Published OnlineFirst January 28, 2011; DOI:10.1158/1078-0432.CCR-10-2169

Clinical Cancer Research

ERCC1 and *ERCC2* Polymorphisms Predict Clinical Outcomes of Oxaliplatin-Based Chemotherapies in Gastric and Colorectal Cancer: A Systemic Review and Meta-analysis

Ming Yin, Jingrong Yan, Eva Martinez-Balibrea, et al.

Clin Cancer Res 2011;17:1632-1640. Published OnlineFirst January 28, 2011.

Published OnlineFirst January 28, 2011; DOI:10.1158/1078-0432.CCR-10-2169

Clinical Cancer Research

ERCC1 and *ERCC2* Polymorphisms Predict Clinical Outcomes of Oxaliplatin-Based Chemotherapies in Gastric and Colorectal Cancer: A Systemic Review and Meta-analysis

Ming Yin[1], Jingrong Yan[2], Eva Martinez-Balibrea[4], Francesco Graziano[5], Heinz-Josef Lenz[3], Hyo-Jin Kim[6], Jacques Robert[9], Seock-Ah Im[7], Wei-Shu Wang[8], Marie-Christine Etienne-Grimaldi[10], and Qingyi Wei[1]

Abstract

Purpose: Nucleotide excision repair (NER) modulates platinum-based chemotherapeutic efficacy by removing drug-produced DNA damage. To summarize published data on the association between polymorphisms of NER genes (*ERCC1* and *ERCC2*) and responses to oxaliplatin-based chemotherapies, we carried out a meta-analysis of gastric and colorectal cancer for commonly studied polymorphisms *ERCC1* rs11615C>T and *ERCC2* rs13181T>G.

Patients and Methods: In 17 previously published studies, 1,787 cancer patients were treated with the oxaliplatin-based regimen. Primary outcomes included therapeutic response (TR; i.e., complete response + partial response vs. stable disease + progressive disease), progression-free survival (PFS), and overall survival (OS). We calculated OR or HR with 95% CIs to estimate the risk or hazard.

Results: We found consistent and clinically substantial risk or hazard for TR, PFS, and OS in the oxaliplatin-treated gastric and colorectal cancer patients with an ethnic discrepancy. For *ERCC1* rs11615C>T, the T allele was associated with reduced response and poor PFS and OS in Asians (TR: OR = 0.53 and 95% CI = 0.35–0.81; PFS: HR = 1.69 and 95% CI = 1.05–2.70; and OS: HR = 2.03 and 95% CI = 1.60–2.59). For *ERCC2* rs13181T>G, the G allele was associated with reduced response and poor PFS and OS in Caucasians (TR: OR = 0.56 and 95% CI = 0.35–0.88; PFS: HR = 1.41 and 95% CI = 1.02–1.95; and OS: HR = 1.42 and 95% CI = 1.11–1.81).

Conclusions: NER *ERCC1* rs11615C>T and *ERCC2* rs13181T>G polymorphisms are useful prognostic factors in oxaliplatin-based treatment of gastric and colorectal cancer. Larger studies and further clinical trials are warranted to confirm these findings. *Clin Cancer Res; 17(6); 1632–40. ©2011 AACR.*

Introduction

Fluoropyrimidines are essential in the treatment of gastric and colorectal cancer in advanced stages and have shown survival benefit compared with the best supportive care (1, 2). Oxaliplatin is the new generation of platinum drugs that improve response rate and survival after adding to the 5-fluorouracil (5-Fu)/leucovorin (LV) regimen. Combination treatment with 5-Fu/LV plus oxaliplatin (FOLFOX) is now considered the standard treatment of gastric and colorectal cancer, with a response rate of more than 40% for the first-line treatment (3, 4). Despite the efficacy of combined chemotherapies, a large proportion of patients display varying levels of resistance, indicating that the therapeutic efficacy has a remarkable interindividual variability. Since DNA kinking is the major feature of platinum–DNA adducts that block DNA replication and lead to cancer cell death (5, 6), which is recognized and repaired by the nucleotide excision repair (NER) pathway, it is conceivable that the interindividual difference in the NER capacity may influence the efficacy of oxaliplatin-based chemotherapy and clinical outcomes of the treated cancer 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* rs11615 and rs3212986 SNPs (C118T and C8092A) have some effects on *ERCC1* mRNA expression (7), whereas *ERCC2* rs1799793 and rs13181 SNPs [Asp312Asn (G>A) and Lys751Gln (T>G), respectively] SNPs are associated with

Authors' Affiliations: [1]Department of Epidemiology, M.D. Anderson Cancer Center, The University of Texas; [2]Department of Pediatrics, Baylor College of Medicine, Houston, Texas; [3]Department of Medical Oncology, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, California; [4]Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; [5]Medical Oncology Unit, Azienda Ospedale San Salvatore, Pesaro, Italy; [6]Department of Internal Medicine, Dong-A University College of Medicine, Busan, South Korea; [7]Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; [8]School of Medicine, National Yang-Ming University, Taipei, Taiwan; [9]Universite Victor Segalen, Institut Bergonie, Bordeaux-cedex, Bordeaux, France; and [10]Centre Antoine Lacassagne, Oncopharmacology Unit, Nice, France

Corresponding Author: Qingyi Wei, Department of Epidemiology, M.D. Anderson Cancer Center, The University of Texas, 1515 Holcombe Blvd, Unit 1365, Houston, TX 77030. Phone: 713-792-3020; Fax: 713-563-0999; E-mail: qwei@mdanderson.org

doi: 10.1158/1078-0432.CCR-10-2169

Published OnlineFirst January 28, 2011; DOI:10.1158/1078-0432.CCR-10-2169

Translational Relevance

Combination treatment with oxaliplatin and fluoropyrimidines is the standard treatment of gastric and colorectal cancer which improves patient response and overall survival. The nucleotide excision repair (NER) pathway is responsible for the removal of DNA adducts caused by oxaliplatin and thus may influence chemotherapeutic efficacy. Our meta-analysis provided evidence of an association between NER *ERCC1* rs11615C>T and *ERCC2* rs13181T>G single nucleotide polymorphisms and clinical outcomes in gastric and colorectal cancer patients, both Asians and Caucasians, receiving oxaliplatin-based chemotherapy. Our results suggest that it is feasible to use a pharmacogenomic approach to predict clinical outcomes of oxaliplatin-treated gastric and colorectal cancer patients.

suboptimal DNA repair capacity (8, 9). Previous studies have 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 (10). Therefore, these *ERCC1* and *ERCC2* SNPs may be useful prognostic 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, we conducted a systemic review and meta-analysis to assess the evidence of effects of *ERCC1* rs11615C>T and *ERCC2* rs13181T>G SNPs on the efficacy of oxaliplatin-based chemotherapy in gastric and colorectal cancer patients.

