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No evidence of an association of *ERCC1* and *ERCC2* polymorphisms with clinical outcomes of platinum-based chemotherapies in non-small cell lung cancer: a meta-analysis

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Abstract

Background—The nucleotide excision repair (NER) pathway modulates platinum-based chemotherapeutic efficacy by removing drug-induced DNA damage.

Methods—To summarize published data on the association between NER genes and responses to platinum-based chemotherapies in non-small cell lung cancer (NSCLC), we performed a meta-analysis of 17 published studies of *ERCC1* C118T/C8092A and *ERCC2* Lys751Gln/Asp312Asn polymorphisms, including 2,097 cancer patients. Primary outcomes included objective response (TR) (i.e., complete response + partial response vs. stable disease + progressive disease), progression-free survival (PFS) and overall survival (OS). We calculated odds ratio (OR) or hazard ratio (HR) with 95% confidence interval (CI) to estimate the risk or hazard.

Results—We found that none of the *ERCC1* C118T/C8092A and *ERCC2* Lys751Gln/Asp312Asn polymorphisms alone was statistically significantly associated with objective response, PFS and OS in NSCLC patients.

Conclusion—There is no evidence to support the use of NER *ERCC1* C118T/C8092A and *ERCC2* Lys751Gln/Asp312Asn polymorphisms as prognostic predictors of platinum-based chemotherapies in NSCLC.

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Keywords

Chemotherapy; DNA repair; Meta-analysis; Pharmacogenetics; Platinum

1. Introduction

Platinum is one of the most extensively used chemotherapeutic agents since its clinical introduction in the 1970s, and to date it remains the treatment of choice in various types of cancer, representing a major landmark in the history of anticancer drugs. Platinum-based double-agent chemotherapy is the cornerstone for non-small cell lung cancer (NSCLC) patients of advanced stages, whose effect did not differ significantly with the second drug used in the regimen. Two types of platinum drugs, cisplatin and carboplatin, are currently used, with almost the same working mechanisms but different toxicity profile. Previous studies demonstrated that the efficacy of platinum-based chemotherapy has a remarkable inter-individual variability, with a response rate from 26-60% in NSCLC patients [1]. Therefore, it is important to identify those whose tumors are susceptible to platinum drugs in order to provide individualized therapy.

Platinum cytotoxicity results from formation of platinum-DNA adducts that block transcription and lead to cell death of the tumors. Resistance to platinum has been associated with increased removal of platinum from cancer cells and repair/removal of platinum-DNA adducts by tolerance mechanisms [2]. Since the nucleotide excision repair (NER) pathway is the major DNA repair system to remove those DNA adducts, modification of the NER capacity would be expected to influence the anticancer effect of platinum drugs and therefore the clinical outcomes of NSCLC patients. ERCC1 and ERCC2 proteins are major components of the NER complex, acting as the rate-limiting enzymes in the NER pathway. Several common and putatively functional single nucleotide polymorphisms (SNPs) of *ERCC1* and *ERCC2* have been identified, of which *ERCC1* C118T and C8092A SNPs have been reported to have some effects on *ERCC1* mRNA expression [3,4], whereas *ERCC2* Asp312Asn and Lys751Gln (G>A and T>G, respectively) SNPs are associated with a suboptimal DNA repair capacity [5,6]. Previous studies have also suggested that *ERCC1* is a promising predictive marker for response to the platinum-based chemotherapy, because of its low expression associated with increased chemotherapeutic sensitivity [7]. Therefore, these *ERCC1* and *ERCC2* SNPs may be useful predictive markers for treatment with platinum agents.

Because published reports of an association between NER SNPs and clinical outcome of platinum-based chemotherapy from individual studies are not consistent [8,9], we performed a systemic review and meta-analysis to assess the evidence of effects of *ERCC1* and *ERCC2* SNPs on the efficacy of platinum-based chemotherapy in NSCLC patients.

