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RESEARCH ARTICLE

Clinical outcome of cisplatin-based chemotherapy is associated with the polymorphisms of GSTP1 and XRCC1 in advanced non-small cell lung cancer patients

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Abstract
Introduction This study is to evaluate the association of polymorphisms of glutathione S-transferase P1 (GSTP1), copper-transporting P-type adenosine triphosphatase A (ATP7A) and X-ray repair cross-complementing group 1 (XRCC1) with the efficacy and toxicity of cisplatin-based treatment in advanced non-small cell lung cancer (NSCLC) patients.
Materials and methods The outcomes of 97 advanced non-small cell lung cancer patients treated with cisplatin-based chemotherapy were estimated. GSTP1, ATP7A, and XRCC1 genetic polymorphisms were determined via polymerase chain reaction of restriction fragment length polymorphism (PCR–RFLP) and DNA sequencing. Association of the polymorphisms with the efficacy and toxicity of cisplatin was analyzed, respectively.
Results Significant associations were observed between GSTP1 A313G and response rate (RR) ($p = 0.027$), disease control rate (DCR) ($p = 0.019$), and progression-free survival (PFS) ($p = 0.044$), respectively. Patients with AG and GG of GSTP1 have notably lower risk of anemia ($p = 0.046$). XRCC1 A1196G was associated with the incidence of lymphopenia ($p = 0.024$) and diarrhea ($p = 0.020$). ATP7A C2299G was not related with RR, DCR, PFS, and the risk of toxicity.
Conclusions Advanced NSCLC patients with AA genotype of GSTP1 would obtain better curative effect followed with more risk of anemia when treated by cisplatin-based chemotherapy. ATP7A C2299G does not impact the efficacy and toxicity of cisplatin-based chemotherapy. XRCC1 1196A allele could predict the incidence of lymphopenia and diarrhea.

Keywords GSTP1 · ATP7A · XRCC1 · Cisplatin · Non-small cell lung cancer

Introduction

Lung cancer, one of the most common cancer, is the main cause of cancer-related mortality [1]. Up to 80–85 % of patients that diagnosed with lung cancer are non-small cell lung cancer (NSCLC) in an advanced status. Although the outcome of patients with NSCLC improves significantly by cisplatin-based chemotherapy, the efficacy and toxicity are largely individual. Relevant evidences reveal that hereditary factors play a crucial role in individual differences of cisplatin-based chemotherapy [2]. SNPs may lead to the changes in the activity of enzymes and transporters which involve in cisplatin elimination.

Glutathione S-transferase P1 (GSTP1), a glutathione S-transferase class member, is widely expressed in different human tissues including lung and liver. It contributes to phase II metabolism of xenobiotics, which involves in the key process of cisplatin biotransformation [3]. GSTP1 A313G mutant alleles, causing an Ile to Val at codon 105 of the substrate-binding site of GSTP1 protein, decrease the

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biotransformation activity of GST proteins, followed by increasing the intracellular cisplatin-GSH-conjugates and inhibiting the metabolism of cisplatin [4, 5].

Copper-transporting P-type adenosine triphosphatase A (ATP7A), responding for the biological balance of copper, is indicated to participate in transportation of cisplatin. ATP7A is one of the mainly composed of copper-transporting ATPase. It is demonstrated that there is a negative relationship between the mRNA expression of ATP7A and the susceptibility to cisplatin in NSCLC cells in vitro [6].

X-ray repair cross-complementing group 1 (XRCC1) is a major member of the base excision repair pathway, which plays a prominent role in both single-strand break repair and base excision repair. XRCC1 protein interacts with ligase III and poly (ADP-ribose) polymerase to efficiently repair DNA damage including cisplatin-induced damage [7]. The XRCC1 A1196G allele variant is associated with lung cancer, of which patients suffer smoking-induced genotoxic damage, implying that the polymorphisms of A1196G may alter the phenotype of the XRCC1 protein to cause the variant response to cisplatin-based chemotherapy [8]. However, excision repair cross complementation 1 (ERCC1) and xeroderma pigmentosum complementary group (XPD) were well defined in the genotype and the response of cisplatin chemotherapy [9].

In this study, we investigated the relationship between the clinical outcome and the SNPs of GSTP1, ATP7A, and XRCC1 in advanced NSCLC patients with cisplatin-based chemotherapy.