Patients and Methods

Study selection

We searched for relevant publications before June 1, 2010, in English literature by using electronic MEDLINE and EMBASE databases with the following terms: "ERCC1," "ERCC2 or XPD," or "ERCC," "gastric or stomach cancer," "colon or colorectal cancer," "polymorphism or variant," 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 gastric or colorectal cancer; treated purely by regimens of FOLFOX (oxaliplatin plus 5-Fu/leucovorin) or XELOX (oxaliplatin plus capecitabine, a drug which converts to 5-Fu *in vivo*), excluding neoadjuvant chemotherapy; cancer histologically or pathologically confirmed; East Asian (China, Korea, and Japan) or Caucasian (European descendents) ethnicities; and *ERCC1* rs11615C>T and or *ERCC2* rs13181T>G 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 sample size less than 45 or written in non-English language were also excluded.

Statistical methods

We estimated the OR for objective response versus no response after platinum-based chemotherapy [CR (complete response) + PR (partial response) vs. PD (progressive disease) + SD (stable disease), using the WHO criteria, ref. 11, or RECIST (Response Evaluation Criteria in Solid Tumors) criteria, ref. 12]. Progression-free survival (PFS) and overall survival (OS) were evaluated by pooled Cox proportional HRs and 95% CIs by published methods (13), because a meta-analysis of summary results is statistically as efficient as a joint analysis of individual participant data (14). We assessed the between-study heterogeneity by the Cochran Q test with a significance level of $P < 0.05$. We carried out 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 test to examine the effect of publication bias. We compared the difference in the effect estimates between subgroups as described previously (15). All *P* values were 2-sided, and all analyses were carried out using the Stata software (Stata Corporation) and Review Manager (v5.0).

Results

We identified 65 related publications by initial screening (as of June 1, 2010), of which 21 publications seemed to meet the inclusion criteria. We excluded 1 study, in which data were inestimable and authors were unreachable (16), 2 studies that used other chemotherapeutic agents (i.e., irinotecan and cetuximab) in addition to FOLFOX or XELOX (17, 18), and 1 study with study sample size less than 45 (ref. 19; Fig. 1). As a result, the final data pool consisted of 17 studies, including 1,787 cancer patients (Table 1).

ERCC1 rs11615C>T

Objective response. Nine studies including 855 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 vs. C/C: OR = 0.89; 95% CI = 0.50–1.57; Fig. 2A) and no single study altered the result substantially by the sensitivity test. However, stratified analysis by ethnicity showed a significant difference in the estimates of effect between Asians and Caucasians ($P = 0.002$) and the T allele was associated with a significantly lower objective response rate in Asians (OR = 0.53; 95% CI = 0.35–0.81). When only colorectal cancer was included, the OR was similar to that of the overall patients (OR = 0.88; 95% CI = 0.42–1.87; Table 2). No publication bias was detected by either the funnel plot or the Egger test (data not shown).

Progression-free survival. Eleven studies including 1,230 patients were eligible for the final analysis. The T allele was associated with a nonsignificant increase of hazard for PFS in all patients (T/T + C/T vs. C/C: HR =

Published OnlineFirst January 28, 2011; DOI:10.1158/1078-0432.CCR-10-2169

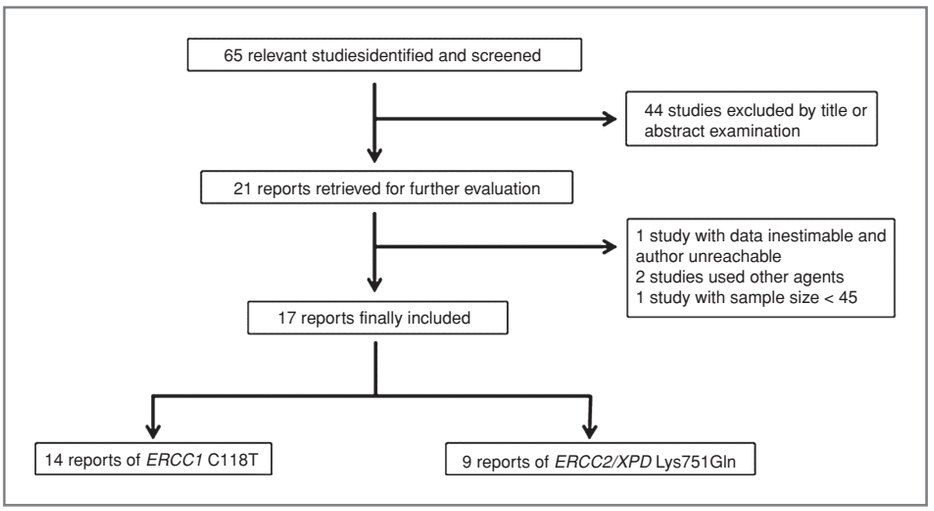

Figure 1. Study flow chart for the process of selecting the eligible publications.

