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Methylenetetrahydrofolate reductase C677T polymorphism predicts response and time to progression to gemcitabine-based chemotherapy for advanced non-small cell lung cancer in a Chinese Han population*

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Abstract: Objective: The aim of this study was to evaluate the association between the methylenetetrahydrofolate reductase (*MTHFR*) C677T excision repair cross-complementation group 1 (*ERCC1*) genetic polymorphisms and the clinical efficacy of gemcitabine-based chemotherapy in advanced non-small cell lung cancer (NSCLC). Methods: A total of 135 chemonaive patients with unresectable advanced NSCLC were treated with gemcitabine/platinum regimens. The polymorphisms of *MTHFR* C677T, *ERCC1* C8092A, and *ERCC1* C118T were genotyped using the TaqMan methods. Results: The overall response rate was 28.9%. Patients with *MTHFR* CC genotype had a higher rate of objective response than patients with variant genotype (TT or CT) (41.2% versus 19.1%, P=0.01). Median time to progression (TTP) of patients with *MTHFR* CC genotype was longer than that of patients with variant genotype (7.6 months versus 5.0 months, P=0.003). No significant associations were obtained between *ERCC1* C118T and C8092A polymorphisms and both response and survival. Conclusions: Our data suggest the value of *MTHFR* C677T polymorphism as a possible predictive marker of response and TTP in advanced NSCLC patients treated with gemcitabine/platinum.

Key words: Non-small cell lung cancer, Single nucleotide polymorphism, Methylenetetrahydrofolate reductase, Gemcitabine, Excision repair cross-complementation group 1

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1 Introduction

Lung cancer is now the leading cause of cancer mortality, and more than one million people are known to die from the disease every year (Guilbert, 2003). Approximately 80% of lung cancer patients are non-small cell lung cancer (NSCLC), of which nearly two-thirds are diagnosed with advanced stages (Spiro and Silvestri, 2005).

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Double platinum-containing regimens represent the gold standard of treatment in advanced NSCLC. Platinum/gemcitabine combination is one of the most used regimens in routine clinical practice (le Chevalier *et al*., 2005; Azzoli *et al*., 2009). Analysis showed an absolute benefit of one-year survival rate of 4.2% in favor of gemcitabine/platinum as compared to the combination of platinum and other third-generation agents (le Chevalier *et al*., 2005). However, large inter-individual variability in clinical response and survival has been observed. Therefore, new biomarkers with predictive power are urgently wanted to assess different clinical outcomes in patients treated with gemcitabine/platinum.

Methylenetetrahydrofolate reductase (MTHFR) plays an important role in folate metabolism and DNA methylation. It catalyzes the irreversible conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (Choi and Mason, 2002). A common single-nucleotide polymorphism (SNP) (CT at nucleotide position 677) in the *MTHFR* gene, resulting in a substitution of an alanine with a valine, led to decreased enzyme activity, which may affect chemosensitivity. *MTHFR* 677T allele carriers show better response to either fluorouracil (5-FU)-based chemotherapy (Cohen *et al*., 2003; Fernández-Peralta *et al*., 2010) or FOLFOX therapy (Etienne-Grimaldi *et al*., 2010) than patients with other genotype in colorectal cancer (CRC). Patients with *MTHFR* TT genotype had increased progression-free survival in pemetrexed-treated NSCLC (Smit *et al*., 2009). However, despite these studies on the associations between these antimetabolic agents and *MTHFR* C677T polymorphism, the predictive value of the *MTHFR* C677T polymorphism on the effect of gemcitabine-based chemotherapy remains unclear.

