Int J Clin Exp Med 2015;8(11):20918-20924
www.ijcem.com /ISSN:1940-5901/IJCEM0015317

Original Article

Predictive potential role of GSTs gene polymorphisms in the treatment outcome of advanced non-small cell lung cancer patients

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Received August 30, 2015; Accepted November 19, 2015; Epub November 15, 2015; Published November 30, 2015

Abstract: This study aimed to investigate the possible association between GSTP1, GSTM1, and GSTT1 polymorphisms and treatment outcome of advanced NSCLC. Between October 2009 and October 2011, a total of 308 patients of NSCLC on stage IIIA, IIIB or IV, treated with cisplatin-based chemotherapy were included. Polymerase chain reaction-restriction fragment length polymorphism was used to genotype the GSTP1 and GSTM1, and GSTT1 polymorphisms. We found that the Ile/Val and Val/Val genotypes of GSTP1 showed more CR+PR to chemotherapy in advanced NSCLC when compared with Ile/Ile genotype, and the Ors (95% CI) were 0.37 (0.18-0.71) and 0.15 (0.07-0.38). The Ile/Val and Val/Val genotypes of GSTP1 were associated with longer overall survival of advanced NSCLC when compared with the Ile/Ile genotype (For Ile/Val vs Ile/Ile, 37.63 ± 2.01 months vs 30.25 ± 2.06 months; for Val/Val vs Ile/Ile, 39.84 ± 3.36 months vs 30.25 ± 2.06 months). In the Cox proportional hazards model, the Ile/Val and Val/Val genotypes significantly decreased risk of death from all causes in patients with advanced NSCLC, and the HRs (95% CIs) were 0.51 (0.28-0.94) and 0.35 (0.16-0.78), respectively. We found that the GSTP1 polymorphisms might affect the clinical outcome of patients with advanced NSCLC, and our results could help us to facilitate therapeutic decision for individualized therapy.

Keywords: GSTP1, GSTM1, GSTT1, polymorphism, NSCLC

Introduction

Lung cancer is a worldwide common malignancy both among men and women, and this cancer arises from lung tissue and has become one of the most common factor leading to human deaths [1]. In 2012, lung cancer is the first cause of death among people with malignant tumors in China [2]. Statistics show that morbidity for lung cancer is high and the 5-year survival rate for lung cancer is approximately 14% [3]. 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 [4]. Although many treatment methods including immune or medication therapy, surgery and genetic therapy have played crucial roles in NSCLC treatment, the cure results still remain unsatisfactory due to the unknown complicate pathogenesis of NSCLC [5, 6]. TNM classification is the basis for prognostic management of NSCLC; however, it does not provide sufficient information about biological tumor progression [7]. There is still demanding for revealing biomarkers for patients' survival.

The human glutathione S-transferases (GSTs) is one superfamily of dimeric phase II metabolic enzymes, and it plays an important role in the cellular defense system [8]. It is reported that the GSTs enzymes could detoxify chemotherapeutic drugs or their metabolites by catalyzing the reduction of these compounds through its conjugation with glutathione. GSTμ1 (GSTM1), GSTθ1 (GSTT1), and GSTπ1 (GSTP1) are three common enzymes belonging to the GST superfamily. Allelic deletions in the *GSTM1* and *GSTT1* genotypes are correlated with reduced enzyme production [8]. Polymorphisms in *GSTP1* are associated with lower substrate-

Table 1. Baseline characteristics of patients with advanced NSCLC

Parameter	Patients	%
Age, years		
< 60	109	41.60
≥ 60	153	58.40
Gender		
Female	85	32.44
Male	177	67.56
Tobacco smoking		
Never	97	37.02
Ever	165	62.98
Family history of cancer		
No	245	93.51
Yes	17	6.49
Histological types		
Squamous Carcinoma	146	55.73
Adenocarcinoma	116	44.27
TNM stage		
IIIA and IIIB	193	73.66
IV	69	26.34
Location		
Left	109	41.60
Right	140	53.44
Other	13	4.96
Response to chemotherapy		
CR+PR	171	65.27
SD+PD	91	34.73

