GSTP1 as a potential predictive factor for adverse events associated with platinum-based antitumor agent-induced peripheral neuropathy

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Abstract. Glutathione S-transferase (GST) exhibits antidotal effects on numerous drugs, including platinum-based antineoplastic drugs. Furthermore, GST Pi 1 (*GSTP1*) polymorphism is associated with peripheral neuropathy. In the present study, it was determined whether *GSTP1* can predict adverse events associated with platinum-based antitumor agent-induced peripheral neuropathy among Japanese patients. The subjects included 122 patients, among whom 105 patients had colorectal, 16 had gastric, and one patient had pancreatic cancer. It was indicated that wild type (AA) *GSTP1* was expressed in 99 patients (81.1%), whereas heterozygous (AG) and homozygous (GG) *GSTP1* polymorphisms were present in 22 (18.0%) and 1 (0.8%) patients, respectively. Among patients with colorectal cancer, the expression of homozygous *GSTP1* was observed in 88 patients (83.8%), whereas that of heterozygous *GSTP1* was observed in 17 patients (16.2%). Peripheral neuropathy of grade ≥3 occurred in 10 patients (9.5%) receiving mFOLFOX therapy (a biweekly cycle consisting of a 2-h infusion of 85 mg/m^2 oxaliplatin and 200 mg/m^2 leucovorin followed by a bolus administration of 400 mg/m^2 5-fluorouracil and a continuous 48-h infusion of 2,400 mg/m^2 5-fluorouracil) for colorectal cancer, which included 6 patients with the AA allele (6.8%) and 4 patients with the AG allele (23.5%). The number of peripheral neuropathy cases of grade ≥3 was increased among patients with the AG allele, compared with patients with the AA allele (P=0.032). In patients with gastric cancer, the AA and AG types of *GSTP1* were expressed in 11 (68.8%) and 5 (31.2%) patients, respectively. Cisplatin, administered to patients with gastric cancer, did not induce peripheral neuropathy. The aforementioned indicated that *GSTP1* genetic polymorphism is associated with peripheral neuropathy induced by oxaliplatin treatment for colorectal cancer, and therefore serves as a predictive marker. Furthermore, early dose reduction or drug withdrawal should be implemented depending on the severity of peripheral neuropathy as a potential method for reducing the number of patients discontinuing the drug, due to adverse events involving peripheral neuropathy.

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Introduction

Platinum-containing drugs, platinum-based drugs, vinca alkaloid, taxane-based drugs and bortezomib, a proteasome inhibitor, are cytocidal anticancer agents, which can induce peripheral neuropathy (1). Treatment using the aforementioned drugs must be discontinued when the symptoms of peripheral neuropathy are severe. Furthermore, these adverse events may persist for a long period of time, even following discontinuation of the drug (2). Therefore, management of peripheral neuropathy is important for patients who are treated with the aforementioned drugs.

Glutathione S-transferase (GST) has antidotal effects on numerous drugs, including platinum-based anticancer agents, and genetic polymorphism of GST Pi 1 *(GSTP1)* has been reported to be associated with the occurrence of peripheral neuropathy (3). *GSTP1* is involved in the metabolism of platinum-based anticancer drugs (4), and an association with neurotoxicity has been indicated when large amounts of cisplatin (CDDP) are administered for cancer treatment (5). A study has indicated that FOLFOX therapy using oxaliplatin, which is similar to the platinum anticancer drug CDDP, has a high response rate to colorectal cancer (6). Globally, *GSTP1* is considered as an indicator of response to chemotherapy and its adverse effects (7), although no definite conclusions have been derived. Reports on the expression of *GSTP1* polymorphisms in Japanese patients with gastrointestinal cancer indicated a negligible association with chemotherapy (8-11). In the present study, it was determined whether *GSTP1* polymorphism is a

predictive factor of peripheral neuropathy, which occurs as an adverse effect of exposure to platinum-based anticancer drugs, in Japanese patients with gastric, colorectal, and pancreatic cancer.

