

## RESEARCH ARTICLE

# Association of GSTP1 and RRM1 Polymorphisms with the Response and Toxicity of Gemcitabine-cisplatin Combination Chemotherapy in Chinese Patients with Non-small Cell Lung Cancer

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## Abstract

**Background:** Previous studies showed that genetic polymorphisms of glutathione S-transferase P1 (GSTP1) were involved in glutathione metabolism and genetic polymorphisms of ribonucleotide reductase (RRM1) were correlated with DNA synthesis. Here we explored the effects of these polymorphisms on the chemosensitivity and clinical outcome in Chinese non-small cell lung cancer (NSCLC) patients treated with gemcitabine-cisplatin regimens. **Materials and Methods:** DNA sequencing was used to evaluate genetic polymorphisms of GSTP1 Ile105Val and RRM1 C37A-T524C in 47 NSCLC patients treated with gemcitabine-cisplatin regimens. Clinical response was evaluated according to RECIST criteria after 2 cycles of chemotherapy and toxicity was assessed by 1979 WHO criteria (acute and subacute toxicity graduation criteria in chemotherapeutic agents). **Results:** There was no statistical significance between sensitive and non-sensitive groups regarding the genotype frequency distribution of GSTP1 Ile105Val polymorphism ( $p>0.05$ ). But for RRM1 C37A-T524C genotype, sensitive group had higher proportion of high effective genotype than non-sensitive group ( $p=0.009$ ). And according to the joint detection of GSTP1 Ile105Val and RRM1 C37A-T524C polymorphisms, the proportion of type A (A/A + high effective genotype) was significantly higher in sensitive group than in non-sensitive group ( $p=0.009$ ). Toxicity showed no correlation with the genotypes between two groups ( $p>0.05$ ). **Conclusions:** Compared with single detection of genetic polymorphisms of GSTP1 Ile105Val or RRM1 C37A-T524C, joint detection of both may be more helpful for patients with NSCLC to receive gemcitabine-cisplatin regimens as the first-line chemotherapy. Especially, genetic polymorphism of RRM1 is more likely to be used as an important biomarker to predict the response and toxicity of gemcitabine-cisplatin combination chemotherapy in NSCLC.

**Keywords:** Non-small cell lung cancer - glutathione S-transferase P1 - ribonucleotide reductase subunit M1

*Asian Pac J Cancer Prev*, 16 (10), 4347-4351

## Introduction

As we all know, variations in genes encode important proteins participating in metabolism of chemotherapeutic agents, or the target of chemotherapeutic agents. Promising results have been obtained in recent pharmacogenomics research that variations in genes may modify the efficacy of chemotherapeutic agents, thereby influencing the sensitivity and toxicity of chemotherapy for non-small cell lung cancer (NSCLC). The glutathione S-transferases (GSTs), a super-family of phase II metabolizing enzymes, play an important role in the detoxification of mutagenic and cytotoxic DNA-reactive molecules mediated by glutathione conjugation. Currently, growing evidence indicates that GSTs enzyme determines the cytotoxicity of a variety of chemotherapeutic agents (Kabler et al.,

2009; Sharma et al., 2011), especially the platinum drugs (Fuertes et al., 2003). Five subclasses of the GSTs super-family exist, and glutathione S-transferase P1 (GSTP1) is the most abundant GSTs isoform in the lung (Singh et al., 2015; Ou et al., 2015). GSTP1, directly participating in the detoxification of platinum compounds is an important mediator of both intrinsic and acquired resistance to platinum (Parker et al., 2011; De Luca et al., 2013). Previous studies have also suggested the importance of the allelic status of GSTP1 for platinum metabolism. It is showed that at codon 105 the variants of the enzymes with valine (Val) have higher activity against cisplatin and carboplatin than enzymes with isoleucine (Ile), and hence polymorphic Ile105Val of GSTP1 is linked to the sensitivity of cancer cells to platinum (Booton et al., 2006; Lu et al., 2006; Pecklak-Scott et al., 2008).