specific catalytic activity. Therefore, polymorphisms in the *GSTM1*, *GSTT1*, and *GSTP1* genes could alter the metabolism of chemotherapeutic drugs and modify the effectiveness of therapy. Previous studies have reported that GSTs polymorphisms could influence the effectiveness of detoxifying cytotoxins generated by cisplatin-based chemotherapy in several kinds of cancers, including osteosarcoma, cervical cancer and gastric cancer [9-11]. Previous studies reported the GSTs polymorphisms and prognosis of NSCLC, but the results are in consistent [12-15]. Therefore, this study aimed to investigate the possible association between GSTP1, GSTM1, and GSTT1 polymorphisms and treatment outcome of advanced NSCLC.

Material and methods

Patients

Between October 2009 and October 2011, a total of 308 patients of NSCLC on stage IIIA, IIIB or IV, treated with cisplatin-based chemotherapy were included. All the patients were pathological- and radiological-based diagnosed by stage IIIA, IIIB or IV and inoperable NSCLC. Patients who did not receive systemic anticancer chemotherapy previously, had severe complications, including cardiovascular and pulmonary diseases, bone marrow suppression, liver and renal dysfunctions, and/or organ failure and brain metastasis were excluded from our study. Finally, 262 patients agreed to participate in the present study, and the participation rate was 85.06%.

Chemotherapy

All patients received cisplatin-based combination chemotherapy. The chemotherapy was repeated at three-weekly intervals for up to six cycles unless unacceptable toxicity, disease progression or patients' refusal to continue treatment. The objective tumor response was assessed locally by the attending physician using Response Evaluation Criteria in Solid Tumors (RECIST) [16]. (RECIST 1.1) (Therasse et al., 2000). Patients who showed complete response (CR) and partial response (PR) to chemotherapy were considered as responders, and patients who, despite chemotherapy, presented stable disease (SD) or progressive disease (PD) characteristics, were regarded as non-responders. NSCLC cancer patients were subjected to chemotherapy at intervals of 3 weeks for up to six cycles, unless unacceptable toxicity levels were reached, or in case of disease progression.

Follow-up

For long-term survival, overall survival (OS) was defined as the period between the date of chemotherapy and the data of death from any cause. Patients with NSCLC were followed up by return visit and telephone manners. Up to the October 2014, patients with NSCLC were followed up for 2.30-60 months with the median follow-up time of 31.16 months. A total of 251 cases were followed up, while 11 cases lost follow-up.

DNA extraction and genotyping

Each patient with advanced NSCLC was asked to provide 5 ml peripheral blood sample, and the samples were stored in -20°C until use. Genomic DNA was isolated from peripheral

Table 2. Association between GSTP1, GSTM1 and GSTT1 polymorphisms and response to chemotherapy in advanced NSCLC

Genotypes	Patients	%	CR+PR	%	SD+PD	%	OR (95% CI)[1]	*P* value
GSTM1								
Present	155	59.16	105	61.40	50	54.95	1.0 (Ref.)	-
Null	107	40.84	66	38.60	41	45.05	0.77 (0.44-1.33)	0.31
GSTT1								
Present	141	53.82	95	55.56	46	50.55	1.0 (Ref.)	-
Null	121	46.18	76	44.44	45	49.45	0.82 (0.48-1.41)	0.44
GSTP1								
Ile/Ile	101	38.55	82	47.95	19	20.88	1.0 (Ref.)	-
Ile/Val	116	44.27	71	41.52	45	49.45	0.37 (0.18-0.71)	0.001
Val/Val	45	17.18	18	10.53	27	29.67	0.15 (0.07-0.38)	< 0.001

[1]Adjusted for age, sex and TNM stage.

