

Mini Review: Relationship Between Platinum Induced Toxicities and Nucleotide Excision Repair (NER) Pathway Polymorphisms in Non-Small Cell Lung Cancer (NSCLC) Patients and Beyond

Shuai Guo, Qi Xu, Chen-Chen Wang, Zhen-Shan Qi, Xiao-Lin Xiao

Shuai Guo, Northeastern University, Boston, MA, 02114, the United States

Shuai Guo, Qi Xu, Xiao-Lin Xiao, Central South University, 410083, Hunan, China

Qi Xu, Test Centre, 361 Yinpen South Road, 410013, Hunan, China

Chen-Chen Wang, Department of Oncology, Third Hospital of Chengdu, Chengdu, 610015, Sichuan, China

Chen-Chen Wang, Medical University of Guangxi, 541000, Nanning, Guangxi, China

Zhen-Shan Qi, Department of Oncology, People's hospital of Fuzhou, Fuzhou, 350004, Fujian, China

Zhen-Shan Qi, College of Medicine, National Taiwan University, 10051, Taipei, Taiwan

Xiao-Lin Xiao, MRC Clinical Sciences Centre, Faculty of Medicine, Imperial College, London, W12 0NN, the United Kingdom

Correspondence to: Xiaolin Xiao, PhD, MRC Clinical Sciences Centre, Faculty of Medicine, Imperial College London, Du Cane Road, London, UK, zip code: W12 0NN.

Email: xiaolin.xiao@csc.mrc.ac.uk

Received: September 15, 2013 Revised: October 15, 2013

Accepted: October 20, 2013

Published online: December 18, 2013

ABSTRACT

Platinum-induced toxicities severely impede successful chemotherapy in non-small cell lung cancer (NSCLC) patients. The nucleotide excision repair (NER) pathway is considered as one of the major factors contributing to platinum effects. Furthermore, genetic variances of the NER pathway influence platinum toxicities. Several genetic loci have recently been reported to contribute to the susceptibility of platinum-induced toxicities. In order to further understand the genetic influence on the risk of platinum-induced toxicities in NSCLC patients, we reviewed and collected articles from PUBMED for genes that reported by recent clinical pharmacogenetic studies. At the conclusion of our search, we summarized the publications about relative clinical trials and summarized five candidate genes, which might relate with platinum-induced toxicities in NSCLC patients. Despite the findings of this and other similar, contemporary research projects, many of the special details and underlying mechanisms in this field of study are still, to a

great extent, unknown. As a result, future studies are needed to gain a full appreciation regarding the identification of high toxicity risk in human beings

© 2013 ACT. All rights reserved.

Key words: DNA repair; Nucleotide excision repair (NER) pathway; Non-small cell lung cancer (NSCLC); Platinum; Toxicity; Copper transport protein 1 (CTR1)

Guo S, Xu Q, Wang CC, Qi ZS, Xiao XL. Mini Review: Relationship Between Platinum Induced Toxicities and Nucleotide Excision Repair (NER) Pathway Polymorphisms in Non-Small Cell Lung Cancer (NSCLC) Patients and Beyond. *Journal of Tumor* 2013; 1(7): 66-72 Available from: URL: <http://www.ghrnet.org/index.php/JT/article/view/544>

INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide, with a total five-year survival rate of about 15%^[1]. There are two major histological subtypes of lung cancer, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The most common types of NSCLC are squamous cell carcinoma, large cell carcinoma and adenocarcinoma^[2]. The incidence of NSCLC is continues growing up rapidly recently years^[3].

Platinum-based chemotherapy is considered as the first-line treatment for lung cancer, but NSCLC is relatively insensitive to chemotherapy compare to SCLC^[4]. Thus, more attention has been paid to improve the chemotherapy efficacy in NSCLC patients^[5]. Cisplatin, carboplatin and oxaliplatin are the first-, second- and third-generation of platinum-containing anti-cancer chemotherapy drugs, respectively^[6]. However, both of the chemotherapy resistance and platinum-induced toxicities are common and constitute the major obstacle for successful chemotherapy in NSCLC patients^[7]. Basically, the most common severe platinum-induced toxicities include nephrotoxicity, ototoxicity, neurotoxicity, myelosuppression, electrolyte disturbances, nausea and anaphylactic reactions^[7].

Chemotherapy induced toxicities are multifactorial: they depend on several internal and external factors, such as health status, disease stage, patient age and smoking status^[5]. Furthermore, genetic factors,

such as single-nucleotide polymorphism (SNP), are important determinants of platinum induced side effects^[6]. Personalized medicine, which tailors intervention to individual variation in risk and treatment response, has been considered as one of the potential medicine models that will greatly improve the clinical efficacy of platinum-based chemotherapy, and the use of genetic information has been played a major role in the design of personalized medicine^[8]. Personalized medicine have been widely researched in several complex diseases, such as diabetes^[9-11], seizures^[12-14], and so on. As the rapid development of SNP detection technologies^[15] and integrative network-based computational methods^[16,17] more researches has investigated the potential ability of using certain SNPs to predict the chemo toxicities in cancer patients^[18].

Nucleotide excision repair (NER) pathway, as a major form of DNA repair pathway, has been suggested to be the main cellular defense mechanism against platinum-induced intra-strand cross-links in DNA repair pathway^[19]. Genes involve in NER pathway, including its up-stream genes, are considered as candidate genes for prediction of different response to platinum-based chemotherapy in NSCLC patients^[20]. Some SNPs have been described as important factors contributing to the activity of NER pathways, thus it would influence platinum-based chemotherapeutic toxicities in NSCLC patients^[19].

