



# ***GSTP1 Ile105Val* and *XRCC1 Arg399Gln* gene polymorphisms contribute to the clinical outcome of patients with advanced non-small cell lung cancer**

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**ABSTRACT.** Glutathione S-transferase P1 (*GSTP1*) and X-ray repair cross-complementing group 1 (*XRCC1*) genetic variations may influence the efficacy of chemotherapy in various cancers. We investigated the possible roles of *GSTP1 Ile105Val* and *XRCC1 Arg194Trp*, and *Arg399Gln* gene polymorphisms in the prognosis of advanced non-small cell lung carcinoma (NSCLC) patients with cisplatin-based chemotherapy. Between January 2010 and December 2012, this study consecutively recruited 141 patients with advanced NSCLC from the First People's Hospital of Yunnan Province. Logistic regression analysis showed that individuals carrying the GG genotype were associated with a better response to chemotherapy than those with the wide-type genotype, with an adjusted odds ratio (95% confidence interval, CI) of 4.07 (1.06-25.06). Moreover, we observed that the AA genotype of

*XRCC1 Arg399Gln* was correlated with a greater complete response + partial response to chemotherapy than that with the GG genotype (odds ratio = 2.71, 95%CI = 1.13-10.08). Based on the Cox hazard proportional model, the GG genotype of *GSTP1 Ile105Val* was found to be associated with a lower risk of death from all causes as compared to that with the AA genotype (hazard ratio = 0.07, 95%CI = 0.01-0.34). In summary, we suggest that *GSTP1 Ile105Val* and *XRCC1 Arg399Gln* polymorphisms could influence the response to chemotherapy and survival of advanced NSCLC.

**Key words:** Clinical outcome; *GSTP1 Ile105Val*; *XRCC1 Arg194Trp*; Non-small cell lung carcinoma; *XRCC1 Arg399Gln*

## INTRODUCTION

Lung cancer is a worldwide common malignancy that arises from lung tissue and has become one of the most common factor leading to human deaths (IARC, 2012). Non-small cell lung cancer (NSCLC) and small cell lung cancer are the two types for lung cancer based on the histological characteristics, in which NSCLC accounts for about 80% of lung cancer (Beadle et al., 2014). NSCLC is typically diagnosed at an advanced stage, and the 5-year survival rate for lung cancer is approximately 15% (Henley et al., 2014). Current studies have shown that the prognosis of NSCLC can be attributed to a variety of environmental and genetic factors, such as TNM stage, therapy method, and genetic factors (Gou et al., 2015; Ramalingam and Khuri, 2015; Wei et al., 2015). Therefore, it is important to understand the role of various cancer-related genes in the development and prognosis of NSCLC, so as to identify the prognosis markers for NSCLC.

Previous studies have reported that glutathione S-transferase P1 (*GSTP1*) and X-ray repair cross-complementing group 1 (*XRCC1*) genetic variations may influence the efficacy of chemotherapy in various cancers, such as colon cancer, gastric cancer, and ovarian cancer (Khrunin et al., 2010; Ji et al., 2013; Lai et al., 2013; Zaanani et al., 2014). Currently, many studies reported the role of *GSTP1* and *XRCC1* genetic polymorphisms in the clinical outcome of NSCLC, but the results are inconclusive. In this study, we investigated the possible roles of *GSTP1 Ile105Val* and *XRCC1 Arg194Trp*, and *Arg399Gln* gene polymorphisms in the prognosis of advanced NSCLC patients with cisplatin-based chemotherapy.

## MATERIAL AND METHODS

Between January 2010 and December 2012, this study consecutively recruited 141 patients with advanced NSCLC from the First People's Hospital of Yunnan Province. All the NSCLC patients were histopathologically confirmed and newly diagnosed. All patients with advanced NSCLC did not receive anticancer therapies before surgery and had adequate hematology, renal, and liver function with an Eastern Cooperative Oncology Group performance status 0 or 1. Patients that receive anticancer therapies prior to enrollment and have acute and chronic infection disease were excluded from this study. The patients were routinely followed up every 4 weeks during disease progression.

