

ORIGINAL ARTICLE

Carboplatin/taxane-induced gastrointestinal toxicity: a pharmacogenomics study on the SCOTROC1 trial

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Carboplatin/taxane combination is first-line therapy for ovarian cancer. However, patients can encounter treatment delays, impaired quality of life, even death because of chemotherapy-induced gastrointestinal (GI) toxicity. A candidate gene study was conducted to assess potential association of genetic variants with GI toxicity in 808 patients who received carboplatin/taxane in the Scottish Randomized Trial in Ovarian Cancer 1 (SCOTROC1). Patients were randomized into discovery and validation cohorts consisting of 404 patients each. Clinical covariates and genetic variants associated with grade III/IV GI toxicity in discovery cohort were evaluated in replication cohort. Chemotherapy-induced GI toxicity was significantly associated with seven single-nucleotide polymorphisms in the ATP7B, GSR, VEGFA and SCN10A genes. Patients with risk genotypes were at 1.53 to 18.01 higher odds to develop carboplatin/taxane-induced GI toxicity ($P < 0.01$). Variants in the VEGF gene were marginally associated with survival time. Our data provide potential targets for modulation/inhibition of GI toxicity in ovarian cancer patients.

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INTRODUCTION

In United States, 21 980 new cases and 14 270 deaths of ovarian cancer were reported in 2014 according to the most recent survey by the American Cancer Society.¹ It ranks fifth as the cause of cancer death in women and over 2 billion dollars are spent every year in the US on its treatment.² In combination with surgical cytoreduction-, platinum (cisplatin or carboplatin)-based chemotherapy in combination with a taxane agent (paclitaxel or docetaxel) is a standard treatment for ovarian cancer.^{3,4} Despite the therapeutic impact of platinum in conjunction with taxane agents in the management of ovarian cancer, 20–30% of patients will face grade III/IV peripheral neuropathy, 30–40% grade IV neutropenia and 20% grade III/IV gastrointestinal (GI) toxicity.⁵ Carboplatin/taxane-induced mucositis, diarrhea and vomiting represent a major GI toxicity that patients encountered in the SCOTROC1 trial, which recruited 1077 ovarian cancer patients to treatment with either docetaxel–carboplatin or paclitaxel–carboplatin.⁶ Acute GI toxicity represents a substantial negative impact on patients' quality of life.⁷ However, there are no genetic markers that have been shown to be associated with a higher risk of GI toxicity after carboplatin/taxane therapy.

In this study, we investigated 1261 selected polymorphisms with described functional effects in 60 genes to identify any genetic variants associated with carboplatin/taxane-induced GI toxicities in ovarian cancer patients. The inclusion criteria of these genes were described previously.⁸ The findings of this study provide new biologic insights and potential predictive factors for risk of GI toxicity in ovarian cancer patients receiving carboplatin/taxane-based chemotherapy.

PATIENTS AND METHODS

Patients

A randomized phase III study, SCOTROC1, recruited 1077 ovarian cancer patients to treatment with docetaxel–carboplatin ($n=539$) or with paclitaxel–carboplatin ($n=538$).⁶ The trial has been described in detail previously, but is summarized here. All patients had no prior chemotherapy or radiotherapy and received six cycles of chemotherapy at 3-week intervals. Clinical response and toxicity were graded at baseline, and after cycles 3 and 6 according to Southwest Oncology Group criteria and National Cancer Institute Common Toxicity Criteria (NCI–CTC, version 2.0). Of the 1077 patient samples, 880 samples had germline DNA of sufficient quality for gene chip analysis.⁸ The GI toxicity including mucositis, vomiting and diarrhea was documented. Written informed consent was collected from all patients. Details of SCOTROC1 trial, patients' demographic characteristics and clinical assessments were described previously.⁶ Clinical characteristics are displayed in Table 1.