Platinum agents exert their activity through the formation of DNA adducts. Excision repair cross-complementation group 1 (ERCC1) is the lead enzyme in the nucleotide excision repair (NER) DNA repair pathway. Preclinical data suggests that the *ERCC1* C8092A and C118T polymorphisms could affect the *ERCC1* mRNA and protein levels, thus leading to different platinum sensitivity and increased DNA repair capacity (Chen *et al*., 2000; Yu *et al*., 2000; Park *et al*., 2002). *ERCC1* polymorphisms have been reported to predict better response (Su *et al*., 2007; Kalikaki *et al*., 2009; Li *et al*., 2010) or survival in NSCLC patients treated with platinum-based chemotherapy (Isla *et al*., 2004; Ryu *et al*., 2004; Zhou *et al*., 2004). However, published reports of the associations between *ERCC1* SNPs and clinical efficacy from individual studies are controversial (de las Peñas *et al*., 2006; Tibaldi *et al*., 2008; Wang *et al*., 2010).

In addition, a significant difference between Japanese and US patients in genotypic distribution for *ERCC1* 118, *ERCC2* K751Q, CYP3A4*1B, CYP3A5*3C, and CYP2C8 R139K was observed by Gandara *et al*. (2009). The purpose of this study was to assess the predictive value of genetic polymorphisms potentially related to gemcitabine-platinum in patients of Chinese Han ethnicity.

2 Subjects and methods

2.1 Subjects

Initially, a total of 135 patients from Zhejiang Cancer Hospital were recruited for this study. Patients who were diagnosed with histologically or cytologically confirmed unresectable advanced NSCLC and had a measurable lesion by computed tomography (CT) scan were eligible. They must meet the following criteria: age ≥18 years, life expectancy ≥3 months, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2, adequate bone marrow reserve, and adequate liver function and renal function. Patients enrolled in the study were all given gemcitabine/platinum regimens.

Patients were excluded if they had the following reasons: they had serious infection or organic disease; they had other malignant tumors except basal cell carcinoma of the skin and carcinoma of the cervix uteri in situ; they were pregnant or lactating women; they had central nervous system (CNS) metastasis; they had any other reasons that could influence the trial.

All written patients gave informed consent and the protocol was approved by the Ethics Committee of Zhejiang Cancer Hospital. The trial was adhered to Good Clinical Practice (GCP) guidelines.

2.2 Chemotherapy regimens

Patients had received one of the following chemotherapy regimens: cisplatin 75 mg/m^2 on Day 1

plus gemcitabine 1250 mg/m^2 on Days 1 and 8, every 3 weeks, or cisplatin was replaced with carboplatin [area under curve (AUC)=5 mg/(ml·min)] on Day 1. Each regimen was repeated with up to six cycles, unless the disease progressed, or there was unacceptable toxicity, or according to the patient's or physician's decision.

2.3 Evaluation criteria

Pretreatment evaluation included medical history, physical examination, physical performance assessment, complete blood count (CBC), serum biochemistry, urinalysis, electrocardiogram (ECG), and CT scan of the chest and abdomen. In addition, magnetic resonance imaging (MRI) and single photoemission computed tomography (SPECT) were also performed. Tumor response was assessed every two cycles. Responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (Therasse *et al*., 2000), which classify the response into four categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). All responses had to be confirmed 28 d or more after the initial response and reviewed by an independent radiologist.

2.4 Sample collection and DNA isolation

Genomic DNA was extracted from blood (2 ml) drawn from an antecubital vein before drug administration. The blood samples were collected in ethylenediamine tetraacetic acid (EDTA) vacutainer tubes and stored at −80 °C. DNA was isolated using the Wizard Genomic DNA Purification kit (Promega, Madison, WI, USA) according to the manufacturer's protocol. DNA yields and integrity were checked by the absorbance at 260 nm with a spectrophotometer, whereas testing for proteins contamination was done by measuring the absorbance at 280 nm and calculating the absorbance ratio at 260/280 nm.

2.5 SNP genotyping

SNPs in *ERCC1* C8092A (rs3212986), *ERCC1* C118T (rs11615), and *MTHFR* C677T (rs1801133) were analyzed with TaqMan assays using the ABI 7500 (Applied Biosystems Inc., Darmstadt, Germany) real-time polymerase chain reaction (PCR) system. Primers, probes, and TaqMan universal PCR master mix were purchased from ABI. The TaqMan assays were performed as previously reported by Su *et al*. (2007). Genotyping was done by authors blinded to case status, and the genotyping results were independently reviewed.

