Cancer Chemother Pharmacol (2013) 72:305–314
DOI 10.1007/s00280-013-2194-x

ORIGINAL ARTICLE

Association between GSTP1 Ile105Val polymorphism and oxaliplatin-induced neuropathy: a systematic review and meta-analysis

Zhi Peng · Qianqian Wang · Jing Gao · Zhaoning Ji · Jiajia Yuan · Ye Tian · Lin Shen

Received: 28 February 2013 / Accepted: 11 May 2013 / Published online: 22 May 2013

Abstract
Background and aims The association between glutathione-S-transferase P1 (GSTP1) Ile105Val polymorphism and oxaliplatin-induced neuropathy has been investigated in a number of published studies. However, most of these studies were based on small sample sizes and the results remained inconsistent. To assess the relationship between GSTP1 gene Ile105Val polymorphism and its susceptibility to oxaliplatin-induced neuropathy, a meta-analysis of previous studies was conducted.
Methods Two investigators independently searched studies published up to December 2012 from the databases of PubMed, EMBASE and The Cochrane Library. The pooled effect was calculated as odds ratio (OR) and corresponding 95 % confidence intervals (CIs) using fixed-effect or random-effect model.
Results Twelve prospective trials and two retrospective clinical trials involving 2,191 participants met the inclusion criteria. Combined analyses of these studies showed no significant associations between GSTP1 Ile105Val polymorphism and oxaliplatin-induced neuropathy, yielding OR of 1.08 (95 %CI 0.67–1.74, $P = 0.754$) in dominant model. Similar results were also obtained in recessive model (OR = 1.67, 95 %CI 0.56–4.93, $P = 0.357$) and allelic analysis (OR = 1.22, 95 %CI 0.67–2.24, $P = 0.513$). Since significant heterogeneity across studies, the pooled effects were calculated by random-effect model. No evidence of publication biases was identified in this meta-analysis.
Conclusion This meta-analysis did not support the hypothesis that GSTP1 Ile105Val polymorphism was related to the occurrence of neurotoxicity in oxaliplatin-treated patients. Given the limited number of studies and potential bias, large-scale and well-designed clinical trials should be needed to confirm these hypotheses.

Keywords GSTP1 · Polymorphism · Neuropathy · Meta-analysis

Zhi Peng and Qianqian Wang contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s00280-013-2194-x) contains supplementary material, which is available to authorized users.

Z. Peng · J. Gao · J. Yuan · Y. Tian · L. Shen (✉)
Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Gastrointestinal Oncology, Peking University Cancer Hospital and Institute, FuCheng Road 52, HaiDian District, Beijing 100142, China
e-mail: lin100@medmail.com.cn

Z. Peng · Z. Ji
Department of Medical Oncology, Yijishan Hospital, Wannan Medical College, Wuhu, Anhui, China

Q. Wang
Department of Epidemiology, Beijing Institute of Traumatology and Orthopaedics, Beijing 100035, China

Introduction

Oxaliplatin, or *trans*-L-dach (1R, 2R-diaminocyclohexane) oxalatoplatinum (L-OHP), is a third-generation platinum analog similar to carboplatin and cisplatin [1]. In 1976, this drug was discovered in the Nagoya City University by Yoshinori Kidani, and subsequently it was developed as drug for colorectal cancer treatment [2]. The therapeutic spectrum of oxaliplatin has been extended to other malignancies such as gastric [3], pancreatic [4] and non-small cell lung cancers [5].

Peripheral neuropathy is one of the most frequent and clinically relevant adverse events associated with the use of oxaliplatin [6]. Although there are several approaches to reduce oxaliplatin-induced neuropathy such as stop-and-go strategy, calcium and magnesium infusions, venlafaxine [7], using neuroprotective agents [6], no well-accepted therapy to prevent oxaliplatin-induced neuropathy has been identified [8, 9].

In recent years, the pharmacogenomic approach has been proposed for the identification of people at high risk of development of chemotherapy-induced peripheral neurotoxicity [10]. Genetic variations in drug-targeted genes, or polymorphisms of genes encoding DNA repair enzymes, metabolism, and detoxification pathways may influence the neurotoxicity of oxaliplatin. Some studies have discovered the connection between genetic polymorphisms and oxaliplatin-induced neuropathy, such as ERCC1 C118T [11], GSTP1 Ile105Val [12], AXGT haplotype [13], SCN2A R19K polymorphism [14], ITGB3 L33P [15], polymorphic CAG motif of the SK3 gene [16], ABCC1/2 [17], whereas other polymorphisms such as GSTM1 deletion, ABCB1 Ser893Ala/Thr were not found to be associated with oxaliplatin-induced neuropathy [10]. Up to now, the most studied polymorphism related with oxaliplatin-induced neuropathy is GSTP1 Ile105Val.

The glutathione-S-transferases (GSTs), a superfamily of dimeric phase II metabolic enzymes, play an important role in the cellular defense system. The GST superfamily are divided into six major classes (α, μ, π, θ, ζ and ω) [18]. These enzymes contribute to the inactivation of various toxic compounds (unsaturated aldehydes, quinines, epoxides and hydroperoxides) by forming secondary metabolites during oxidative stress. Cytosolic human GST exhibits genetic polymorphisms which can increase the susceptibility to carcinogenesis and inflammatory diseases [19, 20]. Glutathione-*S*-transferase pi 1(GSTP1) is one member of GST family, known to strongly affect human's susceptibility to several cancers and metabolite detoxification [21].