2. Patients and methods

2.1. Study selection

We conducted this systematic review using a peer-reviewed, published protocol according to the guidelines of the Cochrane Collaboration. We searched for relevant publications before June 30th, 2010 in English literature by using electronic MEDLINE and EMBASE databases with the following terms “ERCC1”, “ERCC2 or XPD” or “ERCC”, “lung”, “cancer”, “carcinoma”, “adenocarcinoma”, “malignancy”, “polymorphism or variant”, “platinum”, and “treatment or chemotherapy”. References of the retrieved articles were further screened for earlier original studies. The inclusion criteria were as follows: advanced, recurrent, or metastatic cancers treated by any of the aforementioned platinum drugs (excluding

neoadjuvant chemotherapy); platinum drugs given through systemic chemotherapy (i.e. intravenous infusion); cancer histologically or pathologically confirmed; East Asian (China, Korea and Japan) or Caucasian (European descendents) ethnicities; and *ERCC1* C118T and C8092A (rs11615 and rs3212986) or *ERCC2* Lys751Gln and Asp312Asn (rs13181 and rs1799793) genotyped. The corresponding authors were contacted to obtain missing information, and some studies were excluded, if critical missing information was not obtained by our repeated requests. Abstracts, unpublished reports and articles with study sample size less than 30 or written in non-English language were also excluded.

2.2. Statistical methods

We estimated the odds ratio (OR) for objective response versus no response after platinum-based chemotherapy [CR+PR vs. PD+SD, using the WHO criteria [10] or the Response Evaluation Criteria in Solid Tumors criteria (RECIST) [11]] associated with *ERCC1* and *ERCC2* SNPs. Progression-free survival (PFS) and overall survival (OS) were evaluated by calculating pooled Cox proportional hazard ratios (HRs) and 95% confidence intervals (CIs) as relevant effect measures using published methods, when related data were not available from some of the studies but appropriate summary statistics or Kaplan-Meier curves were provided [12], because it has been reported that a meta-analysis of summary results is statistically as efficient as a joint analysis of individual participant data [13]. We then investigated the between-study heterogeneity by using the Cochran's Q test, using a significance level of $P < 0.05$. We performed initial analyses with a fixed-effect model and confirmatory analyses with a random-effect model, if there was significant heterogeneity. We used inverted funnel plots and the Egger's test to examine the effect of publication bias (linear regression analysis). All P values were two-sided, and all analyses were performed using the Stata software (Stata Corporation, College Station, Texas) and Review Manager (v5.0; Oxford, England).

3. Results

We identified 53 related publications by initial screening (as of June 30th, 2010), of which 18 publications met the inclusion criteria (Fig. 1). We excluded one study [14], in which data were inestimable and authors unreachable. As a result, the final data pool consisted of 17 studies, including 45 stage I/II and 2,052 stage III/IV (total 2,097) NSCLC patients (Table 1).

3.1. ERCC1 C118T

3.1.1. Objective response—Eight studies including 765 patients were eligible for the final analysis. In the dominant model, the minor variant T allele was not associated with objective response in all patients (T/T+C/T versus C/C: OR, 0.82; 95% CI, 0.47-1.43; $P = 0.012$ for heterogeneity, $I^2 = 60\%$). (Fig. 2A). Stratified analysis by ethnicity showed no association in both Asians and Caucasians (OR, 0.88; 95% CI, 0.42-1.86; $P = 0.005$ for heterogeneity, $I^2 = 73\%$ for Asians; OR, 0.67; 95% CI, 0.33-1.36; $P = 0.382$ for heterogeneity, $I^2 = 0\%$ for Caucasians) (Table 2). No publication bias was detected by either the funnel plot or Egger's test (data not shown).

3.1.2. Progression-free survival—Three studies including 259 patients were eligible for the final analysis. The T allele was not associated with any hazard change of PFS in our study (T/T+C/T versus C/C: HR, 0.88; 95% CI, 0.33 to 2.35; $P = 0.004$ for heterogeneity, $I^2 = 82\%$) (Fig. 2B and Table 2). No publication bias was detected by either the funnel plot or the Egger's test (data not shown).