The aim of the study is to provide a comprehensive assessment on the association between genetic polymorphism within NER pathway and platinum-based chemotherapy toxicity in NSCLC, and further appraise the prediction ability of these potential biomarkers.

METHODS

We searched the relative literatures about NER pathway genetic polymorphisms and platinum induced toxicities in NSCLC patients through PubMed, with key words “gene name + NSCLC + toxicity/toxicities”. Gene names included a total of 23 genes associated with NER pathway, with the detailed gene information listed in table 1. The time period for literature searching was from the first available article to September 1st 2013. Publications meeting the following criteria were including: (1) patients were diagnosed with NSCLC; (2) patients had been received platinum-based chemotherapy; (3) the data of toxicity rate stratified by polymorphisms could be obtained from the original article. Candidate NER genes were selected as the genes had been reported by more than one qualified literature to show its potential relationship with platinum-induced toxicities, thus three genes were remained. Besides three candidates NER genes, one up-stream gene of NER pathway and a copper transport family gene were also selected, due to the emerging evidence of their relationship with platinum response. Figure 1 illustrates the literatures and candidate genes selection process. And the detailed summarized information about these studies was presented in table 2-4.

Genetic polymorphism in NER pathway

Nucleotide excision repair includes certain key steps and there are some core proteins that should significantly influence the DNA repair ability^[21]. After literature selection, this study focused on three core genes in NER pathway^[22].

Table 1 Nucleotide excision repair (NER) pathway associated genes.

Gene names	Location	Full names
CCNH	5q13.3-q14	Cyclin H
CDK7	5q12.1	Cyclin-dependent kinase 7
CETN2	Xq28	Centrin, EF-hand protein, 2
CSA	5q12.1	Excision repair cross-complementing rodent repair deficiency, complementation group 8
CSB	10q11.23	Excision repair cross-complementing rodent repair deficiency, complementation group 6
DDB1	11q12-q13	Damage-specific DNA binding protein 1, 127kDa
DDB2	11p12-p11	Damage-specific DNA binding protein 2, 48kDa
ERCC1	19q13.32	Excision repair cross-complementing rodent repair deficiency, complementation group 1
LIG1	19q13.2-q13.3	Ligase I, DNA, ATP-dependent
MMS19	10q24-q25	MMS19 nucleotide excision repair homolog
MNAT1	14q23	CDK-activating kinase assembly factor 1
RAD23A	19p13.2	RAD23 homolog A
RAD23B	9q31.2	RAD23 homolog B
RPA1	17p13.3	Replication protein A1, 70kDa
RPA2	1p35	Replication protein A2, 32kDa
RRM1	11p15.5	Ribonucleotide reductase M1
XAB2	19p13.2	XPA binding protein 2
XPA	9q22.3	Xeroderma pigmentosum, complementation group A
XPB	2q21	Xeroderma pigmentosum, complementation group B
XPC	3p25	Xeroderma pigmentosum, complementation group C
XPD	19q13.3	Xeroderma pigmentosum, complementation group D
XPF	16p13.12	Xeroderma pigmentosum, complementation group F
XPG	13q33	Xeroderma pigmentosum, complementation group G

Table 2 Previous publications about genetic polymorphisms of ERCC1 gene and platinum induced toxicities in NSCLC patients.

Publications	Year	Treatment	n	Ethnicity	Genes/SNPs ¹	Related toxicities ²	P-value ²
Joerger M <i>et al</i> ^[58]	2012	Platinum-based	197	White, Black Asian, Others	C118T	NA	NS
Ludovini V <i>et al</i> ^[25]	2011	Cisplatin -base	192	Italian	C118T	NA	NS
KimCurran <i>et al</i> ^[24]	2011	Platinum-based	300	Chinese	C8092A	NA	NS
Vinolas N <i>et al</i> ^[29]	2011	Cisplatin + vinorelbine	94	Spanish	C118T	NA	NS
Chen S <i>et al</i> ^[27]	2010	Platinum-based	95	Chinese	C118T	NA	NS
Gandara DR <i>et al</i> ^[28]	2009	Platinum-based	526	Japanese	C118T	NA	NS
Kalikaki A <i>et al</i> ^[19]	2009	Platinum-based	119	Greek	C118T	NA	NS
Tibaldi C <i>et al</i> ^[26]	2008	Cisplatin-gemcitabine	65	Italian	C119T	NA	NS
Suk R <i>et al</i> ^[23]	2005	Platinum-based	214	White	C118T C8029A	NA gastrointestinal (grade 3~4)	NS P=0.03

¹ ERCC1: excision repair cross-complementing rodent repair deficiency, complementation group 1, ERCC1 C118T (ERCC1 Asn119Asn, rs11615), ERCC1 C8029A (rs3212986) ² NA: not applicable, NS: no significant.

