Gln locus, there were 64 cases with GG genotype (61.54%), 32 cases with GA genotype (30.77%) and 8 cases with AA genotype (7.69%). At *XPD* Lys751Gln locus, there were 82 cases (78.85%) with AA genotype, 19 cases (18.27%) with AC genotype, 3 cases (2.88%) with CC genotype. At *GSTP1* Ile105Val locus, there were 66 cases (63.64%) with GG genotype, 33 cases (31.73%) with GA genotype and 5 cases (4.81%) with AA genotype. By chi-square test, frequency distribution of alleles at all three SNP locus fitted Hardy-Weinberg equilibrium (p>0.05), indicating that enrolled patients had representativeness of the population.

Correlation between gene polymorphism and treatment efficacy of chemotherapy

After combined therapy mainly using platinum-based drugs, treatment efficiency of all 104 patients were evaluated based on RECIST standard. There were 4 cases achieving CR, 58 PR, 31 SD and 11 PD, with overall effective rate of 59.61%.

Chi-square analysis was used to analyse the correlation between clinical pathology indexes of patients and gene polymorphism with treatment efficacy of platinum based drugs. As shown in Table 3, no significant correlations existed between sex, age, body status, Eastern Cooperative Oncology Group (ECOG) score and *XPD* Lys751Gln locus with effective rate of platinum treatment (p>0.05). Differentiation grade of tumors, polymorphism at *XRCC1* Arg399Gln and *GSTP1* Il3105Val locus was significantly correlated with the effective rate of platinum treatment (p<0.05). Those patients with higher differentiation grade of tumors, and those with *XRCC1* Arg399Gln GA+AA and *GSTP1* Ile105Val AG+GG carriers had remarkably higher effective rate than those with lower differentiated tumors, as well as those carrying *XRCC1* Arg399Gln GG and *GSTP1* Ile105Val AA (p<0.05).

To invade possible confounding factors, unconditional Logistic regression was used for multi-variant analysis. As shown in Table 4, except sex, age, ECOG score and *XPD* Lys751Gln locus polymorphism, those patients with moderate or low differentiated tumor tissues, CRCC1Arg399Gln GG and *GSTP1* Ile105Val AA carriers had lower possibility of beneficial effects (p<0.05).

Relationship between post-chemotherapy survival time and genotype

Kaplan-Meier method was used to analyse the correlation between survival time of patients after chemotherapy and genotypes. Setting the survival time as variable, and survival status as 0 whilst survive as 1. Analysis was then performed using genotypes at three loci as grouping variables. Log-rank test was employed for statistical analysis, in parallel with survival curve plotting. As shown in Figure 1, significant difference existed for survival time among different genotypes at *XRCC1* Arg399Gln locus (χ^2=4.17, p=0.04). Patients with GA+AA genotype had higher survival time than individuals

with GG genotype. No significant difference existed for survival time among different genotypes at *XPD* Lys751Gl locus (χ^2=0.03, p=0.86). Patients with AG+GG genotypes at *GSTP1* Ile105Val loci had significantly longer survival time than those carrying AA genotype (χ^2=4.35, p=0.03).
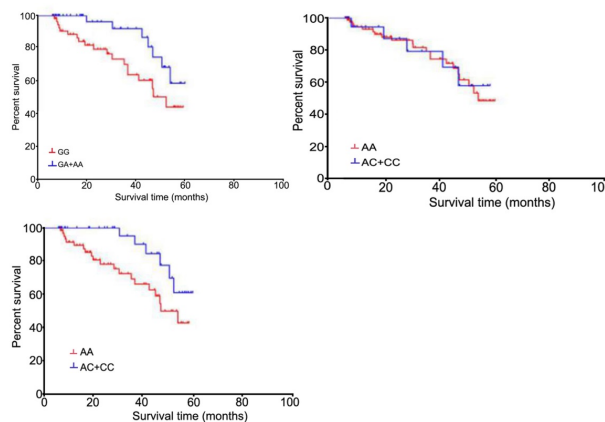
Figure 1. *Survival curve after chemotherapy of patients with different genotypes at three SNP loci.*

Screening of independent factors affecting patient survival by Cox regression analysis

In Cox multi-variant analysis, sex, age, differentiation grade, ECOG score and expression of three SNP loci were analysed. Results showed that differentiation grade, polymorphism at *XRCC1* Arg399Gln and *GSTP1* Ile105Val locus were independent risk factors affecting patient survival (Table 5).