The gene coding for GSTP1 is located on chromosome 11q13, and the most studied polymorphism of GSTP1 is an A>G substitution in position 313 in exon 5 that gives rise to missense substitution Ile105Val (GSTP1*B alleles, 313A>G, I105V, rs1695) [22]. It is speculated that GSTP1 Ile105Val polymorphism displays a significantly lower enzyme activity, leading to less effective capability of detoxification [23]. Over the past two decades, a number of studies were conducted to investigate the relationship between GSTP1 codon 105 polymorphism and oxaliplatin-induced neuropathy [11–13, 17, 24–33]. However, these studies have reported conflicting results. For example, significant associations between the GSTP1 genotype and oxaliplatin-induced neuropathy were observed in several studies [11, 12, 24, 25, 27, 28, 31, 33], whereas no statistically significant association was found in other studies [12, 13, 17, 26, 29, 30, 32]. This systematic review and meta-analysis was designed to assess existing evidences concerning the clinical effectiveness of GSTP1 Ile105Val and neurotoxicity induced by oxaliplatin in cancer chemotherapy.

Materials and methods

Search strategy and selection criteria

We performed electronic searches of the English-language literatures on GSTP1 polymorphisms and oxaliplatin-induced neuropathy in PubMed, EMBASE and The Cochrane Library using the combined text words "GSTP1" and neuropathy-related words (e.g. neuropathy or neurotoxicity). The latest search was undertaken in December 2012. We also manually screened the reference lists of the retrieved articles to identify other relevant publications.

The including criteria were the followings: (1) they must be clinical researches; (2) the exposure of interest included GSTP1 Ile105Val; (3) the outcome of interest included oxaliplatin-induced neurotoxicity; and (4) the studies provided the numbers of patients with and without neurotoxicity in different genotypes. Studies that were published as reviews or involved children (<18 years) were excluded from analysis.

Based on clinical relevance, the primary endpoint was defined as the incidence of grade ≥2 neurotoxicity in OSS or grade ≥3 neurotoxicity in NCI-CTC (in OSS, grade 2 indicates moderate motor symptoms and sensory symptoms extended to ankle and wrist, and grade 3 indicates motor symptoms requiring help/assistance and sensory symptoms extended to knee and elbow; in NCI-CTC, grade ≥3 indicates sensory alteration or paresthesia interfering with activity of daily living (ADL), disabling or death).

Data extraction

Two investigators (Peng and Wang) independently did the search and data extraction. Any discrepancies were resolved by discussion. The following data elements were extracted from each study: first author, year of publication, racial descent, design of the study, source of population, sample size, mean age and gender percentage of cases and controls, type of tumors, chemotherapy regiments, oxaliplatin dosages, neuropathy criteria, genotype frequencies and genotyping methods.

Statistical analysis

In view of unknowing exact genetic model for the polymorphism, we examined contrasts for dominant model

(assuming heterozygotes have the same increased risk as minor homozygous genotypes), as well as recessive model (only minor homozygous genotype having the effect) and allele frequencies (the minor allele frequency vs. the major allele frequency). The effect of associations was estimated as odds ratio (OR) with the corresponding 95 % confidence intervals (CI). Firstly, fixed-effect model was used for calculating pooled ORs. If there was significant heterogeneity across studies, random-effect model was selected. The existence of heterogeneity between studies was evaluated using the Dersimonian and Laird's Q test [34]. I^2 was used to quantify heterogeneity; this measure describes the percentage of the observed between-study variability attributable to heterogeneity rather than chance. I^2 takes values between 0 and 100 %. Important heterogeneity was defined while $I^2 > 50$ % [35].

We used sensitivity analysis in which each study was excluded once at a time to examine the influence of one study on the overall summary estimate. In order to investigate the source of heterogeneity, studies were subdivided by ethnicity (Caucasian, including Caucasian of European origin; East Asian, including Chinese, Japanese, Korean), dosage ($\leq$85 mg/m^2 or >85 mg/m^2) and the criteria for evaluating the oxaliplatin-induced toxicity (NCI-CTC or OSS) for subgroup analysis. We also used meta-regression to examine the effect of study-level predictor variables such as study design and mean age of study population on the effect size.

Publication bias was evaluated using inverted funnel plot and Egger's test [36]. All analyses were carried out using Stata software (version 9.0). All P values were two-sided and the significance level was 0.05.

Results

Study characteristics

Three hundred and one studies were identified from online databases and the reference lists, of which 14 studies involving 2,191 patients (1,354 men and 837 women) were in accordance with the inclusive criteria and included in meta-analysis (Fig. 1). The characteristics of the studies are listed in Table 1. Individuals involved in these 14 studies received oxaliplatin-based chemotherapy regimens in terms of FOLFOX4, FOLFOX6, mFOLFOX6, FLOFOX7, CAPOX, IROX, oxaliplatin plus S1, FLO or FLP. All of these patients had not received oxaliplatin or other platinum agents previously. Sample size ranged from 51 to 520. Five trials were conducted in Asians [11, 24, 25, 27, 29] and the other 9 studies in Caucasians [12, 13, 17, 26, 28, 30–33]. Twelve trials were designed to be prospective and the other two studies to be retrospective [11, 12]. The mean age of patients ranged from 55 to 68. The patients of ten trials were mCRC, and the others were patients with advanced gastric cancer [24, 31], gastrointestinal solid tumors [12] or advanced carcinomas [13]. Single chemotherapy regimen was applied in 12 trials while more than 3 regimens in the other 2 trials [12, 28]. Oxaliplatin dosage included 85 mg/m^2/day biweekly, 100 mg/m^2/day biweekly, 130 mg/m^2/day biweekly and 130 mg/m^2/day every 3 weeks. The patients of 12 trials received the same oxaliplatin dose, while the dose varied among patients in the other one trial [12]. Eight trials [11, 13, 25, 27, 28, 30–32] applied National Cancer Institute Common Toxicity Criteria (NCI-CTC) to evaluate the neurotoxicity, while other six studies [12, 17, 24, 26, 29, 33] depending on oxaliplatin-specific scale (OSS).

Two oxaliplatin-containing regimens in McLeod's [28] and Boige's [32] studies were separated into 2 independent trials for analysis. We also analyzed the patients experiencing acute and chronic neuropathy as two separated samples in Gamelin's study [13].