Materials and methods

Patient sample. A total of 122 patients (mean age 65 years; range 35-81 years), whose *GSTP1* status was determined at the Tokyo Medical University Hospital (Tokyo, Japan) between April 2005 and December 2008, were included in the present study. Among the following 122 patients: 105 (78 male and 27 female) patients had advanced recurrent colorectal cancer and were receiving mFOLFOX6 therapy (Table I); 16 (12 male and 4 female) patients had advanced recurrent gastric cancer and were receiving chemotherapy, including CDDP (Table II); and 1 female patient had advanced recurrent pancreatic cancer. Chemotherapy for gastric cancer included treatments of 10 patients with S-1/CDDP (SP), 4 patients with CPT-11/CDDP, 1 patient with 5-FU/CDDP (FP) and 1 patient with paclitaxel/CDDP. Treatment with 5-FU/CDDP was used as a chemotherapeutic agent for pancreatic cancer, but this case was firstly treated as pancreatic invasion of stomach cancer; however, the results of the autopsy changed the diagnosis to stomach invasion of pancreatic cancer.

The inclusion criteria were the following: ≥18 years of age, presence of metastatic or non-resectable locally advanced colorectal cancer, gastric and pancreatic cancer, exposure to platinum drugs for chemotherapy and Eastern Cooperative Oncology Group performance status ≤2 (12). The exclusion criteria included the presence of other active cancer types. In patients with colorectal cancer, the expression pattern of *GSTP1* was examined and the objective tumor response and adverse events that required discontinuation of mFOLFOX6 chemotherapy were identified. In patients with gastric and pancreatic cancer, the expression patterns of *GSTP1* and adverse events associated with CDDP chemotherapy were examined. Clinical antitumor effects, according to the Response Evaluation Criteria in Solid Tumors 1.1 guideline (13), and adverse event, according to the National Cancer Institute Common Toxicity Criteria 4.0, were evaluated (14).

The present study was approved by the Ethics Committee of the Tokyo Medical University Hospital (Tokyo, Japan). Furthermore, written informed consent was obtained from the patients prior to the trial. Patients were informed with all the necessary details concerning the study. Direct sequencing was used to analyze *GSTP1* polymorphism in 18 healthy individuals and was compared with the results of polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), in order to verify consistency of the results obtained using the two methods. The healthy individuals consisted of 14 males and 4 females (median age, 34 years) and they were tested between April and June 2005.

Determination of GSTP1 polymorphism. A single nucleotide substitution (A→G) at position 313 of *GSTP1* results in Ile-to-Val substitution at amino acid position 105. Depending on the zygosity [homozygous for the A allele (AA), heterozygous (AG) and homozygous for the G allele (GG)] of the allele, three common *GSTP1* variants, AA/wild type, AG and GG are generated, with the substitution decreasing or abolishing the activity of the encoded enzyme. Genomic DNA was extracted from 200 μl whole blood using a QiaAmp kit (Qiagen Inc., Valencia, CA, USA), according to the manufacturer's protocols. The Ile105Val polymorphism was analyzed using PCR-RFLP as described by Harries *et al* (15). The 40 μl reaction mixture contained 5 μl cell lysate, which was used as a template, 200 ng of each primer, 105 forward, 5'-ACCCCAGGCTCTATGGGAA-3' and 105 reverse, 5'-TGAGGGCACAAGAAGCCCCT-3'. The primerse were made and supplied by Eurofinsgenomics (Ohta, Tokyo, Japan), 2.0 mM magnesium chloride and 1.5 U Taq DNA polymerase (both from Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA, USA). Initial denaturation was performed at 95˚C for 5 min. The thermocycling conditions (30 cycles) were: Primer annealing at 55˚C for 30 sec, polymerization at 72˚C for 30 sec, and strand separation at 94˚C for 30 sec. A final polymerization step at 72˚C for 5 min was included to complete elongation. At the annealing temperature, the sample was digested using 5 U/ml *Bsm*AI (New England Biolabs, Inc., Ipswich, MA, USA), and the fragments were separated on a 3.0% Metaphor agarose gel (FMC BioProducts, Philadelphia, PA, USA) and visualized following staining with ethidium bromide at 55˚C for 12 h.