Patients and methods

Study population

Ninety-seven patients of NSCLC on stage IIIB or IV, median age 57 years (31–79 years), treated with cisplatin-based chemotherapy were included (Table 1), and all patients participated in the study for the whole length of therapy. All of the patients recruited were ethnic Han, and diagnosed with at least bidimensionally measurable CT scan according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). All patients did not receive systemic anticancer chemotherapy previously and were enrolled with signed an informed consent form for blood sample collection to establish the clinical significance of genetic polymorphisms in the cisplatin-based chemotherapy. Patients with an estimated life expectancy of $\geq$12 weeks and with Eastern Cooperative Oncology Group (ECOG, PS) status $\leq$2, KPS $\geq$ 70 were eligible for this study. Meanwhile, adequate bone marrow reserve, normal renal function, liver function, and cardiac function before chemotherapy were necessary for the patients. And other eligible criteria included leukocyte count $\geq 4.0 \times 10^9$/L, neutrophil count $\geq 2.0 \times 10^9$/L, lymphocyte count $\geq 1.2 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, serum alkaline phosphatase (ALP) $< 1.5 \times$ ULN (upper limits of normal), alanine aminotransferase (ALT) $< 1.5 \times$ ULN, creatinine $\leq 1.2 \times$ ULN, and blood urea nitrogen (BUN) $\leq 1.2 \times$ ULN. Exclusion criteria included any serious concomitant systemic disorder unable to receive chemotherapy, concurrent chemo-radiotherapy; brain metastasis with symptoms; without comprehensive data; developing other diseases (e.g., gastric ulcer, neutral system diseases) which may affect the safety of patients or the evaluation of results. All human studies have been approved by the ethics committee of the hospital and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. In this study, all patients signed an informed consent form for cisplatin-based chemotherapy and blood sample collection.

Table 1 Patient characteristics

Characteristics	No. of patients	Percentage (%)
Age (years)		
≥60	43	44.3
<60	54	55.7
Gender		
Male	66	68.0
Female	31	32.0
Smoking		
No	58	59.8
Yes	39	40.2
TNM stage		
IIIB	23	23.7
IV	74	76.3
Histology		
Adenocarcinoma	57	58.8
Squamous carcinoma	36	37.1
Other	4	4.1
Chemotherapy regimens		
Gemcitabine + Cisplatin	48	49.5
Vinorelbine + Cisplatin	9	9.3
Paclitaxel + Cisplatin	16	16.5
Docetaxel + Cisplatin	24	24.7

Chemotherapy regimens

All participants received one of the following cisplatin-based combination chemotherapy regimen: cisplatin 75 mg/m^2 on d2–4 plus gemcitabine 1200 mg/m^2 on d1 and d7 (GP regimen), plus vinorelbine 30 mg/m^2 on d1 and d8 (NP regimen), plus paclitaxel 210 mg/m^2 on d1 (TP regimen), or plus docetaxel 75 mg/m^2 on d1 (DP regimen).

The chemotherapy was repeated at three-weekly intervals for up to six cycles unless unacceptable toxicity, disease progression or patients' refusal to continue treatment.

Clinical evaluation

The patients were required to complete two cycles of chemotherapy at least to evaluate treatment response according to RECIST 1.1. The percentage of patients with complete response (CR) and partial response (PR) after treatment represents response rate (RR). The percentage of patients with CR, PR, and stable disease (SD) after treatment represents disease control rate (DCR). For long-term response, progression-free survival (PFS) was defined as the period between the date of chemotherapy and the data of confirmed progression or death from any cause. Toxicity including hematotoxicity, alimentary canal toxicity, and dermal toxicity were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE, V2.0).

DNA extraction and genotyping

Genomic DNA was isolated from peripheral blood lymphocytes using Qiagen blood mini kit (Qiagen, Germany) by the manufacturer's protocol. The genotypes of GSTP1 A313G, ATP7A C2299G, and XRCC1 A1196G were analyzed by DNA pyrosequencing on an ABI Prism 3100 DNA analyzer (Applied Bio-systems, USA). The positive and reverse primer sequences of GSTP1 A313G were 5′-ACC CCA GGG CTC TAT GGG AA-3′ and 5′-TGA GGG CAC AAG AAG CCC CT-3′, respectively. The positive and reverse primer sequences of ATP7A C2299G were 5′-TGC AGC AAT TTG AAT ACC TCC C-3′ and 5′-AAA GCA TGT ATT TCC AAT GAT TGG-3′, respectively. The positive and reverse primer sequences of XRCC1 A1196G were 5′-TTG TGC TTT CTC TGT GTC CA-3′ and 5′-TCC TCC AGC CTT TTC TGA TA-3′, respectively.