3.1.3. Overall survival—Eight studies including 971 patients were eligible for the final analysis. Consistent with the results of objective response and PFS, there were no evidence for an influence of *ERCC1* C118T polymorphism on OS of NSCLC patients (T/T+C/T versus C/C: HR, 1.08; 95% CI, 0.75 to 1.56; $P = 0.001$ for heterogeneity, $I^2 = 71\%$) (Fig. 2C). Stratified analysis by ethnicity also showed null association in both Asians and Caucasians (HR, 1.16; 95% CI, 0.61-2.23; $P = 0.003$ for heterogeneity, $I^2 = 78\%$ for Asians; and HR, 1.03; 95% CI, 0.63-1.68; $P = 0.041$ for heterogeneity, $I^2 = 61\%$ for Caucasians) (Table 2). No publication bias was detected by either the funnel plot or the Egger's test (data not shown).

3.2. XPD Lys751Gln

3.2.1. Objective response—Eight studies including 694 patients were eligible for the final analysis, three of which included Asians. There were no evidence for an association between the Gln (G) allele and objective response in all patients (Gln/Gln+Gln/Lys versus Lys/Lys: OR, 0.82; 95% CI, 0.57-1.18; $P = 0.622$ for heterogeneity, $I^2 = 0\%$) (Fig. 3A). Stratified analysis by ethnicity also showed null association in both Asians and Caucasians (OR, 0.55; 95% CI, 0.28-1.07; $P = 0.766$ for heterogeneity, $I^2 = 0\%$ for Asians; and OR, 0.99; 95% CI, 0.63-1.56; $P = 0.558$ for heterogeneity, $I^2 = 0\%$ for Caucasians) (Table 2). No publication bias was detected by either the funnel plot or the Egger's test (data not shown).

3.2.2. Progression-free survival—Four eligible studies of 640 patients were included in the final analysis, one of which included both ethnicities [15]. Overall, there was no effect of the Gln (G) allele on progression hazard in all patients (HR, 1.00; 95% CI, 0.79 to 1.25; $P = 0.348$ for heterogeneity, $I^2 = 9\%$) (Fig. 3B). When only Caucasians were included, the results were not significantly changed (HR, 0.93; 95% CI, 0.71 to 1.22; $P = 0.288$ for heterogeneity, $I^2 = 20\%$) (Table 2). No publication bias was detected by either the funnel plot or the Egger's test (data not shown).

3.2.3. Overall survival—Seven studies included 975 patients were eligible for the final analysis. The Gln (G) allele was not associated with the hazard of death in all patients (HR, 0.88; 95% CI, 0.72 to 1.07; $P = 0.668$ for heterogeneity, $I^2 = 0\%$) (Fig. 3C). When only Caucasians were included, the results were not changed (HR, 0.89 and 95% CI, 0.70-1.13; $P = 0.811$ for heterogeneity, $I^2 = 0\%$) (Table 2). No publication bias was detected by either the funnel plot or the Egger's test (data not shown).

3.3. *ERCC1* C8092A and *ERCC2* Asp312Asn

Objective response, progression-free survival and overall survival—As shown in Table 3, we did not find any significant associations with objective response, PFS and OS.

4. Discussion

In this meta-analysis, we did not find any statistical evidence for an association, nor an ethnic difference, between four NER SNPs (*ERCC1* C118T/C8092A and *ERCC2* Lys751Gln/Asp312Asn) and clinical outcomes of NSCLC patients receiving platinum-based chemotherapy.

Platinum agents are activated intracellularly, covalently binding to DNA to induce DNA adducts that block DNA replication and ultimately leading to cell death. Various signal transduction pathways, including DNA-damage recognition and repair, cell-cycle arrest and apoptosis, are activated in this process to exert antitumor effects. With an enhanced DNA repair capacity, some cancer cells are able to resist against the platinum-based

chemotherapy, particularly when the NER pathway is highly activated to remove those DNA adducts caused by platinum drugs. There is evidence that cancer patients with congenital NER mutations are sensitive to platinum treatment and that NSCLC patients with a lower NER capacity had an increased overall survival after the first-line platinum-based chemotherapy [16,17].

SNPs can contribute directly to the variation in phenotypic drug sensitivity by modifying functions of the related genes. ERCC1 and ERCC2 are two key rate-limiting enzymes in the multistep NER process. ERCC1, in collaboration with its partner XPF protein, is involved in the DNA lesion recognition, whereas ERCC2 is a subunit of human transcriptional initiation factor TFIIH with an ATP-dependent helicase activity. Studies have found an effect of some *ERCC1* and *ERCC2* variants on the NER capacity, probably through regulation of mRNA expression [18,19]. Therefore, functional *ERCC1* and *ERCC2* SNPs may reveal platinum sensitivity as an inborn trait, and prognostic values of NER SNPs may differ among individuals.