Quality assessment

The use of quality scoring system in meta-analyses of observational studies is controversial [37]. We did not assign a single grade or score to represent the quality of a study. Instead, we focused on certain items that were reflective of methodological and reporting quality of the studies. Study year, country, race, study design, source of population, number of patients, age, type of tumors, chemotherapy regimens, oxaliplatin dose/schedule and grade criteria were considered in our evaluation of the quality of an included study (Table 1).

The role of GSTP1 polymorphism on oxaliplatin-induced neuropathy

GSTP1 AA or AG versus GG

All of 14 included trials reported the relevant data for the comparison of the risk of severe oxaliplatin-induced neuropathy between patients with GSTP1 AA or AG genotype and those with GSTP1 GG genotype. We did not find significant associations between GSTP1 G allele and the risk of oxaliplatin-induced neuropathy in dominant model (OR = 1.08, 95 %CI 0.67–1.74, $P = 0.754$). Statistical significance of heterogeneity was detected across all studies ($I^2 = 67.9$ %, $P < 0.05$). We carried out influence analyses to explore the source of heterogeneity. The results were not significantly affected by the removal of any study (supplement Fig. 1), and we failed to find out the source of heterogeneity after subgroup analysis where the studies were stratified by study characteristics, such as ethnicity,

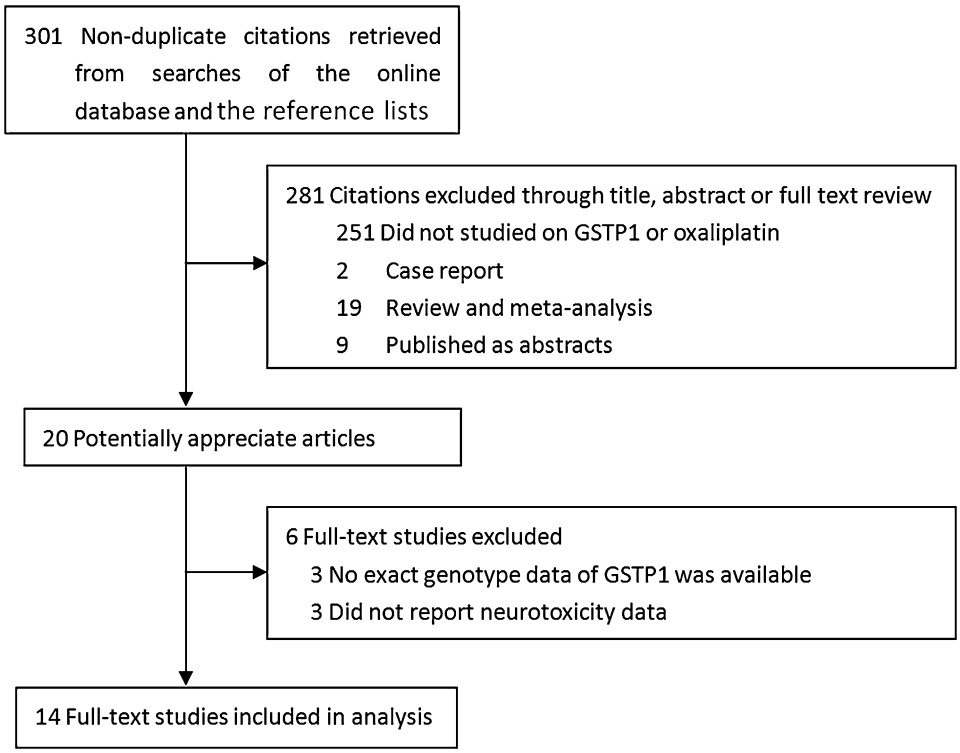

Fig. 1 Study selection process for the meta-analysis of GSTP1 Ile105Val polymorphism and oxaliplatin-induced neuropathy

dosage of oxaliplatin, the grade criteria (Table 2) and meta-regression analysis (data not shown) (Fig. 2).

GSTP1 AA versus AG or GG

There were seven clinical trials for these analyses. The risk of severe neuropathy was not significantly different between patients with GSTP1 AA genotype and those with AG or GG genotype (OR = 1.67, 95 %CI 0.56–4.93, $P = 0.357$). There was significant heterogeneity between studies ($I^2 = 59.7$ %, $P < 0.05$) (Fig. 3). However, no statistical heterogeneity was detected in the patients received >85 mg/m^2 dosage of oxaliplatin, although the risk was similar to the original result (OR = 0.58, 95 %CI 0.12–2.72, $P = 0.951$) (Table 2).

GSTP1 A allele versus G allele

We compared the risk of oxaliplatin-induced neuropathy between GSTP1 A allele and G allele in seven trials including 1,043 patients. There were also no significant differences between the two groups (OR = 1.22, 95 %CI 0.67–2.24, $P = 0.513$). Heterogeneity was statistically significant across studies ($I^2 = 73.6$ %, $P < 0.05$). No statistical heterogeneity was detected in the subgroup of studies using NCI-CTC criteria, and the result did not change materially (OR = 1.12, 95 %CI 0.71–1.76, $P = 0.636$) (Table 2; Fig. 4).

Publication bias

For publication bias estimating, we did not observe visually or statistically significant asymmetry according to the inverted funnel plot (supplement Fig. 2) and Egger's test in all analyses (data not shown).

Discussion

Present study is the first meta-analysis examining the effect of GSTP1 Ile105Val polymorphism on the risk of oxaliplatin-induced neuropathy. Fourteen articles including 2,191 patients were used for final analysis. There was no evidence supporting the hypothesis that the GSTP1 Ile105Val polymorphism is significantly associated with oxaliplatin-induced neuropathy.