Statistical analysis

The clinical information on efficacy and toxicity was compared across genotype, using χ^2 tests for categoric variables and one-way analysis of variance for continuous variables. Survival curves were analyzed by the Kaplan–Meier method, and the impact of the SNPs on PFS was assessed using the log-rank test. Meanwhile, baseline characteristics (age, sex, smoking history, histological types, and TNM stage at entry) were adjusted in order to avoid potential confounding effects. The association between RR, DCR, and the SNPs were described as odds ratio (ORs) and 95 % confidence interval (CI) in unconditioned Logistic regression. The prognostic value of different SNPs for the PFS was estimated by multivariate analysis using the Cox proportional hazards models, describing as the hazard ratio (HR) and 95 % CI. P values <0.05 with two-sided were considered statistical differences. Data were performed by the statistical software SPSS Statistics (version 19.0, SPSS Inc., Chicago, IL, USA).

Results

Allele frequencies

The patient characteristics, such as age, sex, smoking, TMN stage, histology, and chemotherapy regimens, were shown in Table 1. The allele frequencies of polymorphisms were GSTP1 (A: 85.6 %, G: 14.4 %), ATP7A (G: 80.9 %, C: 19.1 %), and XRCC1 (G: 73.7 %, A: 26.3 %), respectively (Table 2). Genotype frequencies of both GSTP1, ATP7A, and XRCC1 polymorphisms were found to be in Hardy–Weinberg equilibrium ($p > 0.05$).

Relationship between the SNPs and treatment outcome

RR was obviously increased in AA carriers than that in AG + GG carriers when adjusted for age, sex, smoking, TMN stage, pathological type, and chemotherapy regimens in patients with GSTP1 polymorphisms ($p = 0.026$, Table 3). There was a relationship between DCR and genotypes ($p = 0.036$), moreover, it is more obvious after adjusted by Logistic regression test ($p = 0.019$, Table 4). The Kaplan–Meier curve of the PFS was shown in Fig. 1a, and the Log-rank test showed that the PFS was not affected by genotypes ($p = 0.076$). However, PFS was longer in AA genotype patients by adjusted with the Cox multivariate analysis ($p = 0.042$, Table 5).

Table 2 The distribution of genotypes

Genotypes	No. of patients	Percentage (%)
GSTP1 A313G		
AA	70	72.2
AG	26	26.8
GG	1	1.0
ATP7A C2299G		
GG	66	68.0
CG	25	25.8
CC	6	6.2
XRCC1 A1196G		
GG	53	54.6
AG	37	38.1
AA	7	7.2

Table 3 Relationship between the genotypes and response rate

Genotypes	CR + PR (%)	SD + PD (%)	Chi-square test		Binary logistic regression analysis		
			χ^2	p	OR	95 % CI	p
GSTP1 A313G							
AA	24 (34.3)	46 (65.7)			1		
AG + GG	4 (14.8)	23 (85.2)	3.597	0.058	4.302	1.193–15.515	0.026
ATP7A C2299G							
GG	18 (27.3)	48 (72.7)			1		
CG + CC	10 (32.3)	21 (67.7)	0.255	0.613	0.579	0.202–1.655	0.308
XRCC1 A1196G							
GG	17 (32.1)	36 (67.9)			1		
AG + AA	11 (25.0)	33 (75.0)	0.586	0.444	1.407	0.539–3.675	0.485

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Table 4 Relationship between the genotypes and disease control rate

Genotypes	CR + PR + SD (%)	PD (%)	Chi-square test		Binary logistic regression analysis		
			χ^2	p	OR	95 % CI	p
GSTP1 A313G							
AA	58 (82.9)	12 (17.1)			1		
AG + GG	17 (63.0)	10 (37.0)	4.397	0.036	3.740	1.238–11.298	0.019
ATP7A C2299G							
GG	53 (80.3)	13 (19.7)			1		
CG + CC	22 (71.0)	9 (29.0)	1.048	0.306	1.683	0.571–4.966	0.345
XRCC1 A1196G							
GG	41 (77.4)	12 (22.6)			1		
AG + AA	34 (77.3)	10 (22.7)	0.000	0.992	0.973	0.352–2.690	0.958

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

For ATP7A SNPs, RR in GG carriers and GC + CC carriers was 28.8 and 22.6 %, respectively ($p = 0.226$, Table 3). There was no association between DCR and ATP7A C2299G polymorphisms ($p = 0.338$, Table 4), meanwhile, the similar result was observed in the Kaplan–Meier curve of the PFS ($p = 0.808$, Fig. 1b) and in the Cox multivariate analysis ($p = 0.818$, Table 5).