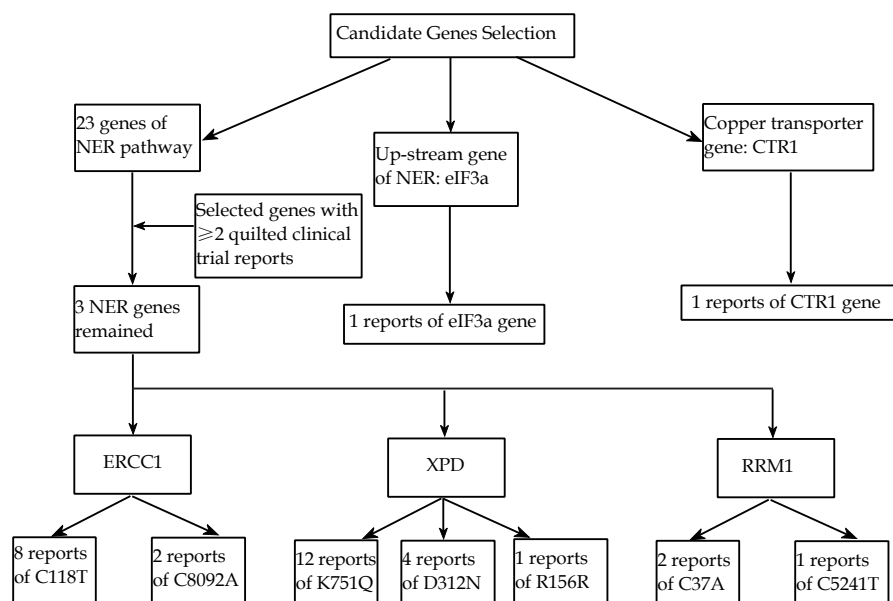


Figure 1 Candidate gene selection.

Table 3 Previous publications about genetic polymorphisms of XPD gene and platinum induced toxicities in NSCLC patients.

Publications	Year	Treatment	n	Ethnicity	Genes/SNPs ¹	Related toxicities ²	P-value ²
Provencio M <i>et al</i> ^[33]	2012	Cisplatin+vinorelbine	180	Spanish	K751Q D312N	NA NA	NS NS
Tiseo M <i>et al</i> ^[35]	2012	Carboplatin based	208	Italian	K751Q	NA	NS
Ludovini V <i>et al</i> ^[25]	2011	Cisplati -base	192	Italian	K751Q	NA	NS
Li Y <i>et al</i> ^[36]	2011	Cisplatin+vinorelbine	115	Chinese	K751Q	NA	NS
Vinolas N <i>et al</i> ^[29]	2011	Cisplatin+vinorelbine	94	Spanish	K751Q	NA	NS
Wu W <i>et al</i> ^[30]	2009	Platinum-based	209	Chinese	R156R	hematologic	p=0.009
					D312R	NA	NS
					K715Q	NA	NS
					R156R & D312R ³	hematologic (grade 3~4)	p=0.025
Kalikaki A <i>et al</i> ^[19]	2009	Platinum-based	119	Greek	K751Q	NA	NS
Gandara DR <i>et al</i> ^[28]	2009	Platinum-based	526	Japanese	C118T	NA	NS
Tibaldi C <i>et al</i> ^[26]	2008	Cisplatin-gemcitabine	65	Italian	D312R K751Q	NA	NS
Giachino DF <i>et al</i> ^[34]	2007	Platinum-based	203	Italian	K751Q	NA	NS
Petty WJ <i>et al</i> ^[31]	2007	Platinum-based	49	White & Black	K751Q	neutropenia (grade 4)	NS
					D312R	NA	NS
Booton R <i>et al</i> ^[32]	2006	Platinum-based	108	White	K751Q	NA	NS
					D312R & K751Q ³	neutropenia (grade 4)	p=0.05

¹XPD: Xeroderma Pigmentosum D, XPD Lys751Gln (XPD K751Q, rs1052559), XPD Asp312Asn (XPD D312N, rs1799793), XPD Arg156Arg (XPD R156R, rs238406); ²NA: not applicable, NS: no significant; ³ R156R & D312R: haplotype of XPD R156R and XPD D312R, D312R & K751Q: haplotype of XPD D312R and XPD K751Q.

Table 4 Previous publications about genetic polymorphisms of RRM1, eIF3a and CTR1 gene and platinum induced toxicities in NSCLC patients.

Publications	Year	Treatment	n	Ethnicity	Genes/SNPs ¹	Related toxicities ²	P-value ²
Zhang L <i>et al</i> ^[37]	2012	Platinum-based	388	Chinese	RRM1, C37A	vomiting (grade 3~4) hematological & non-hematologic (grade 3~4)	0.046 0.047
Vinolas N <i>et al</i> ^[29]	2011	Cisplatin + vinorelbine	94	Spanish	RRM1, C37A	NA	NS
Ludovini V <i>et al</i> ^[25]	2011	Cisplatin -base	192	Italian	RRM1, C524T	NA	NS
Xu X <i>et al</i> ^[43]	2012	Platinum-based	282	Chinese	eIF3a, Arg803Lys	Nephrotoxicity (grade 3~4)	p=0.02
Xu X <i>et al</i> ^[48]	2013	Cisplatin -base	204	Chinese	CTR1, rs10981694	ototoxicity (grade 3~4)	p=0.01

¹ RRM1: ribonucleotide reductase M1, RRM1 C37A (rs1042858), RRM1 C524T (rs11030813), eIF3a: eukaryotic translation initiation factor 3, subunit A, CTR1: copper transport protein 1; ²NA: not applicable, NS: no significant.