2.6 Statistical analysis

The Hardy-Weinberg equation for the equilibrium of allele distributions was used to evaluate our data along with the χ^2 test or Fisher's exact test. Multivariate analyses were performed by using logistic regression analysis to assess the association between each genetic polymorphism and treatment response while adjusting for patient gender, age, tumor histology, and history of cigarette smoking.

Time to progression (TTP) was calculated from the registration date to the day of radiological or clinical evidence of progression or death, whichever occurred first, whereas overall survival (OS) was calculated from the date of treatment start to the end point (death or censoring). The Kaplan-Meier method was used to plot TTP and OS, and the log-rank test was used in univariate analysis.

Factors included in univariate analysis were age (≥65 years versus <65 years), sex (male versus female), genotypes, clinical stage (IIIB versus IVa/IVb), histology (other versus adenocarcinoma), and smoking history (never versus former and current smokers). Factors with *P*-values <0.1 in univariate analysis were included in multivariate analysis. In multivariate analysis, hazard ratios were calculated to estimate the direction and the magnitude of the effect.

All *P*-values reported were two-sided, and a probability of 0.05 or smaller was considered statistically significant. Statistical analyses were performed with SPSS software (Version 13.0, SPSS Inc., Chicago, USA).

3 Results

3.1 Clinical characteristics of patients

Patient clinical characteristics are summarized in Table 1. A total of 135 patients were enrolled in this study. The median age was 56 years (ranged from 25 to 72 years). Ninety patients (66.7%) were male and 45 patients (33.3%) were female. All of these patients had advanced unresectable diseases, and the TNM (tumor, node, metastasis) stages were 64.4% of Stage

IVb, 26.7% of Stage IVa, and 8.9% of Stage IIIB. Histological types included adenocarcinoma (59.3%), squamous cell carcinoma (28.9%), and unspecified or other NSCLC (11.9%). Cigarette smokers accounted for 57%. Most of the patients (85.9%) had the ECOG PS of 1.

Table 1 Patient clinical characteristics (*n*=135)

Characteristics	Patient number	Percent (%)
Age		
≥65 years	23	17.0
<65 years	112	83.0
Gender		
Male	90	66.7
Female	45	33.3
Smoking history		
Smokers	77	57.0
Never smokers	58	43.0
Clinical stage		
IIIB	12	8.9
IVa	36	26.7
IVb	87	64.4
ECOG PS		
0	11	8.2
1	116	85.9
2	8	5.9
Histology		
Adenocarcinoma	80	59.3
Squamous cell carcinoma	39	28.9
Unspecified or other NSCLC	16	11.9

No significant correlation was found between the genotypes and age, gender, histology, smoking status, PS, or clinical stage (data not shown).

3.2 Genotype and genetic equilibrium test

For the *ERCC1* codon 118 polymorphism, the frequencies of TT, CT, and CC genotypes were 5.9%, 48.1%, and 45.9%, respectively. The *ERCC1* C8092A CC polymorphism was found in 44.4% of the cases, whereas the CA and AA genotypes were observed in 43.0% and 12.6% of the cases, respectively. For the polymorphism of *MTHFR* C677T, CC allele had a frequency of 37.8%, whereas the heterozygous and homozygous variants had a frequency of 40.0% and 22.2%, respectively (Table 2).

The genotype distributions of the three sites were determined to be in Hardy-Weinberg equilibrium with a *P*-value >0.05. Thus, this sample could represent a Mendelian population with a genetic equilibrium (Table 2).