No association existed between XRCC1 SNPs and RR, DCR whatever by adjusted or not ($p = 0.444$ and $p = 0.992$, respectively, Tables 3, 4). Also, there was no connection between PFS and genotypes ($p = 0.600$ and $p = 0.617$, respectively, Table 5) in the Kaplan–Meier curve of the PFS (Fig 1c), and either by the Log-rank test or by Cox multivariate analysis.

Relationship between the SNPs and toxicity

A significant difference in anemia was observed in patients with GSTP1 A313G ($p = 0.046$), however, the association disappeared after adjusted by Logistic regression analysis ($p = 0.998$) (Supplementary Table 1). A weak relationship was observed between the GSTP1 SNPs and toxicity of lymphopenia, leucopenia, neutropenia, thrombocytopenia, nausea, vomiting, diarrhea, and erythra. Whereas, no obvious toxicity was recorded in patients with ATP7A SNPs (Supplementary Table 2). XRCC1 SNPs was significantly linked with the incidence of lymphopenia ($p = 0.024$) and diarrhea ($p = 0.020$) by both Chi-square test and logistic regression analysis, while the other toxicity of cisplatin-based chemotherapy were not related (Supplementary Table 3).

Discussion

Patients with advanced NSCLC have an individual response to cisplatin-based chemotherapy. Many researchers suggest that genetic factors maybe play an important role in the individual response [10, 11]. It is demonstrated that this response results from hereditary factors by increased the

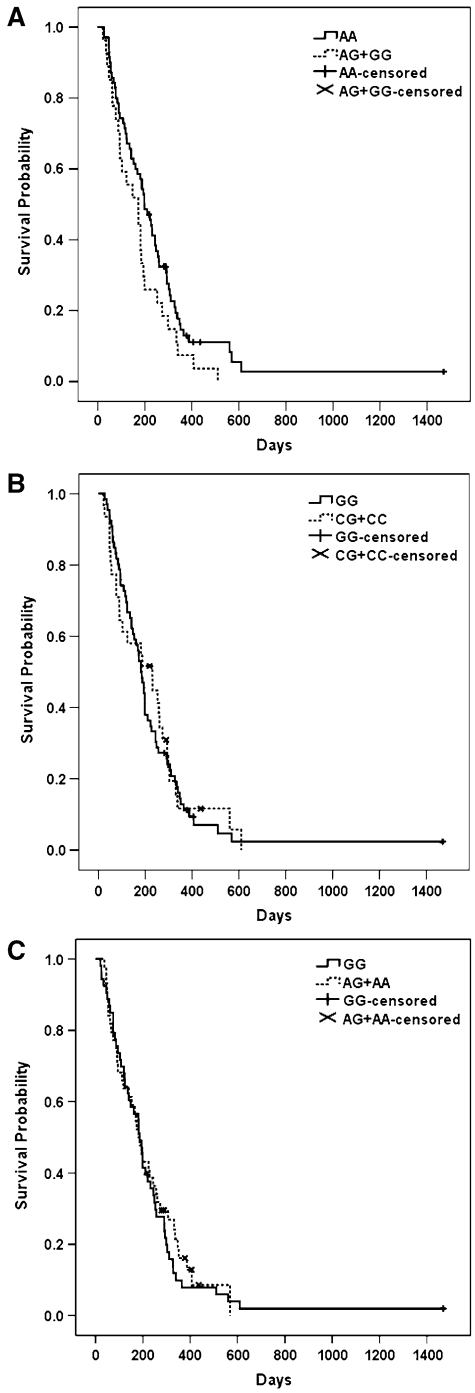

Fig. 1 **a** Progress-free survival (days) in patients with GSTP1 A313G. **b** Progress-free survival (days) in patients with ATP7A C2299G. **c** Progress-free survival (days) in patients with XRCC1 A1196G

cell activity of biotransformation, accumulation of intracellular cisplatin, and the weakened capacity of DNA repairing [12–14].