ERCC1 (excision repair cross-complementing rodent repair deficiency, complementation group 1)

ERCC1 is a component of the 5' endonuclease of the nucleotide excision repair complex, and it is crucial for the repair of DNA damage caused by interstrand and intrastrand cross-links that prevent both replication and transcription. Two major polymorphisms have been widely tested in pervious pharmacogenetic studies. These two SNPs include ERCC1 C118T (ERCC1 Asn119Asn, rs11615), as

well as ERCC1 C8029A (rs3212986), with the detailed descriptions shown in table 2.

For ERCC1 C8029A, Suk R *et al*^[23] reported a significant relationship between ERCC1 C8029A and grade 3~4 gastrointestinal toxicity (p=0.03) in white population. But the other Chinese study^[24] in 300 patients did not replicate the results.

For ERCC1 C118T, a total of eight studies failed to find a significant association between this polymorphism and any platinum-

induced toxicity. These eight clinical studies were composed of the followings: two of them were Italian studies, with one enrolled^[25] 192 patients and the other^[26] enrolled 65 patients; another two were Asian studies, with one^[27] enrolled 95 Chinese and the other one^[28] enrolled 526 Japanese; the remaining four studies were a Greek study^[19] enrolled 119 patients, a Spanish study^[29] enrolled 94 subjects, a white study^[23] enrolled 214 patients and a multi-ethnicities study (White, Black, Asian and others) enrolled 137 subjects in Netherland.

Among these published studies, only Suk R *et al*^[23] reported a significant relationship between C8029A and gastrointestinal toxicity in white population, which has not been successfully replicated. As far as we know from our literature research, there is no evidence to show the significant effect of ERCC1 C118T on platinum induced toxicities.

XPD (Xeroderma Pigmentosum D)

XPD is also known as ERCC2 (excision repair cross completing group 1 gene product). It helps unwind DNA and generates a junction between the double-stranded and single-stranded DNA around the transcription bubble. There are three major genetic polymorphisms within XPD gene which has been widely studied. These three SNPs include XPD Lys751Gln (XPD K751Q, rs1052559), XPD Asp312Asn (XPD D312N, rs1799793), and XPD Arg156Arg (XPD R156R, rs238406). Their detailed study information was shown in table 3.

In recent years, some relevant studies reported some significant relationships between XPD genotypes and platinum toxicities. Wu W *et al*^[30] enrolled 209 Chinese NSCLC patients and reported a significant relationship between XPD R156R and grade 3~4 hematologic toxicity ($p=0.009$), especially severe leukopenia toxicity ($p=0.005$). Moreover, they reported that the haplotype “CG” (D312N and R156R) revealed a protective effect of on the risk of grade 3~4 hematologic toxicity ($p=0.025$). On the other hand, Petty WJ *et al*^[31] reported a study included 49 patients (whites and blacks), and found the XPD genotype was associated with a significant higher risk of grade 4 neutropenia ($p=0.02$). Another study reported by Booton R *et al*^[32] found a significant association between XPD D312N/K751Q haplotype and grade 4 neutropenia ($p=0.05$) in white NSCSL patients.

However, there were another nine studies that did not find any significant relationship between XPD genotypes and platinum-induced toxicities. These nine studies were composed of the followings: three of them were Spanish studies, one enrolled 180 and analyzed XPD K751Q and XPD D312N mutations^[33], one enrolled 94 patients and carried out the analysis of XPD K751Q genotype^[29], the another one enrolled 203 patients and also tested XPD K751Q genotype^[34], three of them were Italian studies, one enrolled 208 patients and tested XPD K751Q genotype^[35], one enrolled 65 patients and carried out the test of XPD K751Q and XPD D312R genotype^[26], and another one enrolled 192 patients and tested XPD K751Q genotype^[25]; one of the nine studies was a Chinese study included 115 patient and tested XPD K751Q genotype^[36]; one of the nine studies was a Greek study^[19] included 119 patients and carried out the test of XPD K751Q genotype; the last one was published by Gandara DR *et al*^[28] and enrolled 256 Japanese NSCLC patients.

Based on the aforementioned studies, only Wu W *et al*^[30] and Petty WJ *et al*^[31] found a significant association between XPD polymorphism and hematologic toxicity. Although some ethnicity difference might exist, the relationship between XPD genotypes and platinum induced toxicities needs to be further confirmed by larger and multi-ethnicity based studies.

RRM1 (regulatory subunit of ribonucleotide reductase 1)

RRM1 functions as the regulatory subunit of ribonucleotide reductase and controls substrate specificity and the on/off function of ribonucleotide reductase, whereas the catalytic subunit (RRM2) converts nucleoside diphosphates to the corresponding deoxynucleotides. As shown in table 4, two major polymorphisms of RRM1 gene, RRM1 C37A (RRM1 rs1042858) and RRM1 C524T (RRM1 rs11030918), have been tested in recent studies.

Zhang L *et al*^[37] investigated the relationship between RRM1 C37A and platinum-induced toxicities in 388 Chinese stage IIIB-IV NSCLC patients. The patients received cisplatin/carboplatin based chemo together with vinorelbine/gemcitabine/gocetaxcel/paclitaxel. They found this C37A genotype was significantly related with the total grades 3~4 adverse events ($P=0.047$), including hematological toxicity and non-hematologic toxicity. On the other hand, Zhang L *et al*^[37] reported that this SNPs also related with grade 3~4 vomiting ($P=0.046$), whereas a clinical study of Spain, Vinolas N *et al*^[29] did not replicate the results. In this Spanish study, a total of 94 NSCLC patients in stage III-IV were enrolled and they were treated with cisplatin and vinorelbine. The study^[23] did not find any significant relationship between RRM1 C37A and platinum-induced toxicities. In addition, Ludovini V *et al*^[25] published an Italian study that enrolled 192 chemotherapy-native NSCLC patients in advance stages. This study analyzed the relationship between RRM1 C524T and platinum toxicities, but no significant relationship was found in this study.