Table 2 Results of genetic equilibrium tests

Genotype	Patient*	χ^2	*P*
ERCC1 C118T			
C/C	62 (45.9%)	2.89	0.09
C/T	65 (48.2%)		
T/T	8 (5.9%)		
ERCC1 C8092A			
C/C	60 (44.4%)	1.15	0.22
C/A	58 (43.0%)		
A/A	17 (12.6%)		
MTHFR C677T			
C/C	51 (37.8%)	0.20	0.66
C/T	54 (40.0%)		
T/T	30 (22.2%)		

Data are expressed as number (percentage)

3.3 Genotype and treatment response

Table 3 shows the association of treatment response with genotypes. No significant associations were found between *ERCC1* genotypes and objective response. The overall response rate of 135 patients enrolled in this study was 28.9% (39/135). A significant correlation was found between *MTHFR* C677T and response to platinum-gemcitabine: 41.2% (21/51) of patients carrying *MTHFR* CC experienced PR, whereas only 25.9% (14/54) of *MTHFR* CT and 13.3% (4/30) of *MTHFR* TT responded to therapy (*P*=0.01).

3.4 Correlation between polymorphisms and clinical outcome

Table 4 shows TTP and OS analysis data according to the examined polymorphisms. The overall median TTP was 5.9 months (95% confidence interval (CI): 5.19–6.61 months) and the median OS was 10.4 months (95% CI: 9.15–11.65 months). Patients genotype analysis demonstrated that those who were homozygous for the *MTHFR* 677C allele had a better TTP compared with those carrying at least one T allele (CT or TT) (log-rank test, *P*=0.003; Table 4, Fig. 1). Even when considering the CT and TT genotypes separately, with median TTP of 5.7 months (95% CI: 4.48–6.92 months) and 4.0 months (95% CI: 2.01–5.99 months), respectively, the log-rank test was still significant (hazard ratio (HR) 4.55, *P*=0.003).

Table 3 Response according to *ERCC1* and *MTHFR* genotypes

Genotype	CR+PR[a]	SD+PD[a]	Crude OR (95% CI)	*P*	Adjust OR (95% CI)[b]	*P*[b]
ERCC1 C118T						
C/C	20 (51.3%)	42 (43.8%)	0.70 (0.13–3.78)	0.68	0.71 (0.12–3.91)	0.69
C/T	17 (43.6%)	48 (50.0%)	0.94 (0.17–5.12)	0.94	1.01 (0.20–6.02)	0.76
T/T	2 (5.1%)	6 (6.2%)	1		1	
ERCC1 C8092A						
C/C	17 (43.6%)	43 (44.8%)	0.54 (0.14–2.13)	0.38	0.50 (0.13–2.58)	0.43
C/A	19 (48.7%)	39 (40.6%)	0.44 (0.11–1.72)	0.24	0.47 (0.12–1.97)	0.22
A/A	3 (7.7%)	14 (14.6%)	1		1	
MTHFR C677T						
C/C	21 (53.8%)	30 (31.3%)	4.55 (1.38–14.95)	0.01	4.74 (1.46–18.63)	0.009
C/T	14 (35.9%)	40 (41.7%)	2.00 (0.88–4.57)	0.10	1.87 (0.85–5.38)	0.15
T/T	4 (10.3%)	26 (27.1%)	1		1	

[a] Data are expressed as number (percentage); [b] Adjusted for gender, age, histology, and history of cigarette smoking

Table 4 TTP and OS according to *ERCC1* and *MTHFR* genotypes

Genotype	TTP (month)*	*P*	OS (month)*	*P*
Overall	5.9 (5.19–6.61)		10.4 (9.15–11.65)	
ERCC1 C118T				
C/C	5.8 (4.84–6.77)	0.80	11.3 (8.29–14.30)	0.73
C/T	5.9 (4.61–7.19)		10.0 (8.19–11.81)	
T/T	3.1 (0.00–8.57)		9.9 (4.55–15.25)	
ERCC1 C8092A				
C/C	5.7 (4.88–6.52)	0.70	9.9 (7.62–12.18)	0.44
C/A	6.4 (5.37–7.43)		11.3 (8.88–13.71)	
A/A	5.0 (3.50–6.50)		8.8 (9.15–11.65)	
MTHFR C677T				
C/C	7.6 (5.92–9.28)	0.003	12.0 (9.88–14.12)	0.19
C/T	5.7 (4.48–6.92)		10.4 (8.53–12.27)	
T/T	4.0 (2.01–5.99)		8.3 (7.46–9.14)	
T/T+C/T	5.0 (4.16–5.84)	0.003	9.6 (8.72–10.48)	0.53

* Data are expressed as median (95% CI)

The univariate analysis revealed *MTHFR* C677T polymorphism was significantly associated with TTP, whereas sex (*P*=0.09) and smoking history (*P*=0.07) had a trend to associated with TTP (Table 5).