Genotyping

A total of 60 candidate genes (Supplementary table 1) with 1536 single-nucleotide polymorphisms (SNPs) were genotyped with an Illumina GoldenGate custom SNP array (Illumina, San Diego, CA, USA; Supplementary Table 2a) and an additional 33 SNPs not suitable for the Illumina assay were genotyped using pyrosequencing (Biotage, Uppsala, Sweden; Supplementary Table 2b). Specific genotyping methods were described previously.⁸

Quality control

To ensure high genotyping quality, only SNPs with >90% efficiency for all patients were included in the analysis. Of the 1569 SNPs genotyped, 1303 SNPs passed standards of genotyping efficiency. Of the 1303 SNPs, we evaluated potential deviations from Hardy–Weinberg proportions⁹ using a

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Table 1. Clinical characteristics by cohort

Variable	Level	Replication set (N = 404)		Discovery set (N = 404)		Total (N = 808)	
		N	%	N	%	N	%
FIGO stage	IC	27	6.7	25	6.2	52	6.4
	II	57	14.1	41	10.1	98	12.1
	III	257	63.6	281	69.6	538	66.6
	IV	63	15.6	57	14.1	120	14.9
Tumor grade	Well differentiated	27	6.7	30	7.4	57	7.1
	Moderate	103	25.5	108	26.7	211	26.1
	Poor/undifferentiated	222	55.0	221	54.7	443	54.8
	Unknown	52	12.9	45	11.1	97	12.0
ECOG status	0	142	35.1	126	31.2	268	33.2
	1	211	52.2	215	53.2	426	52.7
	2	51	12.6	63	15.6	114	14.1
CA125 response	No response	59	14.6	71	17.6	130	16.1
	Response	213	52.7	211	52.2	424	52.5
	Not evaluated	132	32.7	122	30.2	254	31.4
Treatment	Paclitaxel/Carboplatin	196	48.5	204	50.5	400	49.5
	Docetaxel/Carboplatin	208	51.5	200	49.5	408	50.5
Worst grade of GI toxicity	0	19	4.7	18	4.5	37	4.6
	1	105	26.0	107	26.5	212	26.2
	2	208	51.5	208	51.5	416	51.5
	3	66	16.3	64	15.8	130	16.1
	4	6	1.5	7	1.7	13	1.6
Worst grade of neuropathy	0	143	35.4	142	35.1	285	35.3
	1	169	41.8	172	42.6	341	42.2
	2	64	15.8	71	17.6	135	16.7
	3	26	6.4	18	4.5	44	5.4
	4	2	0.5	1	0.2	3	0.4
First cycle of grade 2 neuropathy	1	16	4.0	9	2.2	25	3.1
	2	21	5.2	16	4.0	37	4.6
	3	37	9.2	21	5.2	58	7.2
	4	27	6.7	29	7.2	56	6.9
	5	21	5.2	22	5.4	43	5.3
	Censored	282	69.8	307	76.0	589	72.9
Survival status	Alive	252	62.4	262	64.9	514	63.6
	Dead	152	37.6	142	35.1	294	36.4
Median survival time (months)		20.05		20.30		20.24	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal.

χ^2 -test of association with a Bonferroni multiple testing correction for the significance cutoff. A total of 42 SNPs showed significant deviations (after multiple testing correction) and were removed from the subsequent analysis (for a total of 1261 SNPs evaluated). Principle Components Analysis was performed on the remaining SNPs to evaluate potential population substructure. As expected given the self-reported ethnicity in the current cohort, no substructure was observed (data strongly grouped into a single cluster, and eigenvalues from the first three components were not significantly related to toxicity, data not shown). In addition, subjects

for which grade of GI toxicity was missing were excluded from analysis and greater than 90% complete observations for all SNPs were included in the association analysis. 880 patient samples were initially available, and 808 passed completeness standard filters. The patients were randomly assigned into test/discovery and replication/validation cohorts, stratified by case/control status to achieve equal numbers of cases in both sets: 71 cases (grade III/IV GI toxicity) and 333 controls (grade I/II GI toxicity) were included in the testing/discovery set, and 72 cases and 332 controls in the validation/replication set (Figure 1).