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Ribonucleotide reductase (RR) is a dimeric enzyme. As the major rate-limiting enzyme of DNA replication and repair, it plays an important role in deoxynucleotide production, which is a crucial step in DNA synthesis and repair. Ribonucleotide reductase subunit M1 (RRM1), the regulatory subunit of RR, is a nucleotide-binding site. RRM1 has been identified as a potential tumor suppressor gene and controls the substrate specificity and overall activity of the enzyme. Previous data showed that RRM1 was also the primary target for gemcitabine (Qiu et al., 2014), and was involved in sensitivity to gemcitabine in NSCLC (Gray et al., 2007; Zhang et al., 2012; Li et al., 2014). Consistently, many clinical studies have demonstrated that higher levels of RRM1 are associated with gemcitabine resistance, thus proving a predictive value as well (Nakahira et al., 2007; Zhang et al., 2013; Dong et al., 2014). Recently, the research of correlation between expression levels and genetic polymorphisms of RRM1 gene and the efficacy of gemcitabine is a central issue in patients with NSCLC.

Lung cancer is one of the malignant tumors with the highest incidence and mortality in the world. Every year, NSCLC accounts for 75% 80% among all the patients diagnosed as lung cancer in the first time (Zhang et al., 2014). Except for a minority's cancer that could be resected, the majority of patients with NSCLC are diagnosed at an advanced stage (stage III or IV), which requires systemic-based combination chemotherapy. And one of the standard therapies for advanced NSCLC is gemcitabine-cisplatin combination chemotherapy at present (Wang et al., 2007; Wang et al., 2007). However, it is suggested by the research of modern pharmacogenetics and genomics that the genetic diversity of cells results in the heterogeneity of tumor cells, and considerable inter-individual differences in therapeutic and adverse effects still exist among NSCLC patients, even with the same pathological types, clinical staging and chemotherapy. And the single nucleotide polymorphism and expression of genes are closely related to the prognosis and toxicity. The mechanism underlying the variations is still unclear. It is hypothesized that the genetic polymorphisms of genes, which code drug metabolizing enzymes or targets, may partially account for inter-individual variation in therapeutic efficacy of chemotherapy.

All in all, in view of the fact that polymorphic Ile105Val of GSTP1 is linked to the platinum metabolism, and that RRM1 expression related to the efficacy of gemcitabine is affected by RRM1 C37A-T524C polymorphism (Rodriguez et al., 2011), we aimed to assess the association of GSTP1 Ile105Val and RRM1 C37A-T524C polymorphisms with the response and toxicity of gemcitabine-cisplatin combination chemotherapy in Chinese patients with NSCLC, thereby providing a molecular biological basis for clinical individualized chemotherapy in NSCLC.

## Materials and Methods

### General data

Forty-seven initial-treated Chinese patients (aged 29~74, with the median age of 59; 5 females and 42

males), diagnosed pathologically with advanced NSCLC, were recruited from Hunan Cancer Hospital from 2008 to 2013. All patients did not receive any other chemotherapy, but only 2~4 cycles in Medical Department of Veteran Cadre in this hospital. To avoid the confounding factor of differences in clinical staging, of 47 patients with advanced NSCLC, 27 at stage III and 20 at stage IV were included in the research. And there were 10 cases of adenocarcinoma, 33 cases of squamous carcinoma, 3 cases of adenosquamous carcinoma, and 1 case of poorly-differentiated carcinoma in total. According to Eastern Cooperative Oncology Group (ECOG) criteria, no patient's ECOG status was higher than 2, and all patients were expected to live longer than 3 months. With no severe organ damage, the status of every patient's electrocardiogram, haemogram, blood chemistries, hepatic and renal function was normal before the initiation of chemotherapy. And every patient was informed and signed an informed consent before study.

### Methods

**Chemotherapy regimens:** All patients received gemcitabine-cisplatin combination chemotherapy for 2~4 cycles. Concrete dosage: gemcitabine 1 000 mg/m<sup>2</sup>, d1, d8; cisplatin 75 mg/m<sup>2</sup>, d1 or 25 mg/m<sup>2</sup>, d1~3. All chemotherapeutic drugs were injected intravenously, and the treatment cycles were repeated every 3 weeks. 128 cycles of chemotherapy were given totally, with an average of 2.7 cycles for each patient. The therapy would be terminated in case of disease progression or unacceptable toxicity.

