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Glutathione-S-transferase pi (GSTP1) codon 105 polymorphism is not associated with oxaliplatin efficacy or toxicity in advanced colorectal cancer patients

Dina M. Kweekel[a,*], *Hans Gelderblom*[b], *Ninja F. Antonini*[c], *Tahar Van der Straaten*[a], *Johan W.R. Nortier*[b], *Cornelis J.A. Punt*[d], *Henk-Jan Guchelaar*[a]

[a]*Leiden University Medical Center (LUMC), Department of Clinical Pharmacy and Toxicology (L-0-P), Albinusdreef 2, 2300 RC Leiden, The Netherlands*
[b]*Department of Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands*
[c]*Biometrics Department, Netherlands Cancer Institute (NKI), Amsterdam, The Netherlands*
[d]*Department of Oncology, University Nijmegen Medical Center, Nijmegen, The Netherlands*

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ABSTRACT

Purpose: Oxaliplatin is detoxified by conjugation to glutathione via the enzyme Glutathione-S-transferase pi (GSTP1). The aim of this study is to investigate the association of GSTP1 Ile105Val genetic polymorphism with oxaliplatin efficacy and toxicity in advanced colorectal cancer (ACC) patients.

Experimental design: A total of 91 ACC patients received capecitabine and oxaliplatin (CAPOX) as a part of a multicentre phase-III study of the Dutch Colorectal Cancer Group. Tumour response was evaluated according to RECIST, toxicity was graded using CTC, and GSTP1 Ile105Val was determined by pyrosequencing.

Results: Overall survival after CAPOX was similar for patients with the Ile/Ile (11.5 mo), Ile/Val (11.6 mo) and Val/Val (12.6 mo) genotypes ($p = 0.602$). Likewise, there were no statistically significant differences in progression-free survival ($p = 0.252$). Overall grades 3–4 toxicity was not related to genotype ($p = 0.313$). There were no differences in any grade or grades 3–4 neurotoxicity amongst the patients who received $\geqslant 500\ mg/m^2$ of oxaliplatin (p-values of 0.376 and 0.772, respectively).

Conclusions: The results of this study indicate that the GSTP1 genotype is not predictive for progression-free survival or overall survival in ACC patients treated with CAPOX. Moreover, overall neurotoxicity and neurotoxicity in patients receiving $\geqslant 500\ mg/m^2$ of oxaliplatin was not associated with GSTP1 genotype.

1. Introduction

The platinum analogue oxaliplatin is frequently used in the treatment of advanced colorectal cancer (ACC) in combined drug regimens with capecitabine. One of the metabolic routes of oxaliplatin involves the conjugation of the platinum-diaminocyclohexane metabolite to glutathione (GSH). This conjugation reaction is catalysed by the enzyme glutathione-S-transferase (GST) of which the P1 (π) subclass of this enzyme is highly expressed in the intestine.[1] The importance of this

* *Corresponding author:* Tel.: +31 71 526 2790; fax: +31 71 524 8101.
E-mail address: d.m.kweekel@lumc.nl (D.M. Kweekel).
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metabolic route is underscored by the fact that up to 18% of the oxaliplatin dose is excreted in urine as a GSH derivative.[2] *GSTP1* is a polymorphic gene, and the codon 105 polymorphism (313A > G or Ile105Val) has a relatively high prevalence: Ile/Ile (45–50%), Ile/Val (42–46%) and Val/Val (9–11%).[1] 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.[3]

The role of the *GSTP1* as a predictor of oxaliplatin efficacy and toxicity is not clear. The Val/Val genotype has been associated with a superior overall survival (OS) after oxaliplatin chemotherapy in refractory ACC.[4] Likewise, other studies report an inferior OS or progression-free survival (PFS) in gastric cancer patients with the Ile/Ile-genotype treated with cisplatin.[5,6] However, two recent studies in patients with advanced colorectal cancer treated with oxaliplatin, fluorouracil and leucovorin (FOLFOX) report no association of *GSTP1* genotype with PFS.[7,8] In addition, contradicting results were reported with regard to the association of *GSTP1* with (neuro)toxicity. Ruzzo and colleagues found an increased incidence of neurotoxicity in Val/Val genotype patients,[8] whereas Lecomte et al. found the opposite in patients receiving $\geqslant$500 mg/m^2 of oxaliplatin as a part of various FOLFOX regimens for gastrointestinal solid tumours.[9]