Table 1. Studies on oxaliplatin-based chemotherapy and *ERCC1* (rs11615C>T) and *ERCC2* (rs13181T>G) polymorphisms included in the meta-analysis

Study	Country	Tumor	Drug	*n*	Biomarkers	SNPs	Allele frequency[a]
Asians							
Chang et al. (21)	Taiwan	Colorectal	FOLFOX	168	TR, OS, PFS	rs11615	T: 0.254
Lai et al. (34)	Taiwan	Colorectal	FOLFOX	188	TR, OS, PFS	rs13181	G: 0.080
Keam et al. (22)	Korea	Gastric	FOLFOX	73	TR, OS, PFS	rs11615	T: 0.260
						rs13181	G: 0.082
Liang et al. (35)	China	Colorectal	FOLFOX or XELOX	99	TR, PFS	rs11615	T: 0.288
Seo et al. (36)	Korea	Gastric	FOLFOX	75	TR, OS, PFS	rs11615	T: 0.240
Huang et al. (37)	China	Gastric	FOLFOX	89	OS, PFS	rs11615	T: 0.281
Liang et al. (38)	China	Colorectal	FOLFOX or XELOX	113	OS	rs11615	T: 0.323
Caucasians							
Le Morvan et al. (39)	France	Colorectal	FOLFOX or XELOX	59	TR, OS, PFS	rs13181	G: 0.381
Paré et al. (20)	Spain	Colorectal	FOLFOX	126	TR, OS, PFS	rs11615	T: 0.586
						rs13181	G: 0.384
Park et al. (40)	USA	Colorectal	FOLFOX	70	TR	rs13181	G: 0.421
Chua et al. (41)	Australia	Colorectal	FOLFOX	115	TR, OS, PFS	rs11615	T: 0.635
Spindler et al. (42)	Denmark	Colorectal	XELOX	66	TR, PFS[b]	rs11615	T: 0.652
Viguier et al. (43)	France	Colorectal	FOLFOX	61	TR	rs11615	T: 0.557
Ruzzo et al. (44)	Italy	Colorectal	FOLFOX	166	PFS	rs11615	T: 0.557
						rs13181	G: 0.443
Stoehlmacher et al. (45)	USA	Colorectal	FOLFOX	106	OS, PFS	rs11615	T: 0.505
						rs13181	G: 0.373
Martinez-Balibrea et al. (46)	Spain	Colorectal	FOLFOX or XELOX	96	PFS	rs11615	T: 0.615
						rs13181	G: 0.354
Etienne-Grimaldi et al. (47)	France	Colorectal	FOLFOX	117	TR, OS, PFS	rs11615	T: 0.538
						rs13181	G: 0.385
HapMap[c]	China	(normal)		137		rs11615	T: 0.243
				136		rs13181	G: 0.095
	Europe	(normal)		113		rs11615	T: 0.642
				113		rs13181	G: 0.332

Abbreviation: TR, therapeutic response.

[a]Allele frequencies are shown as the T allele of *ERCC1* rs11615 and the G allele of *ERCC2* rs13181.

[b]PFS data were not available.

[c]Data from http://hapmap.ncbi.nlm.nih.gov/cgi-perl/gbrowse/hapmap3r3_B36/.