Data analysis

The aim of this study was to discover variants associated with chemotherapy-induced GI toxicity rather than building a predictive model, with an emphasis on whether genetic information had influence after accounting for clinical variables. Clinical covariates and genetic variants significantly associated with grade III/IV GI toxicity in the first discovery cohort were evaluated in the second replication cohort. Important clinical covariates significantly associated with the response were selected with stepwise logistic regression to minimize AIC (Akaike's Information Criteria).¹⁰ Covariates considered were bulk of residual disease, FIGO stage, tumor grade, Eastern Cooperative Oncology Group (ECOG) performance status, clinical/radiological response, CA125 response, histology, treatment arm, haematological toxicity, neurotoxicity, first cycle of neurotoxicity, survival status and progression-free survival status; selected covariates included pretreatment ECOG performance status, CA125 response, treatment arm, survival status and first cycle at which neuropathy was experienced. Subjects with missing values for the selected covariates were excluded from subsequent analyses. Single-SNP analyses including important clinical covariates were performed using logistic regression to test for association of each SNP with toxicity; no genetic model of inheritance was assumed, and a genotypic model was used that included dummy variables for the SNP genotypes. SNPs with nominal *P*-values < 0.05 were evaluated in the validation set. This two-stage analysis identifies SNPs that replicate in independent data, which reduces possible false-positive associations. Across both independent replication sets, we calculate a joint *P*-value and ascribe statistical significance using permutation testing (repeating the entire variable selection and two-stage approach). A corrected *P*-value was obtained from this permutation test that can be compared with the usual 5% significance level to account for multiple testing and our two-stage design.

To further reduce potential false-positive findings, only the SNPs that met these strict criteria and also were consistent in direction of the risk effect for each genotype (positive vs negative estimated odds ratio) were considered true replications. In addition, to further examine the cumulative effect of genetic risk variants, we constructed a genetic risk score equal to the number of independent risk genotypes possessed by each individual, based on the four independent genetic signals (risk genotypes at SNPs in high linkage disequilibrium (LD) were counted only once). Therefore, the genetic risk score could take on values of 0, 1, 2, 3 or 4; because only one individual possessed four risk genotypes, the genetic risk score was modeled as an ordinal variable with categories 0, 1, 2 and 3+. This score was examined as an exploratory data analysis and does not represent a predictive model; the predictive ability of this score should be evaluated in an independent cohort. As sensitivity analyses, a genetic risk score was also calculated where the sum of the risk genotypes was weighted by the log odds ratio estimate.

We also investigated whether the SNPs significantly associated with GI toxicity were also associated with either overall survival or progression-free survival time after controlling for important clinical covariates (ECOG performance status, CA125 response, FIGO stage, histology, presence of neuropathy, bulk of residual disease, and clinical response) using a Cox Proportional Hazards model. All data analysis was performed in the freely available R-software (<http://www.r-project.org/>).¹¹

RESULTS

SNPs associated with grade III/IV GI toxicity

The regression modeling of the clinical data identified the following variables as covariates for further analysis of the risk of developing grade III/IV GI toxicity: treatment arm, first cycle of grade 2 neuropathy, CA125 response, overall survival and ECOG status. From the 1261 SNPs that passed quality control standards, 81 SNPs were significant in the test set at the *P* < 0.05 level. Of