**DNA isolation and genotyping:** Genomic DNA was isolated from peripheral blood leukocytes using phenol-chloroform followed by ethanol precipitation and then stored at 4°C before use. In this study, the genetic polymorphisms of GSTP1 Ile105Val and RRM1 C37A-T524C in 47 patients with NSCLC were detected using Sanger sequencing (Chu et al., 2009). According to the results of DNA sequencing for the polymorphism of GSTP1 Ile105Val, there were homozygous for A/A wild genotype, heterozygous for A/G genotype and homozygous for G/G genotype; for RRM1 C37A-T524C genotype, there were high effective genotype (37AC-524CT) and non-high effective genotype (37AA-524CC, 37AA-524CT, 37AA-524TT, 37AC-524CC, 37AC-524TT, 37CC-524CC, 37CC-524CT, 37CC-524TT) (Rodriguez et al., 2011). Based on the analyzed results above, the genotypes was classified into six types: A (A/A+high effective genotype), B (A/G+high effective genotype), C (G/G+high effective genotype), D (A/A+non-high effective genotype), E (A/G+non-high effective genotype) and F (G/G+non-high effective genotype).

### Evaluation on therapeutic effects

The patient's response to treatment was assessed every 2 cycles according to WHO criteria (response evaluation criteria in solid tumors, RECIST), which classified the response into four categories: complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). Those with responses as CR and PR, which contributed to objective response rate (ORR),

should be verified by further examination a month later, while responses as SD and PD were considered ineffective. According to the response to chemotherapy, all patients were divided into two groups: responders (sensitive group, CR+PR) and non-responders (non-sensitive group, SD+PD). Toxicity was observed and assessed by 1979 WHO criteria (acute and subacute toxicity graduation criteria in chemotherapeutic agents).

#### Statistical data analysis

Statistical analysis was performed using SPSS 18.0 software package. The baseline characteristics between responders and non-responders were compared using  $\chi^2$  test and Fisher probabilities.  $\chi^2$  test and Fisher probabilities were also applied to determine the frequencies of genotypes between two groups and test the significant differences between genotypes and clinical response. Before assessing clinical association, deviations from Hardy-Weinberg equilibrium for each SNP genotype were assessed using the  $\chi^2$  test. All statistical tests were two-sided, and  $p < 0.05$  was considered statistically significant.

## Results

#### Comparison on the baseline characteristics of responders and non-responders

Both genotypes of GSTP1 and RRM1 were determined in 47 patients with NSCLC. There were 2 cases of CR, 22 of PR, 19 of SD and 4 of PD. Therefore, responders and non-responders were 24 and 23 cases, respectively, and the total effective rate was 51.1%. There was no statistical significance between responders and non-responders regarding the gender, age and clinical staging ( $p=0.171$ , 0.308, 0.292), but significant difference was presented in terms of pathological types ( $p=0.002$ ) (Table 1).

#### GSTP1 genotype and treatment response

The genotypic distribution frequencies of G/G, A/G,

and A/A in GSTP1 Ile105Val polymorphism were 4.3%, 31.9% and 63.8%, respectively. There was no statistical significance between sensitive and non-sensitive groups regarding the gene distribution frequency of GSTP1 A105G polymorphism, and no associations were detected between genotypes and response to gemcitabine-cisplatin regimens ( $p=0.116$ ) (Table 2).

#### RRM1 genotype and treatment response

For RRM1 C37A-T524C, the distribution frequencies of high and non-high effective genotypes were 36.2% and 63.8%, respectively. The genotype of RRM1 C37A-T524C polymorphism was associated with the response to gemcitabine-cisplatin regimens, and the proportion of RRM1 C37A-T524C high effective genotype in sensitive group was higher than in non-sensitive group dramatically ( $p=0.009$ ) (Table 3).