GSTP1 is a kind of phase II detoxification enzymes, which is involved in the detoxification of cisplatin. Over expression of GSTP1 in NSCLC patient decreased the sensitivity to platinum agents in vitro [15]. The polymorphism of GSTP1 A313G changes the thermal stability and conjugation capacity of GSTP1, which alters the ability of GSTP1 to detoxify chemotherapeutic agents and modulates drug responses. Therefore, enzyme activity with the GSTP1 A313G is more effective on cisplatin than that with wild-type in vitro [16]. Meanwhile, the mutation frequency of GSTP1 A313G is 20.35 % in lung cancer patients. However, it is a controversy that the A or G allele would enhance clinical response of cisplatin-based chemotherapy. Several studies have pointed out that patients with genotypes of GG and GA were more susceptive to platinum and had a better prognosis and PFS than that with wild-type AA carriers [17–21]. Noteworthy, Khrunin et al. [22] found that patients with AA genotype survived longer than that with GG after platinum chemotherapy in ovarian cancer. In the present study, the higher RR, DCR, and the longer PFS were observed by the AA carriers than that by the AG + GG carriers with the GSTP1 SNPs. Ke et al. [23] hinted at the same tendency that the mutation carriers exhibited a shorter survival time. At least some of the confusion between the previous researches is due to the different adjusted factors which included the other genotypes assessed at the same researches. It is reminded that the various genotypes related to the curative effect of cisplatin should be evaluated comprehensively in the clinical practice.

Meanwhile, the relationship between the SNPs of GSTP1 A313G and the toxicity of cisplatin-based chemotherapy was clear. Except for anemia, the risk of hematotoxicity, gastrointestinal toxicity, and dermal toxicity was not reduced in patients with 313G. However, it is reported that G allele carriers had lower risk of leukocyte decrease than that of wild-type carriers in advanced NSCLC patients treated by platinum-based regimens in all of 108 patients [12]. The individual differences of cisplatin-induced toxicity may be due to alterations in GSTP1 proteins activity by reducing the transport capacity for cisplatin in patients with 313G.

ATP7A is associated with copper transport across the cell. ATP7A mediates the transport of platinum drugs across the cellular membranes, and is considered to sequester platinum agents in intracellular compartments and to prevent their reaction with nuclear DNA [24, 25]. A correlation between the expression of ATP7A and the degree of acquired resistance to platinum drug in cultured cells and tumor samples suggests that the copper transporters are important constituents of the program that regulates sensitivity to platinum drugs [26, 27]. ATP7A C2299G, mutated in high frequency of 23.2 % in Chinese population, can change the gene functions. Clinical data showed that ATP7A C2299G was associated with toxicity of chemotherapeutics using docetaxel and thalidomide [28]. It is highly necessary to investigate the association of

Table 5 Relationship between the genotypes and progression-free survival

Genotypes	PFS (days, 95 % CI)	Log-tank test		Cox regression analysis		
		χ^2	*p*	HR	95 % CI	*p*
GSTP1 A313G						
AA	198 (158.2–237.8)			1		
AG + GG	171 (82.8–259.2)	3.153	0.076	1.639	1.014–2.650	0.044
ATP7A C2299G						
GG	182 (154.1–209.9)			1		
CG + CC	229 (87.2–370.8)	0.059	0.808	0.924	0.570–1.497	0.748
XRCC1 A1196G						
GG	187 (153.1–220.9)			1		
AG + AA	182 (148.4–215.6)	0.275	0.600	0.896	0.582–1.379	0.617

PFS progression-free survival

ATP7A SNPs with the efficacy and toxicity of cisplatin for advanced NSCLC patients. In the present study, there is no effect of ATP7A C2299G on the treatment outcome including RR, DCR and PFS, and drug toxicity such as hematological and skin toxicity in advanced NSCLC patients by cisplatin-based chemotherapy.