Multivariate Cox regression analysis adjusted for gender and smoking status revealed a significant effect of *MTHFR* C677T (CT/TT versus CC; HR 1.89, 95% CI: 1.23–2.91; *P*=0.004) on patients' TTP (Table 6).

No other association could be identified between the remaining polymorphisms and TTP or OS.

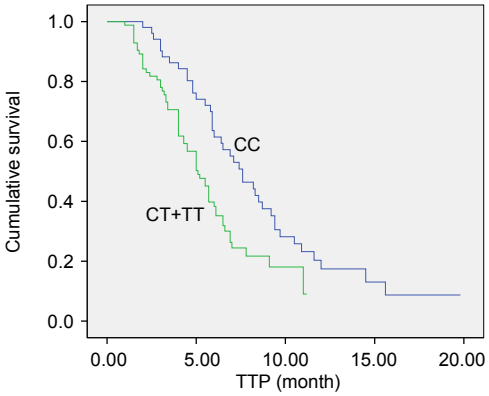

Fig. 1 Kaplan-Meier curves for time to progression (TTP) according to genetic polymorphism of *MTHFR* C677T
log-rank test, *P*=0.003

Table 5 Univariable analysis of TTP

Variables	HR	95% CI	*P*
Age (≥65 years/<65 years)	1.01	0.60–1.60	0.97
Gender (male/female)	1.44	0.94–2.22	0.09
Smoking status (former or current/never)	1.45	0.97–2.17	0.07
Histological type (other/ adenocarcinoma)	1.29	0.87–1.92	0.20
Performance status (2/0–1)	1.33	0.58–3.04	0.50
Stage (IIIB or IVa/IVb)	0.88	0.58–1.33	0.54
MTHFR C677T (CT or TT/CC)	1.88	1.23–2.89	0.004*
ERCC1 C118T (CT or TT/CC)	0.90	0.61–1.34	0.90
ERCC1 C8092A (AA/CA or CC)	1.03	0.59–1.82	0.91

* Statistically significant in Cox proportional hazard model analysis, *P*<0.05

Table 6 Multivariable analysis of TTP

Variables	HR	95% CI	*P*
Gender (male/female)	1.216	0.574–2.573	0.610
Smoking status (ever/never)	1.250	0.618–2.530	0.535
MTHFR C677T (CT or TT/CC)	1.891	1.230–2.905	0.004*

* Statistically significant in Cox proportional hazard model analysis, *P*<0.05

4 Discussion

The great interindividual variability in drug effects is one of the most challenging issues in the clinical management of NSCLC patients. Platinum/gemcitabine combination is one of the most used regimens in the clinical practice. Two types of platinum drugs, cisplatin and carboplatin, are popularly used in clinical practice with similar mechanisms and efficacy but different toxicities. However, predictive markers for response to this regimen are still limited. Our recent study showed that T393C polymorphism of Gs protein α subunit (*GNAS1*) gene was a predictor for clinical outcomes in advanced NSCLC patients treated with gemcitabine/platinum (Xie *et al*., 2012). In the current study, we tried a combination of gene polymorphisms potentially related with the effect of this regimen. We found that inter-individual variations of the *MTHFR* C677T polymorphism help to predict chemotherapy efficiency and prognosis in advanced NSCLC. Our data showed that patients carrying the CC genotype at *MTHFR* C677T had a favorable response and longer TTP to gemcitabine-based treatment compared with those carrying TT or CT genotype.