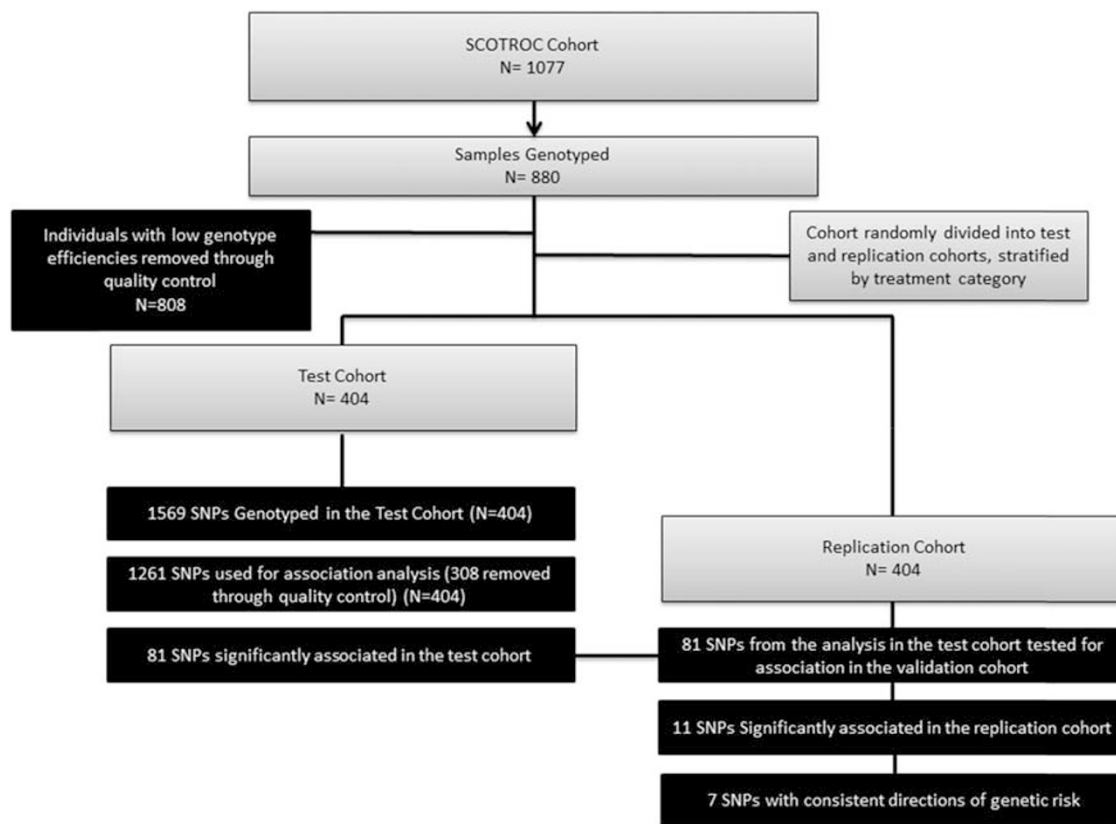


Figure 1. Workflow of the data analysis, with processing of the samples shown in gray, and the workflow related to the SNPs shown in black. SNPs, single-nucleotide polymorphisms.

Table 2. SNPs significantly associated with significant gastrointestinal toxicity in the discovery and replication cohorts. Analyses are adjusted for ECOG performance status, CA125 response, treatment arm, survival status, and first cycle at which neuropathy was experienced

SNP	Gene	Polymorphism	P-value discovery set (N = 404)	P-value replication set (N = 404)	Joint P-value	Corrected P-value (compare with 0.05)	Odds ratio (N = 808)	95% CI (N = 808)	Risk genotype
rs1061472	<i>ATP7B</i>	A→G	0.004	0.031	1.22E−04	0.00111	1.70	1.02, 2.84	AA
rs1801249	<i>ATP7B</i>	A→G	0.003	0.032	8.64E−05	0.00081	1.53	0.93, 2.51	AA
rs3594	<i>GSR</i>	A→G	0.035	0.030	1.05E−03	0.00848	2.83	1.45, 5.52	CC
rs6900017	<i>VEGFA</i>	A→G	0.037	0.040	1.47E−03	0.01162	9.97	1.85, 53.72	AA
rs879825	<i>VEGFA</i>	A→G	0.036	0.014	4.97E−04	0.00417	18.01	2.78, 116.56	GG
rs9369421	<i>VEGFA</i>	A→G	0.040	0.037	1.47E−03	0.01162	9.91	1.83, 53.52	GG
rs9825762	<i>SCN10A</i>	A→G	0.018	0.022	3.90E−04	0.00335	1.90	0.76, 4.77	AA