All the advanced NSCLC patients underwent the cisplatin-based chemotherapy after

enrollment. Response to chemotherapy of the NSCLC patients was assessed according to RECIST criteria in 2000 (Duffaud and Therasse, 2000). A good response to chemotherapy was defined as a complete response (CR) and partial response (PR) to chemotherapy, and a poor response to chemotherapy was defined as a stable disease (SD) and progressive disease (PD). The overall survival was used as the endpoint index, and it was calculated by the time between the date of undergoing chemotherapy and the date of death from any cause or the end of the study. Routine follow-ups of all patients were ended in December 2014, and patients were followed up every 4 weeks through telephone interview.

### DNA extraction and genotyping

DNA was extracted from peripheral blood lymphocytes using the Qiagen blood mini-kit (Qiagen, Hilden, Germany) following the manufacturer instructions. The *GSTP1 Ile105Val* and *XRCC1 Arg194Trp* and *Arg399Gln* genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. DNA samples were amplified using two different primer pairs specific for *GSTP1 Ile105Val* and *XRCC1 Arg194Trp* and *Arg399Gln* genes. The forward and reverse primers were designed using the Sequenom Assay Design 3.1 software (San Diego, CA, USA). PCR was conducted with an initial melting step of 94°C for 5 min, followed by 30 cycles of denaturation at 94°C for 45 s, annealing at 62°C for 45 s, extension at 72°C for 45 s, and a final extension at 72°C for 5 min. PCR amplification was checked by using 1.5% agarose gel electrophoresis. Further, the amplified products were digested with 5 U of each restriction enzyme. Around 10% of the samples containing all genotypes for *GSTP1 Ile105Val* and *XRCC1 Arg194Trp* and *Arg399Gln* genes were repeated for PCR-RFLP polymorphism and all were matched to their genotype.

### Statistical analysis

The association between the response to chemotherapy and *GSTP1 Ile105Val*, *XRCC1 Arg194Trp*, and *Arg399Gln* polymorphisms was tested using odds ratio (OR) and 95% confidence interval (95%CI) in logistic regression analysis, and the wide-type genotype was taken as a reference group. The overall survival time of advanced NSCLC patients carrying *GSTP1 Ile105Val*, *XRCC1 Arg194Trp*, and *Arg399Gln* polymorphisms were tested using the Kaplan-Meier method. Cox hazard proportional model was used to calculate the overall survival of advanced NSCLC. The results are reported using hazard ratio and 95%CI with adjustments for potential confounding factors. All P values were based on a 2-tailed test and P < 0.05 was considered significant. The SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA) was carried out for statistical analysis.

## RESULTS

The mean age of patients with advanced NSCLC was 55.95 ± 7.83 years (Table 1). This study was comprised of 41 (29.08%) females and 100 (70.92%) males in the present study. In advanced NSCLC patients, 93 (65.96%) were smokers, 51 (36.17%) were drinkers, 62 (43.97%) were at III TNM stage, 79 (56.03%) were at IV TNM stage, 62 (43.97%) were adenocarcinoma type, 79 (56.03%) were squamous carcinoma type, 71 (50.35%) showed CR+PR to chemotherapy, and 70 (49.65%) showed SD+PD to chemotherapy.