Published OnlineFirst January 28, 2011; DOI:10.1158/1078-0432.CCR-10-2169

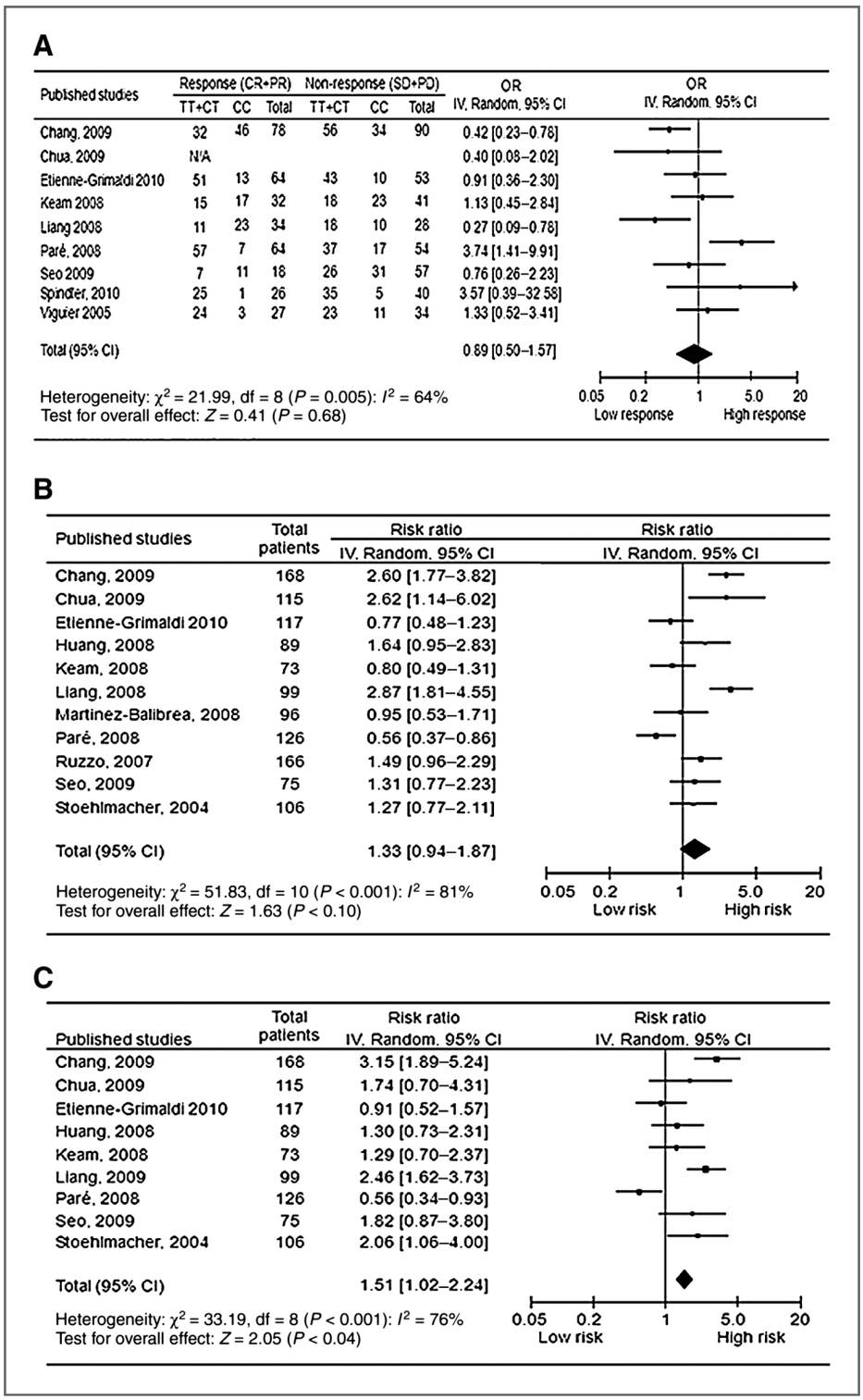

Figure 2. Forest plot of (A) objective response; (B) PFS; and (C) OS in gastric and colorectal cancer patients treated with oxaliplatin-based therapies by *ERCC1* rs11615C>T polymorphism (T/T + C/T vs. C/C, reference group = C/C).

1.33; 95% CI = 0.94–1.87; Fig. 2B), and the single study by Paré and colleagues (20) showed substantial influence over the pooled result, the exclusion of which elevated the HR significantly (HR = 1.46; 95% CI = 1.07–1.99). Although stratified analysis by ethnicity showed a clinically substantial and statistically significant increase in the hazard of progression in Asian patients (HR = 1.69; 95% CI = 1.05–2.70), further comparison did not show significant

Published OnlineFirst January 28, 2011; DOI:10.1158/1078-0432.CCR-10-2169

Table 2. Analysis of the association between *ERCC1* rs11615C>T and *ERCC2* rs13181T>G polymorphisms and objective response, PFS, and OS

	Objective response				PFS				OS			
	Study[a] (cases)	T/T + T/C vs. C/C		Phet[b]	Study (cases)	T/T + T/C vs. C/C		Phet[b]	Study (cases)	T/T + T/C vs. C/C		Phet[b]
		Fixed effect	Random effect			Fixed effect	Random effect			Fixed effect	Random effect	
***ERCC1* rs11615C>T**												
All	9 (855)	0.81 (0.58–1.12)	0.89 (0.50–1.57)	0.005	11 (1,230)	1.33 (1.15–1.54)	1.33 (0.94–1.87)	<0.001	9 (968)	1.53 (1.27–1.85)	1.51 (1.02–2.24)	<0.001
Asian	4 (378)	0.53 (0.35–0.81)	0.55 (0.31–0.98)	0.158	5 (504)	1.79 (1.45–2.21)	1.69 (1.05–2.70)	<0.001	5 (504)	2.03 (1.60–2.59)	1.95 (1.37–2.78)	0.078
Caucasian	5 (477)	1.47 (0.89–2.43)	1.44 (0.68–3.02)	0.103	6 (726)	1.00 (0.81–1.23)	1.07 (0.72–1.59)	0.004	4 (464)	0.97 (0.72–1.32)	1.10 (0.60–2.03)	0.012
Colorectal only	7 (707)	0.77 (0.54–1.12)	0.88 (0.42–1.87)	0.002	8 (993)	1.38 (1.17–1.64)	1.39 (0.89–2.17)	<0.001	6 (731)	1.58 (1.27–1.98)	1.55 (0.87–2.77)	<0.001
***ERCC2* rs13181T>G**		G/G + G/T vs. T/T	G/G + G/T vs. T/T			G/G + G/T vs. T/T	G/G + G/T vs. T/T			G/G + G/T vs. T/T	G/G + G/T vs. T/T	
All	6 (625)	0.53 (0.37–0.78)	0.53 (0.36–0.78)	0.588	8 (931)	1.37 (1.15–1.63)	1.41 (1.06–1.89)	0.010	6 (669)	1.61 (1.29–2.00)	1.54 (0.96–2.50)	<0.001
Asian	2 (261)				2 (261)				2 (261)			
Caucasian	4 (364)	0.56 (0.35–0.88)	0.56 (0.35–0.89)	0.368	6 (670)	1.33 (1.09–1.62)	1.41 (1.02–1.95)	0.022	4 (408)	1.42 (1.11–1.81)	1.42 (1.06–1.90)	0.236
Colorectal only	5 (552)	0.52 (0.35–0.77)	0.52 (0.35–0.77)	0.472	7 (858)	1.42 (1.19–1.71)	1.50 (1.11–2.02)	0.008	5 (596)	1.70 (1.36–2.13)	1.77 (1.11–2.84)	0.002

[a]Study: the number of studies included in the analysis.
[b]Phet: *P* value of between-study heterogeneity.

Published OnlineFirst January 28, 2011; DOI:10.1158/1078-0432.CCR-10-2169

difference in the estimates of effect between Asians and Caucasians ($P = 0.147$). When only colorectal cancer was included, the HR was similar to that of overall patients (HR = 1.39; 95% CI = 0.89–2.17; Table 2). No publication bias was detected by either the funnel plot or the Egger test (data not shown).

Overall survival. Nine studies including 968 patients were eligible for the final analysis. There seemed a significant effect of *ERCC1* rs11615C>T polymorphism on OS in all patients (T/T + C/T vs. C/C: HR = 1.51; 95% CI = 1.02–2.24; Fig. 2C). Further analysis showed substantial influence from the single study of Chang and colleagues (21), the exclusion of which led to the loss of significance of the pooled result (HR = 1.36; 95% CI = 0.92–2.02). Stratified analysis indicated a more pronounced effect in Asian patients (HR = 2.03; 95% CI = 1.60–2.59) than in the Caucasian patients (HR = 1.10; 95% CI = 0.60–2.03) and a marginally significant difference existed in the estimates of effect between these two ethnicities ($P = 0.064$). When only colorectal cancer was included, the T allele was associated with a nonsignificant increased hazard of death (HR = 1.55; 95% CI = 0.87–2.77; Table 2). No publication bias was detected by either the funnel plot or the Egger test (data not shown).