GSTP1 is directly involved in the detoxification of cisplatin by the formation of cisplatin–glutathione adducts, indicating that GSTP1 plays a role in the acquisition of resistance to this platinum compound [38, 39]. Amino acid 105 of GSTP1 lies in close proximity to the active center and may directly influence GSTP1's catalytic activity. The Val allele causes a variant GSTP1 protein with a lower enzymatic capacity for the conjugation of various cytotoxic drugs as compared to the wild-type Ile allele [22, 40]. However, the precise mechanism has not been well clarified yet. Kweekel et al. [30] summarized two theories

Table 1 Main characteristics of clinical trials included in meta-analysis

References	Years	Country	Race	Study design	Source of population	No. of patient (male/female)	Age (mean or median)	Type of tumors	Chemotherapy regiments	Oxaliplatin dose (mg/m^2)/schedule	Grade criteria
Li et al. [24]	2010	China	Asian	Prospective	Single center	89 (64/25)	55	Advanced gastric cancer	Oxaliplatin plus 5-FU	85/biweekly	OSS
Chen et al. [25]	2009	Taiwan	Asian	Prospective	NR	166 (104/62)	>50	Unresectable metastatic CRC	FOLFOX-4	85/biweekly	NCI-CTC
Pare et al. [26]	2008	Spain	Caucasian	Prospective	NR	126 (81/45)	66	Metastatic CRC	mFOLFOX6	85/biweekly	OSS
Hong et al. [27]	2011	Korea	Asian	Prospective	Multicenter	52 (37/15)	63	Metastatic CRC	Oxaliplatin plus S-1	85/biweekly	NCI-CTC
McLeod et al. [28]	2010	Canada	Caucasian	Prospective	Multicenter	520 (306/214)	61	Metastatic CRC	FOLFOX or IROX	85/biweekly	NCI-CTC
Kanai et al. [29]	2010	Japan	Asian	Prospective	Multicenter	82 (51/31)	64	Colorectal cancer	mFOLFOX6	85/biweekly	OSS
Lecomte et al. [12]	2006	France	Caucasian	Retrospective	Single center	90 (52/38)	64	Gastrointestinal solid tumors	FOLFOX4 or FOLFOX7 or FOLFOX6 or GEMOX or TOMOX	85–130/biweekly	OSS
Kweekel et al. [30]	2008	Netherlands	Caucasian	Prospective	Multicenter	91 (57/34)	61	Advanced CRC	CAPOX	130/every 3 weeks	NCI-CTC
Goekkurt et al. [31]	2009	Germany	Caucasian	Prospective	Multicenter	134 (92/42)	64	Advanced gastric cancer	FLO or FLP	85/biweekly or 50/biweekly	NCI-CTC
Boige et al. [32]	2010	France	Caucasian	Prospective	Multicenter	345 (214/131)	68	Metastatic CRC	FOLFOX6	100/biweekly	NCI-CTC
Ruzzo et al. [33]	2007	Italy	Caucasian	Prospective	Multicenter	166 (87/79)	66	Advanced CRC	FOLFOX4	85/biweekly	OSS
Gamelin et al. [13]	2007	France	Caucasian	Prospective	Multicenter	135 (93/42)	62	Advanced carcinomas	FOLFOX	85/biweekly	NCI-CTC
Cecchin et al. [17]	2012	Italy	Caucasian	Prospective	Multicenter	144 (82/62)	59	CRC	FOLFOX4	85/biweekly	OSS
Inada et al. [11]	2007	Japan	Asian	Retrospective	Single center	51 (34/17)	65	Colorectal cancer	mFOLFOX-6	85/biweekly	NCI-CTC

NR not report, *CRC* colorectal cancer, *NCI-CTC* National Cancer Institute Common Toxicity Triteria, *OSS* oxaliplatin-specific scale, *5-FU* 5-fluorouracil, *FOLFOX* oxaliplatin plus 5-FU and leucovorin, *IROX* irinotecan plus oxaliplatin, *GEMOX* oxaliplatin and gemcitabine, *TOMOX* oxaliplatin plus raltitrexed, *CAPOX* capecitabine plus oxaliplatin, *FLO* fluorouracil, leucovorin and oxaliplatin, *FLP* fluorouracil, leucovorin and cisplatin

Table 2 Effect of GSTP1 Ile105Val polymorphism on oxaliplatin-induced neuropathy by prespecified study characteristics in different genetic model

Compared genotypes of GSTP1	No. of trials	OR (95 %CIs)	*P* value	Test for heterogeneity	
				I^2	*P* value
AG + GG versus AA					
Race					
Asian	5	1.64 (0.56, 4.75)	0.334	78.8	0.004
Caucasian	12	0.87 (0.47, 1.60)	0.650	60.9	0.001
Dosage					
≤85	13	1.07 (0.54, 2.13)	0.846	75.0	<0.001
>85	4	0.97 (0.32, 2.92)	0.963	63.4	0.042
Criteria					
NCI-CTC	11	1.25 (0.66, 2.36)	0.494	63.6	0.003
OSS	6	0.77 (0.24, 2.49)	0.665	81.0	<0.001
GG versus AG + AA					
Dosage					
≤85	5	2.59 (0.62, 10.78)	0.191	74.6	0.003
>85	4	0.58 (0.12, 2.72)	0.489	0.0	0.951
Criteria					
NCI-CTC	6	1.25 (0.59, 2.69)	0.560	0.0	0.984
OSS	3	2.41 (0.06, 74.89)	0.616	84.5	0.002
G allele versus A allele					
Dosage					
≤85	5	1.48 (0.67, 3.26)	0.336	80.2	<0.001
>85	4	0.88 (0.31, 2.52)	0.817	65.7	0.033
Criteria					
NCI-CTC	6	1.12 (0.71, 1.76)	0.636	30.9	0.204
OSS	3	1.39 (0.25, 7.58)	0.706	89.2	<0.001

NCI-CTC National Cancer Institute Common Toxicity Criteria, *OSS* oxaliplatin-specific scale, *OR* odds ratio, *CI* confidence interval

