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ORIGINAL ARTICLE

Pharmacogenetic association between *GSTP1* genetic polymorphism and febrile neutropenia in Japanese patients with early breast cancer

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Abstract
Background Genetic risk factors for febrile neutropenia (FN), the major adverse event of perioperative chemotherapy for early breast cancer, remain unclear.
Methods This study retrospectively explored pharmacogenetic associations of single nucleotide polymorphisms (SNPs) of the uridine glucuronosyltransferase 2B7 (*UGT2B7*, rs7668258), glutathione-*S*-transferase pi 1 (*GSTP1*, rs1695), and microcephalin 1 (*MCPH1*, rs2916733) genes with chemotherapy-related adverse events in 102 Japanese women who received epirubicin and cyclophosphamide as perioperative chemotherapy for early breast cancer.
Results The allele frequencies for all of the SNPs were in concordance with the Hap-Map data of Japanese individuals. Among the 24 patients who had FN at least once during all courses of chemotherapy, 23 had the A/A genotype, and 1 had the A/G genotype of the *GSTP1* polymorphism (rs1695, $P = 0.001$); 23 of the 70 patients with the A/A genotype had FN, as compared with only 1 of the 32 patients with the A/G and G/G genotypes. The genotype distributions of the *UGT2B7* and *MCPH1* polymorphisms did not differ between the patients who had FN or grade 3/4 neutropenia and those who did not.
Conclusion Among Japanese women who received epirubicin and cyclophosphamide as perioperative chemotherapy for early breast cancer, those with the A/A genotype of the *GSTP1* polymorphism (rs1695) were more likely to have FN.

Keywords Breast cancer · Polymorphism · GSTP1 · Epirubicin · Cyclophosphamide

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Introduction

Genetic risk factors for febrile neutropenia (FN), the major adverse event of perioperative chemotherapy for early breast cancer, remain unclear. Combination chemotherapy with epirubicin and cyclophosphamide is a widely used perioperative regimen for early breast cancer. Epirubicin, an anthracycline drug associated with neutropenia, FN, and cumulative cardiac toxicity, is predominantly glucuronidated and inactivated by the drug metabolizing enzyme uridine glucuronosyltransferase 2B7 (UGT2B7) [1]. The enzymatic activity of UGT2B7 thus plays an important role in interindividual variation in the pharmacological effects of epirubicin. Previous in vitro experiments using microsomes from human liver have shown that polymorphisms of the *UGT2B7* gene account

for interindividual variation in the formation of morphine 3-glucuronide [2]. A study of 123 patients with breast cancer showed that a single nucleotide polymorphism (SNP), a transition (T to C) at position -161 in the *UGT2B7* gene (rs7668258), decreased epirubicin clearance and exacerbated grade 3/4 neutropenia among patients who had the C/C genotype as compared with those who had the C/T and T/T genotypes [3]. On the other hand, cyclophosphamide, an alkylating agent, is bioactivated by cytochrome P450 in vivo to its active metabolites, which are also associated with neutropenia, nausea or vomiting, and anorexia. The active metabolites are subsequently detoxified by conjugation with glutathione, a step catalyzed by glutathione-*S*-transferase pi 1 (GSTP1) [4]. Genetic polymorphism involving an A to G transition (rs1695) at codon 105 of the *GSTP1* gene results in amino acid substitution from isoleucine (IIe) to valine (Val), decreasing the enzymatic activity of GSTP1 and altering the pharmacokinetics of cyclophosphamide [5]. A study of 405 patients with early breast cancer showed that the A/A genotype of rs1695 is associated with a higher risk of grade 3/4 neutropenia than the A/G and G/G genotypes [6]. Moreover, a genome-wide association study (GWAS) analysis of 270 Japanese patients with breast cancer found that a polymorphism involving a transition (T to C, rs2916733) in intron 9 of the microcephalin 1 (*MCPH1*) gene encoding a DNA damage response protein is associated with an increased risk of epirubicin-related neutropenia. Patients with the T/C or C/C genotypes had higher risks of neutropenia than those with the T/T genotype [7].

To confirm and extend these findings, we investigated the *UGT2B7*, *GSTP1*, and *MCPH1* polymorphisms in DNA samples from Japanese women who received epirubicin and cyclophosphamide as perioperative chemotherapy for early breast cancer to test the hypothesis that these polymorphisms are related to toxicity and disease-free survival (DFS).