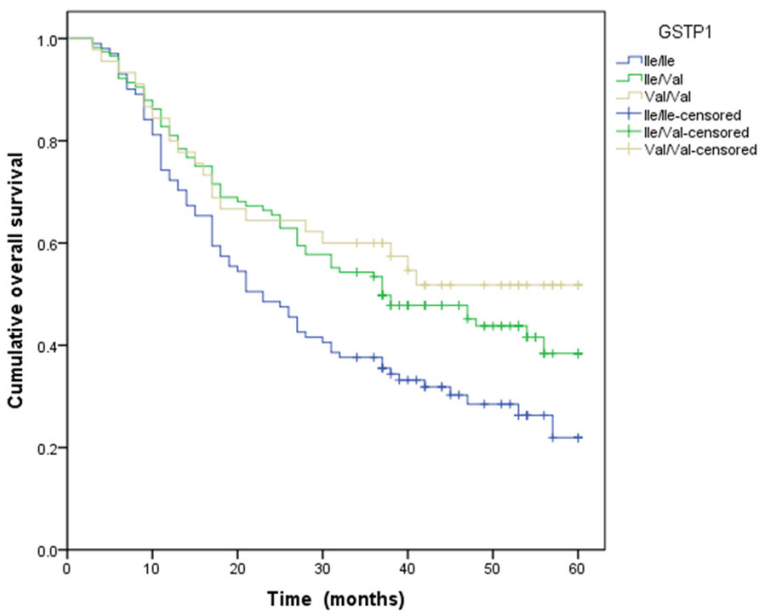

Figure 1. Kaplan-Meier survival curves for overall survival of advanced NSCLC by GSTP1 polymorphism.

blood lymphocytes using Qiagen blood mini kit (Qiagen, Germany) by the manufacturer's protocol. Polymerase chain reaction-restriction fragment length polymorphism was used to genotype the GSTP1 and GSTM1, and GSTT1 polymorphisms. The primer sequences of GSTM1 were 5'-TTGGTTACTCCTGGTGAGATGTG-3' and 5'-TCAGGCCATGATCCGGACGA-3'. The primer sequences of GSTT1 were 5'-TTGG-TTACTCCTGGTCACATCTC-3' and 5'-TCAGGCCA-TCATGGCCACGA-3'. The primer sequences of GSTP1 were 5'-AGG GGA CCC CTC TAT CCC AA-3' and 5'-TGA CCC GAG AACAAC GGG CT-3'. The reaction for PCR was conducted at 95°C for 5 min for the initial denaturation, following 30 cycles of denaturation at 95°C for 30 s, annealing at 59°C for 45 s, extension at 72°C for 30 s and final extension at 72°C for 5 mins. A 136, 480 and 215 bp amplicons represents the GSTP1, GSTT1 and GSTM1 genes. The PCR-RFLP results were confirmed by sequencing of the PCR amplified product using Genetic Analyzer 3500, Applied Biosystems (Molecular Medicine Lab, Department of Biotechnology, Assam University, Silchar, India).

Statistical analysis

The demographic and clinical data were shown as the mean ± standard deviation (SD) or frequency (N) and percentage (%). Association between GSTP1, GSTM1, and GSTT1 polymorphisms and response to chemotherapy were calculated by computing the odds ratio (OR) and 95% confidence intervals (95% CI) from multivariate regression analysis. Survival curves were analyzed by the Kaplan-Meier method, and the impact of the GSTP1, GSTM1, and GSTT1 polymorphisms on OS was assessed using the log-rank test. Multivariable Cox proportional hazards model was used to assess effect of the GSTP1, GSTM1, and GSTT1 polymorphisms on

Table 3. Association between GSTP1, GSTM1 and GSTT1 polymorphisms and OS of advanced NSCLC

Genotypes	Patients	%	Survival time	P for Log-rank test	Death	%	Alive	%	HR (95% CI)[1]	P
GSTM1										
Present	155	59.16	35.16 ± 1.72		96	60.76	59	56.73	1.0 (Ref.)	-
Null	107	40.84	35.19 ± 2.16	0.55	62	39.24	45	43.27	0.85 (0.50-1.45)	0.52
GSTT1										
Present	141	53.82	34.81 ± 1.83		87	55.06	54	51.92	1.0 (Ref.)	-
Null	121	46.18	35.58 ± 2.00	0.07	71	44.94	50	48.08	0.88 (0.52-1.49)	0.62
GSTP1										
Ile/Ile	101	38.55	30.25 ± 2.06		72	45.57	29	27.88	1.0 (Ref.)	-
Ile/Val	116	44.27	37.63 ± 2.01		65	41.14	51	49.04	0.51 (0.28-0.94)	0.02
Val/Val	45	17.18	39.84 ± 3.36	< 0.001	21	13.29	24	23.08	0.35 (0.16-0.78)	0.004

[1]Adjusted for age, sex and TNM stage.