Abbreviation: CI, confidence interval.

those significant in the test set, 11 were also significant in the validation set. Seven of these SNPs passed further assessment for direction of effect and a genotypic model was selected as the most likely genetic model for all SNPs (Figure 1). These seven SNPs reside in or near four genes: *ATP7B*, *GSR*, *VEGFA*, and *SCN10A* (Table 2). The odds of developing platinum/taxane-induced GI toxicity in patients with risk genotypes ranged from 1.53 to 18.01 times for each risk SNP (corrected $P < 0.05$; Table 2). For each SNP, genotype counts by GI toxicity status are displayed for each cohort (Table 3). The independence of each significant SNP from other SNP signals was assessed by evaluating LD between the markers (quantified as R^2 values) (Shown in Table 4). Rs1061472 and rs1801249 are both in *ATP7B* and are in strong LD ($R^2 = 91.78\%$) and rs6900017, rs879825 and rs9369421 are all in

VEGFA and are in strong LD (Table 4); therefore, these five SNPs represent only two independent genetic signals.

Genetic risk score analysis

After calculating a risk genotype composite score for each individual (equal to the number of independent risk genotypes that individual carries), a strong association between the number of risk genotypes and GI toxicity was observed (Figure 2a). The number of risk genotypes was associated with a multiplicative increase in the odds of developing GI toxicity, with the odds of developing GI toxicity estimated to increase by an average of 1.89 for every subsequent risk genotype ($P = 1.62E - 7$), although this is only marginally significant after permutation correction ($P = 0.056$).

Table 3. Genotype counts by GI toxicity status for each cohort

SNP	Genotype	Discovery set		Validation set		Total	
		Grade I/II	Grade III/IV	Grade I/II	Grade III/IV	Grade I/II	Grade III/IV
rs1061472	AA	54	19	58	21	112	40
rs1061472	AG	177	31	166	24	343	55
rs1061472	GG	93	19	97	24	190	43
rs1801249	AA	52	18	57	20	109	38
rs1801249	AG	172	28	167	23	339	51
rs1801249	GG	106	24	105	28	211	52
rs3594	AA	58	7	56	5	114	12
rs3594	AC	152	27	138	32	290	59
rs3594	CC	114	34	132	35	246	69
rs6900017	AA	2	2	1	1	3	3
rs6900017	AG	41	7	48	13	89	20
rs6900017	GG	286	62	283	58	569	120
rs879825	AA	298	64	293	61	591	125
rs879825	AG	30	4	37	9	67	13
rs879825	GG	1	2	1	1	2	3
rs9369421	AA	287	62	277	59	564	121
rs9369421	AG	44	6	52	12	96	18
rs9369421	GG	2	2	1	1	3	3
rs9825762	AA	189	53	196	53	385	106
rs9825762	AG	124	16	117	15	241	31
rs9825762	GG	20	2	17	4	37	6

Abbreviation: GI, gastrointestinal.

Table 4. LD correlation matrix (R^2) for the seven SNPs associated with significant gastrointestinal toxicity

		rs1061472	rs1801249	rs3594	rs6900017	rs879825	rs9369421	rs9825762
Chr.13	rs1061472	1.0000	0.9178	0.0003	0.0045	0.0058	0.0046	0.0003
Chr.13	rs1801249	0.9178	1.0000	0.0000	0.0051	0.0060	0.0052	0.0002
Chr.8	rs3594	0.0003	0.0000	1.0000	0.0000	0.0001	0.0000	0.0003
Chr.6	rs6900017	0.0045	0.0051	0.0000	1.0000	0.7420	0.9706	0.0001
Chr.6	rs879825	0.0058	0.0060	0.0001	0.7420	1.0000	0.7724	0.0001
Chr.6	rs9369421	0.0046	0.0052	0.0000	0.9706	0.7724	1.0000	0.0000
Chr.3	rs9825762	0.0003	0.0002	0.0003	0.0001	0.0001	0.0000	1.0000

Abbreviations: Chr., chromosome; LD, linkage disequilibrium; SNP, single-nucleotide polymorphism.