In summary, earlier reports show either a superior overall survival for *GSTP1* Val/Val patients treated with oxaliplatin, or no association of genotype and survival. Similarly, the studies of neurotoxicity were non-conclusive. Therefore, our aim was to investigate the possible associations of the *GSTP1* codon 105 polymorphism with (1) overall and progression-free survival and (2) (neuro)toxicity in ACC patients treated with capecitabine and oxaliplatin.

2. Patients and methods

2.1. Subjects

Blood samples were obtained from patients enroled in a multicentre phase-III trial, the CAIRO study of the Dutch Colorectal Cancer Group (DCCG).[10] We refer to this article for a detailed description of eligibility criteria and response or toxicity evaluation. Briefly, patients with ACC were allocated to sequential (regimen A)[10] or combination treatment (regimen B) with capecitabine and irinotecan, followed by capecitabine (1000 mg/m^2/d b.i.d. on days 1–14 every 3 weeks) and oxaliplatin (130 mg/m^2 on day 1 every 3 weeks), CAPOX. In this study only patients who received regimen B were included for reasons of study group homogeneity. First line regimen B combination therapy consisted of capecitabine (1000 mg/m^2/d b.i.d. on days 1–14, every 3 weeks) plus irinotecan (250 mg/m^2/d on day 1 every 3 weeks). Dose reductions were performed for capecitabine in the case of grades 2–4 toxicity as described previously.[11] Oxaliplatin dose reductions of 25% were carried out in the case of grade 4 haematological toxicity, febrile neutropaenia and for persistent paresthesias ($\geqslant$14 d) or painful temporary paresthesias (7–14 d). If haematological and non-haematological toxicities had not recovered before the next treatment cycle, oxaliplatin dose was delayed for a maximum of 2 weeks. If still not recovered by that time, patients went off-study. Prophylactic use of haematological growth factors was not permitted. The accrual period was from January 2003 to December 2004, and EDTA blood samples for genotyping were collected from December 2003 to March 2005 after a protocol amendment. The objective of this amendment was to perform genetic association studies regarding drug efficacy and toxicity. The study protocol and the amendment were approved by the local ethics committees. Written informed consent was obtained from all the patients participating in the genetic association study prior to blood collection. We obtained DNA material from a total of 91 patients who received oxaliplatin-based chemotherapy in regimen B. Tumour evaluation was performed every three cycles according to RECIST criteria[12] and toxicity was graded according to the United States (US) National Cancer Institute (NCI) Common Toxicity Criteria, version 2.0. We performed a subgroup analysis of neurotoxicity in patients who received a cumulative oxaliplatin dose of $\geqslant$500 mg/m^2 since higher cumulative dosages have been associated with an increased incidence of this adverse effect.[9,13] All the results were blinded with respect to genotype.

2.2. Genotyping

Genomic DNA was isolated form peripheral blood cells (MagnaPure Total Nucleic Acid Isolation Kit I on MagnaPure LC (Roche Diagnostics, Mannheim, Germany)). Chromosomal DNA was quantified using Nanodrop (Isogen, IJsselstein, The Netherlands) and was diluted to 10 ng/μl. Primers for the GSTP Ile105Val polymorphism (rs1695) and pyrosequence materials were obtained from Isogen Life Sciences (IJsselstein, The Netherlands), Sepharose beads from Amersham (Uppsala, Sweden). PCRs were done using Hotstart PCR mastermix (Qiagen, Hilden, Germany) on the MyCycler (Biorad, Veenendaal, The Netherlands). Pyrosequence analysis was performed on a Pyrosequencer 96MA (Biotage, Sweden). PCRs were as follows: each reaction contained 10 ng of DNA, and 5 pmole of each PCR primer (forward: 5′-AGGACCTCCGCTGCAAATAC-3′, reverse 5′-CTGGTGCAGATGCTCACATAGTT-3′) in a total of 12 μl. Cycle conditions were initial denaturation for 15 min at 95 °C, 35 cycles of 95 °C–55 °C–72 °C each for 30 s, ended by 10 min at 72 °C. The pyrosequence reactions were performed according to the manufacturers' protocol. The sequence to analyse was **A/G**TCTCCCTCAT using the forward sequence primer 5′-CTCCGCTGCAAATAC-3′.