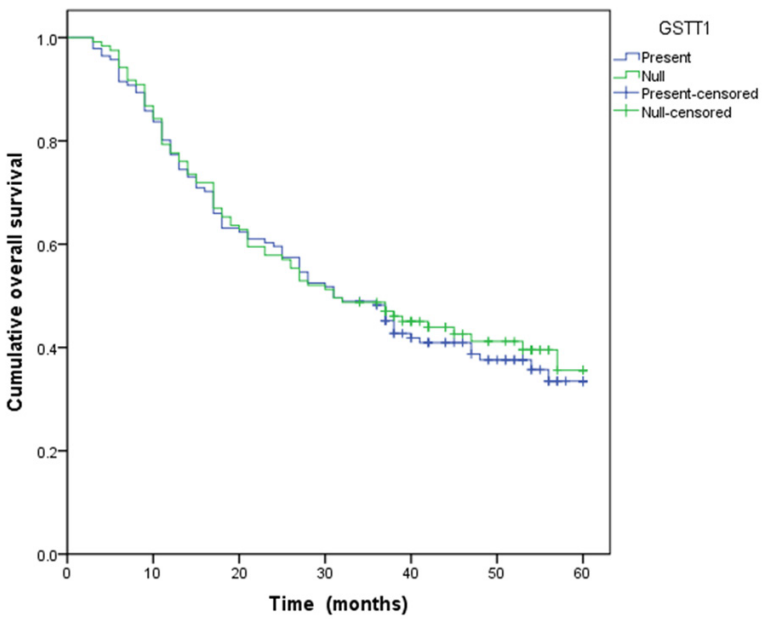

Figure 2. Kaplan-Meier survival curves for overall survival of advanced NSCLC by GSTT1 polymorphism.

overall survival of advanced NSCLC in the presence of other potential predictive and prognostic factors. *P* values < 0.05 with two-sided were considered statistical differences. SPSS Statistics (version 16.0, SPSS Inc., Chicago, IL, USA) was applied for statistical analysis. Data were performed by the statistical software.

Results

The demographic and clinical characteristics of the advanced NSCLC patients are shown in **Table 1**. There were 85 females and 177 males, and their mean age was 66.12 ± 10.32 years. Of the 262 NSCLC patients, 165 (62.98%) had a habit of tobacco smoking, 17 (6.49%) had a family history of cancer, 146 (55.73%) were squamous carcinoma, 116 (44.27%) were adenocarcinoma, 193 (73.66%) were IIIA and IIIB TNM stage, 69 (26.34%) were IV TNM stage, 109 (41.60%) were at left lung, 140 (53.44%) were at right lung, 171 (65.27%) showed CR+PR to chemotherapy and 91 (34.73%) showed SD+PD to chemotherapy.

After adjustment for clinical variables, the Ile/Val and Val/Val genotypes of GSTP1 showed more CR+PR to chemotherapy in advanced NSCLC when compared with Ile/Ile genotype, and the Ors (95% CI) were 0.37 (0.18-0.71) and 0.15 (0.07-0.38), respectively (**Table 2**). However, no significant association was found between GSTM1 and GSTT1 polymorphisms and chemotherapy to chemotherapy in advanced NSCLC.

Until the end of follow-up, a total of 158 patients with NSCLC died from all causes, and the 5-years overall survival rate was 39.69%. The Ile/Val and Val/Val genotypes of GSTP1 were associated with longer overall survival of NSCLC when compared with the Ile/Ile genotype (For Ile/Val vs Ile/Ile, 37.63 ± 2.01 months vs 30.25 ± 2.06 months; for Val/Val vs Ile/Ile, 39.84 ± 3.36 months vs 30.25 ± 2.06 months) (**Figure 1**). In the Cox proportional hazards model, the

