RESEARCH ARTICLE

Effect of the ERCC1 (C118T) Polymorphism on Treatment Response in Advanced Non-Small Cell Lung Cancer Patients Undergoing Platinum-Based Chemotherapy

Walennee Kaewbubpa[1], Nutthada Areepium[1]*, Virote Sriuranpong[2]

Abstract

For advanced non-small-cell lung cancer (NSCLC) cases, a platinum-based regimen is the first-line chemotherapy treatment. The excision repair cross-complementing group 1 (ERCC1) plays an important role in DNA repair and has been related to resistance to platinum chemotherapy. This study aimed to investigate the effects of the ERCC1 (C118T) polymorphism on treatment response in 26 Thai advanced NSCLC patients receiving first line platinum-based chemotherapy during January to July 2015 at King Chulalongkorn Memorial Hospital (KCMH). DNA was extracted from peripheral blood lymphocytes and the single nucleotide polymorphism of ERCC1 was genotyped using a real-time PCR method with the TaqMan assay. The distribution of C/C, C/T and T/T genotypes was 57.7 %, 34.6 % and 7.7 %, respectively. The response rate to platinum-based chemotherapy in the wild type (C/C) of ERCC1 (C118T) was better than with the variant types (C/T and T/T) but the difference was not statistically significant (29.7% vs 9.1%, P=0.274). The results showed that a genetic polymorphism in ERCC1 might influence patient response to platinum-based chemotherapy. Further multicenter studies are now required to confirm the results of our study.

Keywords: ERCC1- SNP- platinum- non-small-cell lung cancer- response to chemotherapy

Asian Pac J Cancer Prev, **17 (11)**, 4917-4920

Introduction

Lung cancer is the most common cause of cancer deaths worldwide. Approximately 80% of lung cancer cases are non-small cell lung cancer (NSCLC). The majority of NSCLC patients are diagnosed at an advanced stage (Spiro and Silvestri, 2005). Platinum-based chemotherapy is the first line treatment for advanced NSCLC. Platinum-based chemotherapy including cisplatin or carboplatin is used in combination with the third generation cytotoxic drugs (gemcitabine, paclitaxel or docetaxel) (Ettinger et al., 2012). Although, platinum cytotoxicity results from the formation of platinum-DNA adducts that affect cancer cell death but some patients do not respond well enough to this treatment for many reasons. Platinum compounds induces the bulky DNA adducts that are removed via the nucleotide excision repair (NER) pathway. The removal of DNA adducts leads to resistance to chemotherapy. ERCC1 is one of most important genes in the NER pathway (Ardizzoni et al., 2007; Gossage and Madhusudan, 2007; Rabik and Dolan, 2007; Martin et al., 2008). Therefore, single nucleotide polymorphism of an ERCC1 gene is suspected to influence individual variations in chemotherapy response.

Previous studies indicated that patients with C/C genotype of the ERCC1 tended to have better outcomes than other genotype in Asian people (Su et al., 2007; Cheng et al., 2012). Among the advanced NSCLC, patients with C/C allele had higher response rate of platinum-based chemotherapy than those who had ERCC1 polymorphism (C to T) (Su et al., 2007). Moreover, patients with C/C genotype showed significantly longer survival than those with C/T or T/T genotypes (Cheng et al., 2012). In contrast, response rate to platinum-based chemotherapy of patients who are not carrying T allele was lower than those who carry at least one T allele (Li et al., 2010). Therefore, these studies had shown the correlation between ERCC1 polymorphism and effectiveness of cancer treatment.

At present, there are no studies explore the genetic polymorphism of ERCC1 gene on treatment response in Thai patients. For that reason, we investigated the effect of ERCC1 (C118T) polymorphism on treatment response in Thai advanced NSCLC patients treated with platinum-based chemotherapy.

Material and Methods

Patients

In this prospective cohort study, we included a total a total of 26 eligible patients during January to July 2015 at King Chulalongkorn Memorial Hospital (KCMH). Inclusion criteria included patients with histologically

*[1]Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, [2]Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. *For Correspondence: Nutthada.A@pharm.chula.ac.th*

or cytologically diagnosed stage IIIB or IV of NSCLC and were treated with cisplatin or carboplatin-based chemotherapy, patients were treated with the following chemotherapy for at least 2 cycles, age > 18 years, adequate renal, hematologic and hepatic function and Eastern Cooperative Oncology Group (ECOG) performance status 0-2. Patients with brain metastases, unsuitable for adequate follow-up, treated with radiotherapy or surgical therapy for lung cancer were excluded. The study was approved by Institutional Review Board, faculty of medicine, Chulalongkorn University, Bangkok, Thailand and all participants provided informed consent, which was conducted in accordance with the Declaration of Helsinki.

Methods

The demographic and clinical data were collected from medical records. We followed up eligible patients from the first cycle who received platinum-based chemotherapy until at the end of study.