Patients with a composite score of 2 had an estimated odds ratio for GI toxicity of 3.56 (2.21–5.72) compared with individuals with a composite score of 0. The number and percentage of patients in each genetic risk score category by GI toxicity/no toxicity status are presented in Table 5, along with the model odds ratios.

On the basis of the four-locus weighted risk score, the odds of developing GI toxicity increased by a factor of 2.15 (uncorrected $P=4.30E-7$) for each additional weighted risk genotype (range 0–4). Because the VEGFA locus was more rare than the other loci (only six subjects possessed the risk genotype), this locus was also removed from the weighted genetic risk score to avoid potential biases. For the remaining three loci, the odds of developing GI toxicity increased by a factor of 1.65 (uncorrected $P=4.33E-6$) for each additional weighted risk genotype (range 0–3).

Survival time analysis

Patients with a high-risk genotype score (2–3+ risk genotypes) had the same progression-free survival ($P=0.98$) and overall survival ($P=0.90$) as patients with the lower risk composite score (0–1 risk genotypes; Figures 2b and c, respectively). In addition, Cox proportional hazards analysis for both survival time and progression-free survival for each individual genotype indicate no association with progression-free or overall survival. The only SNP in association

with patient's survival time is VEGFA rs9369421, where genotype GG is associated with high risk of GI toxicity (Figure 3). However, the G allele is associated with increased survival; the hazard, or risk of death, for patients with genotype AA ($n=685$) is 1.58 times higher than patients with either AG or GG genotype ($n=120$; $P=0.012$).

DISCUSSION

In this study, seven SNPs from four genes (*ATP7B*, *GSR*, *VEGFA* and *SCN10A*) were found to be associated with platinum/taxane-induced grade III/IV GI toxicity in ovarian cancer patients. The odds for a patient to develop severe GI toxicity are 18 times higher in VEGFA rs879825 GG carriers than A allele carriers. There is also evidence that variants in the four genes may exhibit a cumulative effect, as the odds of developing GI toxicity increased by a factor of 1.89 for each additional risk genotype that a patient possessed. This estimate increased to 2.15 when the risk genotype score was weighted by the effect size of each locus, which appears to be driven by the VEGFA. Weighted risk scores have been shown to have higher power to detect association, although little is known about their bias and variance characteristics; because the weights being utilized were derived from the sample being analyzed, the