Patients and methods

Patients

Japanese women with early breast cancer who had received adjuvant chemotherapy before or after breast surgery at Nagoya University Hospital were retrospectively studied. All patients had been treated at the outpatient chemotherapy center and gave written informed consent to participate in this study. The study protocol was approved by the Institutional Review Board of Nagoya University Hospital, and the study was conducted in accordance with the Declaration of Helsinki.

Treatment and supportive care in routine practice

All patients received either FEC100 or EC regimens administered in accordance with standardized procedures, including infusion volume and rate. The FEC100 regimen consisted of epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2, and 5-fluorouracil (5-FU) 500 mg/m^2, given on day 1 of a 21-day cycle. The EC regimen consisted of epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2, given on day 1 of a 21-day cycle. The patients were scheduled to receive 4 or 6 cycles of the FEC100 regimen or 4 cycles of the EC regimen, depending on their risk of relapse.

Granulocyte colony-stimulating factor (G-CSF) was usually used in accordance with the package insert: e.g., in patients with an absolute neutrophil count of <500/μl or <1,000/μl during a febrile state. Prophylactic antibiotics were not used to prevent FN, and other supportive treatments in individual patients were essentially left to the discretion of the treating physicians. In patients with FN, the clinical need for hospitalization for the treatment of toxicity was assessed by the assigned physician, in principle.

Toxicity assessments

Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Grade 2, 3, and 4 neutropenia was defined as an absolute neutrophil count of <1,500–1,000/μl, <1,000–500/μl, and <500/μl, respectively. Grade 3 FN was defined as the occurrence of at least one episode of fever with an axillary temperature higher than 38.0 °C accompanied by an absolute neutrophil count of <1,000/μl during treatment. Body temperature was routinely measured at the outpatient chemotherapy center immediately before the administration of each course of chemotherapy and at home by the patients themselves ad libitum. The worst grade toxicity that occurred during the first course of chemotherapy and all courses of chemotherapy was recorded and included in analysis. Blood tests were performed at least once immediately after starting the first course of chemotherapy. Nonhematologic toxicity was evaluated according to the CTCAE by well-trained oncology nurses and medical oncologists who dedicated themselves to routine practice in an outpatient chemotherapy center. A standardized checklist was used to assess toxicity and maintain grading consistency.

Data collection

Clinical information relevant to chemotherapy was obtained from the patients' medical charts and included the

worst grade toxicity (FN, neutropenia, and other major toxicity) during the first course and all courses of chemotherapy, DFS, the prophylactic use of G-CSF for neutropenia, and hospitalization.

Genomic analysis

The genotypes of *GSTP1* (Ile105Val, rs1695), *UGT2B7* (C-161T, rs7668258), and *MCPH1* (rs2916733) were determined using TaqMan® SNP Genotyping Assays (Applied Biosystems, Foster City, CA). *UGT1A1*6* (Gly71Arg, rs4148323) was also evaluated as a control [8]. Genomic DNA was extracted from whole blood using a QiaAmp Blood Mini kit® (Qiagen, Valencia, CA), following the manufacturer's protocol. Polymerase chain reactions (PCR) were performed using 10 ng of genomic DNA diluted in DNase-RNase-free water, 10 μL of TaqMan® Universal PCR Master Mix (2x) (Applied Biosystems), and 1.0 μL of TaqMan® SNP Genotyping Assays (Assay ID: C-27827970-40, C-3237198-20, C-15850560-10, and C-559715-20, respectively; Applied Biosystems) in a total volume of 20 μL on a StepOnePlus® Real-Time PCR system (Applied Biosystems). The PCR conditions were 95 °C for 20 s, followed by 40 cycles of 95 °C for 3 s and 60 °C for 20 s. We tested the relations of the genotypes of the *UGT2B7*, *GSTP1*, and *MCPH1* genes to clinical events, including toxicity (FN and neutropenia), DFS, the prophylactic and therapeutic use of G-CSF for neutropenia, and hospitalization.

Statistical analysis

Fisher's extract test was used to test the statistical significance of relations between clinical events and genotypes. DFS was defined as the time from the date of operation to the date of documentation of initial recurrence or death from any cause and was estimated according to the Kaplan–Meier method. DFS was compared using the generalized log-rank test. All statistical analyses were performed with IBM® SPSS® Statistics, Version 20 (SPSS Inc., Chicago, IL). *P* values of <0.05 were considered to indicate statistical significance.