Direct sequencing of PCR products. PCR products (~50 μl) were purified using a QIAquick PCR purification kit (Qiagen GmbH, Hilden, Germany), according to the manufacturer's protocols, prior to sequencing. The concentration of the PCR product was estimated on a 2% agarose gel. The product (~250 ng) was used as the template in a double-stranded (ds) cycle sequencing reaction using the ds-DNA cycle sequencing system (Gibco; Thermo Fisher Scientific, Inc.), according to the manufacturer's protocols, and was labeled with (γ32P) dATP. Sequencing was performed from both directions separately following PCR with the 105 forward and 105 reverse primers according to the manufacturer's protocols. Cycling conditions included initial denaturation at 94˚C for 5 min followed by 20 cycles of denaturation at 94˚C for 30 sec, primer annealing at 47˚C for 60 sec and polymerization at 72˚C for 60 sec. The reaction was completed by 10 cycles of denaturation at 94˚C for 30 sec and polymerization at 72˚C for 60 sec. The PCR product sequence was entrusted to commercial-based vendors (Eurofinsgenomics).

Statistical analysis. The data are presented as the mean values. The SPSS 24.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The χ^2 test was performed for comparing response rates between the groups and an unpaired Student's t-test for comparing the means. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Analyzing GSTP1 polymorphism in healthy individuals. Analysis of *GSTP1* polymorphism of 18 healthy individuals using direct sequencing revealed that 15 patients harbored the AA allele, 2 harbored the AG allele and 1 harbored the GG allele (Fig. 1). All *GSTP1* single nucleotide polymorphism

Table I. Clinical information of patients with colorectal cancer.

Factors	Genotype AA (n=88)	Genotype AG (n=17)	P-value
Sex			0.04[a]
Male	62	16	
Female	26	1	
Median age, years	66	60	0.08
Primary site			0.27
Colon	49	7	
Rectum	39	10	
Stage[b]			0.63
II	10	1	
III	28	7	
IV	50	9	
Number of cycles of CDDP treatment			0.05
Adj	3	1	
1st	49	3	
2nd	26	11	
Following 3rd	10	2	
Cycle (median)	10	10	0.81
Timeframe			0.63
Synchronous	47	8	
Metachronous	41	9	
Cancellation reason			0.61
PD	35	4	
Toxicity with PN	25	7	
Toxicity without PN	18	4	
Other	10	2	

[a]P<0.05. [b]Staging according to the International Union Against Cancer Tumor-Node-Metastasis classification 8th edition (39). Adj, adjuvant chemotherapy; PD, progressive disease; PN, peripheral neuropathy.

Table II. Clinical information of patients with gastric cancer.

Factors	Genotype AA (n=11)	Genotype AG (n=5)	P-value
Sex			0.37
Male	9	3	
Female	2	2	
Median age, years	69	62	0.17
Number of cycles of CDDP treatment			0.71
1st	7	4	
2nd	1	0	
Following 3rd	3	1	
Median cycle	2	2	0.77
Cancellation reason			0.48
PD	7	4	
Toxicity with PN	0	0	
Toxicity without PN	4	1	
Other	0	0	

PD, progressive disease; PN, peripheral neuropathy.

Figure 1. Genotyping of GSTP1 polymorphism in healthy volunteers. Polymerase chain reaction-restriction fragment length polymorphism performed on samples collected from 18 healthy volunteers indicated that the homozygous *GSTP1* variant was present in one (arrow in lane 1) and heterozygous *GSTP1* polymorphism in two patients (arrows in lanes 15 and 17). GSTP1, glutathione S-transferase Pi 1.

(SNP) sites contained the ATC sequence for the homozygous AA allele, and the A/GTC (Fig. 2A) and GTC (Fig. 2B) sequences at the SNP position. These results of the direct sequencing were in accordance with those obtained using PCR-RFLP, thereby demonstrating the accuracy of the GST analysis method.