ERCC2 rs13181T>G

Objective response. Six studies including 625 patients were eligible for the final analysis. The G allele was associated with a reduced objective response in all patients (G/G + G/T vs. T/T: OR = 0.53; 95% CI = 0.37–0.78; Fig. 3A), and no single study influenced the pooled result substantially. In stratified analyses (Table 2), the association remained significant in subgroups of Caucasians (OR = 0.56; 95% CI = 0.35–0.88) and colorectal cancer (OR = 0.52; 95% CI = 0.35–0.77). No publication bias was detected by either the funnel plot or the Egger test (data not shown).

Progression-free survival. Eight eligible studies of 931 patients were included in the final analysis, only 2 of which included Asians. Overall, there was a substantial effect of the G allele on progression hazard in all patients (G/G + G/T vs. T/T: HR = 1.41; 95% CI = 1.06–1.89; Fig. 3B and Table 2), and no single study influenced the pooled result substantially. In stratified analyses (Table 2), the significance remained in subgroups of Caucasians (HR = 1.41; 95% CI = 1.02–1.95) and colorectal cancer (HR = 1.50; 95% CI = 1.11–2.02). No publication bias was detected by either the funnel plot or the Egger test (data not shown).

Overall survival. Six studies including 669 patients were eligible for the final analysis; again, only two of which included Asians. The G allele was associated with a nonsignificant increase in the hazard of death in all patients (G/G + G/T vs. T/T: HR = 1.54; 95% CI = 0.96–2.50; Fig. 3C and Table 2), and the single study by Keam and colleagues (22) had a substantial influence over the pooled result, the exclusion of which elevated the HR significantly (HR = 1.77; 95% CI = 1.11–2.84). In stratified analyses, the significance remained in subgroups of Caucasians (HR = 1.42; 95% CI = 1.11–1.81), and colorectal cancer (HR = 1.77; 95% CI = 1.11–2.84). No publication bias was detected by either the funnel plot or the Egger test (data not shown).

Discussion

In this meta-analysis, we provided evidence of an association between *ERCC1* rs11615C>T and *ERCC2* rs13181T>G SNPs and clinical outcomes of Asian and Caucasian patients with gastric and colorectal cancer, respectively, who were treated by oxaliplatin-based chemotherapy.

Previous studies showed that clinical outcomes, measured as either tumor progression or survival, were better in patients susceptible to higher levels of platinum-induced DNA adducts (23, 24). Resistance to platinum may result from numerous mechanisms (25), among which NER is the predominant mechanism for moderate levels of platinum resistance seen clinically (26). There is evidence that cancer patients with congenital NER mutations are sensitive to platinum treatment and that hypersensitivity of testicular cancer to cisplatin is due to DNA repair deficiency (27, 28). ERCC1 and ERCC2 are two key rate-limiting enzymes in the multistep NER process. ERCC1, in collaboration with the XPF protein, is involved in DNA lesion recognition, whereas ERCC2 is a subunit of human transcriptional initiation factor TFIIH with ATP-dependent helicase activity. Therefore, functional *ERCC1* and *ERCC2* SNPs may contribute directly to phenotypes of drug sensitivity by modifying functions of the related genes and reflect platinum sensitivity as an inborn trait.

Our meta-analysis used objective response, PFS, and OS as primary parameters to assess the influence of NER SNPs on clinical outcomes of oxaliplatin-based chemotherapy because these parameters are intrinsically correlated but not necessarily consistent with one another. Most often, a low objective response rate suggests tumor resistance to the chemotherapeutic regimen and a short PFS and OS is very likely the consequence. However, a high objective response rate may lead to an increased PFS and OS or no survival benefit at all (29), showing the necessity of including all 3 parameters to make a comprehensive assessment. In our meta-analysis, *ERCC1* rs11615 T allele was a biomarker of low objective response, a short PFS, and OS in Asian patients, whereas *ERCC2* rs13181 G allele showed significant or marginally significant association with low objective response, a short PFS, and OS in overall patients, Caucasians, and colorectal cancer subgroups. Although some single studies may have influenced the significance of the pooled results, the association tendency was obvious with or without these studies. The consistent changes of 3 parameters strongly suggested that *ERCC1* rs11615C>T and *ERCC2* rs13181T>G both had an effect on oxaliplatin-based chemotherapy and that objective response could be a useful surrogate of survival in oxaliplatin-treated gastric and colorectal cancer patients.

Our results could be reasonably explained by the biological significance of these 2 SNPs. The rs11615 T