#### Correlation between polymorphisms of GSTP1 Ile105Val and RRM1 C37A-T524C and treatment response

Because of the joint detection of GSTP1 Ile105Val and RRM1 C37A-T524C polymorphisms, 47 patients were classified into six types: A, B, C, D, E and F. And the genotypic distribution frequencies were 29.8%, 6.4%, 0.0%, 34.0%, 25.5% and 4.3%, respectively. In sensitive group, type A took the majority ( $p=0.009$ ) (Table 4).

#### Correlation between polymorphisms of GSTP1 Ile105Val and RRM1 C37A-T524C and toxicity

The major toxicities of 47 patients were gastrointestinal reactions, leucopenia, thrombocytopenia and rash, whereas there was no obvious liver and renal dysfunction.

**Table 2. GSTP1 Polymorphism and Gemcitabine-cisplatin Chemotherapy Response [n(%)]**

Groups	n	A/A	A/G	G/G	p
Sensitive group	24	16(66.67)	7(29.17)	1(4.17)	0.116
Non-sensitive group	23	14(60.87)	8(34.78)	1(4.35)	

**Table 1. Comparison on the Baseline Characteristics of Responders and Non-responders[n(%)]**

Baseline Characteristics	n	Responders	Non-responders	$\chi^2$	p
Gender				1.875	0.171
Male	42	20 (47.61)	22 (52.38)		
Female	5	4 (80.00)	1 (20.00)		
Age (years)				1.037	0.308
<59	23	10 (43.48)	13 (56.52)		
≥59	24	14 (58.33)	10 (41.67)		
Clinical staging				1.113	0.292
III	27	12 (44.44)	15 (55.56)		
IV	20	12 (60.00)	8 (40.00)		
Pathological types				14.678	0.002
Adenocarcinoma	10	9 (90.00)	1 (10.00)		
Squamous cell carcinoma	33	14 (42.42)	19 (57.58)		
Adenosquamous carcinoma	3	1 (33.33)	2 (66.67)		
Poorly-differentiated carcinoma	1	0 (0.00)	1(100.00)		

**Table 3. RRM1 Polymorphism and Gemcitabine-cisplatin Chemotherapy Response[n(%)]**

Groups	n	High effective genotype	Non-high effective genotype	$\chi^2$	p	OR(95%CI)
Sensitive group	24	13 (54.17)	11 (45.83)	6.88	0.009	5.614(1.464-21.532)
Non-sensitive group	23	4 (17.39)	19 (82.61)			

**Table 4. Combination of GSTP1 and RRM1 Polymorphisms and Gemcitabine-cisplatin Chemotherapy Response[n(%)]**

Groups	n	Type A	Type D+E	$\chi^2$	p	OR(95%CI)
Sensitive group	24	11(45.83)	10(41.67)	6.857	0.009	6.600(1.484-29.355)
Non-sensitive group	23	3(13.04)	18(78.26)			

**Table 5. Combination of GSTP1 and RRM1 Polymorphisms and Toxicities of Gemcitabine-cisplatin Chemotherapy (n=47)**

Toxicities	Degrees	Type A (n=14)	Type B (n=3)	Type D (n=16)	Type E (n=12)	Type F (n=2)	p
Leucopenia	I-IV	6	3	7	9	1	0.18
	0°	8	0	9	3	1	
Thrombocytopenia	I-IV	3	2	7	5	0	0.412
	0°	11	1	9	7	2	
Nausea/vomiting	I-IV	13	3	16	12	2	0.66
	0°	1	0	0	0	0	
Diarrhea	I-IV	4	3	6	3	0	0.147
	0°	10	0	10	9	2	
Hepatic and renal dysfunction	I-IV	0	0	0	0	0	-
	0°	14	3	16	12	2	
Cardiac dysfunction	I-IV	0	0	0	0	0	-
	0°	14	3	16	12	2	
Skin toxicity	I-IV	1	0	0	0	0	0.66
	0°	13	3	16	12	2	

Toxicity showed no correlation with the genotypes of all patients ( $p>0.05$ ) (Table 5).