Expression of AA type and polymorphic GSTP1. In the entire study group, *GSTP1* harboring the AA allele (Ile/Ile) was expressed in 99 patients (81.2%). Furthermore, the AG (Ile/Val) and GG (Val/Val) variants of *GSTP1* were expressed in 22 (18.0%) and 1 (0.8%) patients, respectively. The mean age of the patients with AA and AG in *GSTP1* were 65.3 and 61.1 years, respectively, indicating no significant difference (P>0.05) between the AA and AG group. In patients with colorectal cancer, the AA (Ile/Ile) and AG (Ile/Val) polymorphic *GSTP1* were expressed in 88 (83.8%) and 17 (16.2%) cases, respectively. In patients with gastric cancer, the AA group and heterozygous polymorphic *GSTP1* were expressed in 11 (68.8%) and 5 (31.2%) cases, respectively.

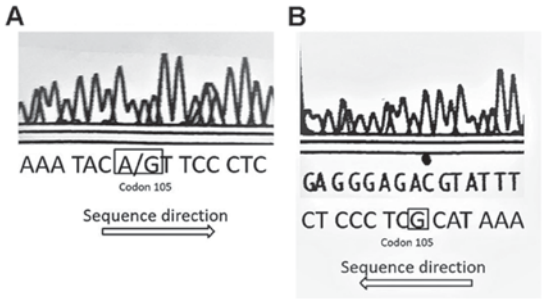

Figure 2. All GSTP1 SNP sites contained the ATC sequence for the homozygous AA allele, and the (A) A/GTC and (B) GTC sequences at the SNP position. SNP, single nucleotide polymorphism.

Patients with colorectal cancer. The proportion of female patients with colorectal cancer carrying the AA genotype of *GSTP1* was significantly higher than those with the AG form (P=0.04; Table I). There was no significant difference in the number of doses of mFOLFOX6 administered between the two groups, 9.6 times for the wild type *GSTP1* and 10.3 times for AG-*GSTP1* (P=0.81; Table I). Chemotherapy was discontinued due to disease progression in 39 patients (37.1%), peripheral neuropathy in 32 patients (30.5%), adverse events other than peripheral neuropathy in 22 patients (21.0%) and for other reasons in 12 patients (11.4%). Blood toxicity of grade ≥3 occurred in 13 cases harboring the AA genotype (14.8%) and 3 cases harboring the AG polymorphism (17.6%); however, the difference was not significant (P=0.76; Table III). Peripheral neuropathy of grade ≥3 was observed in 10 patients (9.5%), of which 6 patients harbored the AA (6.8%) and 4 harbored the AG genotype of *GSTP1* (23.5%). Peripheral neuropathy of grade ≥3 was observed at significantly increased rates in patients with AG polymorphism, compared with patients with the AA genotype (P=0.032; Table IV). The two groups did not indicate a significant difference in terms of non-hematological toxicity other than peripheral neuropathy of grade ≥3, with 12 patients of the AA type (13.6%) and 3 of the AG type (17.6%) indicating this effect (P=0.71; Table V). The therapeutic effect of mFOLFOX6 (complete response/partial response/stable disease/progressive disease/cannot be evaluated) was 7/23/34/21/3, respectively, for the AA type and 0/3/6/5/3, respectively, for the AG type patients. The aforementioned results were not statistically significant (P=0.67; Table VI).

Patients with gastric cancer. In patients with gastric cancer, *GSTP1* with the AA genotype was expressed in 11 patients (68.8%), whereas the AG polymorphic version was expressed in 5 patients (31.2%) (Table II). No significant differences were observed in the clinicoepidemiological data between the two groups. The median number of CDDP treatments was 2 cycles (range, 1-8 cycles). There was no significant difference between AA and AG genotype of *GSTP1* in terms of hematological toxicity during chemotherapy with CDDP, with 4 patients with AA type (36.4%) and no patient with AG type exhibiting hematological toxicity events of grade ≥3 (P=0.12; Table VII). Furthermore, non-hematological toxicity of grade ≥3 occurred in 4 cases harboring the AA allele (36.3%) and 2 cases bearing the AG allele (40.0%), exhibiting no significant difference between the two groups (P=0.89; Table VIII). In the present study, no patient exhibited peripheral neuropathy.