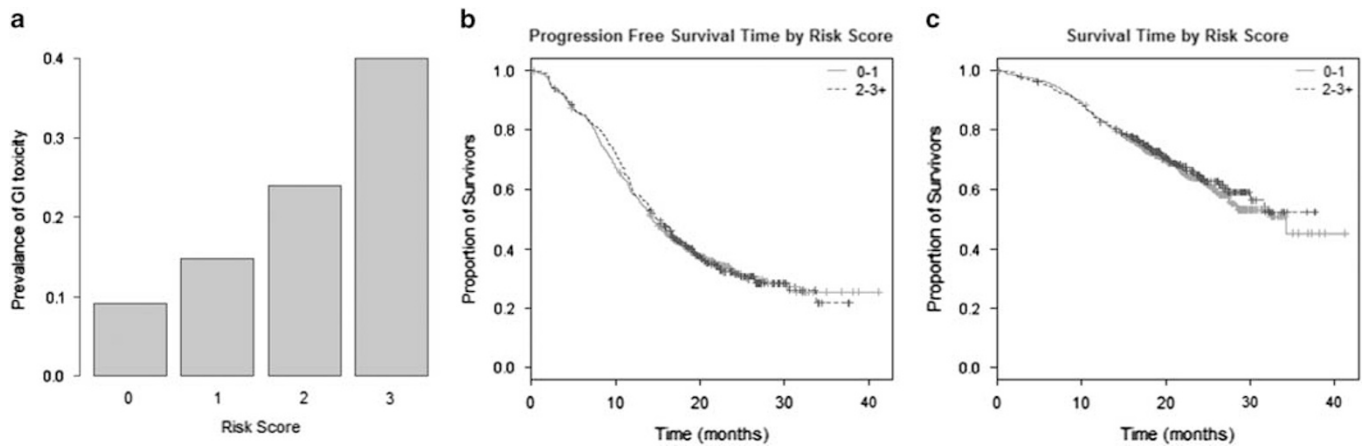


Figure 2. (a) Proportion of ovarian cancer cases experiencing GI toxicity by number of risk genotypes. (b) Progression-free survival. Time by number of risk genotypes. (c) Overall survival time by number of risk genotypes. GI, gastrointestinal.

Table 5. Frequencies (percentages) of cases and controls in each genetic risk category

Risk score	0	1	2	3+	Total
Cases	15 (10%)	54 (38%)	58 (41%)	16 (11%)	143
Controls	148 (22%)	309 (46%)	184 (28%)	24 (4%)	665
Total	163 (20%)	363 (45%)	242 (30%)	40 (5%)	808
Model odds ratio	1.0	1.89	3.56	6.71	

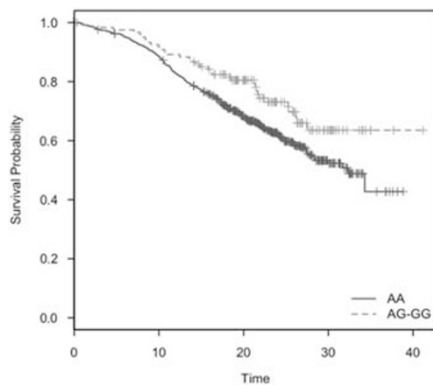


Figure 3. Survival time by rs9369421 genotype (Kaplan-Meier survival curve, log rank analysis).

estimated odds ratios may be overly optimistic. Nevertheless, the results of this study suggest novel genetic variants that increase risk of GI toxicity, which should be the focus of future studies.

To date, the most promising association between gene variants and platinum/taxane-induced grade III/IV GI toxicity in ovarian cancer patients was reported in 118 Korean patients that revealed a strong risk with carriage of the *ABCB1* 2677T or A allele (adjusted odds ratio, 9.74; 95% confidence interval, 1.59–15.85).¹² However, no significant association was found with this variant in our previous small-scale study¹³ and was not validated in this study either. Inconsistent results of *ABCB1* 2677G>T/A pharmacogenetics were seen in breast cancer, nonsmall cell lung cancer and prostate cancer patients receiving platinum/taxane regarding patients' survival time as well.^{14–16} *ABCB1* encodes a cross

membrane protein named P-glycoprotein that effluxes a wide range of structurally diverse substrates including xenobiotics and endogenous compounds.¹⁷ Substrates can interact with chemotherapy agents that may mask the impact of *ABCB1* variants on the pharmacokinetics of drugs,¹⁸ especially in cancer patients that multiple drugs are administered concomitantly. This could be a cause of inconsistent findings of *ABCB1* pharmacogenetics in different cancer patients.

Deeken *et al.*¹⁹ assessed 1256 SNPs in 170 drug metabolism and disposition genes in 74 prostate cancer patients who received either docetaxel and thalidomide, or docetaxel alone. Twenty-three genes were common between DMET 1.0 and the 123 genes assessed in our study (Supplementary Table 3). *ATP7A* and *CYP2D6* genes were correlated with docetaxel-related toxicity in the study by Deeken *et al.* ($P < 0.01$). However, this result was not replicated in either our previous small-scale study or the current, expanded study. *ATP7B* gene was identified as a significant marker for carboplatin/taxane-related GI toxicities ($P < 0.01$). This effect was not seen in the study by Deeken *et al.*¹⁹ Different combinations of chemotherapy may mask the genetic effect on drug response and toxicity. Moreover, the same gene or variants may also have a different role in different cancers when the same drug treatment is applied.