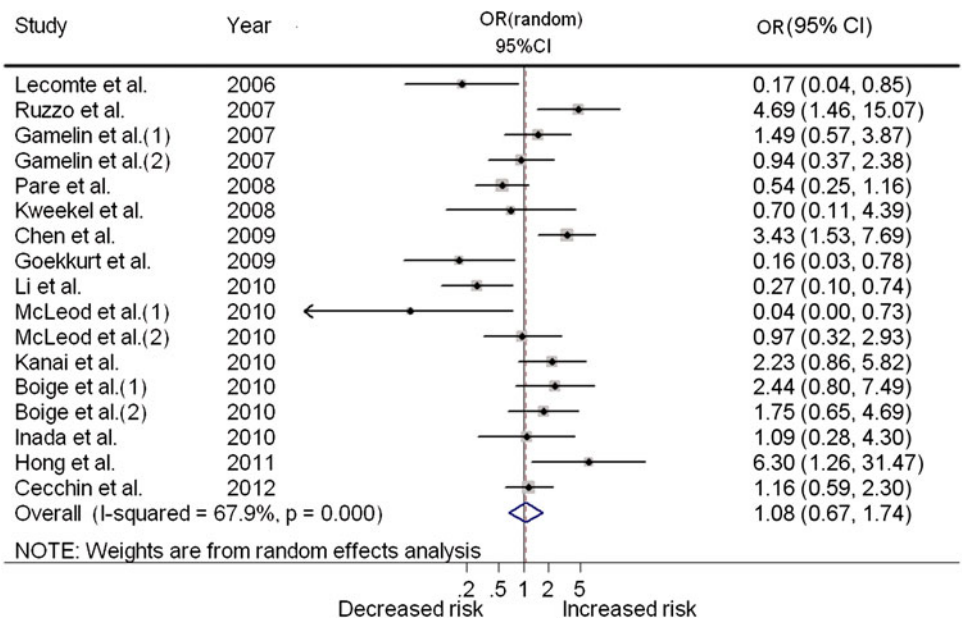

Fig. 2 Meta-analysis for the relationship between GSTP1 Ile105Val polymorphism and oxaliplatin-induced neuropathy risk in dominant model. Dominant model (AA or AG vs. GG). Year represents publish year. The *solid squares* represent odds ratios (ORs) from individual studies; the *diamonds* are shown as overall effect

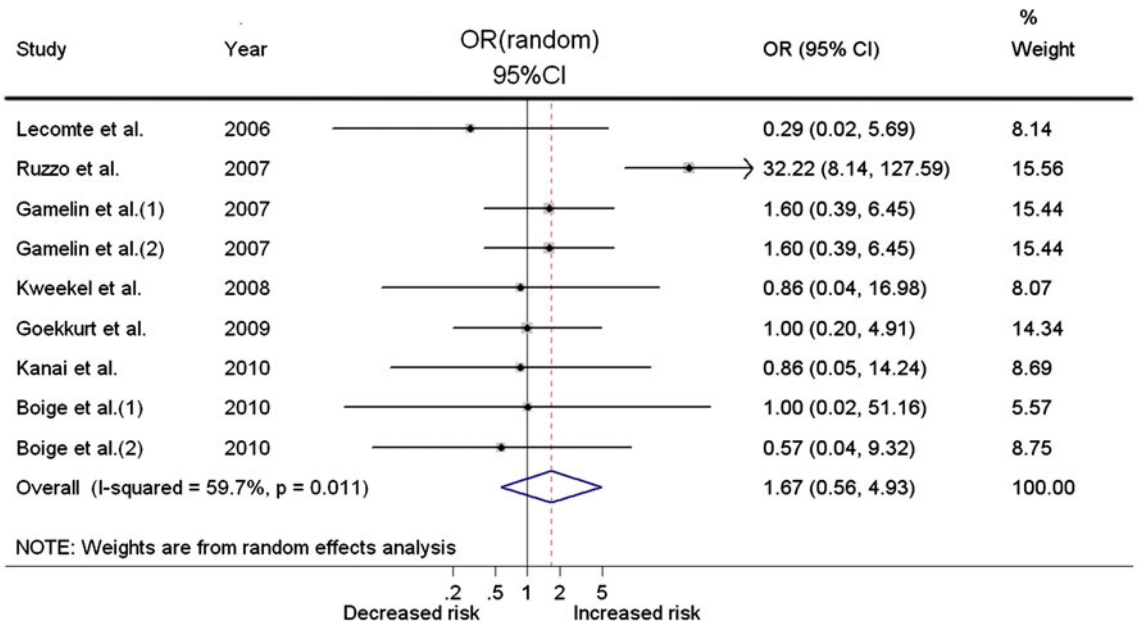

Fig. 3 Meta-analysis for the relationship between GSTP1 Ile105Val polymorphism and oxaliplatin-induced neuropathy risk in recessive model. Recessive model (AA vs. AG or GG). Year represents publish year. The *solid squares* represent odds ratios (ORs) from individual studies; the *diamonds* are shown as overall effect