Table 1. *PCR primer sequence of target fragments.*

Polymorphism loci	Primer sequence (5'-3')
XRCC1 Arg399Gln	F-TTGTGCTTTCTCTGTCTCCA
	R-TCCTCCAGCCTTTCTGATA
XPD Lys751Gln	F-CTCTCCCTTTCCTCTGTTC
	R-CAGGTGAGGGGGATCTG
GSTP1 Ile105Val	F-ACCCCAGGGCTCTATGGGAA
	R-TGAGGGCACAAGAAGCCCCT

Table 2. *Hardy-Weinberg equilibrium test for genotype frequency at polymorphism locus.*

Polymorphism locus	Allele	Genotype			Allele		χ^2	P
		AA (%)	AB (%)	BB (%)	A (%)	B (%)		
XRCC1 Arg399Gln	G/A	64 (61.54)	32 (30.77)	8 (7.69)	160 (76.92)	48 (23.08)	1.85	0.17
XPD Lys751Gln	A/C	82 (78.85)	19 (18.27)	3 (2.88)	183 (87.98)	25 (12.02)	1.93	0.16
GSTP1 Ile105Val	A/G	66 (63.46)	33 (31.73)	5 (4.81)	165 (79.33)	43 (20.67)	0.11	0.74

Note: A/B represents G/A, A/C and A/G allele at XRCC1 Arg399Gln, *XPD* Lys751Gln and *GSTP1* Ile105Val loci.

Table 3. *Correlation between clinical pathology indexes and gene polymorphism and efficacy of chemotherapy.*

Index	n	PR+CR (n=62)	SD+PD (n=42)	Effective rate (%) (PR+CR)/n	χ^2	P
Sex						
Male	65	37	28	56.92	0.52	0.47
Female	39	25	14	64.1		
Age						
≥ 60 y	72	47	25	65.28	3.12	0.08
<60 y	32	15	17	46.88		
Differentiation						
High	82	56	26	68.29	12.12	<0.001*
Low/middle	22	6	16	27.27		
ECOG score						
0	17	12	5	70.59	1.04	0.59
1	58	33	25	56.9		
2	29	17	12	58.62		
*XRCC1*Arg399Gln						
GG	64	32	32	50	6.39	0.01*
GA+AA	40	30	10	75		
XPD Lys751Gln						
AA	82	50	32	60.98	0.3	0.59
AC+CC	22	12	10	54.55		
GSTP1 Ile105Val						
AA	66	34	32	51.52	4.92	0.03*
AG+GG	38	28	10	73.68		

Note: *$p<0.05$.

Table 4. *Unconditional logistic regression analysis of factors for chemotherapy efficiency.*

Parameter	P	OR	95% CI
Sex	0.76	1.17	0.44~31.2
Age	0.31	1.03	0.98~1.08
Differentiation grade	0.001*	0.14	0.04~0.46
ECOG score	0.64	0.84	0.41~1.73
*XRCC1*Arg399Gln GG/ GA+AA	0.005*	0.21	0.07~0.63
XPD Lys751Gln AA/AC+CC	0.42	1.62	0.51~5.22
GSTP1 Ile105Val AA/AG+GG	0.007*	0.23	0.08~0.67

Note: *$p<0.05$.

Table 5. Analysis of independent risk factors affecting patient survival by Cox regression analysis.