2.3. Statistics

All eligible patients randomised to combination treatment who started second-line treatment were included for the analysis (n = 91). We evaluated differences in adverse events and overall or progression-free survival for the subgroups of patients with Ile/Ile (n = 47), Ile/Val (n = 35), Val/Val (n = 9), Ile/Ile or Ile/Val (n = 47 + 35) and Ile/Val or Val/Val (n = 35 + 9).

The association between *GSTP1* and adverse events (both any grade and grades 3–4 toxicity) and overall grades 3–4 toxicity was investigated by a (exact) Trend test and Chi-squared test.

Progression-free survival was calculated as time between the start of second-line treatment and first progression after the start of second line, death or last follow-up visit. Overall

survival was calculated as time between the start of second-line treatment and death or last follow-up visit. The association between *GSTP1* and survival was investigated by a uni- and multivariate Cox proportional hazard regression analysis and Score test. Stratification factors at randomisation (predominant localisation of primary tumour, prior adjuvant therapy, serum LDH and performance score), age and gender were considered as possible confounding factors.

P-values smaller than 0.05 were considered statistically significant. All analyses were performed in SAS 9.1 and SPLUS 6.2.

3. Results

Genotyping the Ile105Val polymorphism was successful in all 91 patients receiving CAPOX (100%). Overall genotype frequencies for the *GSTP1* Ile105Val polymorphism were as follows: Ile/Ile (AA) 52%, Ile/Val (AG) 38% and Val/Val (GG) 10%. Patient characteristics and genotype distributions are shown in Table 1; there were no statistically significant differences amongst *GSTP1* genotypes. The *GSTP1* genotype distribution is in Hardy–Weinberg equilibrium ($p = 0.514$). Ethnicity data were not collected, but patients in this Dutch study were predominantly of Caucasian origin.

3.1. *Overall and progression-free survival*

Median overall and progression-free survival times are shown in Table 2. Overall survival (OS) did not differ significantly according to genotype: Ile/Ile 11.5, Ile/Val 11.6 and Val/Val 12.6 months, respectively (score test $p = 0.602$). Specifically, Val/Val genotype patients did not have a different OS compared to the other patients ($p = 0.202$). Progression-free survival (PFS) was also similar: Ile/Ile 4.1, Ile/Val 5.2 and Val/Val 4.0 months, respectively (score test $p = 0.252$). PFS of patients with the Ile/Val genotype was longer than that of patients with the Ile/Ile genotype ($p = 0.050$, borderline significance) in multivariable Cox Regression analysis, but the Val/Val genotype experienced a similar survival compared to the Ile/Ile genotype ($p = 0.543$).

Table 1 – Patient characteristics.