Since only a limited numbers of studies are available and the sample size they studied are relatively small, the relationship between RRM1 genetic polymorphism and platinum induced toxicities need to be further investigated in larger clinical pharmacokinetics studies.

Genetic polymorphism in up-stream gene of NER pathway

eIF3a is the largest subunit of eukaryotic translation initiation factor 3 (eIF3), known to be over-expressed in many malignancies, both *in vivo* and *in vitro*^[38,39]. It has been suggested that eIF3a is an upstream gene of NER pathway. The eIF3a knockdown cell line showed increased cellular resistance to cisplatin, increased DNA repair ability and up-expression of DNA repaired proteins^[40], while the eIF3a over expressed cell line showed the opposite results. *In vivo*, the gene expression levels of eIF3a significantly associated with response of lung cancer patients to platinum-based chemotherapy^[41].

Xu X *et al*^[42] explored the association between eIF3a polymorphism and platinum-based chemotherapy response, and further investigated the overall survival in Chinese lung cancer patients. They found that rs3740556 conferred a significant increase in platinum-based chemotherapy response and a favorable survival for NSCLC patients. More importantly, Xu X *et al*^[43] further investigated the role of eIF3a polymorphism in relation to severe platinum toxicity in Chinese NSCLC patients, and found a novel missense SNP Arg803Lys was associated with nephrotoxicity and ototoxicity. Although these results need to be replicated by further larger studies, these results bring the light of the essential role of eIF3a in identification of individuals at risk of severe toxicity, which will lead to more attraction on up-stream genes of NER pathway and to contribute to the improvement of chemotherapeutic efficacy in NSCLC patients.

Genetic polymorphism in copper transport family

Beyond this NER pathway, an interesting possibility has emerged that copper transporter family performs as the major plasma-membrane transporter in platinum uptake as well as exportation^[44]. Both of the platinum cellular uptake and DNA repair ability are

suggested as the major cause of severe toxicities in platinum treatment *in vivo*^[45]. Copper transporter family is comprised of CTR1 (copper transport protein 1), ATP7A (copper-transporting ATPase 1), and ATP7B (ATPase, Cu⁺ transporting, beta polypeptide)^[46]. It has been confirmed that CTR1 plays an essential role in platinum influx among these three components^[46].

A multi-institutions based study found that rs7851395 and rs1268377 genotypes of the CTR1 gene affect the platinum-based chemotherapeutics response, as well as the overall survival rate in Chinese NSCLC patients^[47]. Moreover, Xu X *et al*^[48] investigated the role of CTR1 polymorphism in susceptibility to severe platinum toxicities. They found that the rs10,981,694 mutation was associated with platinum induced severe ototoxicity and C allele carrier patients seemed to have poorer toxicity tolerance in Chinese NSCLC patients. On the basis of these findings, it may be possible to use CTR1 in the further as a biomarker to predict the outcomes of personalized platinum chemotherapy.

CONCLUSION

Based on the results of published clinical trials, we have selected these candidate genes (i.e., ERCC1, XPD, RRM1, eIF3a, and CTR1) that are more likely to have effect on platinum-induced toxicities in NSCLC patients. Confounding variables such as environmental influence and unknown gene-gene interaction do undoubtedly exist^[49,50]. Twin modeling based genetic research might also be used to inspire further exploration of potential biomarkers^[51]. Additionally, unidentified associations corresponding to differences in ethnicity, age, study sample sizes, and study-specific methods of analysis do further complicate the situation^[52,53]. Beyond these genetic factors, epigenetics, especially DNA methylation^[54,55], should be considered as another potential biomarker which has been suggested contribute greatly to the variance of individual drug response^[56,57].

In conclusion, the complex occurrence of chemo toxicities and our current lack of knowledge both prevent us from fully explaining the precise mechanism. Consequently, future studies encompassing larger sample sizes and novel perspectives are called for in overcoming current problems. If allowed to transpire, these studies will facilitate a better understanding of the regulatory pathways in chemo toxicities in human beings.

ACKNOWLEDGMENTS

Shuai Guo, Qi Xu, These authors contribute equally.