Patients with pancreatic cancer. With respect to adverse events of FP therapy, the GG version of *GSTP1* was observed only in a 71-year-old female patient with stage IV pancreatic cancer. They had grade 3 myelosuppression and gastrointestinal symptoms without peripheral neuropathy. Following chemotherapy, they developed progressive disease. The ratios of the various forms of *GSTP1* detected in patients with pancreatic cancer were as follows: Wild type, 44.7%; heterozygous polymorphism, 41.7%; and homozygous polymorphism, 13.6% (16).

Table III. *GSTP1* genotypes and hematological toxicity of grade ≥3 in patients with colorectal cancer.

	Hematological toxicity		
GSTP1 genotype	Yes	No	P-value
			0.76
AA	13	75	
AG	3	14	

GSTP1, glutathione S-transferase Pi 1. Grade, National Cancer Institute Common Toxicity Criteria 4.0.

Table IV. *GSTP1* genotypes and peripheral neuropathy in patients of grade ≥3 with colorectal cancer.

	Peripheral neuropathy		
GSTP1 genotype	Yes	No	P-value
			0.032
AA	6	82	
AG	4	13	

GSTP1, glutathione S-transferase Pi 1. Grade, National Cancer Institute Common Toxicity Criteria 4.0.

Table V. *GSTP1* genotypes and adverse events in grade ≥3 patients with colorectal cancer.

	Non-hematological toxicity except peripheral neuropathy		
GSTP1 genotype	Yes	No	P-value
			0.71
AA	12	76	
AG	3	14	

GSTP1, glutathione S-transferase Pi 1. Grade, National Cancer Institute Common Toxicity Criteria 4.0

Discussion

A total of two SNPs in *GSTP1* have been reported (17,18), one of which is the A→G substitution at nucleotide position 313 observed in the present study, where the amino acid Ile is replaced by Val at codon 105. The other is the C→T replacement at the nucleotide 341, in which the amino acid Ala at codon 114 is replaced by Val. These SNPs are associated with the sensitivity and adverse events accompanying oxaliplatin treatment (4). In the present study, the SNP status of *GSTP1* was determined based on the report of Lecomte *et al* (19), who indicated that oxaliplatin-induced neurotoxicity occurs

Table VI. Genotypes and the therapeutic effect of mFOLFOX6.

	Genotype		
Patient response	AA (n=88)	AG (n=17)	P-value
			0.67
CR	7	0	
PR	23	3	
SD	34	6	
PD	21	5	
NE	3	3	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, cannot be evaluated.

Table VII. *GSTP1* genotypes and hematological toxicity of grade ≥3 in patients with gastric cancer.

	Hematological toxicity		
GSTP1 genotype	Yes	No	P-value
			0.12
AA	4	7	
AG	0	5	

GSTP1, glutathione S-transferase Pi 1. Grade, National Cancer Institute Common Toxicity Criteria 4.0

Table VIII. *GSTP1* genotypes and non-hematological toxicity of grade ≥3 in patients with gastric cancer.

	Non-hematological toxicity except peripheral neuropathy		
GSTP1 genotype	Yes	No	P-value
			0.89
AA	4	7	
AG	2	3	

GSTP1, glutathione S-transferase Pi 1.

through the variant codon 105 of *GSTP1*. To the best of our knowledge, this is the first report in which *GSTP1* polymorphism was determined using PCR-RFLP for patients with colorectal, gastric or pancreatic cancer during the same timeframe.