Peripheral blood (10 ml) was collected from each subject and enrolled into EDTA tubes. Genomic DNA was extracted from peripheral blood sample using QIA amp® DNA blood Mini Kit (Qiagen, Hilden, Germany). ERCC1 genotypes at codon 118C/T were analyzed with TaqMan genotyping assay and the real-time polymerase chain reaction (RT-PCR) system. The primers and probes were commercially available (Applied Biosystems Inc., Foster city, CA USA: rs11615). Each reaction mixture in a total volume of 20 µl contains nuclease-free water 7.5 µl + TaqMan® Universal master mix 10 µl + TaqMan® probe with primers 0.5 µl + DNA template 2 µl . TaqMan PCR and fluorescence measurements were performed using the StepOnePlusTM Real time PCR system (Applied Biosystems, USA).

Objective tumor responses were evaluated in accordance with the Response Evaluation Criteria In Solid Tumors (RECIST) criteria after second cycle of chemotherapy and were repeated every two cycles thereafter. Patients with a complete response (CR) or a partial response (PR) were defined as responders. Patients who had stable disease (SD) or progressive disease (PD) were defined as non-responders.

Statistical analysis

Demographic and clinical data was determined and presented as mean ± standard deviation (SD) or frequency (percentage). Response treatment was compared across genotype using Fisher's exact test or chi-square test. Statistic tests provided two sides. P value < 0.05 was considered statistic significant. All analyses were calculated using IBM SPSS software, version 22.0 (SPSS. Co., Ltd, Bangkok, Thailand).

Results

Patient characteristics

Patient characteristics are shown in Table 1. This study includes 26 advanced NSCLC patients with platinum-based chemotherapy. Enrolled patients consist of 10 women and 16 men, whose average age are 63.4 ± 10.7 years. There are 13 (50.0%) non-smokers. Twenty five (96.2%) has stage IV disease and twenty four (92.3%) has adenocarcinoma. 0-1 ECOG status was 23 patients (88.5%).

ERCC1 (C118T) genotype frequencies

ERCC1 (C118T) allele frequencies are present in Table 1. The ERCC1 (C118T) genotypes were in Hardy-Weinberg equilibrium. The wild type (C/C), heterozygous variant (C/T) and homozygous variant (T/T) were 57.7 %, 34.6 %, 7.7 %, respectively.

Treatment response

Among responders, partial response is in 5 (19.2%) and no patient had complete response. For non-responders, stable disease was in 19 (73.1%) and progressive disease in 2 (7.7%) (Table 1).

Patient characteristics and treatment response

We found that the distribution of responders was more frequent in adenocarcinoma tumor and in stage IV. We also observed that non-responders were frequently in older patients, ECOG performance status 0-1 and adenocarcinoma. No association was observed between treatment response and patient age, gender, histological cell type, disease stage, ECOG performance status or

Table 1. Patient Characteristics and Treatment Response

Characteristics	n (%)
Age (years)	
Mean ± SD	63.4 ± 10.7
Gender	
Male	16 (61.5)
Female	10 (38.5)
Histology	
Squamous cell carcinoma	2 (7.7)
Adenocarcinoma	24 (92.3)
Stage	
IIIB	1 (3.8)
IV	25 (96.2)
Smoking status	
Never smoker	13 (50.0)
Smoker	13 (50.0)
ECOG PS	
0-1	23 (88.5)
2	3 (11.5)
ERCC1 (C118T)	
C/C	15 (57.7)
C/T	9 (34.6)
T/T	2 (7.7)
Responders	
Complete response (CR)	0 (0.0)
Partial response (PR)	5 (19.2)
Non-responders	
Stable disease (SD)	19 (73.1)
Progressive disease (PD)	2 (7.7)

Table 2. Association between Patient Parameters and Treatment Response

Parameters	Responders (CR + PR) [n (%)]	Non-responders (SD + PD) [n (%)]	P-value
Age (year)			
< 60	3 (60)	7 (33.3)	0.247
≥ 60	2 (40)	14 (66.7)	
Gender			
Male	2 (40)	14 (66.7)	0.247
Female	3 (60)	7 (33.3)	
Histology			
Squamous cell carcinoma	0 (0)	2 (9.5)	0.646
Adenocarcinoma	5 (100)	19 (90.5)	
Stage			
IIIB	0 (0)	1 (4.8)	0.808
IV	5 (100)	20 (95.2)	
Smoking status			
Never smoker	2 (40)	11 (52.4)	0.500
Smoker	3 (60)	10 (47.6)	
ECOG PS			
0 or 1	5 (100)	18 (85.7)	0.512
2	0 (0)	3 (14.3)	
Genotype			
C/C	4 (80)	11 (52.4)	0.274
C/T + T/T	1 (20)	10 (47.6)	

smoking status (Table 2).