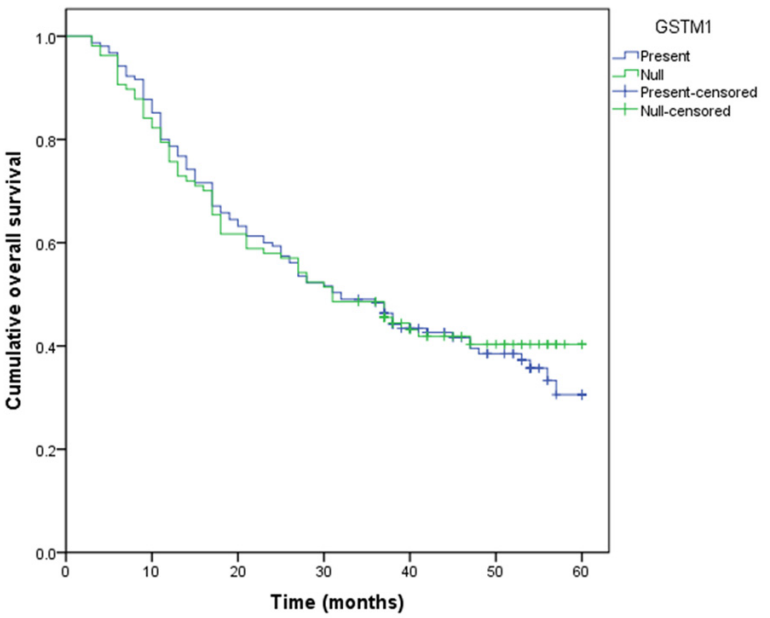

Figure 3. Kaplan-Meier survival curves for overall survival of advanced NSCLC by GSTM1 polymorphism.

Ile/Val and Val/Val genotypes significantly decreased risk of death from all causes in patients with advanced NSCLC, and the HRs (95% CIs) were 0.51 (0.28-0.94) and 0.35 (0.16-0.78), respectively (**Table 3**). No significant association was observed between GSTM1 and GSTT1 polymorphisms and OS of NSCLC (**Figures 2** and **3**).

Discussion

In the present study, we investigated the impact of GSTP1, GSTM1, and GSTT1 polymorphisms on the treatment outcome of advanced NSCLC in a sample of Chinese population. Our findings showed a significant association between GSTP1 polymorphism and response to chemotherapy and OS of advanced NSCLC, and the Ile/Val and Val/Val genotypes decreased the risk of disease progression and death from all causes in comparison with the Ile/Ile genotype. However, no significant association was found between GSTM1 and GSTT1 polymorphisms and response to chemotherapy and survival of advanced NSCLC.

The isoenzyme of GSTs with the most overexpression in cancer or precancerous tissues is GSTP1 [17]. Polymorphisms in the GSTP1 results in sequence change of amino acid located in site of 105 (Ile105Val) of which the amino acid substitution changes the volume and hydroliphobicity of amino acid and thus decreasing of enzymatic stability and catalytic capability. The wild-type homogeneous Ile/Ile has the highest enzymatic activities while the mutant homogeneous Val/Val has the lowest enzymatic activities [17].

Recently, several studies have indicated that GSTP1 has association with chemotherapy outcome. The study by Liu et al. showed the association between the gene polymorphism and prognosis of breast cancer patients, and they found that the polymorphism of GSTP1 Ile105Val is associated with response to chemotherapy and PFS and OS of breast cancer patients, and this gene polymorphism could help in design of individualized therapy [18]. One meta-analysis conducted by Pu et al. and pooled with six studies involving 898 particpants, and reported that GSTP1 polymorphism might influence the chemotherapy response and overall survival of osteosarcoma [19]. One study was conducted in a Chinese population, and reported that the gene polymorphism of GSTP1 have clinical value for predicting the response to chemotherapy for advanced gastric cancer [20]. Kumamoto et al. conducted a study in a Japanese population, and they reported that GSTP1 polymorphism may be useful markers of colorectal cancer patients treated with 5-FU/oxaliplatin as first-line chemotherapy [21]. The results of these studies reported that GSTP1 polymorphism contributed to chemotherapy sensitivity and prognosis of several kinds of cancers.