Results

Among a total of 480 Japanese women with breast cancer who received FEC100 or EC regimens at Nagoya University Hospital from May 2006 through July 2013, 102 patients (21.3 %) gave informed consent and participated in this study (Table 1). The median number of administered treatment cycles was 4 (range 4–6) among the 61 patients who received FEC100 regimens and 4 (range 2–4) among the 41 who received EC regimens. The median follow-up after surgery was 967 days (range 92–1,859 days) in the FEC100 group and 1,105 days (range 209–1,959 days) in the EC group. The median number of blood tests was 2 (range 1–5; 1 time for 5 patients, 2 for 64, 3 for 27, 4 for 5, and 5 for 1) during the first course of chemotherapy (from day 1 to day 21) and 2 (range 1–5) in every subsequent course. Blood tests were usually performed on day 1 (before chemotherapy) and day 14.

Table 1 Patient characteristics ($n = 102$)

Characteristic	Patients	
	N	%
Age (years) median age (years, range)	56 (31–77)	
Menopausal status		
Premenopausal	43	42.2
Postmenopausal	59	57.8
Estrogen-receptor status		
Positive	56	54.9
Negative	46	45.1
HER2 status		
Positive	49	48.0
Negative	53	52.0
Chemotherapy		
Neoadjuvant FEC100	12	11.8
Adjuvant FEC100	49	48.0
Adjuvant EC	41	40.2
Performance status		
0	99	97.0
1	3	3.0
Median ejection fraction (%) (range)		62.9 (57.7–84.8)

FEC100 5-fluorouracil/epirubicin/cyclophosphamide, *EC* epirubicin/cyclophosphamide

During the first course of chemotherapy, 22 patients (22 %) had FN, and 78 (76 %) had grade 3/4 neutropenia (Table 3). The median time to the neutrophil nadir was 14 days (range 7–14) during the first course, albeit laboratory monitoring was not strictly standardized in this study. During the entire treatment period, 24 patients (24 %) had FN and 90 (88 %) had grade 3/4 neutropenia (Table 4). G-CSF was used to manage grade 3/4 neutropenia at least once in 45 patients (44.1 %) during the first course and in 56 patients (54.9 %) during the entire treatment period. Although G-CSF was used primarily when patients had FN, the patients in this study frequently received it for prophylaxis against infection if they had non-FN (29 patients during the first course, 35 patients during the entire treatment period) or if they had had severe

Table 2 UGT2B7, GSTP1, MCPH1, and UGT1A1 polymorphisms

Genotype	*N*	%	Hap-Map JPT (%)
UGT2B7 (rs7668258)			
C/C	52	51.0	48.2
C/T	40	39.2	42.2
T/T	10	9.8	9.4
GSTP1 (rs1695)			
A/A	70	68.6	82.6
A/G	26	25.5	16.3
G/G	6	5.9	1.2
MCPH1 (rs2916733)			
T/T	24	23.5	20.9
T/C	51	50.0	57.0
C/C	27	26.5	22.1
UGT1A1*6 (rs4148323)			
G/G	72	70.6	75.3
A/G	28	27.4	23.5
A/A	2	2.0	1.2

neutropenia in their previous cycles of chemotherapy (33 patients). Emergency hospitalization was required for the treatment of grade 3 nausea or vomiting in 2 patients (1 patient during all courses and 1 from the second to fourth courses) and for the treatment of a non-pathological fracture of the heel bone that was unrelated to chemotherapy in 1 patient. Because only 2 patients were admitted for the treatment of toxicity, hospitalization was not evaluated further. Other adverse events, such as anemia, thrombocytopenia, diarrhea, and fatigue, were all grade 2 or milder.