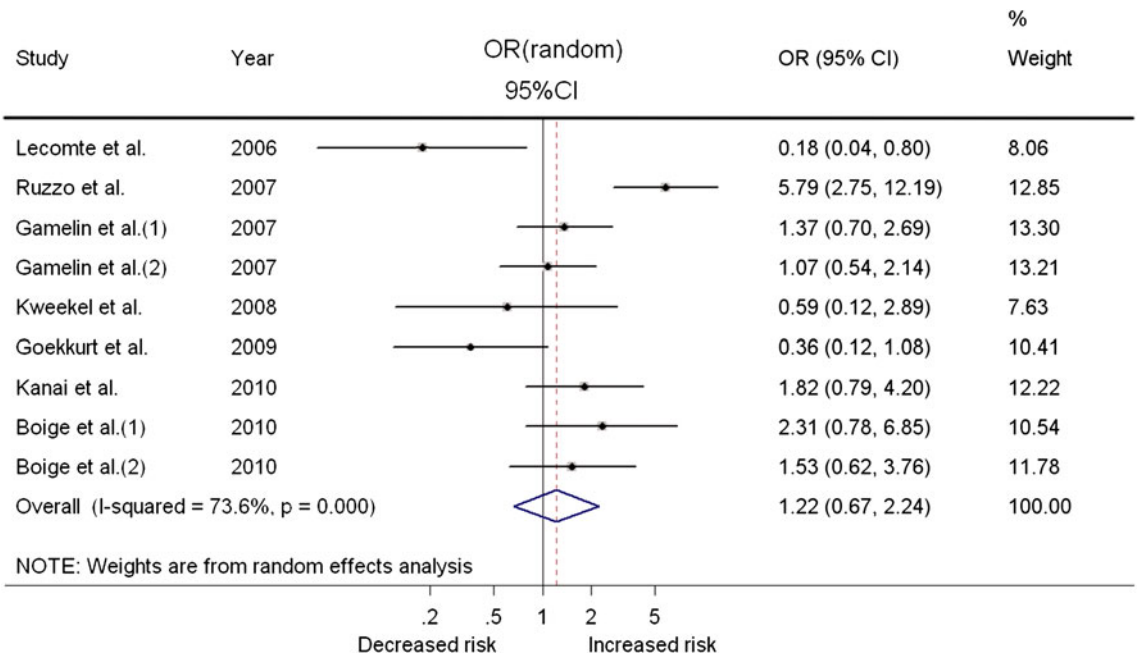

Fig. 4 Meta-analysis for the relationship between GSTP1 Ile105Val polymorphism and oxaliplatin-induced neuropathy risk in allelic analysis. Allele model (A allele vs. G allele). Year represents publish year. The *solid squares* represent odds ratios (ORs) from individual studies; the *diamonds* are displayed as overall effect

postulated to explain the association between the GSTP1 Ile105Val polymorphism and oxaliplatin-induced neuropathy. Firstly, previous studies indicated that the Ile105Val polymorphism decreased the substrate affinity of the GSTP1 enzyme [22]. The protective effect of GSTP1*G allele on platinum may result in a lower incidence of neurotoxicity in Val/Val carriers [23]. Secondly, GSTP1*A reduces cellular proliferation and protects against apoptosis through a JNK-independent mechanism. In contrast, GSTP1*G did not influence cellular proliferation but

protected cells from apoptosis through JNK-mediated mechanisms, which are involved in protecting the cells from platinum-induced toxicity [41]. In addition, Mir et al. [42] discovered a significant correlation between GSTP1 105Ile/105Ile genotype and the occurrence of grade ≥ 2 docetaxel-induced peripheral neuropathy (DIPN). These findings strongly suggested 105Ile/105Ile variants playing a role of oxidative stress in the pathophysiology of DIPN. However, which signaling pathway or additional pathway is more important for the pathophysiologic effects is still not well known. And the results of our study also did not contribute to explaining the pathophysiologic effects of GSTP1 Ile105Val polymorphism and oxaliplatin-induced neuropathy. It might be explained by the fact that the effect of a gene polymorphism depends on its complicated genetic background, and expression of compensatory functions of other genes or proteins could mask the effect of one GSTP1 mutation [21].

The difference of criteria used to evaluate oxaliplatin-induced neuropathy may partly account for the result. There is a wide discrepancy in the literature on how to measure and grade oxaliplatin-induced neuropathy, such as NCI-CTC, Total Neuropathy Score (TNS), Eastern Cooperative Oncology Group (ECOG) toxicity criteria, OSS and criteria from individual studies or World Health Organization [6]. Most clinical trials evaluated oxaliplatin-induced neuropathy based on NCI-CTC or OSS criteria. However, after subgroup analysis by different criteria, no significant association between GSTP1 Ile105Val polymorphism and oxaliplatin-induced neuropathy was observed in both NCI-CTC and OSS groups (Fig. 4).

Some limitations of this meta-analysis must be considered. Firstly, extreme heterogeneity was still observed between studies although we performed subgroup analysis stratified by study characteristics, such as ethnicity, dosage of oxaliplatin, the grade criteria and meta-regression analyses. Since the limited detailed presented data in the included studies, other potential confounding effects such as selection bias, population stratification, population-specific gene–gene or gene–environment interaction, genotyping errors or chance that might be contributable to the source of heterogeneity across studies were not well examined [43]. Secondly, oxaliplatin-induced neuropathy is usually cumulative. More cycles of chemotherapy and more doses of oxaliplatin might account for a higher incidence of severe neuropathy after treatment with oxaliplatin. Chen et al. [25] found that the statistically significant only shows after 12 cycles but not after 4 or 8 cycles. Whereas due to limited data, we were unable to further examine the effect of cycles of chemotherapy on the association between GSTP1 and neuropathy. Thirdly, oxaliplatin dosage was an important factor to be considered. Although study-level dosage of oxaliplatin was extracted from each study and was used for subgroup and meta-regression analyses, individual-level was more influential on the relationship, which was not available. Fourthly, the neurotoxicity induced by oxaliplatin can manifest as two distinct syndromes: a transient, acute syndrome that can appear during or shortly after infusion, and a dose-limiting, cumulative sensory neuropathy [44]. In this meta-analysis, there was only one study that separated into two samples based on acute or chronic neuropathy. However, the result did not change materially after we included the patients with acute neuropathy or not (data not shown).

In conclusion, this is the first meta-analysis to examine the effect of GSTP1 Ile105Val polymorphism on the risk of oxaliplatin-induced neuropathy. No significant association between the GSTP1 Ile105Val polymorphism and the risk of oxaliplatin-induced neuropathy was identified in the present study. Given the limited number of studies and potential bias, large-scale and well-designed, controlled clinical trials will be required to confirm these hypotheses.