The accumulated evidence suggests that diminished folate status predisposes to the development of several malignancies, including pancreas cancer, lung cancer, as well as breast cancer and gastric cancer (Kim, 1999). The mechanisms for folate associated carcinogenesis include altered DNA methylation, disruption of DNA repair or DNA integrity (Choi and Mason, 2000). Folate is a critical coenzyme for both nucleotide synthesis and biological methylation and plays a central role in one-carbon metabolism (Choi and Mason, 2002). MTHFR is a key enzyme in folate metabolism which catalyzes the irreversible conversion of 5,10-methylenetetrahydrofolate, which is necessary for thymidylate and purine synthesis, to 5-methyltetrahydrofolate, which is used for biological methylation (Choi and Mason, 2002). The *MTHFR* gene is located at 1p36.3. *MTHFR* 677C→T transition causes an alanine-to-valine substitution (Ala222Val), leading to 30%–60% reduction in enzyme activity (Kim *et al*., 2009). Increasing evidence showed the involvement of *MTHFR* C677T polymorphism in cancer treatment and prognosis, while the association between this polymorphism and patient's response and prognosis may vary in different drugs. An earlier similar study showed patients with the *MTHFR* 677CC genotype had a trend of longer TTP (but not response) to cisplatin/gemcitabine in Stage IV NSCLC (Alberola *et al*., 2004). Other recent reports showed that acute lymphoblastic leukaemia (ALL) patients with 677TT genotype had a significantly higher incidence of relapse compared to other genotypes after the consolidation methotrexate therapy (D′Angelo *et al*., 2011; Salazar *et al*., 2011). However, other studies showed *MTHFR* 677T allele carriers had a higher response rate to 5-FU-based chemotherapy (Cohen *et al*., 2003; Fernández-Peralta *et al*., 2010) or FOLFOX therapy (Etienne-Grimaldi *et al.*, 2010). Patients with *MTHFR* 677T allele had improved outcome to pemetrexed-based chemotherapy in NSCLC (Smit *et al*., 2009).

In summary, this is the first study to identify SNP marker in the *MTHFR* gene predictive to gemcitabine/platinum treatment in advanced NSCLC patients. There are no other loci in the same region that have been reported to associate with survival and/or response to gemcitabine among lung cancer patients. The molecular mechanism of this polymorphism on MTHFR activity remains unclear. Additional studies are warranted to find out the molecular mechanisms underlying the significance of the C677T genotypes to different drugs.

The *ERCC1* gene is located at region q13.2–q13.3 of chromosome 19. In the NER cascade, ERCC1 up-regulation occurs at first (Reed *et al*., 2000). Polymorphisms in *ERCC1* C118T and C8092A are common, and have been found to be associated with the response or survival of patients with NSCLC after platinum-based chemotherapy along with discrepant findings.

Previous studies had reported that patients carrying the *ERCC1* CC genotype or C allele at C118T had a higher response rate to platinum-based chemotherapy (Su *et al*., 2007; Kalikaki *et al*., 2009; Li *et al*., 2010). Isla *et al*. (2004) and Ryu *et al*. (2004) both found that advanced NSCLC patients with the *ERCC1* 118 CC genotype had better survival, but no relationships were found between the response and 118 CC genotype after platinum-based treatment. Zhou *et al*. (2004) found a statistically significant association between the 8092 CC genotype and better OS. However, another similar study found the A

allele associated with better survival (Kalikaki *et al*., 2009), but not 8092 CC genotype.

We found no significant association between the polymorphisms of *ERCC1* C118T and C8092A and response or survival in our work. These results were in agreement with recent studies (de las Peñas *et al*., 2006; Tibaldi *et al*., 2008; Wang *et al*., 2010). Our data were also in accordance with a recent meta-analysis (Yin *et al*., 2011).