**Table 1.** Demographic and clinical characteristics of the recruited patients and control subjects.

Variables	Patients	%	Survival time
Age (years)	55.95 ± 7.83		
<60	93	65.96	21.10 ± 1.47
≥60	48	34.04	21.94 ± 1.52
Gender			
Female	41	29.08	20.52 ± 2.05
Male	100	70.92	21.38 ± 1.40
Smoking status			
Never	48	34.04	21.48 ± 1.72
Ever	93	65.96	21.60 ± 1.53
Drinking status			
Never	90	63.83	21.51 ± 1.41
Ever	51	36.17	21.82 ± 2.04
TNM stage			
III	62	43.97	22.53 ± 1.68
IV	79	56.03	20.24 ± 1.58
Histology			
Adenocarcinoma	62	43.97	20.83 ± 1.71
Squamous carcinoma	79	56.03	22.14 ± 1.59
Response to chemotherapy			
CR+PR	71	50.35	25.52 ± 1.67
SD+PD	70	49.65	17.55 ± 1.48

The association between *GSTP1 Ile105Val*, *XRCC1 Arg194Trp*, and *Arg399Gln* and the response to chemotherapy in advanced NSCLC is shown in Table 2. Based on logistic regression analysis, we observed that the GG genotype of *GSTP1 Ile105Val* were associated with a greater CR+PR response to chemotherapy compared to the common genotype, and the adjusted OR (95%CI) was 4.07 (1.06-25.06). Moreover, the AA genotype of *XRCC1 Arg399Gln* was associated with a greater CR+PR response to chemotherapy compared to the wide-type genotype (OR = 2.71, 95%CI = 1.13-10.08). However, we did not observe a significant correlation between the *XRCC1 Arg194Trp* polymorphism and the response to chemotherapy in advanced NSCLC patients.

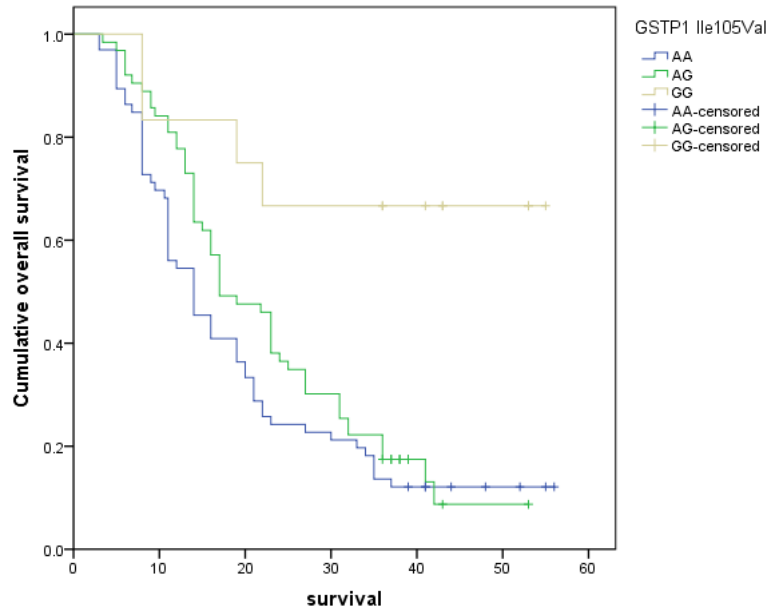
**Table 2.** Association between *GSTP1 Ile105Val*, *XRCC1 Arg194Trp*, and *Arg399Gln* and response to chemotherapy in advanced NSCLC.

Genes	N	%	Good response	%	Poor response	%	OR (95%CI) <sup>1</sup>	P value
<i>GSTP1 Ile105Val</i>								
AA	66	46.81	28	39.44	38	54.29	1.0 (Ref.)	-
AG	63	44.68	34	47.89	29	41.43	1.59 (0.75-3.38)	0.19
GG	12	8.51	9	12.68	3	4.29	4.07 (1.06-25.06)	0.03
<i>XRCC1 Arg194Trp</i>								
CC	64	45.39	29	40.85	35	50.00	1.0 (Ref.)	-
CT	58	41.13	31	43.66	27	38.57	1.39 (0.64-3.01)	0.37
TT	19	13.48	11	15.49	8	11.43	1.66 (0.52-5.42)	0.34
<i>XRCC1 Arg399Gln</i>								
GG	61	43.26	26	36.62	35	50.00	1.0 (Ref.)	-
GA	53	37.59	24	33.80	29	41.43	1.11 (0.50-2.50)	0.78
AA	27	19.15	21	29.58	6	8.57	2.71 (1.13-10.08)	0.01

<sup>1</sup>Ajusted for age, gender, smoking status, drinking status, TNM stage, and histology.