Currently, platinum-based agents are being used as key drugs in chemotherapy for colon and gastric cancer. Oxaliplatin in mFOLFOX therapy is commonly used for non-resectable and advanced colon cancer (20). Similarly, CDDP and oxaliplatin are frequently used as important chemotherapeutic drugs for gastric cancer (21). However, it was repeatedly observed that one of the adverse effects of using platinum-based agents was the development of peripheral neuropathy, which significantly determined the course of subsequent treatment.

GST is a detoxification enzyme that eliminates drugs and toxins by binding to them *in vivo* (4). Any abnormality in GST affects platinum detoxification, which is presumed to result in an increased frequency of peripheral neuropathy (19). Administration of large doses of glutathione also reduces the frequency of neuropathy (5). Furthermore, GST-π, a sub-class of GST, is associated with the sensitivity of platinum-based agents (4). Moscow *et al* (22) reported that in all cases of colorectal cancer, GST-π expression was increased by 3.7-fold in the tumor tissue, compared with its matched control tissue. DNA-damaging agents crosslink the DNA in the cell, and intracellular glutathione eliminates DNA-damaging agents via ATP-binding cassette transporters. Therefore, GST-π serves an important role in mediating the interaction between the agent and glutathione (23). Additionally, glutathione administration suppresses neurotoxicity and blocks apoptotic cell death induced by tumor protein p53-dependent activation (24).

AA (Ile/Ile), AG (Ile/Val) and GG (Val/Val) types of *GSTP1* were observed in 58, 35, and 7% of Europeans, respectively in 2007 (7). According to the North American Gastrointestinal Intergroup Trial N9741 in USA, AA, AG and GG included 194 (41.9%), 220 (47.5%) and 49 (10.6%) patients out of the 463 patients included in the trial (25).

The prevalence of AA, AG and GG genotypes was 75.3, 22.9 and 1.8%, respectively, in Chinese populations (26). It was lower ratio in AG and GG than Europeans and American. The present study also identified an increased proportion of AA type patients (81.1%), compared with AG (18%) and GG (0.8%) type patients in Japan. It may be a racial difference. Genetic polymorphism of *GSTP1* is a predictive factor of oxaliplatin-induced peripheral neuropathy in patients with colorectal cancer (27). Furthermore, patients with GG polymorphism of *GSTP1* were more likely to discontinue FOLFOX due to neurotoxicity (24 vs. 10%; P=0.01) (7). AG or GG type genetic polymorphism has been reported to develop stronger disorder (Grade 3 and 4) for neuropathy (25). The results of the present study also revealed a significantly increased onset of peripheral neuropathy of grade 3 or 4 in AG type patients, compared with AA type patients (P=0.032), indicating that *GSTP1* may serve as a potential marker of adverse events. If *GSTP1* status could be used to determine patients with an increased likelihood of peripheral neuropathy onset, it would be easier for physicians and pharmacists to provide accurate instructions and check for subjective symptoms. To prevent adverse effects, a 'stop and go' method involving withdrawal of oxaliplatin alone (28) may be effective. Furthermore, this would help pre-determine the number of cycles of FOLFOXIRI-Bev, for which a maximum of 12 cycles was currently used in the Triplet plus Bevacizumab trial (29). FOLFIRI treatment, without oxaliplatin, as the first-line therapy may be therapeutically beneficial. Evaluating the risk of peripheral neuropathy based on the background of the patient and deciding on an individualized treatment strategy are also important. However, peripheral neuropathy of grade ≥3 has been reported to be more common for individuals with AA (Ile/Ile) type, compared with AG (Ile/Val) and GG (Val/Val) types (19), however these results are controversial.

These conflicting results may be attributed to the involvement of external factors other than *GSTP1*, which may include the following: *XRCC1* genetic polymorphism (30), exacerbation of symptoms due to hand-foot syndrome and weakened antidotal effects of oxaliplatin owing to hepatic failure. Therefore, this aspect warrants further investigation.