GSTP1 number of patients (%)		Ile/Ile *N* = 47 (52%)	Ile/Val *N* = 35 (38%)	Val/Val *N* = 9 (10%)	Total *N* = 91 (100%)
Age	Median (range)	59 (41–81)	62 (37–78)	61 (45–72)	61 (37–81)
Gender	Male	27 (57%)	23 (66%)	7 (78%)	57 (63%)
	Female	20 (43%)	12 (34%)	2 (22%)	34 (37%)
Performance score (PS) at randomisation	PS $\leqslant$ 1	44 (94%)	33 (94%)	9 (100%)	86 (95%)
	PS 2	3 (6%)	2 (6%)	–	5 (5%)
Serum LDH at randomisation	Normal	31 (66%)	18 (51%)	7 (78%)	56 (62%)
	>UNL	16 (34%)	17 (49%)	2 (22%)	35 (38%)
Predominant localisation at randomisation	Liver	33 (70%)	24 (69%)	7 (78%)	64 (70%)
	Extrahepatic	14 (30%)	11 (31%)	2 (22%)	27 (30%)
Prior adjuvant therapy	No	42 (89%)	31 (89%)	8 (89%)	81 (89%)
	Yes	5 (11%)	4 (11%)	1 (11%)	10 (11%)
Localisation of primary tumour	Colon	27 (57%)	21 (60%)	5 (56%)	53 (58%)
	Rectum	20 (43%)	14 (40%)	4 (44%)	38 (42%)
Months between randomisation and the start of oxaliplatin		8.7 (2.1–27.6)	9.7 (1.6–37.5)	10.3 (3.2–15.0)	9.2 (1.6–37.5)
Number of cycles oxaliplatin received	Median (range)	4 (1–13)	6 (1–20)	6 (1–10)	5 (1–20)
	1–3	21 (45%)	9 (26%)	3 (33%)	33 (36%)
	4–6	16 (34%)	10 (29%)	4 (44%)	30 (33%)
	>6	10 (21%)	16 (46%)	2 (22%)	28 (31%)
Performance score World Health Organisation (WHO) at the start of oxaliplatin	PS0	21 (45%)	22 (63%)	4 (44%)	47 (52%)
	PS1	23 (49%)	11 (31%)	5 (56%)	39 (43%)
	PS2	3 (6%)	2 (6%)	–	5 (5%)
ERCC1 C118T	CC	16 (34%)	11 (31%)	4 (44%)	31 (34%)
	CT	22 (47%)	21 (60%)	5 (56%)	48 (53%)
	TT	7 (15%)	1 (3%)	–	10 (11%)
	Missing	2 (4%)	3 (9%)	–	2 (2%)
ERCC2 Lys751Gln	Lys/Lys	12 (26%)	12 (34%)	2 (22%)	26 (29%)
	Lys/Gln	22 (47%)	19 (54%)	6 (67%)	47 (52%)
	Gln/Gln	11 (23%)	1 (3%)	–	12 (13%)
	Missing	2 (4%)	3 (9%)	1 (11%)	6 (7%)
TS 28 bp repeat	2R/2R	13 (28%)	5 (14%)	1 (11%)	19 (21%)
	2R/3R	23 (49%)	15 (43%)	4 (44%)	42 (46%)
	3R/3R	9 (19%)	13 (37%)	3 (33%)	25 (27%)
	Missing	2 (4%)	2 (6%)	1 (11%)	5 (5%)

Baseline characteristics of patients receiving second-line treatment with oxaliplatin combination chemotherapy for advanced colorectal cancer (all $p > 0.05$). UNL, upper limit of normal; PS, performance status; bp (nucleotide) base pair.

Table 2 – Median PFS and OS (months).

	N	Progression-free survival (95% CI)		Univariate Cox regression	Multivariate Cox regression*	Overall survival (95% CI)		Univariate Cox regression	Multivariate Cox regression*
Overall	91	4.1	(3.8; 5.1)	–	–	11.6	(9.6; 13.6)	–	–
Ile/Ile	47	4.1	(2.4; 4.5)	Reference	Reference	11.5	(8.0; 14.0)	Reference	Reference
Ile/Val	35	5.2	(3.7; 6.5)	0.126	0.050	11.6	(9.6; 14.6)	0.918	0.955
Val/Val	9	4.0	(1.9; 7.3)	0.814	0.543	12.6	(6.0; 15.5)	0.210	0.323
Ile/Ile+Ile/Val	82	4.2	(3.7; 5.8)	0.509 (versus Val/Val)	0.952 (versus Val/Val)	11.5	(9.6; 13.7)	0.202 (versus Val/Val)	0.290 (versus Val/Val)
Ile/Val+Val/Val	44	5.0	(3.9; 6.5)	0.197	0.058	12.0	(9.6; 14.6)	0.651	0.815

Median progression-free survival (PFS) and overall survival (OS) of patients after starting second-line treatment with oxaliplatin-based chemotherapy for advanced colorectal cancer. CI: confidence interval.

* Adjusted for: serum LDH, tumour origin, previous adjuvant treatment, gender, age and performance score.