REFERENCES

- Herbst RS, Heymach JV, Lippman SM, Lung cancer. *N Engl J Med* 2008; **359**(13): 1367-1380
- Hoffman PC, Mauer AM, Vokes EE, Lung cancer. *Lancet* 2000; **355**(9202): 479-485
- Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010; **60**(5): 277-300
- Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**(2): 69-90
- Harrington SE, Smith TJ, The role of chemotherapy at the end of life: "when is enough, enough?". *JAMA* 2008; **299**(22): 2667-2678
- Program NT, Cisplatin. *Rep Carcinog* 2011; (12): 110-101
- Monneret C, Platinum anticancer drugs. From serendipity to rational design. *Ann Pharm Fr* 2011; **69**(6): 286-295
- Conti R, Veenstra DL, Armstrong K, Lesko LJ, Grosse SD. Personalized medicine and genomics: challenges and opportunities in assessing effectiveness, cost-effectiveness, and future research priorities. *Med Decis Making* 2010; **30**(3): 328-340
- Yu M, Xu XJ, Yin JY, Wu J, Chen X, Gong ZC, Ren HY, Huang Q, Sheng FF, Zhou HH, Liu ZQ. KCNJ11 Lys23Glu and TCF7L2 rs290487(C/T) polymorphisms affect therapeutic efficacy of repaglinide in Chinese patients with type 2 diabetes. *Clin Pharmacol Ther* 2010; **87**(3): 330-335
- Sheng, F.F., et al., NAMPT -3186C/T polymorphism affects repaglinide response in Chinese patients with Type 2 diabetes mellitus. *Clin Exp Pharmacol Physiol* 2011; **38**(8): 550-554
- Gong ZC, Huang Q, Dai XP, Lei GH, Lu HB, Yin JY, Xu XJ, Qu J, Pei Q, Dong M, Zhou BT, Shen J, Zhou G, Zhou HH, Liu ZQ. NeuroD1 A45T and PAX4 R121W polymorphisms are associated with plasma glucose level of repaglinide monotherapy in Chinese patients with type 2 diabetes. *Br J Clin Pharmacol* 2012; **74**(3): 501-509
- Qu J, Zhou BT, Yin JY, Xu XJ, Zhao YC, Lei GH, Tang Q, Zhou HH, Liu ZQ. ABCC2 polymorphisms and haplotype are associated with drug resistance in Chinese epileptic patients. *CNS Neurosci Ther* 2012; **18**(8): 647-651
- Zhou BT, Zhou QH, Yin JY, Li GL, Xu XJ, Qu J, Liu D, Zhou HH, Liu ZQ. Comprehensive analysis of the association of SCN1A gene polymorphisms with the retention rate of carbamazepine following monotherapy for new-onset focal seizures in the Chinese Han population. *Clin Exp Pharmacol Physiol* 2012; **39**(4): 379-384
- Zhou BT, Zhou QH, Yin JY, Li GL, Qu J, Xu XJ, Liu D, Zhou HH, Liu ZQ. Effects of SCN1A and GABA receptor genetic polymorphisms on carbamazepine tolerability and efficacy in Chinese patients with partial seizures: 2-year longitudinal clinical follow-up. *CNS Neurosci Ther* 2012; **18**(7): 566-572
- Xu X, Zeng H, Xiao D, Zhou H, Liu Z. Genome wide association study of obesity. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2013; **38**(1): 95-100
- Xiao, XL, Dawson N, MacIntyre L, Morris BJ, Pratt JA, Watson DG, Higham DJ, Exploring metabolic pathway disruption in the subchronic phencyclidine model of schizophrenia with the Generalized Singular Value Decomposition. *Bmc Systems Biology* 2011; **5**: 72
- Dawson N, Xiao X, McDonald M, Higham DJ, Morris BJ, Pratt JA., Sustained NMDA Receptor Hypofunction Induces Compromised Neural Systems Integration and Schizophrenia-Like Alterations in Functional Brain Networks. *Cerebral cortex* 2012 Oct 18. [Epub ahead of print]
- Yin JY, Han LF, Huang Q, Xu XJ, Zhou HH, Liu ZQ. ABCC1 polymorphism Arg723Gln (2168G> A) is associated with lung cancer susceptibility in a Chinese population. *Clin Exp Pharmacol Physiol* 2011; **38**(9): 632-637
- Kalikaki A, Kanaki M, Vassalou H, Souglakos J, Voutsina A, Georgoulas V, Mavroudis D. DNA repair gene polymorphisms predict favorable clinical outcome in advanced non-small-cell lung cancer. *Clin Lung Cancer* 2009; **10**(2): 118-123
- Behera M, Heine JJ, Sica GL, Fowler EE, Tran H, Fu RW, Gal AA, Hermann R, Mayfield W, Khuri FR, Owonikoko TK, Ramalingam SS. Survival Analysis of Patients With Stage I Non-Small-Cell Lung Cancer Using Clinical and DNA Repair Pathway Expression Variables. *Clin Lung Cancer* 2012; **14**(2): 128-138
- Ryu JS, Hong YC, Han HS, Lee JE, Kim S, Park YM, Kim YC, Hwang TS. Association between polymorphisms of ERCC1 and XPD and survival in non-small-cell lung cancer patients treated with cisplatin combination chemotherapy. *Lung Cancer* 2004; **44**(3): 311-316
- Wang, G., et al., The involvement of XPC protein in the cisplatin DNA damaging treatment-mediated cellular response. *Cell Res*, 2004. **14**(4): p. 303-14.
- Suk R, Gurubhagavatula S, Park S, Zhou W, Su L, Lynch TJ,