With a pooled dataset of 2,097 patients treated by cisplatin-, and carboplatin-based regimens, we performed a comprehensive evaluation of clinical outcomes by objective response, PFS and OS, because these parameters are correlated but not necessarily consistent with one another. In a dominant model fitted for each of the minor variants, we found none of the four SNPs (*ERCC1* C118T/C8092A and *ERCC2* Lys751Gln/Asp312Asn) in most frequently published studies was associated with clinical outcomes of NSCLC patients treated with platinum-based chemotherapy. Further stratified analyses by ethnicity also yielded no differences. Our results are different from those of a previous meta-analysis, which showed an association between the CC genotype of the *ERCC1* C118T polymorphism with an increased objective response (CC vs. CT+TT: OR, 2.17; 95% CI, 1.43-3.33; $P < 0.001$) [20]. This is because: (1) the authors mistakenly reported a very strong association between the CC genotype and objective response in the study by Kalikaki *et al.* [21], because they extracted the *ERCC1* C118T response data in the format of CC vs. CT+TT (OR: 9.56, 95% CI, 1.22-74.74), which, however, was presented as CC+CT vs. TT in the original study with a correct OR of 1.89 with 95% CI, 0.68-5.26 (CC vs. CT+TT) or 0.53 with 95% CI, 0.19-1.46 (CT+TT vs. CC) as we presented in our Figure 2A; (2) our present analysis consisted a larger sample size ($n=765$), including some new publications that reported T allele to be associated higher objective response [22], compared with the previously published one ($n=526$).

A more recent meta-analysis by Chen *et al.* found a significant association of low/negative tissue expression of ERCC1 with higher objective response and median survival in advanced NSCLC patients [23]. These discrepant findings may be due to the differences in study designs, patient populations, treatment modalities, and genetic background as well as biological significance between surrogate and target tissues. For example, SNPs could reflect the inter-individual difference in the systemic NER ability, while tissue ERCC1 expression was a more direct measurement of the NER capacity in the target tissues that can be affected by other factors such as epigenetic mechanism of methylation of the genes. However, the importance of SNPs could result not only from their direct modification of the related gene functions but also their genetic linkage with other causative germ-line mutations. In general, the overall effect from a SNP is expected to be weak or moderate. In contrast, tissue levels of NER are heavily influenced by numerous factors, including genetic alterations in cancer, chemotherapy (e.g. platinum itself), and environmental factors, such as tobacco carcinogens and other oxidants [24], in addition to methylation. Therefore, although *ERCC1/ERCC2* SNPs may modify expression of the related genes, they are not surrogates of gene expression. Given these results, an examination of the association between *ERCC1/*

ERCC2 SNPs and tissue level of gene expression would be helpful to provide additional useful information.

Despite our efforts in performing a comprehensive analysis, limitations of our meta-analysis need to be addressed. First, our analysis used published international studies, of which one study [14] was excluded from the analysis because of loss of contact for original data. We did not include the data of *ERCC1* C118T and objective response of *ERCC2* Lys751Gln SNP from the study by Gandara *et al* [15], because the result of *ERCC1* C118T was not in the T dominant model and because objective response was not reported as odds ratio. This could cause some bias in our estimates, but it is unlikely to change our major conclusions due to their negative findings or opposite result from that of our pooled analysis. For example, *ERCC2* Gln allele was significantly associated with an increased objective response in the study by Gandara, but favored a reduced objective response in our study. Second, most of the included studies were retrospective and differed significantly in their study designs, such as patient selection, chemotherapeutic protocol and follow-up time. Some studies included patients receiving surgery or radiotherapy in addition to the platinum-based chemotherapy, thus adding confounding factors that may have caused wide and significant heterogeneity between studies. Stratified analyses by some important host-, or treatment-related factors, such as smoking history, tumor histology, and therapeutic method, would be helpful to reduce the heterogeneity and provide additional useful information. However, few of these studies reported genotype distribution by subgroups, thus making such analyses impossible. Third, our analysis largely used unadjusted estimates, because not all published studies presented adjusted estimates, or when they did, the estimates were not adjusted by the same potential confounders, such as age, sex, ethnicity and exposures. However, when the available adjusted estimates were used in our analysis, the conclusions were not significantly changed (data now shown). Fourth, the management of platinum toxicity is important for safe administration of the platinum-based chemotherapy. However, we were unable to analyze the association between *ERCC1* and *ERCC2* SNPs and platinum toxicities, because few studies provided this information or used different toxicity profiles.