The genotype distributions were in accordance with Hardy–Weinberg equilibrium, and the allele frequencies were in concordance with the Hap-Map data of Japanese individuals (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi? [9], Table 2). During the first course of chemotherapy, the incidence of FN was higher in the patients who had A/A genotype than in those with A/G and G/G genotypes for the *GSTP1* polymorphism rs1695 ($P = 0.002$), but no clear associations with FN were found for the other polymorphisms (Table 3). For the *GSTP1* polymorphism, G-CSF use during the first course was more frequent in the patients with the A/A genotype than in those with the A/G and G/G genotypes of rs1695 ($P = 0.033$). During the entire treatment period, FN and G-CSF use were more common in patients with the A/A genotype of rs1695 ($P = 0.001$, $P = 0.02$, respectively), but were unrelated to the other polymorphisms (Table 4), similar to the first course. Among the 70 patients with the A/A genotype of rs1695, 21 and 23 had FN during the first and all courses of chemotherapy, respectively. In contrast, only 1 of the 32 patients with the A/G and G/G genotypes had FN during the first course of chemotherapy. The proportion of patients who received the FEC100 regimen was higher among those with the A/G and G/G genotypes ($n = 25$, 78 %), who were less likely to have FN in this study, than those with the A/A genotype ($n = 36$, 51 %), who were more likely to have FN. None of the polymorphisms investigated in this study were significantly associated with grade 3/4 neutropenia during either the first course or the entire treatment period (Tables 3, 4). The associations were also not significant when the analysis was limited to the 61 patients who had grade 4 neutropenia. The *UGT1A1*6* polymorphism was not significantly associated with grade 3/4 neutropenia, FN, or G-CSF use.

None of the SNPs were associated with DFS. Among the 102 patients, 12 (11.8 %) had recurrence (lung, 4; bone, 3; liver, 2; pleura, 2; lymph nodes, 2; brain, 1). For the *GSTP1* polymorphism of rs1695, DFS did not differ between patients with the A/A genotype and those with the A/G and G/G genotypes (median, 1102 and 559 days, respectively, $P = 0.844$, Fig. 1).

Discussion

This study investigated pharmacogenetic relations of the *UGT2B7*, *GSTP1*, and *MCPH1* polymorphisms to toxicity, such as FN and neutropenia, and DFS among Japanese women who received epirubicin and cyclophosphamide as perioperative chemotherapy for early breast cancer. Patients with the A/A genotype of the *GSTP1* polymorphism rs1695 were more likely to have FN than those with the A/G and G/G genotypes during both the first course of chemotherapy and the treatment period as a whole; however, no clear associations with FN were found for the other polymorphisms. On the other hand, none of the polymorphisms investigated in this study were significantly associated with grade 3/4 neutropenia during the first course or the entire treatment period, despite the increased incidence of FN among patients with the A/A genotype of rs1695. The discrepancy between the incidence of FN and that of neutropenia might have been attributed to sporadic and unscheduled blood testing during chemotherapy, potentially resulting in missing the neutrophil nadir in some patients and underestimation of the severity of neutropenia in others. During the first course as well as all courses of chemotherapy, G-CSF was more commonly used in patients with the A/A genotype of rs1695, which reflected the higher incidence of FN among patients with this genotype.

The phenotypic effects of the *GSTP1* polymorphism of rs1695 have been inconsistent among studies. Lack of consistent results is most likely attributed in part to the different patient characteristics among studies. Our finding that the A/A genotype is related to increased toxicity agrees

Table 3 Associations between the polymorphisms and neutropenia, FN, and G-CSF use (the worst grade during the first course)

Genotype	*n*	FN		*P*	Neutropenia		*P*	G-CSF		*P*
		− ($n = 80$)	+ ($n = 22$)		G1/2 ($n = 24$)	G3/4 ($n = 78$)		− ($n = 57$)	+ ($n = 45$)	
UGT2B7 (rs7668258)										
C/C	52	41	11	1.000	15	37	0.246	30	22	0.842
C/T and T/T	50	39	11		9	41		27	23	
GSTP1 (rs1695)										
A/A	70	49	21	0.002	17	53	1.000	34	36	0.033
A/G and G/G	32	31	1		7	25		23	9	
MCPH1 (rs2916733)										
T/T	24	20	4	0.583	5	19	0.791	16	8	0.249
T/C and C/C	78	60	18		19	59		41	37	
*UGT1A1*6* (rs4148323)										
G/G	72	55	17	0.599	17	55	1.000	41	31	0.828
A/G and A/A	30	25	5		7	23		16	14	

FN febrile neutropenia, *G-CSF* granulocyte colony-stimulating factor

Table 4 Associations between the polymorphisms and neutropenia, FN, and G-CSF use (the worst grade during the entire treatment period)