XRCC1 serves as a scaffold factor in base excision repair, for which functional polymorphisms have been identified. The A1196G allele variant with high frequency ranged from 20–38 % of lung cancer population are the hot spot in the research of XRCC1 polymorphisms, which especially links with the change of XRCC1 protein activity to impact DNA repair capacity [29]. DNA damage severity induced by cisplatin has relevance with the efficiency and toxicity of cisplatin-based chemotherapy. It is predicted that XRCC1 A1196G affects the response to cisplatin-based chemotherapy; however, as the changes of DNA repair capacity caused by the SNPs of XRCC1 could take place in normal tissue as well as tumor tissue, there existed different results on the effect of XRCC1 polymorphisms. Giachino et al. [30] observed A variant allele carriers had a higher risk of toxicity of cisplatin followed with a longer survival time in NSCLC patients. AA genotype in XRCC1 1196 was significantly associated with the toxicity of cisplatin on neutropenia [22]. In the present study, there was no association between the XRCC1 A1196G and RR, DCR and PFS, while the A allele was linked with the higher incidence of lymphopenia and diarrhea.

There were some deficiencies in this study, such as the small samples and a bit confounding factors. The weak relationship between the genotypes and the toxicity may result from the bias of the small samples and the lower incidence of toxicity. It is worth mentioning that the patients in this study delayed treatments when they can not tolerate the toxicity of cisplatin-based chemotherapy. Besides, heterogeneous cisplatin-based chemotherapy and histology maybe prevent drawing a firm conclusion despite the result was adjusted by the affecting factors. Anyhow, further study needed to be performed with a large number of cases or with multiple centers.

Our results suggest that the polymorphism of GSTP1 A313G but not ATP7A C2299G might affect the clinical outcome, moreover, the GSTP1 A313G is a useful predictor of lymphopenia, and XRCC1 A1196G could dope out the incidence of lymphopenia and diarrhea by cisplatin-based chemotherapy in the advanced NSCLC patients.

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References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012;62(1):10–29.
2. Zhou F, Yu Z, Jiang T, Lv H, Yao R, Liang J. Genetic polymorphisms of GSTP1 and XRCC1: prediction of clinical outcome of platinum-based chemotherapy in advanced non-small cell lung cancer (NSCLC) patients. Swiss Med Wkly. 2011;141:w13275.
3. Hirano T, Kato H, Maeda M, Gong Y, Shou Y, Nakamura M, et al. Identification of postoperative adjuvant chemotherapy responders in non-small cell lung cancer by novel biomarker. Int J Cancer. 2005;117(3):460–8.
4. Wang D, Lippard SJ. Cellular processing of platinum anticancer drugs. Nat Rev Drug Discov. 2005;4(4):307–20.
5. Peklak-Scott C, Smitherman PK, Townsend AJ, Morrow CS. Role of glutathione S-transferase P1-1 in the cellular detoxification of cisplatin. Mol Cancer Ther. 2008;7(10):3247–55.
6. Galluzzi L, Senovilla L, Vitale I, Michels J, Martins I, Kepp O, et al. Molecular mechanisms of cisplatin resistance. Oncogene. 2012;31(15):1869–83.
7. Zhu G, Lippard SJ. Photoaffinity labeling reveals nuclear proteins that uniquely recognize cisplatin–DNA interstrand cross-links. Biochemistry. 2009;48(22):4916–25.
8. Schneider J, Classen V, Bernges U, Philipp M. XRCC1 polymorphism and lung cancer risk in relation to tobacco smoking. Int J Mol Med. 2005;16(4):709–16.
9. Li F, Sun X, Sun N, Qin S, Cheng H, Feng J, et al. Association between polymorphisms of ERCC1 and XPD and clinical response to platinum-based chemotherapy in advanced non-small cell lung cancer. Am J Clin Oncol. 2010;33(5):489–94.
10. Wheeler HE, Gamazon ER, Stark AL, O'Donnell PH, Gorsic LK, Huang RS, et al. Genome-wide meta-analysis identifies variants associated with platinating agent susceptibility across populations. Pharmacogenom J. 2013;13(1):35–43.
11. Tiseo M, Bordi P, Bortesi B, Boni L, Boni C, Baldini E, et al. ERCC1/BRCA1 expression and gene polymorphisms as prognostic and predictive factors in advanced NSCLC treated with or without cisplatin. Br J Cancer. 2013;108(8):1695–703.