The findings of this study provides novel genes that may be correlated with platinum/taxane-based therapy, although it remains unclear given that few reports have disclosed an important role of any of the above genes in the metabolism or disposition of either agent. Moreover, the gene variations that are known to be involved in detoxification, disposition and response to carboplatin/taxane, including the seven genes overlapped in our previous study, were not associated with either toxicity or survival time. Although these genes may play a role in platinum/taxane metabolism pathways directly or indirectly, we can only speculate the mechanism of gene-drug interactions. For instance, the function of rs9825762of *SCN10A* gene was unclear but the rs3594 of glutathione reductase, *GSR*, gene was associated with oxidative stress status of children infected by malaria, which suggested a potential function of this variant.²⁰ The *ATP7B* (ATPase, Cu⁺⁺ transporting, beta polypeptide) gene encodes a protein called copper-transporting ATPase 2. This protein is found primarily in the liver and has a role in transporting copper from the liver to other organs. It is also important for the elimination of excess copper from the body through bile.²¹ *ATP7B* gene mutations may cause copper accumulation in tissues. As a result, toxic level of copper could impair the lining of the gastrointestinal tract and trigger nausea and vomiting when chemotherapy was

applied. Molecular genetic testing for *ATP7B* mutations is available in clinic, which is applied for diagnosis/prediction of a disease caused by *ATP7B* mutations, Wilson's disease.²² A study in preschool kids found that rs6900017 of *VEGFA* gene was associated with their lung function at school age, but not at birth that suggested a potential function of *VEGFA* variants in lung development.²³ Although no studies of the function of rs879825 and rs9369421 so far, they are in high linkage disequilibrium with rs6900017 as we found in our study. *VEGFA* also has been identified as the primary tumor angiogenesis factor and targeted by several newly developed agents for patients with metastatic carcinoma. However, these novel *VEGF* targeting agents including bevacizumab, sorafenib, sunitinib, brivanib and cilengitide have had only modest effect on human cancers.²⁴ In combination with standard chemotherapy, carboplatin–paclitaxel and bevacizumab moderately improved progression-free survival time in ovarian cancer patients according to two randomized phase III studies, GOG218 and ICON7.^{25,26} In addition, *VEGFA* gene variants were found to be related to the therapeutic outcome of oxaliplatin-based chemotherapy in metastatic colorectal cancer patients.²⁷ However, these variants were not associated with the GI toxicity of carboplatin-based chemotherapy in ovarian cancer patients. In this study, three variants of *VEGFA* gene were found highly correlated with chemotherapy-induced GI toxicity, which indicated a critical role of *VEGFA* in ovarian cancer patients who received a standard chemotherapy.

In summary, this study is the first step in defining a pharmacogenetics model for platinum/taxane-induced GI toxicity in ovarian cancer patients. Seven SNPs from four genes increased the risk of developing platinum/taxane-induced grade III–IV GI toxicity, whereas *VEGFA* gene was associated with patients' survival time. Our data suggest new genetic markers associated with platinum/taxane GI toxicity in ovarian cancer patients and the risk may vary between populations because the minor allele frequency of these risk variants are quite different in Caucasian, Asian and African populations. These genetic markers provide potential targets to modulate/inhibit GI toxicity in ovarian cancer patients. Further studies are required to validate these risk factors from *in vitro* models to independent clinical trials in multiple ethnic groups to clarify the potential role they might have in predicting chemotherapy-induced GI toxicity and to evaluate the value of these risk variants as therapeutic markers.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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