3.2. *Toxicity*

Overall grades 3–4 toxicity did not differ significantly amongst genotypes: Ile/Ile 34.0%, Ile/Val 28.6% and Val/Val 55.6% ($p = 0.313$, Table 3). For further analysis, we selected the following toxicities with an incidence rate of at least 5% (at grades 3–4 severity level): diarrhoea ($n = 7$), fatigue ($n = 8$), sensory neurotoxicity ($n = 5$) and vomiting ($n = 5$). Of these, only grades 3–4 vomiting was associated with genotype. Grades 3–4 vomiting occurred in 1 patient of the Ile/Ile genotype (2.1%), 2 patients of the Ile/Val genotype (5.7%) and 2 (22.2%) of the Val/Val patients; although these are very small numbers, we found a trend: $p = 0.053$. The incidence of severe vomiting of Val/Val patients was significantly higher than that of Ile-carriers ($p = 0.020$).

Additionally, we performed association analysis of neurotoxicity in patients who received a cumulative oxaliplatin dose of $\geqslant 500\ mg/m^2$ ($n = 56$, Table 3). Of the 58 patients receiving $\geqslant 4$ cycles, 2 patients received $<500\ mg/m^2$ of oxaliplatin as a result of dose reductions; these are not included in the cumulative neurotoxicity analysis. A total of 25 of 47 patients with the Ile/Ile genotype (53.2%) were qualified for this subgroup analysis, as well as 25 of 35 (71.4%) patients with the Ile/Val and 6 of 9 (66.7%) patients with the Val/Val genotype ($p = 0.231$). Grades 3–4 neurotoxicity was found in 4 of 56 (7.1%) of patients. Grades 3–4 neurotoxicity only occurred in the Ile/Ile (2 of 25) and Ile/Val (2 of 25) genotypes, overall $p = 0.772$. Any grade neurotoxicity was found in 17/25 (68.0%) of Ile/Ile patients, compared to 21/25 (84.0%) of Ile/Val patients and 5/6 (83.3%) of Val/Val patients, $p = 0.376$.

4. Discussion

In this study, we found no evidence for an association of the *GSTP1* codon 105 polymorphism with PFS, OS or toxicity. Similarly, when we performed a subgroup analysis of patients who received a cumulative oxaliplatin dose of $\geqslant 500\ mg/m^2$, no association of the *GSTP1* Ile > Val polymorphism with neurotoxicity was detected.

Table 3 – Adverse events in advanced colorectal cancer patients receiving second-line combination chemotherapy with oxaliplatin.

		Ile/Ile N = 47	Ile/Val N = 35	Val/Val N = 9	Three groups Chisq.[a]	Three groups Trend[b,c]	Ile/Ile versus Ile/Val + Val/Val[a]	Ile/Ile + Ile/Val versus Val/Val[a]
Overall grades 3–4		16 (34.0%)	10 (28.6%)	5 (55.6%)	0.313	0.517[b], 0.620[c]	0.996	0.152
Diarrhoea	Any grade	19 (40.4%)	15 (42.9%)	2 (22.2%)	0.521	0.525[b], 0.631[c]	0.862	0.262
	Grades 3–4	3 (6.4%)	3 (8.6%)	1 (11.1%)	0.861	0.585[b], 0.770[c]	0.628	0.685
Fatigue	Any grade	37 (78.7%)	26 (74.3%)	5 (55.6%)	0.341	0.190[b], 0.209[c]	0.364	0.565
	Grades 3–4	4 (8.5%)	4 (11.4%)	0 (0.0%)	0.556	0.713[b], 0.792[c]	0.922	0.327
Vomiting	Any grade	23 (48.9%)	15 (42.9%)	5 (55.6%)	0.751	0.989[b], 1.000[c]	0.740	0.599
	Grades 3–4	1 (2.1%)	2 (5.7%)	2 (22.2%)	0.053	0.859[b], 1.000[c]	0.145	0.020
Sensory neuropathy	Any grade	29 (61.7%)	26 (74.3%)	5 (55.6%)	0.388	0.725[b], 0.745[c]	0.379	0.914
	Grades 3–4	3 (6.4%)	2 (5.7%)	0 (0.0%)	0.742	0.527[b], 0.738[c]	0.701	0.446
Sensory neuropathy, $\geqslant 500\ mg/m^2$	Any grade	17 (68.0%)	21 (84.0%)	5 (83.3%)	0.376	0.614[b], 0.201[c]	0.162	0.688
	Grades 3–4	2 (8.0%)	2 (8.0%)	0 (0.0%)	0.772	0.216[b], 0.247[c]	0.823	0.472

This table describes all adverse events with $\geqslant 5\%$ reported incidence of grades 3–4 toxicity. The %s refer to the relative amount of patients of a particular genotype who experienced an adverse event. In total, 25 patients of the Ile/Ile, 25 patients of the Ile/Val and 6 patients of the Val/Val genotype received $\geqslant 500\ mg/m^2$ of oxaliplatin.

a Chi-square.

b Trend test.

c Exact trend test.