The median overall survival time was 23.55 months. At the end of the study, 112 advanced NSCLC patients died from all causes. The GG genotype of *GSTP1 Ile105Val* was associated with a longer overall survival time compared to the wide-type genotype (P value for log-rank test = 0.001; Figure 1). After adjusting for age, gender, smoking status, drinking

status, TNM stage, and histology, we observed that the GG genotype of *GSTP1 Ile105Val* was correlated with a lower risk of death compared to the wide type genotype (hazard ratio = 0.07, 95%CI = 0.01-0.34) (Table 3). The *XRCC1 Arg194Trp*, and *Arg399Gln* polymorphisms did not exhibit a significant association with the survival of advanced NSCLC patients.



**Figure 1.** Cumulative overall survival of advanced NSCLC by the *GSTP1 Ile105Val* polymorphism.

**Table 3.** Association between *GSTP1 Ile105Val*, *XRCC1 Arg194Trp*, and *Arg399Gln* and overall survival of patients with advanced NSCLC.

Genes	N	%	Death	%	Alive	%	Adjusted HR (95%CI) <sup>1</sup>	P value
<i>GSTP1 Ile105Val</i>								
AA	66	46.81	58	50.00	8	30.77	1.0 (Ref.)	-
AG	63	44.68	54	46.55	9	34.62	0.83(0.26-2.62)	0.72
GG	12	8.51	4	3.45	8	30.77	0.07(0.01-0.34)	<0.001
<i>XRCC1 Arg194Trp</i>								
CC	64	45.39	56	48.28	8	30.77	1.0 (Ref.)	-
CT	58	41.13	45	38.79	13	50.00	0.49(0.16-1.43)	0.15
TT	19	13.48	15	12.93	4	15.38	0.54(0.12-2.79)	0.35
<i>XRCC1 Arg399Gln</i>								
GG	61	43.26	51	43.97	10	38.46	1.0 (Ref.)	-
GA	53	37.59	37	31.90	16	61.54	0.45 (0.16-1.21)	0.08
AA	27	19.15	19	16.38	8	30.77	0.47 (0.14-1.59)	0.16

<sup>1</sup>Ajusted for age, gender, smoking status, drinking status, TNM stage, and histology.

## DISCUSSION

The present case-control study investigated the role of the *GSTP1 Ile105Val*, *XRCC1 Arg194Trp*, and *Arg399Gln* polymorphisms in the response to cisplatin-based chemotherapy and the survival of advanced NSCLC patients. We found that the *GSTP1 Ile105Val* and *XRCC1*

*Arg399Gln* genetic polymorphisms promoted the response to chemotherapy and the survival time in the advanced NSCLC patients.

The amino acid substitution changes of *GSTP1 Ile105Val* gene could cause hydrophobicity of amino acids, which alters the enzymatic stability and catalytic function. The *GSTP1 Ile105Val* polymorphism is reported to be associated with the efficacy of chemotherapy in various cancers, such as breast cancer, bladder cancer, osteosarcoma, non-small cell lung cancer, and gastric cancer (Deng et al., 2015a,b; Liu et al., 2013, 2015; Pu et al., 2015; Yuan et al., 2015). Liu et al. (2013) revealed that *GSTP1 Ile105Val* and *XRCC1 Arg399Gln* polymorphisms may contribute to the clinical outcome of gastric cancer patients receiving oxaliplatin-based adjuvant chemotherapy. Liu et al. (2015) carried out a study in a Chinese advanced NSCLC and reported that *GSTP1 Ile105Val* and *XRCC1 Arg399Gln* polymorphisms might influence the clinical outcome of patients with advanced NSCLC receiving cisplatin-based chemotherapy. Deng et al. (2015b) suggested that patients with the *GSTP1 Ile105Val* Val allele were associated with a favorable recurrence-free survival of advanced NSCLC. Pu et al. (2015) conducted a meta-analysis with six studies involving 898 participants, and indicated that *GSTP1* polymorphisms may influence the prognosis of osteosarcoma patients treated with chemotherapy. Yuan et al. (2015) carried out a study in a Chinese population and reported that the GG genotype of *GSTP1 Ile105Val* was significantly correlated with better response to chemotherapy and longer survival time in breast cancer.