For the association between GSTP1 polymorphism and NSCLC, many studies have reported their association, but the results are inconsistent [22-26]. Han et al. and Lv et al. conducted studies in a Chinese population, and they reported that GSTP1 polymorphism are correlated with response to chemotherapy and have prognostic value for NSCLC [22, 23]. Vlachogeorgos et al. conducted a study in a

Greek population, and they reported that GSTP1 polymorphism may predict the response to treatment and the survival of patients with advanced NSCLC [24]. Lu et al. conducted a study in a American population, and the reported that GSTP1 may be associated with improved survival among patients with advanced NSCLC [25]. The above mentioned studies are in line with our results. However, Kalikaki et al. did not find significant association between GSTP1 polymorphism and treatment outcome of advanced NSCLC [26]. The inconsistent results may be caused by the differences in ethnicities, source of patients and sample size.

We identified three limitations in our study. First, patients were selected from a single hospital, which might not be representative of the general population. Second, other genetic polymorphisms might have influenced the treatment outcome of advanced NSCLC in addition to GSTT1, GSTM1 and GSTP1 polymorphisms. Third, the sample size of this study was relatively small, which could limit the statistical power to identify the differences between groups. Further studies with large sample sizes are greatly needed to clarify the association of glutathione S-transferases gene polymorphisms with the prognosis of advanced NSCLC.

In conclusion, we found that GSTP1 polymorphism might affect the clinical outcome of patients with advanced NSCLC, and our results could help us to facilitate therapeutic decision for individualized therapy.

Disclosure of conflict of interest

None.

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References

[1] International Agency for Research on Cancer (2012). Lung Cancer. Estimated Incidence, Mortality and Prevalence Worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Access in 2015-08-01.

[2] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: Globocan 2008. Int J Cancer 2010; 127: 2893-2917.

[3] Henley SJ, Richards TB, Underwood JM, Eheman CR, Plescia M, McAfee TA; Centers for Disease Control and Prevention (CDC). Lung cancer incidence trends among men and women-united states, 2005-2009. MMWR Morb Mortal Wkly Rep 2014; 63: 1-5.

[4] Beadle J, Coats A, Ho G, Prabhash K, von Haeling S, Brown R, Anker S. 487psurvival and quality of life data from the act one randomised, double-blind, placebo-controlled, phase ii study of espindolol for the treatment and prevention of cachexia in patients with stage iii/iv non-small cell lung cancer or colorectal cancer. Ann Oncol 2014; 25: iv162-iv163.

[5] Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: Epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008; 83: 584-594.

[6] Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I. Gefitinib or chemotherapy for non–small-cell lung cancer with mutated egfr. N Engl J Med 2010; 362: 2380-2388.

[7] Chansky K, Sculier JP, Crowley JJ, Giroux D, Van Meerbeeck J, Goldstraw P; International Staging Committee and Participating Institutions. The international association for the study of lung cancer staging project: Prognostic factors and pathologic tnm stage in surgically managed non-small cell lung cancer. J Thorac Oncol 2009; 4: 792-801.

[8] Strange RC, Fryer AA. The glutathione S-transferases: influence of polymorphism on cancer susceptibility. IARC Sci Publ 1999; 231-249.

[9] Goričar K, Kovač V, Jazbec J, Zakotnik B, Lamovec J, Dolžan V. Genetic variability of DNA repair mechanisms and glutathione-S-transferase genes influences treatment outcome in osteosarcoma. Cancer Epidemiol 2015; 39: 182-188.

[10] Daukantienė L, Kazbarienė B, Valuckas KP, Didžiapetrienė J, Krikštaponienė A, Aleknavičius E. The significance of reduced glutathione and glutathione S-transferase during chemoradiotherapy of locally advanced cervical cancer. Medicina (Kaunas) 2014; 50: 222-229.

[11] Yu P, Du Y, Yang L, Fan S, Wu J, Zheng S. Significance of multidrug resistance gene-related proteins in the postoperative chemotherapy of gastric cancer. Int J Clin Exp Pathol 2014; 7: 7945-7950.