## Discussion

At present, pharmacogenetics is becoming more and more popular in the study of cancer chemotherapy. Individual differences in response to cancer chemotherapy, especially drug resistance, represent a major problem. There is growing evidence implying that the polymorphisms in genes involved in metabolizing enzymes and DNA synthesis may explain the inter-individual variability of response and toxicity to chemotherapy partly (Allen et al., 2005). Therefore, assessing the correlation between genetic polymorphisms and sensitivity or resistance to chemotherapy is very important in selecting the most effective first-line treatment.

It is acknowledged that genetic polymorphisms of GSTP1 and RRM1 are involved in the metabolism of cisplatin. In this study, we attempted to explore whether these genetic polymorphisms could be used as predictors of the clinical outcome of Chinese patients with advanced NSCLC who were treated with gemcitabine-cisplatin combination chemotherapy. Certainly, some findings have been achieved in this study. Firstly, we found that GSTP1 Ile105Val mutation had no association with the clinical outcome of gemcitabine-cisplatin treatment, which was not in agreement with those from some previous studies (Sun et al., 2010; Zhou et al., 2011; Lv et al., 2012). The major reasons for this discrepancy are as follows: (1) Besides the variants of the enzyme with valine (Val) at codon 105, maybe there are some other mutations which impact on the metabolic pathways and/or efficiency of chemotherapeutic agents; (2) The sample size is relatively small and the course of treatment is short; (3) Genetic polymorphisms of GSTP1 may not play a leading role

in some populations or races since the metabolism of chemotherapeutic agents is affected by many enzymes and relevant genes. Therefore, it is revealed that to study on the characteristics of the metabolism of chemotherapeutic agents, the factors including multiple relevant genes and characteristics of tumor cell DNA repair should be put into consideration for comprehensive evaluation. Secondly, the data from this study also showed that the distribution frequency of high effective genotype in 24 sensitive cases was significantly higher than in 23 non-sensitive cases, and that carriers with high effective genotype for genetic polymorphisms of RRM1 C37A-T524C in patients with NSCLC had noticeably better sensitivity. With respect to RRM1 C37A-T524C polymorphism, the result of our study was consistent with a previous study (Rodriguez et al., 2011). The potential mechanism may be that RRM1 C37A-T524C polymorphism could impact on gene expression, thereby changing the therapeutic efficacy. However, the therapeutic effect of gemcitabine-cisplatin regimens is insensitivity, even in some patients who carry with high effective genotype for genetic polymorphisms of RRM1 C37A-T524C. Hence, it further suggests that it's inappropriate to formulate individual chemotherapy program based on the characteristics of single gene. Thirdly, through the joint detection of GSTP1 Ile105Val in peripheral blood and SNP in RRM1 C37A-T524C of 47 patients with advanced NSCLC, whose genotypes could be classified into six types: A, B, C, D, E and F, it was found that the data were unevenly distributed in these types. That was mainly distributed in types A, D and E, while no distribution in type C. Therefore, this research focused on the analysis of the influence from gene combination of types A, D and E on chemotherapeutic efficacy. The data showed that type A was associated with chemo-sensitivity, and that toxicity had no correlation with genotypes, suggesting that high effective genotype

for RRM1 C37A-T524C polymorphism may play a more dominant role.

Therefore, compared with single detection of genetic polymorphism in GSTP1 or RRM1, joint detection of both is more helpful for the patients with NSCLC to receive gemcitabine-cisplatin regimens as the first-line chemotherapy. Particularly, RRM1 C37A-T524C gene polymorphism is more likely to be an important biomarker for predicting the chemotherapeutic effect of patients with NSCLC to gemcitabine-cisplatin regimen, which contributes to individual therapeutic strategies of NSCLC. Further studies are necessary to predict whether our findings will be replicated in larger populations and to determine whether these differences in therapeutic efficacy of gemcitabine-cisplatin combination chemotherapy are caused by the differences in the plasma concentrations of drugs.

## Acknowledgements

The research was supported by Hunan Provincial Science and Technology Department Science and Technology Plan Project Foundation (06JT3008), Hunan Provincial Science and Technology Department Vital Foundation (S2012S2032) and Scientific Research Project of Hunan Province Health Protection Special Foundation (B2012-06). We also thank the study participants.

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