- Wain JC, Neuberg D, Liu G, Christiani DC. Polymorphisms in ERCC1 and grade 3 or 4 toxicity in non-small cell lung cancer patients. *Clin Cancer Res* 2005; **11(4)**: 1534-1538
- 24 KimCurran V, Zhou C, Schmid-Bindert G, Shengxiang R, Zhou S, Zhang L, Zhang J. Lack of correlation between ERCC1 (C8092A) single nucleotide polymorphism and efficacy/toxicity of platinum based chemotherapy in Chinese patients with advanced non-small cell lung cancer. *Adv Med Sci* 2011; **56(1)**: 30-38
- 25 Ludovini V, Floriani I, Pistola L, Minotti V, Meacci M, Chiari R, Garavaglia D, Tofanetti FR, Flacco A, Siggillino A, Baldelli E, Tonato M, Crinò L. Association of cytidine deaminase and xeroderma pigmentosum group D polymorphisms with response, toxicity, and survival in cisplatin/gemcitabine-treated advanced non-small cell lung cancer patients. *J Thorac Oncol* 2011; **6(12)**: 2018-2026
- 26 Tibaldi C, Giovannetti E, Vasile E, Mey V, Laan AC, Nannizzi S, Di Marsico R, Antonuzzo A, Orlandini C, Ricciardi S, Del Tacca M, Peters GJ, Falcone A, Danesi R. Correlation of CDA, ERCC1, and XPD polymorphisms with response and survival in gemcitabine/cisplatin-treated advanced non-small cell lung cancer patients. *Clin Cancer Res* 2008; **14(6)**: 1797-1803
- 27 Chen S, Huo X, Lin Y, Ban H, Lin Y, Li W, Zhang B, Au WW, Xu X. 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)**: 140-145
- 28 Gandara DR, Kawaguchi T, Crowley J, Moon J, Furuse K, Kawahara M, Teramukai S, Ohe Y, Kubota K, Williamson SK, Gautschi O, Lenz HJ, McLeod HL, Lara PN Jr, Coltman CA Jr, Fukuoka M, Saijo N, Fukushima M, Mack PC. Japanese-US common-arm analysis of paclitaxel plus carboplatin in advanced non-small-cell lung cancer: a model for assessing population-related pharmacogenomics. *J Clin Oncol* 2009; **27(21)**: 3540-3546
- 29 Viñolas N, Provencio M, Reguart N, Cardenal F, Alberola V, Sánchez-Torres JM, Barón FJ, Cobo M, Maestu I, Moreno I, Mesía C, Izquierdo A, Felip E, López-Brea M, Márquez A, Sánchez-Ronco M, Tarón M, Santarpia MC, Rosell R; Spanish Lung Cancer Group. Single nucleotide polymorphisms in MDR1 gen correlates with outcome in advanced non-small-cell lung cancer patients treated with cisplatin plus vinorelbine. *Lung Cancer* 2011; **71(2)**: 191-198
- 30 Wu W, Zhang W, Qiao R, Chen D, Wang H, Wang Y, Zhang S, Gao G, Gu A, Shen J, Qian J, Fan W, Jin L, Han B, Lu D. Association of XPD polymorphisms with severe toxicity in non-small cell lung cancer patients in a Chinese population. *Clin Cancer Res* 2009; **15(11)**: 3889-3895
- 31 Petty WJ, Knight SN, Mosley L, Lovato J, Capellari J, Tucker R, Blackstock AW, Miller MS, Miller AA. A pharmacogenomic study of docetaxel and gemcitabine for the initial treatment of advanced non-small cell lung cancer. *J Thorac Oncol* 2007; **2(3)**: 197-202
- 32 Booton R, Ward T, Heighway J, Taylor P, Power F, Ashcroft L, Morris J, Thatcher N. Xeroderma pigmentosum group D haplotype predicts for response, survival, and toxicity after platinum-based chemotherapy in advanced nonsmall cell lung cancer. *Cancer* 2006; **106(11)**: 2421-2427
- 33 Provencio M, Camps C, Cobo M, De las Peñas R, Massuti B, Blanco R, Alberola V, Jimenez U, Delgado JR, Cardenal F, Tarón M, Ramírez JL, Sanchez A, Rosell R. Prospective assessment of XRCC3, XPD and Aurora kinase A single-nucleotide polymorphisms in advanced lung cancer. *Cancer Chemother Pharmacol* 2012; **70(6)**: 883-890
- 34 Giachino DF, Ghio P, Regazzoni S, Mandrile G, Novello S, Selvaggi G, Gregori D, DeMarchi M, Scagliotti GV. Prospective assessment of XPD Lys751Gln and XRCC1 Arg399Gln single nucleotide polymorphisms in lung cancer. *Clin Cancer Res* 2007; **13(10)**: 2876-2881
- 35 Tiseo M, Giovannetti E, Tibaldi C, Camerini A, Di Costanzo F, Barbieri F, Burgers JA, Vincent A, Peters GJ, Smit EF, Ardizzoni A. Pharmacogenetic study of patients with advanced non-small cell lung cancer (NSCLC) treated with second-line pemetrexed or pemetrexed-carboplatin. *Lung Cancer* 2012; **78(1)**: 92-99
- 36 Li Y, Huang XE, Jin GF, Shen HB, Xu L. Lack of any relationship between chemotherapy toxicity in non-small cell lung cancer cases and polymorphisms in XRCC1 codon 399 or XPD codon 751. *Asian Pac J Cancer Prev* 2011; **12(3)**: 739-742
- 37 Zhang L, Gao G, Li X, Ren S, Li A, Xu J, Zhang J, Zhou C. Association between single nucleotide polymorphisms (SNPs) and toxicity of advanced non-small-cell lung cancer patients treated with chemotherapy. *PLoS One* 2012; **7(10)**: e48350
- 38 Dellas A, Torhorst J, Bachmann F, Bänziger R, Schultheiss E, Burger MM. Expression of p150 in cervical neoplasia and its potential value in predicting survival. *Cancer* 1998; **83(7)**: 1376-1383
- 39 Gong Z, Xu X, Hou R, Guo Y, Sheng F, Ouyang D, Zhou H, Liu Z. Effect of docetaxel on expression of eIF3a in human lung cancer A549 cell line. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2010; **35(8)**: 771-776
- 40 Xu X, H. Zhou, and Z. Liu, Recent research progress of eIF3 in biological function. *Chinese Journal of Clinical Pharmacology and Therapeutics* 2010; **2(15)**: 219-224
- 41 Shen Jie, et al., Expression of eIF3S10 in lung cancer and its relationship with chemotherapy response. *Journal of international pathology and clinical medicine* 2006; **26(5)**: 369-371
- 42 Xu X, Han L, Yang H, Duan L, Zhou B, Zhao Y, Qu J, Ma R, Zhou H, Liu Z. The A/G allele of eIF3a rs3740556 predicts platinum-based chemotherapy resistance in lung cancer patients. *Lung Cancer* 2013; **79(1)**: 65-72
- 43 Xu X, Han L, Duan L, Zhao Y, Yang H, Zhou B, Ma R, Yuan R, Zhou H, Liu Z. Association between eIF3alpha polymorphism and severe toxicity caused by platinum-based chemotherapy in non-small cell lung cancer patients. *Br J Clin Pharmacol* 2013; **75(2)**: 516-523
- 44 Holzer AK, Samimi G, Katano K, Naerdemann W, Lin X, Safaei R, Howell SB. The copper influx transporter human copper transport protein 1 regulates the uptake of cisplatin in human ovarian carcinoma cells. *Mol Pharmacol* 2004; **66(4)**: 817-823
- 45 More SS, Akil O, Ianculescu AG, Geier EG, Lustig LR, Giacomini KM. Role of the copper transporter, CTR1, in platinum-induced ototoxicity. *J Neurosci* 2010; **30(28)**: 9500-9509
- 46 Rabik CA, Maryon EB, Kasza K, Shafer JT, Bartnik CM, Dolan ME. Role of copper transporters in resistance to platinating agents. *Cancer Chemother Pharmacol* 2009; **64(1)**: 133-142
- 47 Xu X, Duan L, Zhou B, Ma R, Zhou H, Liu Z. Genetic polymorphism of copper transporter protein 1 is related to platinum resistance in Chinese non-small cell lung carcinoma patients. *Clin Exp Pharmacol Physiol* 2012; **39(9)**: 786-792
- 48 Xu X, Ren H, Zhou B, Zhao Y, Yuan R, Ma R, Zhou H, Liu Z. Prediction of copper transport protein 1 (CTR1) genotype on severe cisplatin induced toxicity in non-small cell lung cancer (NSCLC) patients. *Lung Cancer* 2012; **77(2)**: 438-442
- 49 Cataldo VD, Gibbons DL, Pérez-Soler R, Quintás-Cardama A. Treatment of non-small-cell lung cancer with erlotinib or gefitinib. *N Engl J Med* 2011; **364(10)**: 947-955
- 50 Stewart DJ. Mechanisms of resistance to cisplatin and carboplatin. *Crit Rev Oncol Hematol* 2007; **63(1)**: 12-31