Acknowledgments This work was supported by Beijing Municipal Science and Technology Commission (D0905001040631), Anhui Natural Science Foundation (10040606Q67), Natural Science Foundation of Department of Education, Anhui Province (KJ2010B244).

Conflict of interest The authors declare no conflicts of interest.

References

1. Raymond E, Chaney SG, Taamma A, Cvitkovic E (1998) Oxaliplatin: a review of preclinical and clinical studies. Ann Oncol 9(10):1053–1071
2. Stein A, Arnold D (2012) Oxaliplatin: a review of approved uses. Expert Opin Pharmacother 13(1):125–137
3. Price TJ, Shapiro JD, Segelov E, Karapetis CS, Pavlakis N, Van Cutsem E, Shah MA, Kang YK, Tebbutt NC (2011) Management of advanced gastric cancer. Expert Rev Gastroenterol Hepatol 6(2):199–208 (quiz 209)
4. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardiere C, Bennouna J, Bachet JB, Khemissa-Akouz F, Pere-Verge D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M (2011) FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364(19):1817–1825
5. Mir O, Boudou-Rouquette P, Giroux J, Chapron J, Alexandre J, Gibault L, Ropert S, Coriat R, Durand JP, Burgel PR, Dusser D, Goldwasser F (2012) Pemetrexed, oxaliplatin and bevacizumab as first-line treatment in patients with stage IV non-small cell lung cancer. Lung Cancer 77(1):104–109
6. Weickhardt A, Wells K, Messersmith W (2011) Oxaliplatin-induced neuropathy in colorectal cancer. J Oncol 2011:201593
7. Durand JP, Deplanque G, Montheil V, Gornet JM, Scotte F, Mir O, Cessot A, Coriat R, Raymond E, Mitry E, Herait P, Yataghene Y, Goldwasser F (2012) Efficacy of venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity: results of EFFOX, a randomized, double-blind, placebo-controlled phase III trial. Ann Oncol 23(1):200–205