Published OnlineFirst January 28, 2011; DOI:10.1158/1078-0432.CCR-10-2169

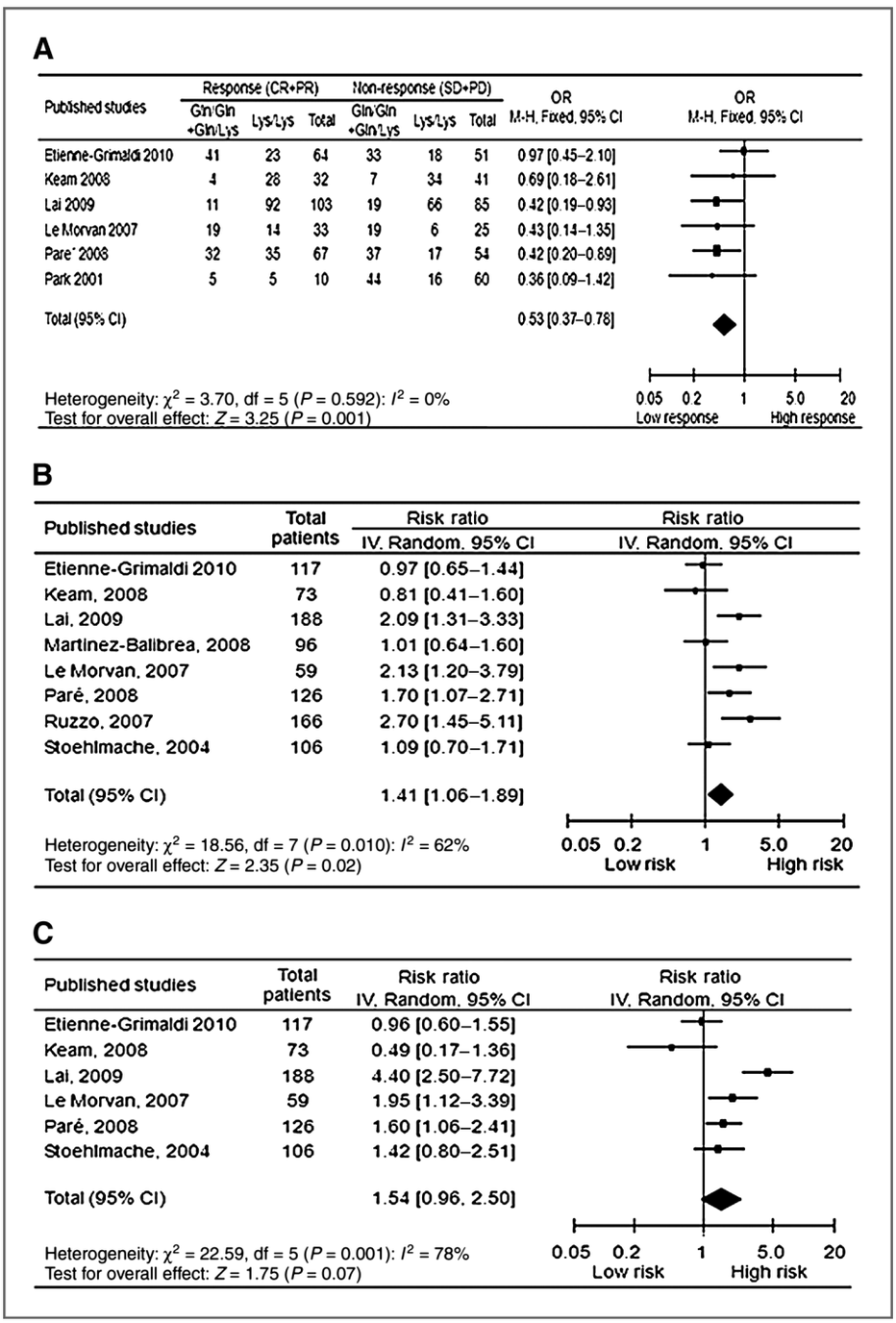

Figure 3. Forest plot of (A) objective response; (B) PFS; and (C) OS in gastric and colorectal cancer patients treated with oxaliplatin-based therapies by *ERCC2* rs13181T>G polymorphism (G/G + G/T vs. T/T, reference group = T/T).

allele of *ERCC1* polymorphism was found to be associated with high mRNA expression of the corresponding gene (30), whereas the rs13181 G allele of *ERCC2* polymorphism was found to be associated with a low number of X-ray–induced chromatid aberrations (8). Functional studies confirmed a substantial influence of the *ERCC1* rs11615C>T and *ERCC2* rs13181T>G SNPs on the phenotype of NER capacity (7, 31, 32), and possessing the TT genotype of *ERCC2* rs13181T>G SNP was associated with the risk of suboptimal DNA repair up to 7-fold, compared with the GG/GT genotypes (8). Hence, patients carrying the *ERCC1* rs11615 T or *ERCC2* rs13181 G allele may have higher DNA repair capacity that could effectively reduce the anticancer effect of oxaliplatin, leading to poor prognosis of these patients.

Notably, there was an apparent ethnic discrepancy in the prognostic values between Asians and Caucasians and statistical test also confirmed the existence of ethnical difference in the estimates of effect for the *ERCC1* rs11615 T

Published OnlineFirst January 28, 2011; DOI:10.1158/1078-0432.CCR-10-2169

allele. As shown in Table 1, there was a remarkably lower prevalence of *ERCC2* rs13181 G allele in Asians than in Caucasians, which might explain the lack of effect of *ERCC2* rs13181T>G SNP in Asian patients. However, it is interesting to find that there was no predictive value of *ERCC1* rs11615C>T SNP in Caucasians, even though the rs11615 T allele was much more common in Caucasians than in Asians. Although the underlying mechanisms are not clear, numerous factors, such as gene–gene interaction from different genetic background and gene–environment interaction from different lifestyles, may have played a role. Additional large studies are warranted to investigate these possibilities.

Despite our efforts to make an accurate and comprehensive analysis, limitations of our meta-analysis need to be addressed. First, some data were excluded from our analysis because of loss of contact (16) or missing data in the original study (33), which could cause some bias in our estimates but was unlikely to change our major conclusions, because Spindler and colleagues showed no association between *ERCC1* rs11615C>T polymorphism and PFS in Caucasians (33) and Liu and colleagues showed no association between *ERCC2* rs13181T>G polymorphism and OS in Asians (16), which were consistent with our findings. Second, most of the included studies were retrospective and differed significantly in study designs. In addition, the frequencies of *ERCC1* rs11615 T and *ERCC2* rs13181 G alleles were also substantially different among patient populations with different ethnicity. All these may have caused wide and significant heterogeneity between studies. 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. However, when only those studies with the available adjusted estimates were used, the conclusions were not significantly changed (data now shown). Fourth, 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. Finally, oxaliplatin is not used as a single compound but in combination with 5-Fu in the regimen, and unfortunately, we were unable to investigate potential gene–gene interactions between NER variants and folate-metabolizing gene variants because of the limited publications available on this topic.

Overall, our meta-analysis showed that *ERCC1* rs11615C>T and *ERCC2* rs13181T>G SNPs might be useful prognostic factors for assessing clinical outcomes of oxaliplatin-based chemotherapies (FOLFOX or XELOX) in gastric and colorectal cancer. However, future prospective studies with large sample sizes and better study designs are required to confirm our findings.

Disclosure of Potential Conflicts of Interest

The authors have declared no conflicts of interest. The contents of the study are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Authors' Contributions

M. Yin, J. Yan, Q. Wei conceived the ideas, conducted literature search, and data collection; E. Martinez-Balibrea, F. Graziano, H-J. Lenz, H-J. Kim, J. Robert, S-A. Im, W-S. Wang, and M-C. Etienne-Grimaldi provided the raw data of their original studies, and all authors contributed to the writing, revising, and approval for final submission.