A number of studies indicate that *GSTP1* is a prognostic factor (4,26,31). The AG and GG types of *GSTP1* have a high response rate to FOLFOX treatment, and longer progression-free (12.0 vs. 6.0 months, P<0.01) and overall (25.0 vs. 16.0 months, P<0.01) survivals were observed in AG and GG types (26); however, other studies have reported that the prognosis of AA homozygotes of *GSTP1*-105 (Ile/Ile) is poor (4,26,31). Furthermore, according to a previous study, there has been no significant association reported between the expression of *GSTP1* and the therapeutic effect, as the group with *GSTP1* overexpression was resistant to platinum-based drugs with poor prognosis (32). This indicates that *GSTP1* may be beneficial in designing treatment strategies.

In the present study, there were no significant differences in hematological or non-hematological toxicity during chemotherapy with CDDP for gastric cancer, with respect to *GSTP1* expression. Furthermore, there were no adverse events of peripheral neuropathy. Peripheral neuropathy associated with CDDP treatment has been reported to occur in a dose-dependent manner, with neurotoxic events starting to appear at a total dose of 250-500 mg/m^2 (body surface) (33). Additionally, these events occur in 50% of patients at a total dose of 900 mg/m^2 and in 100% of patients at a total dose of 1,300 mg/m^2 (33). A single dose of CDDP for gastric cancer in SP therapy is 60 mg/m^2, and therefore, the total dose was not notably high, which may have been one of the reasons that patients did not develop peripheral neuropathy in the present study. Liu *et al* (34) reported that in gastric cancer patients treated with oxaliplatin, they harboring AG and GG polymorphisms of GSTP1 had stronger neurological, gastrointestinal disorders and hematologic toxicity (Grade ≥3) than those of AA.

However, this remains controversial with a number of reports stating that *GSTP1* is not a predictive factor of the efficacy of chemotherapy (35). A number of reports also indicated that *GSTP1* is not a prognostic factor (8,36,37). In addition to the reports on the association of *GSTP1* with the metabolism of anticancer agents, a number of previous studies reported that the GG polymorphism is significantly more common in patients with gastric cancer, compared with healthy individuals, indicating that *GSTP1* is associated with gastric carcinogenesis (9,10). In particular, the aforementioned association was prominent among Asians (11). Furthermore, *GSTP1* has been associated with the onset of gastric cancer (38); however, it was not associated with disease prognosis (35,36). Owing to the increase in the number of novel anticancer drugs and advancements in the methods of administration, cancer prognosis has improved significantly (21). Therefore, *GSTP1* status alone may not be a viable prognostic factor.

The limitation of the present clinical study was that the platinum-based drug was not administered at the same time for patients with colon and gastric cancer as the first-line of treatment. Therefore, it was not possible to achieve a good comparison of progression-free or overall survival between the two groups.

The results of the present study indicate that the *GSTP1* genetic polymorphism is associated with peripheral neuropathy induced by oxaliplatin administered for treating colon cancer, and, therefore may be an effective prognostic marker. Early dose reduction or cessation according to the severity of peripheral neuropathy may reduce the number of patients who discontinued treatment, due to peripheral neuropathy. However, the frequency of peripheral neuropathy in patients harboring the AG polymorphism observed in the present study was low (22%), compared with patients from Western countries (51%) reported in an earlier study (38). Therefore, it is unclear whether clinically sufficient results were obtained. To the best of our knowledge, the number of conclusive reports on factors that predict adverse effects of platinum-based agents for gastric cancer is limited; therefore future investigation on the aforementioned topic is required.

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Availability of data and material

The datasets acquired during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SK designed the study and wrote the initial draft of the manuscript. KK contributed to analysis and interpretation of data and assisted in the preparation of the manuscript. All other authors (YM, KN, MS, TM, ME, TS, TI, MH, YN and AT) contributed to data collection and interpretation, and critically reviewed the manuscript. All authors have approved the final version of the manuscript and have agreed to be accountable for all aspects of the study, including answering of questions related to the accuracy or integrity of the data.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Tokyo Medical University hospital and written informed consent was obtained from all patients.

Patient's consent for publication

Consent for publication was obtained from all participants.

Competing interests

The authors declare that they have no competing interests.

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