8. Hoff PM, Saad ED, Costa F, Coutinho AK, Caponero R, Prolla G, Gansl RC (2012) Literature review and practical aspects on the management of oxaliplatin-associated toxicity. Clin Colorectal Cancer 11(2):93–100
9. Grothey A (2005) Clinical management of oxaliplatin-associated neurotoxicity. Clin Colorectal Cancer 5(Suppl 1):S38–S46
10. Cavaletti G, Alberti P, Marmiroli P (2011) Chemotherapy-induced peripheral neurotoxicity in the era of pharmacogenomics. Lancet Oncol 12(12):1151–1161
11. Inada M, Sato M, Morita S, Kitagawa K, Kawada K, Mitsuma A, Sawaki M, Fujita K, Ando Y (2010) Associations between oxaliplatin-induced peripheral neuropathy and polymorphisms of the ERCC1 and GSTP1 genes. Int J Clin Pharmacol Ther 48(11): 729–734
12. Lecomte T, Landi B, Beaune P, Laurent-Puig P, Loriot MA (2006) Glutathione S-transferase P1 polymorphism (Ile105Val) predicts cumulative neuropathy in patients receiving oxaliplatin-based chemotherapy. Clin Cancer Res 12(10):3050–3056
13. Gamelin L, Capitain O, Morel A, Dumont A, Traore S, le Anne B, Gilles S, Boisdron-Celle M, Gamelin E (2007) Predictive factors of oxaliplatin neurotoxicity: the involvement of the oxalate outcome pathway. Clin Cancer Res 13(21):6359–6368
14. Argyriou AA, Antonacopoulou AG, Scopa CD, Kottorou A, Kominea A, Peroukides S, Kalofonos HP (2009) Liability of the voltage-gated sodium channel gene SCN2A R19K polymorphism to oxaliplatin-induced peripheral neuropathy. Oncology 77(3–4): 254–256
15. Antonacopoulou AG, Argyriou AA, Scopa CD, Kottorou A, Kominea A, Peroukides S, Kalofonos HP (2010) Integrin beta-3 L33P: a new insight into the pathogenesis of chronic oxaliplatin-induced peripheral neuropathy? Eur J Neurol 17(7):963–968
16. Basso M, Modoni A, Spada D, Cassano A, Schinzari G, Lo Monaco M, Quaranta D, Tonali PA, Barone C (2011) Polymorphism of CAG motif of SK3 gene is associated with acute oxaliplatin neurotoxicity. Cancer Chemother Pharmacol 67(5): 1179–1187
17. Cecchin E, D'Andrea M, Lonardi S, Zanusso C, Pella N, Errante D, De Mattia E, Polesel J, Innocenti F, Toffoli G (2012) A prospective validation pharmacogenomic study in the adjuvant setting of colorectal cancer patients treated with the 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX4) regimen. Pharmacogenomics J [Epub ahead of print]
18. Hayes JD, Flanagan JU, Jowsey IR (2005) Glutathione transferases. Annu Rev Pharmacol Toxicol 45:51–88
19. Di Pietro G, Magno LA, Rios-Santos F (2010) Glutathione S-transferases: an overview in cancer research. Expert Opin Drug Metab Toxicol 6(2):153–170
20. McIlwain CC, Townsend DM, Tew KD (2006) Glutathione S-transferase polymorphisms: cancer incidence and therapy. Oncogene 25(11):1639–1648
21. Vasieva O (2011) The many faces of glutathione transferase pi. Curr Mol Med 11(2):129–139
22. Watson MA, Stewart RK, Smith GB, Massey TE, Bell DA (1998) Human glutathione S-transferase P1 polymorphisms: relationship to lung tissue enzyme activity and population frequency distribution. Carcinogenesis 19(2):275–280
23. Ishimoto TM, Ali-Osman F (2002) Allelic variants of the human glutathione S-transferase P1 gene confer differential cytoprotection against anticancer agents in Escherichia coli. Pharmacogenetics 12(7):543–553
24. Li QF, Yao RY, Liu KW, Lv HY, Jiang T, Liang J (2010) Genetic polymorphism of GSTP1: prediction of clinical outcome to oxaliplatin/5-FU-based chemotherapy in advanced gastric cancer. J Korean Med Sci 25(6):846–852
25. Chen YC, Tzeng CH, Chen PM, Lin JK, Lin TC, Chen WS, Jiang JK, Wang HS, Wang WS (2009) Influence of GSTP1 I105V polymorphism on cumulative neuropathy and outcome of FOLFOX-4 treatment in Asian patients with colorectal carcinoma. Cancer Sci 101(2):530–535
26. Pare L, Marcuello E, Altes A, del Rio E, Sedano L, Salazar J, Cortes A, Barnadas A, Baiget M (2008) Pharmacogenetic prediction of clinical outcome in advanced colorectal cancer patients receiving oxaliplatin/5-fluorouracil as first-line chemotherapy. Br J Cancer 99(7):1050–1055
27. Hong J, Han SW, Ham HS, Kim TY, Choi IS, Kim BS, Oh DY, Im SA, Kang GH, Bang YJ, Kim TY (2011) Phase II study of biweekly S-1 and oxaliplatin combination chemotherapy in metastatic colorectal cancer and pharmacogenetic analysis. Cancer Chemother Pharmacol 67(6):1323–1331
28. McLeod HL, Sargent DJ, Marsh S, Green EM, King CR, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Thibodeau SN, Grothey A, Morton RF, Goldberg RM (2010) Pharmacogenetic predictors of adverse events and response to chemotherapy in metastatic colorectal cancer: results from North American Gastrointestinal Intergroup Trial N9741. J Clin Oncol 28(20): 3227–3233
29. Kanai M, Yoshioka A, Tanaka S, Nagayama S, Matsumoto S, Nishimura T, Niimi M, Teramukai S, Takahashi R, Mori Y, Kitano T, Ishiguro H, Yanagihara K, Chiba T, Fukushima M, Matsuda F (2010) Associations between glutathione S-transferase pi Ile105Val and glyoxylate aminotransferase Pro11Leu and Ile340Met polymorphisms and early-onset oxaliplatin-induced neuropathy. Cancer Epidemiol 34(2):189–193
30. Kweekel DM, Gelderblom H, Antonini NF, Van der Straaten T, Nortier JW, Punt CJ, Guchelaar HJ (2009) Glutathione-S-transferase pi (GSTP1) codon 105 polymorphism is not associated with oxaliplatin efficacy or toxicity in advanced colorectal cancer patients. Eur J Cancer 45(4):572–578
31. Goekkurt E, Al-Batran SE, Hartmann JT, Mogck U, Schuch G, Kramer M, Jaeger E, Bokemeyer C, Ehninger G, Stoehlmacher J (2009) Pharmacogenetic analyses of a phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil and leucovorin plus either oxaliplatin or cisplatin: a study of the arbeitsgemeinschaft internistische onkologie. J Clin Oncol 27(17): 2863–2873
32. Boige V, Mendiboure J, Pignon JP, Loriot MA, Castaing M, Barrois M, Malka D, Tregouet DA, Bouche O, Le Corre D, Miran I, Mulot C, Ducreux M, Beaune P, Laurent-Puig P (2010) Pharmacogenetic assessment of toxicity and outcome in patients with metastatic colorectal cancer treated with LV5FU2, FOLFOX, and FOLFIRI: FFCD 2000–05. J Clin Oncol 28(15):2556–2564
33. Ruzzo A, Graziano F, Loupakis F, Rulli E, Canestrari E, Santini D, Catalano V, Ficarelli R, Maltese P, Bisonni R, Masi G, Schiavon G, Giordani P, Giustini L, Falcone A, Tonini G, Silva R, Mattioli R, Floriani I, Magnani M (2007) Pharmacogenetic profiling in patients with advanced colorectal cancer treated with first-line FOLFOX-4 chemotherapy. J Clin Oncol 25(10):1247–1254
34. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7(3):177–188
35. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560
36. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315(7109):629–634
37. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25(9):603–605
38. Townsend DM, Tew KD (2003) The role of glutathione-S-transferase in anti-cancer drug resistance. Oncogene 22(47): 7369–7375
39. Goto S, Iida T, Cho S, Oka M, Kohno S, Kondo T (1999) Overexpression of glutathione S-transferase pi enhances the

adduct formation of cisplatin with glutathione in human cancer cells. Free Radic Res 31(6):549–558
40. Zhong SL, Zhou SF, Chen X, Chan SY, Chan E, Ng KY, Duan W, Huang M (2006) Relationship between genotype and enzyme activity of glutathione S-transferases M1 and P1 in Chinese. Eur J Pharm Sci 28(1–2):77–85
41. Holley SL, Fryer AA, Haycock JW, Grubb SE, Strange RC, Hoban PR (2007) Differential effects of glutathione S-transferase pi (GSTP1) haplotypes on cell proliferation and apoptosis. Carcinogenesis 28(11):2268–2273
42. Mir O, Alexandre J, Tran A, Durand JP, Pons G, Treluyer JM, Goldwasser F (2009) Relationship between GSTP1 Ile(105)Val polymorphism and docetaxel-induced peripheral neuropathy: clinical evidence of a role of oxidative stress in taxane toxicity. Ann Oncol 20(4):736–740
43. Zintzaras E, Ioannidis JP (2005) Heterogeneity testing in meta-analysis of genome searches. Genet Epidemiol 28(2):123–137
44. Saif MW, Reardon J (2005) Management of oxaliplatin-induced peripheral neuropathy. Ther Clin Risk Manag 1(4):249–258