Association of ERCC1 (C118T) polymorphism and treatment response

Regarding the association between ERCC1 (C118T) polymorphism and treatment response are shown in table 2. The platinum-based chemotherapy response rate was 4/15 (26.67 %) in the C/C genotype, 1/11 (9.1 %) in C/T and T/T genotype of ERCC1 (C118T) gene. The response rate of C/T and T/T genotype was lower than that of the C/C genotype, although there was no statistical significance (P=0.274).

Discussion

In this study, we explored the prevalence of ERCC1 (C118T) polymorphism and its effect on the treatment response in Thai advanced NSCLC patients. We found that allele frequency of the ERCC1 (C118T) polymorphism (C to T) was 42.3%. This number corresponded with many studies in Asia such as the studies of Su D et al., (2007), Li et al., (2010) and Cheng J et al., (2012). These studies showed allele frequency of the ERCC1 (C to T) which were 23.1%, 36.5% and 39.4%, respectively. Our result showed the ERCC1 (C118T) polymorphism found extensively in Thai advanced NSCLC patients.

Even though not statistically significant finding due to small number of subjects, we found that C/C genotype was more responsive than other variant types. This results was similar to Su et al., (2007) studies (adjust OR: 4.1, 95% CI:1.31-12.85, CC vs C/T+T/T). Nevertheless, the study we conducted had a different result from Li et al., (2010) which found that patients who did not carry T allele was less responsive than those who carried at least 1 T allele (OR; 0.32, 95% CI:0.13-0.75, CC vs C/T+T/T).

Furthermore, there are a lot of drug resistance mechanisms which are related to the NER system because DNA repair is a complex system including many involved genes (Rabik and Dolan, 2007). It is possible that the correlation between ERCC1 polymorphism and outcomes in advanced NSCLC by several genes such as the the multidrug resistance 1 (MDR1) polymorphism (Yu et al., 2007). Moreover, for some studies, high ERCC1 gene expression level identifies poorer overall survival in advanced NSCLC patients treated with platinum-based chemotherapy (Lord et al., 2002). As mentioned above, further studies should be conducted to learn about the correlation among MDR1 polymorphisms and ERCC1 mRNA expression as well as response rate.

The study is strong in terms of using a prospective type of study, but for its weaknesses, it has sample limitation and the study use only samples from one hospital. This may cause a bias in the selected case we studied. However, in the future study, larger sample size with more genetic polymorphisms and different population are needed to confirm our results.

In conclusion, the present study showed that the ERCC1 (C118T) polymorphism might be prognostic factor on response treatment in advanced NSCLC patients, who receiving platinum-based chemotherapy.

Acknowledgement

This study was supported by THE 90TH ANNIVERSARY OF CHULALONGKORN UNIVERSITY FUND (Ratchadaphiseksomphot Endowment Fund)

References

Ardizzoni A, Boni L, Tiseo M, et al (2007). Cisplatin-versus carboplatin-based chemotherapy in first-line treatment of advanced non–small-cell lung cancer: an individual patient data meta-analysis. *J Natl Cancer Inst*, **99**, 847-57.

Cheng J, Ha M, Wang Y, et al (2012). A C118T polymorphism of ERCC1 and response to cisplatin chemotherapy in patients with late-stage non-small cell lung cancer. *J Cancer Res Clin Oncol*, **138**, 231-8.

Ettinger DS, Akerley W, Borghaei H, et al (2012). Non–small cell lung cancer. *J Natl Compr Canc Netw*, **10**, 1236-71.

Gossage L, Madhusudan S (2007). Current status of excision repair cross complementing-group 1 (ERCC1) in cancer. *Cancer Treat Rev,* **33**, 565-77.

Li F, Sun X, Sun N, et al (2010). 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*, **33**, 489-94.

Lord RV, Brabender J, Gandara D, et al (2002). Low ERCC1 expression correlates with prolonged survival after cisplatin plus gemcitabine chemotherapy in non-small cell lung cancer. *Clin Cancer Res*, **8**, 2286-91.

Martin LP, Hamilton TC, Schilder RJ (2008). Platinum resistance: the role of DNA repair pathways. *Clin Cancer Res*, **14**, 1291-5.

Rabik CA, Dolan ME (2007). Molecular mechanisms of resistance and toxicity associated with platinating agents. *Cancer Treat Rev*, **33**, 9-23.

Spiro SG, Silvestri GA (2005). The treatment of advanced non-small cell lung cancer. *Curr Opin Pulm Med,* **11**, 287-91.

Su D, Ma S, Liu P, et al (2007). Genetic polymorphisms and treatment response in advanced non-small cell lung cancer. *Lung Cancer*, **56**, 281-8.

Yu Q, Han J, Pan J (2007). The relationship between the polymorphisms of gene XGP and MDR1 and the responsiveness of advanced non-small cell lung cancer to platinum-based chemotherapy. *Practical J Cancer*, **22**, 252-6.