Table 4 – Overview of the published studies on GSTP1 and the efficacy or toxicity of platinum derivatives in gastrointestinal tumours.

First author	Sample size	Cancer type	Regimen	Previous	PFS	OS	Overall toxicity	Neurotoxicity
Stoehlmacher et al.[4]	107	CRC	Ox 130 mg/m^2 + 5FU 200 mg/m^2/d for 2 weeks (3 week cycle), second and third line combined	5FU/FA first line (all), IRI second line (79%)	–	↑ in Val/Val	ns	–
Goekkurt et al.[6]	52	GC	First line Cis 50 mg/m^2 + 5FU 2 g/m^2 + FA 500 mg/m^2 (2 week cycle)	Adjuvant 6%, not specified	–	↑ in Val/Val	–	–
Ruzzo et al.[5]	175	GC	5FU + Cis, regimen(s) not specified	Not specified	↑ in Val/Val	↑ in Val/Val	–	–
Lecomte et al.[9]	64	GIC	Mainly (72%) FOLFOX4, first and second line combined	5FU/FA 16%, FOLFIRI 5%	–	–	–	↑ in Ile/Ile[a]
Ruzzo et al.[8]	166	CRC	First line FOLFOX4	Adjuvant without Ox	ns	–	ns	↑ in Val/Val
Le Morvan et al.[7]	59	CRC	Various first line regimens of Ox, mainly combined with 5FU/FA (86%)	Adjuvant 36%, not specified	ns	ns	ns	ns
Current study	91 (56[a])	CRC	Second line Ox 130 mg/m^2 + Cap 1000 mg/m^2/d b.i.d. for 2 weeks (3 week cycle, XELOX)	Each genotype: adjuvant 11%, not specified	ns	ns	ns	ns[a]

PFS, progression-free survival; OS, overall survival; CRC, colorectal cancer; GC, gastric cancer; GIC, gastrointestinal cancer; Ox, oxaliplatin; Cis, cisplatin; 5FU, fluorouracil; FA, folinic acid; IRI, irinotecan; Cap, capecitabine; FOLFOX4, oxaliplatin 85 mg/m^2 + FA (200 mg/m^2/d) + 5FU bolus (400 mg/m^2/d) and 22-h infusion (600 mg/m^2/d) for 2 consecutive days every 2 weeks; ns, not significant; –, not studied.

a Analysed only those patients who received cumulative oxaliplatin doses of at least 500 mg/m^2.

Several previous studies have investigated the association of GTSP1 Ile105Val with oxaliplatin efficacy and toxicity, but the results of these studies were inconclusive (Table 4). Stoehlmacher and colleagues reported a superior OS in Val/Val patients with refractory colorectal cancer treated with oxaliplatin and fluorouracil.[4] This finding was confirmed in two studies of gastric cancer patients using cisplatin.[5,6] In contrast, a more recent smaller study found no association between OS, PFS or toxicity and *GSTP1* genotype.[7]