Overall, our meta-analysis did not support *ERCC1* C118T/C8092A and *ERCC2* Lys751Gln/Asp312Asn as useful prognostic factors for assessing treatment response to platinum-based chemotherapies in NSCLC patients. However, future prospective studies with large sample sizes and better study designs are required to confirm our findings.

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Fig. 1.
Study flow chart for the process of selecting the eligible publications.

Fig. 2. Forest plot of (A) objective response; (B) progression-free survival; and (C) overall survival in NSCLC patients treated with platinum-based therapies by *ERCC1* C118T polymorphism (TT+CT vs CC).

B **C** **Fig. 3.**

Forest plot of (A) objective response; (B) progression-free survival; and (C) overall survival in NSCLC patients treated with platinum-based therapies by *ERCC2* Lys751Gln polymorphism (Gln/Gln+Gln/Lys vs Lys/Lys [GG+TG vs TT]).

Table 1
Studies on platinum-based chemotherapy and *ERCC1* and *ERCC2* polymorphisms included in the meta-analysis.

Study	Country	Ethnicity	Drug	Case No.	Stage	Biomarkers	SNPs
Booton 2006 [25]	UK	Caucasian	Cis or carboplatin	108	III/IV	TR, OS	<i>ERCC2</i> Lys751Gln, Asp312Asn
Camps 2003 [26]	Spain	Caucasian	Cisplatin	33	III/IV	TR	<i>ERCC2</i> Lys751Gln
Isla 2004 [8]	Spain	Caucasian	Cisplatin	62	III/IV	TR, PFS, OS	<i>ERCC1</i> C118T, <i>ERCC2</i> Lys751Gln, Asp312Asn
Kalikaki 2009 [21]	Greece	Caucasian	Platinum	119	III/IV	TR, OS	<i>ERCC1</i> C118T, C8092A, <i>ERCC2</i> Lys751Gln, Asp312Asn
Ryu 2004 [27]	Korea	Asian	Cisplatin	107	III/IV	TR	<i>ERCC1</i> C118T, <i>ERCC2</i> Lys751Gln
Su 2007 [28]	USA	Asian	Cisplatin	76	III/IV	TR	<i>ERCC1</i> C118T
Tibaldi 2008 [9]	Italy	Caucasian	Cisplatin	65	III/IV	TR, OS, PFS	<i>ERCC1</i> C118T, <i>ERCC2</i> Lys751Gln, Asp312Asn
Zhou 2004 [29]	USA	Caucasian	Cis or carboplatin	128	III/IV	OS	<i>ERCC1</i> C118T, C8092A, <i>ERCC2</i> Asp312Asn
Park 2006 [30]	Korea	Asian	Cisplatin	245	III/IV	OS	<i>ERCC1</i> C118T, C8092A
Peñas 2006 [31]	Spain	Caucasian	Cisplatin	132	III/IV	OS, PFS	<i>ERCC1</i> C118T, <i>ERCC2</i> Lys751Gln, Asp312Asn
Okuda 2009 [32]	Japan	Asian	Platinum	90	I-IV	OS	<i>ERCC1</i> C118T, C8092A
Chen 2010 [33]	China	Asian	Cisplatin	95	III/IV	TR	<i>ERCC1</i> C118T
Zhou 2010 [34]	China	Asian	Cis or carboplatin	130	III/IV	TR, OS	<i>ERCC1</i> C118T
Li 2010 [22]	China	Asian	Cis or carboplatin	115	III/IV	TR	<i>ERCC1</i> C118T, C8092A, <i>ERCC2</i> Lys751Gln
Yao 2009 [35]	China	Asian	Platinum	108	III/IV	TR, OS	<i>ERCC2</i> Lys751Gln
Gurubhagavatula 2004 [36]	USA	Caucasian	Cis or carboplatin	103	III/IV	OS	<i>ERCC2</i> Asp312Asn
Gandara 2009 [15]	USA	Both	Carboplatin	381	III/IV	TR [#] , OS, PFS	<i>ERCC1</i> C118T [*] , <i>ERCC2</i> Lys751Gln

* *ERCC1* data of Gandara 2009 were not included in the meta-analysis because the values of dominant comparison were not available.