Currently, some studies have investigated the association between genetic polymorphisms in the *GSTP1 Ile105Val* region and the prognosis of advanced NSCLC, but the results are inconclusive (Ada et al., 2010; Zhou et al., 2011; Ke et al., 2012; Lv et al., 2014; Yang and Zhao, 2014; Deng et al., 2015; Han et al., 2015; Liu et al., 2015). Individuals with *GSTP1* gene polymorphisms display a reduced ability to detoxify drug metabolites, thus promoting the overall survival of NSCLC (Lu et al., 2006; Ke et al., 2012; Lv et al., 2014; Deng et al., 2015; Han et al., 2015). Four studies reported that the Val allele of *GSTP1 Ile105Val* obtained a better response to chemotherapy and a better survival time when compared to Ile allele in Asian population (Ada et al., 2010; Zhou et al., 2011; Ke et al., 2012; Lv et al., 2014; Han et al., 2015). Two studies suggested that the Val allele of *GSTP1 Ile105Val* was more highly correlated with a poor response to chemotherapy than those carrying the Ile genotype (Deng et al., 2015; Liu et al., 2015). However, one study did not find a significant association between *GSTP1 Ile105Val* polymorphism and clinical outcome of advanced NSCLC (Ada et al., 2010). A recent meta-analysis involving nine studies suggested that *GSTP1 Ile105Val* polymorphisms could predict the treatment response of the platinum-based chemotherapy in NSCLC patients. Our study reported the similar results with previous studies.

The function of DNA damage may be affected by cisplatin, and the DNA repair capacity may be correlated with the efficiency and toxicity of cisplatin-based chemotherapy. *XRCC1* gene polymorphisms are reported to be correlated with the treatment outcome of cisplatin-based chemotherapy in several kinds of cancers, such as gastric cancer, colorectal cancer, nasopharyngeal cancer, ovarian cancer, pancreatic cancer, and esophageal cancer (Warnecke-Eberz et al., 2009; Giovannetti et al., 2011; Miao et al., 2012; Chen et al., 2013; Cao et al., 2014; Wu et al., 2014). Currently, several studies have reported the association between *XRCC1* genetic polymorphisms and treatment outcome of advanced NSCLC (Yuan et al., 2006; Wang et al., 2004, 2008; Sun et al., 2009; Li et al., 2011; Ke et al., 2012; Han et al., 2015). Three studies were carried out and reported a significant association between the *XRCC1 Arg194Trp* polymorphism and clinical response to platinum-based chemotherapy in

advanced NSCLC (Wang et al., 2004; Yuan et al., 2006; Ke et al., 2012). Five studies have suggested an significant association of the *XRCC1 Arg399Gln* polymorphism and clinical outcome of advanced NSCLC patients in Asian populations (Wang et al., 2008; Sun et al., 2009; Li et al., 2011; Ke et al., 2012; Han et al., 2015). Our study only reported that the *XRCC1 Arg399Gln* polymorphism could influence the clinical response to platinum-based chemotherapy. Further large scale studies are needed to confirm our results.

In summary, we suggest that *GSTP1 Ile105Val* and *XRCC1 Arg399Gln* were associated with a better response to chemotherapy and longer survival of advanced NSCLC compared to the wild-type genotype. Therefore, studies including larger sample sizes must be performed to confirm our findings.

### Conflicts of interest

The authors declare no conflict of interest.

### ACKNOWLEDGMENTS

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