Acknowledgments

We thank Bhumsuk Keam, Jim Paul, Albert Abad, Denis Smith, Valerie Le Morvan, Dionyssios Katsaros, Nick Thatcher, and Anders Jakobsen for data coordination.

Grant Support

This study was in part supported by the NIH grants R01 CA131274 and R01 ES-011740 (to Q. Wei) and P30 CA016672 (to M. D. Anderson Cancer Center).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received August 12, 2010; revised November 17, 2010; accepted December 3, 2010; published OnlineFirst January 28, 2011.

References

1. Thirion P, Michiels S, Pignon JP, Buyse M, Braud AC, Carlson RW, et al. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: an updated meta-analysis. J Clin Oncol 2004;22:3766–75.
2. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol 2006;24:2903–9.
3. Ajani JA. Evolving chemotherapy for advanced gastric cancer. Oncologist 2005;10 Suppl 3:49–58.
4. Kelly H, Goldberg RM. Systemic therapy for metastatic colorectal cancer: current options, current evidence. J Clin Oncol 2005;23:4553–60.
5. Faivre S, Chan D, Salinas R, Woynarowska B, Woynarowski JM. DNA strand breaks and apoptosis induced by oxaliplatin in cancer cells. Biochem Pharmacol 2003;66:225–37.
6. Reed E. ERCC1 and clinical resistance to platinum-based therapy. Clin Cancer Res 2005;11:6100–2.
7. Yu JJ, Lee KB, Mu C, Li Q, Abernathy TV, Bostick-Bruton F, et al. Comparison of two human ovarian carcinoma cell lines (A2780/CP70 and MCAS) that are equally resistant to platinum, but differ at codon 118 of the ERCC1 gene. Int J Oncol 2000;16:555–60.
8. Lunn RM, Helzlsouer KJ, Parshad R, Umbach DM, Harris EL, Sanford KK, et al. XPD polymorphisms: effects on DNA repair proficiency. Carcinogenesis 2000;21:551–5.
9. Duell EJ, Wiencke JK, Cheng TJ, Varkonyi A, Zuo ZF, Ashok TD, et al. Polymorphisms in the DNA repair genes XRCC1 and ERCC2 and biomarkers of DNA damage in human blood mononuclear cells. Carcinogenesis 2000;21:965–71.
10. Vilmar A, Sorensen JB. Excision repair cross-complementation group 1 (ERCC1) in platinum-based treatment of non-small cell lung cancer with special emphasis on carboplatin: a review of current literature. Lung Cancer 2009;64:131–9.
11. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981;47:207–14.