[12] Ada AO, C Kunak S, Hancer F, Bilgen S, Suzen SH, Alpar S, Gulhan M, Kurt B, Iscan M. CYP and GST polymorphisms and survival in ad-

vanced non-small cell lung cancer patients. Neoplasma 2010; 57: 512-21.
[13] Booton R, Ward T, Heighway J, Ashcroft L, Morris J, Thatcher N. Glutathione-S-transferase P1 isoenzyme polymorphisms, platinum-based chemotherapy, and non-small cell lung cancer. J Thorac Oncol 2006; 1: 679-83.
[14] Lu C, Spitz MR, Zhao H, Dong Q, Truong M, Chang JY, Blumenschein GR Jr, Hong WK, Wu X. Association between glutathione S-transferase pi polymorphisms and survival in patients with advanced nonsmall cell lung carcinoma. Cancer 2006; 106: 441-7.
[15] Oztürk O, Isbir T, Yaylim I, Kocatürk CI, Gürses A. GST M1 and CYP1A1 gene polymorphism and daily fruit consumption in Turkish patients with non-small cell lung carcinomas. In Vivo 2003; 17: 625-32.
[16] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumours. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 3: 205-216.
[17] Johansson AS, Stenberg G, Widersten M, Mannervik B. Structure-activity relationships and thermal stability of human glutathione transferase P1-1 governed by the H-site residue 105. J Mol Biol 1998; 278: 687-698.
[18] Liu J, Luo J, Wang Y, Li L, Yang S. Predictive potential role of glutathione S-transferases polymorphisms on prognosis of breast cancer. Int J Clin Exp Pathol 2014; 7: 8935-8940.
[19] Pu F, Chen F, Chen S, Wang B, Liu J, Shao Z. Association between GSTP1 polymorphisms and prognosis of osteosarcoma in patients treated with chemotherapy: a meta-analysis. Onco Targets Ther 2015; 8: 1835-1842.
[20] Ji M, Xu B, Jiang JT, Wu J, Li XD, Zhao WQ, Zhang HY, Zhou WJ, Wu CP. Relationship between glutathione S-transferase P1 (GSTP1), X-ray repair cross complementing group 1 (XRCC1) and 5,10-methylenetetrahydrofolate reductase (5,10-MTHFR) gene polymorphisms and response to chemotherapy in advanced gastric cancer. Onkologie 2013; 36: 335-340.
[21] Kumamoto K, Ishibashi K, Okada N, Tajima Y, Kuwabara K, Kumagai Y, Baba H, Haga N, Ishida H. Polymorphisms of GSTP1, ERCC2 and TS-3'UTR are associated with the clinical outcome of mFOLFOX6 in colorectal cancer patients. Oncol Lett 2013; 6: 648-654.
[22] Han B, Guo Z, Ma Y, Kang S, Wang Y, Wei Q, Wu X. Association of GSTP1 and XRCC1 gene polymorphisms with clinical outcome of advanced non-small cell lung cancer patients with cisplatin-based chemotherapy. Int J Clin Exp Pathol 8: 4113-4119.
[23] Lv H, Han T, Shi X, Yao Y, Yao Y, Qiu W, Yue L, Liang J. Genetic polymorphism of GSTP1 and ERCC1 correlated with response to platinum-based chemotherapy in non-small cell lung cancer. Med Oncol 2014; 31: 86.
[24] Vlachogeorgos GS, Manali ED, Blana E, Legaki S, Karagiannidis N, Polychronopoulos VS, Roussos C. Placental isoform glutathione S-transferase and P-glycoprotein expression in advanced nonsmall cell lung cancer: association with response to treatment and survival. Cancer 2008; 114: 519-526.
[25] Lu C, Spitz MR, Zhao H, Dong Q, Truong M, Chang JY, Blumenschein GR Jr, Hong WK, Wu X. Association between glutathione S-transferase pi polymorphisms and survival in patients with advanced nonsmall cell lung carcinoma. Cancer 2006; 106: 441-7.
[26] Kalikaki A, Kanaki M, Vassalou H, Souglakos J, Voutsina A, Georgoulias V, Mavroudis D. DNA repair gene polymorphisms predict favorable clinical outcome in advanced non-small-cell lung cancer. Clin Lung Cancer 2009; 10: 118-123.