12. 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(7):679–83.
13. Bradbury PA, Kulke MH, Heist RS, Zhou W, Ma C, Xu W, et al. Cisplatin pharmacogenetics, DNA repair polymorphisms, and esophageal cancer outcomes. Pharmacogenet Genom. 2009;19(8):613–25.
14. Chen S, Huo X, Lin Y, Ban H, Li W, Zhang B, et al. Association of MDR1 and ERCC1 polymorphisms with response and toxicity to cisplatin-based chemotherapy in non-small-cell lung cancer patients. Int J Hyg Environ Health. 2010;213(2):140–5.
15. Oguri T, Fujiwara Y, Katoh O, Daga H, Ishikawa N, Fujitaka K, et al. Glutathione S-transferase-pi gene expression and platinum drug exposure in human lung cancer. Cancer Lett. 2000;156(1):93–9.
16. McIlwain CC, Townsend DM, Tew KD. Glutathione S-transferase polymorphisms: cancer incidence and therapy. Oncogene. 2006;25(11):1639–48.
17. Ginsberg G, Smolenski S, Hattis D, Guyton KZ, Johns DO, Sonawane B. Genetic Polymorphism in Glutathione Transferases (GST): Population distribution of GSTM1, T1, and P1 conjugating activity. J Toxicol Environ Health B Crit Rev. 2009;12(5–6):389–439.
18. Joerger M, Burgers SA, Baas P, Smit EF, Haitjema TJ, Bard MP, et al. Germline polymorphisms in patients with advanced nonsmall cell lung cancer receiving first-line platinum-gemcitabine chemotherapy: a prospective clinical study. Cancer. 2012;118(9):2466–75.
19. Khrunin A, Ivanova F, Moisseev A, Khokhrin D, Sleptsova Y, Gorbunova V, et al. Pharmacogenomics of cisplatin-based chemotherapy in ovarian cancer patients of different ethnic origins. Pharmacogenomics. 2012;13(2):171–8.
20. Saip R, Sen F, Vural B, Ugurel E, Demirkan A, Derin D, et al. Glutathione S-transferase P1 polymorphisms are associated with time to tumor progression in small cell lung cancer patients. J BUON. 2011;16(2):241–6.
21. Yang LM, Li XH, Bao CF. Glutathione S-transferase P1 and DNA polymorphisms influence response to chemotherapy and prognosis of bone tumors. Asian Pac J Cancer Prev. 2012;13(11):5883–6.
22. Khrunin AV, Moisseev A, Gorbunova V, Limborska S. Genetic polymorphisms and the efficacy and toxicity of cisplatin-based chemotherapy in ovarian cancer patients. Pharmacogenom J. 2010;10(1):54–61.
23. Ke HG, Li J, Shen Y, You QS, Yan Y, Dong HX, et al. Prognostic significance of GSTP1, XRCC1 and XRCC3 polymorphisms in non-small cell lung cancer patients. Asian Pac J Cancer Prev. 2012;13(9):4413–6.
24. Safaei R. Role of copper transporters in the uptake and efflux of platinum containing drugs. Cancer Lett. 2006;234(1):34–9.
25. Arnesano F, Scintilla S, Natile G. Interaction between platinum complexes and a methionine motif found in copper transport proteins. Angew Chem Int Ed Engl. 2007;46(47):9062–4.
26. Kuo MT, Chen HH, Song IS, Savaraj N, Ishikawa T. The roles of copper transporters in cisplatin resistance. Cancer Metastasis Rev. 2007;26(1):71–83.
27. Tadini-Buoninsegni F, Bartolommei G, Moncelli MR, Inesi G, Galliani A, Sinisi M, et al. Translocation of platinum anticancer drugs by human copper ATPases ATP7A and ATP7B. Angew Chem Int Ed Engl. 2014;53(5):1297–301.
28. Gu YH, Kodama H, Murata Y, Mochizuki D, Yanagawa Y, Ushijima H, et al. ATP7A gene mutations in 16 patients with Menkes disease and a patient with occipital horn syndrome. Am J Med Genet. 2001;99(3):217–22.
29. Au WW, Salama SA, Sierra-Torres CH. Functional characterization of polymorphisms in DNA repair genes using cytogenetic challenge assays. Environ Health Perspect. 2003;111(15):1843–50.
30. Giachino DF, Ghio P, Regazzoni S, Mandrile G, Novello S, Selvaggi G, et al. Prospective assessment of XPD Lys751Gln and XRCC1 Arg399Gln single nucleotide polymorphisms in lung cancer. Clin Cancer Res. 2007;13(10):2876–81.