Studies revealed that the synonymous C118T polymorphism affected the levels of mRNA and protein, thus leading to differential cisplatin sensitivity (Chen *et al*., 2000; Yu *et al*., 2000; Park *et al*., 2002). Nevertheless, a recent report failed to show an association between *ERCC1* mRNA levels and codon 118 polymorphisms in epithelial ovarian cancer (Smith *et al*., 2007). A possible explanation for this observation has proposed the different translation rate of synonymous polymorphic codons that may affect ERCC1 protein levels and/or cotranslational protein folding, leading to a functionally different protein.

In this study, one of the most important strengths is that all the patients had only received first-line gemcitabine-based chemotherapy, excluding the effects of prior chemotherapy, surgery, and radiotherapy. Such a uniformly treated group of patients enabled us to find out whether the genotype influences the response and survival to this particular regimen.

However, several limitations in this pilot study need to be acknowledged. First, this is a retrospective study, and although we adjusted for various clinical parameters (such as gender, age, histology, and history of cigarette smoking) in our analysis, only 8.9% of patients had Stage IIIB disease and 5.9% of patients had a PS score of 2, a relatively small proportion of patients that might not be adequate to analyze the real effect of tumor stage and PS score on the TTP and OS. Second, because of the relatively small patient population analyzed and the heterogeneity of treatment administered, our findings require further validation studies. To further assess the predictive value of *MTHFR* gene polymorphism, a prospective multicenter study is needed. Hopefully, despite the above limitations, this study contributes significant information on the predictive role of *MTHFR* C677T polymorphism and may allow personalized chemotherapy to optimize clinical outcomes toward individualizing NSCLC treatment strategies.

5 Conclusions

This study suggests that *MTHFR* C677T CC genotype is an independent marker to predict higher response rate and favorable TTP in advanced NSCLC patients treated with gemcitabine/platinum chemotherapy.

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Recommended paper related to this topic

XRCC1 Arg399Gln and clinical outcome of platinum-based treatment for advanced non-small cell lung cancer: a meta-analysis in 17 studies

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Abstract: Objective: *XRCC1* polymorphism is a research hotpot in individual treatment for non-small cell lung cancer (NSCLC). To obtain the association between *XRCC1* polymorphism and clinical outcome of platinum-based treatment for NSCLC, a meta-analysis was conducted. Methods: Databases including PubMed, Embase, Cochrane, and Chinese National Knowledge Infrastructure (CNKI) were searched for publications that met the inclusion criteria. A fixed effect model was used to estimate pooled odds ratio (OR) and hazard ratio (HR) with 95% confidence interval (CI) for the association between *XRCC1* Arg399Gln and response or survival of platinum-based treatment for advanced NSCLC. A chi-squared-based Q-test was used to test the heterogeneity hypothesis. Egger's test was used to check publication bias. Results: Seventeen published case-control studies that focus on the association between *XRCC1* Arg399Gln and response or survival of platinum-based treatment for advanced NSCLC in 2 256 subjects were included in this meta-analysis, of whom 522 were AA genotypes (23.2% frequency), 916 AG genotypes (40.6% frequency), and 818 GG genotypes (36.2% frequency). The overall response rate (ORR) was 45.2% (110/243) for AA genotype patients, 29.9% for AG genotype (73/244), and 30.7% for GG genotype (124/403). The heterogeneity test did not show any heterogeneity and the Egger's test did not reveal an obvious publication bias among the included studies. The meta-analysis indicated that AA genotype patients presented higher response rates toward platinum drug treatment compared with G model (GG+GA) patients (GG vs. AA model: OR=0.489, 95% CI 0.266–0.900, *P*=0.021; AG vs. AA model: OR=0.608, 95% CI 0.392–0.941, *P*=0.026; GA+AA vs. GG model: OR=1.259, 95% CI 0.931–1.701, *P*=0.135; GG+GA vs. AA model: OR=0.455, 95% CI 0.313–0.663, *P*=0.0001). However, no evidence validates *XRCC1* associates with the survival following platinum drug therapy. Conclusions: Our meta-analysis suggested that *XRCC1* Arg399Gln is related with the sensitivity of NSCLC patients to platinum-based treatment. AA genotype patients present more desirable curative effectiveness compared with other patients.