Genotype	*n*	FN		*P*	Neutropenia		*P*	G-CSF		*P*
		− ($n = 78$)	+ ($n = 24$)		G1/2 ($n = 12$)	G3/4 ($n = 90$)		− ($n = 46$)	+ ($n = 56$)	
UGT2B7 (rs7668258)										
C/C	52	39	13	0.817	6	45	1.000	21	31	0.426
C/T and T/T	50	39	11		6	45		25	25	
GSTP1 (rs1695)										
A/A	70	47	23	0.001	7	63	0.510	26	44	0.02
A/G and G/G	32	31	1		5	27		20	12	
MCPH1 (rs2916733)										
T/T	24	19	5	0.791	3	21	1.000	14	10	0.163
T/C and C/C	78	59	19		9	69		32	46	
*UGT1A1*6* (rs4148323)										
G/G	72	54	18	0.798	9	64	1.000	32	40	1.000
A/G and A/A	30	24	6		3	26		14	16	

FN febrile neutropenia, *G-CSF* granulocyte colony-stimulating factor

with the results of several previous studies showing that the A/A genotype is associated with an increased risk of neurotoxicity among patients who receive oxaliplatin and docetaxel [10–12]. On the other hand, among 94 patients with breast cancer who received chemotherapy with cyclophosphamide, epirubicin, and 5-fluorouracil in a previous study, the G/G genotype was associated with a higher risk of grade 3 and 4 hematologic toxicity [13]. Other studies have linked the G allele to increased risks of irinotecan toxicity among patients with colorectal cancer and cyclophosphamide-related toxicity in patients with systemic lupus erythematosus [14, 15]. Preclinical studies have shown that the catalytic activity of GSTP1 is lower in patients with the G/G genotype than in those with the A/A genotype [16, 17]. Because GSTP1 is also involved in the regulation of Jun N-terminal kinase (JNK) signaling pathway, polymorphisms might alter functions related to protecting cells from drug toxicity [18].

Our study found no evidence of a difference in toxicity associated with the *UGT2B7* genotype of rs7668258, which is inconsistent with the results of previous studies showing that rs7668258 had impacts on neutropenia and epirubicin clearance [3], as well as on blood concentrations of morphine and lamotrigine [19, 20]. Given that a GWAS analysis of Japanese patients also found that rs7668258 is not a predictor of epirubicin-related toxicity [7], rs7668258

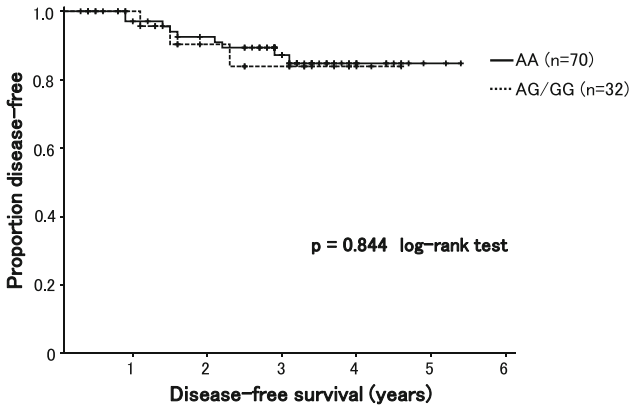

Fig. 1 Kaplan–Meier curves showing the relation between disease-free survival and GSTP1 A313G genotype ($p = 0.844$). The x axis shows the numbers of years from an operation to recurrence

might have different impacts among distinct ethnic populations. Although a previous study of 205 patients with breast cancer reported that rs7439366, another *UGT2B7* polymorphism in complete linkage disequilibrium with rs7668258 [9], is related to DFS after epirubicin-based chemotherapy, none of the SNPs were associated DFS in our study [21].

A previous GWAS analysis of Japanese patients with breast cancer demonstrated that the T/C or C/C genotypes of rs2916733 in *MCPH1* are associated with higher risks of neutropenia than the T/T genotype [7]. In contrast, rs2916733 was not significantly related to toxicity such as FN or neutropenia or to DFS in our study. Because MCPH1 protein is thought to participate in repairing DNA damage, the pharmacogenomic functions of *MCPH1* polymorphism should be further investigated.

This retrospective study had several limitations, including a relatively small number of patients and lack of pharmacokinetic analysis. In addition, blood tests were not performed according to a consistent schedule among the patients. Despite these limitations, our results suggest that the *GSTP1* polymorphism of rs1695 might be a useful predictor of FN and neutropenia.

In conclusion, among Japanese women who received epirubicin and cyclophosphamide for early breast cancer, those with the A/A genotype of the *GSTP1* polymorphism (rs1695) were more likely to have FN than those with the A/G and G/G genotypes. Because our study was retrospective and performed in a single institution, the validity of our findings should be confirmed in independent data sets.

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Conflict of interest The authors declare that they have no conflict of interest.

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