Published OnlineFirst January 28, 2011; DOI:10.1158/1078-0432.CCR-10-2169

12. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
13. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.
14. Lin DY, Sullivan PF. Meta-analysis of genome-wide association studies with overlapping subjects. Am J Hum Genet 2009;85:862–72.
15. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ 2003;326:219.
16. Liu B, Wei J, Zou Z, Qian X, Nakamura T, Zhang W, et al. Polymorphism of XRCC1 predicts overall survival of gastric cancer patients receiving oxaliplatin-based chemotherapy in Chinese population. Eur J Hum Genet 2007;15:1049–53.
17. Zarate R, Rodriguez J, Bandres E, Patiño-Garcia A, Ponz-Sarvise M, Viudez A, et al. Oxaliplatin, irinotecan and capecitabine as first-line therapy in metastatic colorectal cancer (mCRC): a dose-finding study and pharmacogenomic analysis. Br J Cancer 2010;102:987–94.
18. Han SW, Oh DY, Im SA, Park SR, Lee KW, Song HS, et al. Epidermal growth factor receptor intron 1 CA dinucleotide repeat polymorphism and survival of advanced gastric cancer patients treated with cetuximab plus modified FOLFOX6. Cancer Sci 2010;101:793–9.
19. Monzo M, Moreno I, Navarro A, Ibeas R, Artells R, Gel B, et al. Single nucleotide polymorphisms in nucleotide excision repair genes XPA, XPD, XPG and ERCC1 in advanced colorectal cancer patients treated with first-line oxaliplatin/fluoropyrimidine. Oncology 2007;72:364–70.
20. Paré L, Marcuello E, Altes A, del Río E, Sedano L, Salazar J, et al. Pharmacogenetic prediction of clinical outcome in advanced colorectal cancer patients receiving oxaliplatin/5-fluorouracil as first-line chemotherapy. Br J Cancer 2008;99:1050–5.
21. Chang PM, Tzeng CH, Chen PM, Lin JK, Lin TC, Chen WS, et al. ERCC1 codon 118 C–>T polymorphism associated with ERCC1 expression and outcome of FOLFOX-4 treatment in Asian patients with metastatic colorectal carcinoma. Cancer Sci 2009;100:278–83.
22. Keam B, Im SA, Han SW, Ham HS, Kim MA, Oh DY, et al. Modified FOLFOX-6 chemotherapy in advanced gastric cancer: results of phase II study and comprehensive analysis of polymorphisms as a predictive and prognostic marker. BMC Cancer 2008;8:148.
23. van de Vaart PJ, Belderbos J, de Jong D, Sneeuw KC, Majoor D, Bartelink H, et al. DNA-adduct levels as a predictor of outcome for NSCLC patients receiving daily cisplatin and radiotherapy. Int J Cancer 2000;89:160–6.
24. Reed E, Ozols RF, Tarone R, Yuspa SH, Poirier MC. Platinum-DNA adducts in leukocyte DNA correlate with disease response in ovarian cancer patients receiving platinum-based chemotherapy. Proc Natl Acad Sci U S A 1987;84:5024–8.
25. Stewart DJ. Mechanisms of resistance to cisplatin and carboplatin. Crit Rev Oncol Hematol 2007;63:12–31.
26. Shellard SA, Fichtinger-Schepman AM, Lazo JS, Hill BT. Evidence of differential cisplatin-DNA adduct formation, removal and tolerance of DNA damage in three human lung carcinoma cell lines. Anticancer Drugs 1993;4:491–500.
27. Furuta T, Ueda T, Aune G, Sarasin A, Kraemer KH, Pommier Y. Transcription-coupled nucleotide excision repair as a determinant of cisplatin sensitivity of human cells. Cancer Res 2002;62:4899–902.
28. Kelland LR, Mistry P, Abel G, Freidlos F, Loh SY, Roberts JJ, et al. Establishment and characterization of an *in vitro* model of acquired resistance to cisplatin in a human testicular nonseminomatous germ cell line. Cancer Res 1992;52:1710–6.
29. Oye RK, Shapiro MF. Reporting results from chemotherapy trials. Does response make a difference in patient survival? JAMA 1984;252:2722–5.
30. Park D, Stoehlmacher J, Zhang W, Tsao-Wei D, Groshen S, Lenz HJ. *ERCC1* polymorphism is associated with differential *ERCC1* gene expression. In: ASCO Proceedings. San Francisco, CA: American Association for Cancer Research; 2002.
31. Shi Q, Wang LE, Bondy ML, Brewster A, Singletary SE, Wei Q. Reduced DNA repair of benzo[*a*]pyrene diol epoxide-induced adducts and common XPD polymorphisms in breast cancer patients. Carcinogenesis 2004;25:1695–700.
32. Qiao Y, Spitz MR, Shen H, Guo Z, Shete S, Hedayati M, et al. Modulation of repair of ultraviolet damage in the host-cell reactivation assay by polymorphic XPC and XPD/ERCC2 genotypes. Carcinogenesis 2002;23:295–9.
33. Spindler KL, Andersen RF, Jensen LH, Ploen J, Jakobsen A. EGF61A>G polymorphism as predictive marker of clinical outcome to first-line capecitabine and oxaliplatin in metastatic colorectal cancer. Ann Oncol 2010;21:535–9.
34. Lai JI, Tzeng CH, Chen PM, Lin JK, Lin TC, Chen WS, et al. Very low prevalence of XPD K751Q polymorphism and its association with XPD expression and outcomes of FOLFOX-4 treatment in Asian patients with colorectal carcinoma. Cancer Sci 2009;100:1261–6.
35. Liang J LH, Yao R, Liang H, Wu G. ERCC1 Asn118Asn polymorphism as predictor for cancer response to oxaliplatin-based chemotherapy in patients with advanced colorectal cancer. Chin-German J Clin Oncol 2008;7:455–9.
36. Seo BG, Kwon HC, Oh SY, Lee S, Kim SG, Kim SH, et al. Comprehensive analysis of excision repair complementation group 1, glutathione *S*-transferase, thymidylate synthase and uridine diphosphate glucuronosyl transferase 1A1 polymorphisms predictive for treatment outcome in patients with advanced gastric cancer treated with FOLFOX or FOLFIRI. Oncol Rep 2009;22:127–36.
37. Huang ZH, Hua D, Du X, Li LH, Mao Y, Liu ZH, et al. ERCC1 polymorphism, expression and clinical outcome of oxaliplatin-based adjuvant chemotherapy in gastric cancer. World J Gastroenterol 2008;14:6401–7.
38. Liang J, Jiang T, Yao RY, Liu ZM, Lv HY, Qi WW. The combination of ERCC1 and XRCC1 gene polymorphisms better predicts clinical outcome to oxaliplatin-based chemotherapy in metastatic colorectal cancer. Cancer Chemother Pharmacol 2009;66:493–500.
39. Le Morvan V, Smith D, Laurand A, Brouste V, Bellott R, Soubeyran I, et al. Determination of ERCC2 Lys751Gln and GSTP1 Ile105Val gene polymorphisms in colorectal cancer patients: relationships with treatment outcome. Pharmacogenomics 2007;8:1693–703.
40. Park DJ, Stoehlmacher J, Zhang W, Tsao-Wei DD, Groshen S, Lenz HJ. A Xeroderma pigmentosum group D gene polymorphism predicts clinical outcome to platinum-based chemotherapy in patients with advanced colorectal cancer. Cancer Res 2001;61:8654–8.
41. Chua W, Goldstein D, Lee CK, Dhillon H, Michael M, Mitchell P, et al. Molecular markers of response and toxicity to FOLFOX chemotherapy in metastatic colorectal cancer. Br J Cancer 2009;101:998–1004.
42. Spindler KL, Andersen RF, Jensen LH, Ploen J, Jakobsen A. EGF61A>G polymorphism as predictive marker of clinical outcome to first-line capecitabine and oxaliplatin in metastatic colorectal cancer. Ann Oncol ;21:535–9.
43. Viguier J, Boige V, Miquel C, Pocard M, Giraudeau B, Sabourin JC, et al. ERCC1 codon 118 polymorphism is a predictive factor for the tumor response to oxaliplatin/5-fluorouracil combination chemotherapy in patients with advanced colorectal cancer. Clin Cancer Res 2005;11:6212–7.
44. Ruzzo A, Graziano F, Loupakis F, Rulli E, Canestrari E, Santini D, et al. Pharmacogenetic profiling in patients with advanced colorectal cancer treated with first-line FOLFOX-4 chemotherapy. J Clin Oncol 2007;25:1247–54.
45. Stoehlmacher J, Park DJ, Zhang W, Yang D, Groshen S, Zahedy S, et al. A multivariate analysis of genomic polymorphisms: prediction of clinical outcome to 5-FU/oxaliplatin combination chemotherapy in refractory colorectal cancer. Br J Cancer 2004;91:344–54.
46. Martinez-Balibrea E, Abad A, Aranda E, Sastre J, Manzano JL, Díaz-Rubio E, et al. Pharmacogenetic approach for capecitabine or 5-fluorouracil selection to be combined with oxaliplatin as first-line chemotherapy in advanced colorectal cancer. Eur J Cancer 2008;44:1229–37.
47. Etienne-Grimaldi MC, Milano G, Maindrault-Goebel F, Chibaudel B, Formento JL, Francoual M, et al. Methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms and FOLFOX response in colorectal cancer patients. Br J Clin Pharmacol 2010;69:58–66.