There may be several reasons that could explain the discrepancies found in the studies performed so far. First, the OS reported in these studies may be difficult to compare due to the fact that OS can be influenced by (unintended) selective use of second- or third-line treatments which are often not specified by the authors.[14] In that respect, PFS may be a preferable end-point. Secondly, a lack of adjustment for the previous adjuvant treatment may attribute to the discrepancies between the studies. Previous treatment(s) probably confound the results of a study; if, e.g. the Val/Val genotype patients are less heavily pretreated, they may experience more treatment benefit, in terms of PFS or OS, from the studied chemotherapy regimen. Thirdly, one should be careful when combining second- and third-line patients, even if they received the same agents but in different regimens. For example, if we extend the current analysis to patients who received third-line oxaliplatin (regimen A as described in Section 2, $n = 56$), we find that Val/Val patients have a significantly shorter median OS (but not PFS) of 7.1 mo compared to Ile-carriers (11.0 mo, $p = 0.027$). However, combining regimen A patients with the patients of the current analysis (regimen B) is not feasible for two reasons: (1) median OS in regimen B is 11.6 months after the start of oxaliplatin therapy, compared to that in regimen A which is 10.3 months and (2) genotype distributions are different in both regimens. Because relatively few Val/Val patients are in regimen B, combining both regimens would result in a lower OS of Val/Val patients. For this reason, we decided not to combine the patients of regimens A and B, although other studies did combine patients from different lines of therapy or even patients receiving different agents in combination with oxaliplatin.[4,9] Fourthly, an unbalanced distribution of other genetic variants that potentially interfere with a regimen's toxicity or efficacy, such as in the excision repair cross-complementing enzymes 1 (ERCC1) and 2 (ERCC2) or in thymidylate synthase (TS)[15] could influence the study results. As shown in Table 1, these potential confounders were equally distributed amongst the *GSTP1* genotypes. In contrast, most published studies do not include the analysis of potential confounding polymorphisms.

Apart form PFS and OS, we studied oxaliplatin-related neurotoxicity. This is a dose-limiting adverse effect, which occurs as an acute form or as a chronic syndrome. Acute neurotoxicity is seen in >90% of patients, mainly during or shortly after the infusion of the compound. It is characterised by peripheral-nerve hyperexcitability and is triggered or aggravated by exposure to cold. Chronic neurotoxicity manifests as a loss of sensation and dysesthesias in the distal extremities, which may impair daily functioning and increase with the amount of oxaliplatin received. Our data suggest that there is no association between *GSTP1* Ile/Val genotype and neurotoxicity in patients who received $\geqslant 500$ mg/m^2 oxalipla-

tin, although an increased incidence of cumulative neurotoxicity in Ile/Ile patients was reported in an earlier study.[9] However, the incidence of grades 3–4 neurotoxicity was considerably lower (6%) in this study compared to that mentioned in the other report (23%).[9] This difference may be explained, at least partly, by the fact that instead of the oxaliplatin-specific neurotoxicity scale reported by Caussanel and colleagues[16], we used the NCI common toxicity criteria. The application of a different neurotoxicity scale may not only influence the overall incidence of neurotoxicity, but also the association of this clinical end-point with genotype. Another factor influencing chronic neurotoxicity is cumulative oxaliplatin dosage, as this is primarily seen in patients who received 540 mg/m^2 or more.[13] Ruzzo and colleagues[8] report that grade 3 neurotoxicity was more common in advanced colorectal cancer patients with the Val/Val-genotype, but no explicit information was given about cumulative dosages received by the patients. Although from that report it seems that the majority of patients have received >500 mg/m^2 (6 six cycles) of oxaliplatin, we cannot rule out that a number of patients may have received dose reductions or discontinued therapy earlier due to progression, who are nonetheless included in the overall analysis of neurotoxicity. Therefore, we may not be able to compare the outcomes of these investigations.

Two theories have been postulated to explain an association between the *GSTP1* Ile/Ile genotype and chronic neurotoxicity. First, the Val-containing enzyme (at position 105) may have a higher capacity for the detoxification of cisplatin[17] and oxaliplatin, resulting in a lower incidence of neurotoxicity in Val/Val carriers. The other hypothesis is that the Val-containing enzyme shows a decreased inhibition of c-Jun NH_2-terminal kinase (JNK), thereby allowing a higher expression of cellular defence proteins which are involved in protecting the cells from platinum-induced toxicity.[9] However, both theories indirectly contradict the earlier findings of an increased (anti-tumour) efficacy in Val/Val genotype patients.

In conclusion, the results of this study suggest that there is no association of *GSTP1* genotype and PFS or OS in patients with ACC treated with CAPOX. Moreover, no association was found between genotype and the incidence of (grades 3–4) neurotoxicity.

Conflict of interest statement

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