[#]TR (objective response) was reported as hazard ratio, not odds ratio

Table 2

Analysis of the association between *ERCC1* C118T and *ERCC2* Lys751Gln polymorphisms and objective response, PFS and OS.

	Objective response				PFS				OS			
	Study (Cases)	Fixed effect TT +TC vs. CC	Random effect TT+TC vs. CC	Phet [†]	Study (Cases)	Fixed effect TT +TC vs. CC	Random effect TT+TC vs. CC	Phet [†]	Study (Cases)	Fixed effect TT +TC vs. CC	Random effect TT+TC vs. CC	Phet [†]
<i>ERCC1</i> C118T												
All	8 (765)	0.84 [0.61, 1.17]	0.82 [0.47, 1.43]	0.012	3 (259)	0.89 [0.61, 1.32]	0.88 [0.33, 2.35]	0.004	8 (971)	1.12 [0.94, 1.33]	1.08 [0.75, 1.56]	0.001
Asian	5 (523)	0.90 [0.62, 1.30]	0.88 [0.42, 1.86]	0.005	0 (0)				3 (465)	1.22 [0.98, 1.53]	1.16 [0.61, 2.23]	0.003
Caucasian	3 (242)	0.67 [0.33, 1.36]	0.65 [0.31, 1.33]	0.382	3 (259)	0.89 [0.61, 1.32]	0.88 [0.33, 2.35]	0.004	5 (506)	0.97 [0.93, 1.28]	1.03 [0.63, 1.68]	0.041
<i>ERCC2</i> Lys751Gln												
		GG+TG vs. TT	GG+TG vs. TT			GG+TG vs. TT	GG+TG vs. TT			GG+TG vs. TT	GG+TG vs. TT	
All	8 (694)	0.82 [0.57, 1.18]	0.83 [0.57, 1.21]	0.622	4 (640)	1.00 [0.79, 1.25]	1.00 [0.79, 1.28]	0.348	7 (975)	0.88 [0.72, 1.07]	0.88 [0.72, 1.07]	0.668
Asian	3 (323)	0.55 [0.28, 1.07]	0.56 [0.29, 1.10]	0.766	0 (0)				1 (108)			
Caucasian	5 (371)	0.99 [0.63, 1.56]	0.99 [0.63, 1.56]	0.558	3 (259)	0.93 [0.71, 1.22]	0.95 [0.70, 1.30]	0.288	5 (486)	0.89 [0.70, 1.13]	0.89 [0.70, 1.13]	0.811
Mixed	0 (0)				1 (381)				1 (381)			

Phet: P value of between-study heterogeneity.

Association between *ERCC1* C8092A and *ERCC2* Asp312Asn polymorphisms and objective response, PFS and OS.

Table 3

	Patient (study)	<i>ERCC1</i> C8092A ^a	Phet [†]	Patient (study)	<i>ERCC2</i> Asp312Asn ^b	Phet [†]
Objective response	233 (2)			468 (6)		0.681
Fixed effect		N/A			0.91 [0.59, 1.40]	
Random effect		N/A			0.90 [0.58, 1.39]	
PFS	0			259 (3)		
Fixed effect		N/A			1.03 [0.78, 1.34]	0.792
Random effect		N/A			1.03 [0.78, 1.34]	
OS	582 (4)		<0.001	589 (6)		
Fixed effect		0.94 [0.80, 1.10]			0.95 [0.76, 1.18]	0.852
Random effect		1.06 [0.62, 1.82]			0.95 [0.76, 1.18]	

[†] Phet: *P* value of between-study heterogeneity.

^a *ERCC1* C8092A: AA+AC vs. CC

^b *ERCC2* Asp312Asn: AA+AG vs. GG