- 51 Xu X, Ding X, Zhang X, Su S, Treiber FA, Vlietinck R, Fagard R, Derom C, Gielen M, Loos RJ, Snieder H, Wang X. Genetic and environmental influences on blood pressure variability: a study in twins. *J Hypertens* 2013; **31(4)**: 690-697
- 52 Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol* 2002; **31(1)**: 140-149
- 53 Liang ZD, Long Y, Tsai WB, Fu S, Kurzrock R, Gagea-Jurascu M, Zhang F, Chen HH, Hennessy BT, Mills GB, Savaraj N, Kuo MT. Mechanistic Basis for Overcoming Platinum Resistance Using Copper Chelating Agents. *Mol Cancer Ther*, 201; **11(11)**: 2483-2494
- 54 Xu X, Su S, Barnes VA, De Miguel C, Pollock J, Ownby D, Shi H, Zhu H, Snieder H, Wang X. A genome-wide methylation study on obesity: Differential variability and differential methylation. *Epigenetics* 2013; **8(5)**: 522-533
- 55 Wang X, Falkner B, Zhu H, Shi H, Su S, Xu X, Sharma AK, Dong Y, Treiber F, Gutin B, Harshfield G, Snieder H. A genome-wide methylation study on essential hypertension in young African American males. *PLoS One* 2013; **8(1)**: e53938
- 56 Ingelman-Sundberg M, Zhong XB, Hankinson O, Beedana-gari S, Yu AM, Peng L, Osawa Y. Potential Role of Epigenetic Mechanisms in the Regulation of Drug Metabolism and Transport. *Drug Metab Dispos*, 2013; **41(10)**: 1725-1731
- 57 Heil SG. Epigenetic techniques in pharmacogenetics. *Methods Mol Biol* 2013; **1015**: 179-188
- 58 Joerger M, Burgers SA, Baas P, Smit EF, Haitjema TJ, Bard MP, Doodeman VD, Smits PH, Vincent A, Huitema AD, Beijnen JH, Schellens JH. Germline polymorphisms in patients with advanced nonsmall cell lung cancer receiving first-line platinum-gemcitabine chemotherapy: a prospective clinical study. *Cancer* 2012; **118(9)**: 2466-2475

Peer reviewer: Takashi Ogino, Medical Director, Medipolis Proton Therapy and Research Center, 5188 Higashikata, Ibusuki, Kagoshima 891-0304, Japan.