Affecting factor	Regression coefficient (B)	Standard error (S.E)	Wald	P	OR	95% CI
Sex	1.36	0.98	2.31	0.32	2.01	0.66-12.26
Age	1.6	1.11	2.85	0.17	2.43	1.46-11.22
Differentiation	1.11	0.28	15.58	0.025*	3.06	1.69-5.56
ECOG score	1.17	1.26	1.22	0.3	3.15	0.41-13.65

*XRCC1*Arg399Gln	2.19	1.23	3.18	0.04[*]	1.86	1.12-8.67
XPD Lys751Gln	-0.94	1.31	0.67	0.4	0.3	0.06-3.13
*GSTP*1Ile105Val	2.18	0.3	3.78	0.02[*]	3.34	1.20-4.33

Note: [*]p<0.05.

Discussion

Most of EC patients already lost the chance of radical surgery, making chemo- or radio-therapy as major treatment approaches. Previous study revealed similar efficacy of synchronized chemo-and radio-therapy as those of surgery [20]. As the frontline medication for EC chemotherapy, platinum based drug is of critical importance. Therefore, identification of molecular index predicting drug sensitivity may help to guide the application of EC. Polymorphism of Excision Repair Cross-Complementing 1 (*ERCC1*) gene is correlated with treatment efficacy using platinum drug in EC patients [21]. However, few studies have been performed regarding the correlation between *XRCC1*, *XPD* and *GSTP1* gene and platinum drug efficacy against EC. This study thus investigated the polymorphism of these three genes and their correlations with treatment efficacy using platinum in the treatment of EC.

Results showed higher effective rate and longer survival time in EC patients with *XRCC1* Arg399Gln GA+AA and *GSTP1* Ile105Val AG+GG genotypes, compared to those carrying *XRCC1* Arg399Gln GG and *GSTP1* Ile105Val AA patients, suggesting the possible correlation between gene polymorphism of *XRCC1* Arg399Gln and *GSTP1* Ile105Val and treatment efficacy using platinum drug for EC patients. Those patients with *XRCC1* Arg399Gln GA+AA and *GSTP1* Ile105Val AG+GG genotypes are more likely to be satisfied in platinum based chemotherapy. No significant difference was found for effective rate or survival time among different genotypes of *XPD* Lys751Gln, indicating the lack of significant correlation between *XPD* Lys751Gln polymorphism and treatment efficacy of cisplatin in EC patients. Similar reports can be found in a meta-analysis conducted by Gu et al. [10], who showed the correlation between *XRCC1* Arg399Gln polymorphism and efficacy of platinum drug in treating Non-Small Cell Lung Cancer (NSCLC). Similar observations have been found in the treatment of colon cancer [14,22] and ovarian carcinoma [23] using platinum drugs. Kim et al. also found the correlation between polymorphism of Arg399Gln and *GSTP1* Ile105Val locus with treatment efficacy of platinum on colorectal carcinoma [24]. However, the correlation between *XPD* Lys751Gln polymorphism and treatment efficacy of platinum treating tumors is still inconclusive. For example, Li et al. suggested a correlation between *XPD* Lys751Gln polymorphism and overall survival rate or progression-free survival time of NSCLC patients who received platinum drug treatment [15]. Kalikaki et al. however, reported the absence of such correlation [25]. Currently no correlation study has been reported regarding the polymorphism of *XRCC1* Arg399Gln, *GSTP1* Ile105Val and

XPD Lys751Gln and treatment efficacy of platinum drugs against EC. Results from this study showed the correlation between *XRCC1* Arg399Gln, *GSTP1* Ile105Val polymorphism and efficacy of platinum drugs in treating various tumors, making them possible markers for individualized marker in treatment. The debate on *XPD* Lys751Gln loci, however, requires a large cohort clinical study to investigate.

In summary, this study showed better effective rate and longer survival time in EC patients carrying *XRCC1* Arg399Gln GA+AA genotype after treatment using platinum drugs, and higher effective rate and longer survival time in those patients with *GSTP1* Ile105Val AG+GG genotype compared to those with AA genotype. These results provided certain evidences for selecting chemotherapy treatment plan for EC patients. Large-scale clinical trial, however, is required for the application of using these two locus for guiding clinical treatment and drug selection.

Conclusion

EC patients with *XRCC1* Arg399Gln GA+AA genotype and *GSTP1* Ile105Val AG+GG genotype are more sensitive to platinum treatment.

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