RESEARCH COMMUNICATION

Effects of Genetic Polymorphisms in the ABCB1 Gene on Clinical Outcomes in Patients with Gastric Cancer Treated by Second-line Chemotherapy

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Abstract

Objective: Tumor cells that overexpress P-glycoprotein (Pgp) may be resistant to several anticancer agents due to altered pharmacokinetics and reduced intracellular concentrations of the anticancer agents. Pgp is encoded by the ATP binding cassette gene B1 (ABCB1). To our knowledge, only one previous report has evaluated the effect of ABCB1 gene polymorphisms on clinical outcomes of gastric cancer. The purpose of this analysis was to evaluate the impact of genetic polymorphisms of the ABCB1 gene on clinical outcomes in patients with advanced gastric cancer (AGC) treated with second-line chemotherapy. Methods: We retrospectively analyzed the impact of ABCB1 gene polymorphisms (ABCB1 3435C>T) on clinical outcomes in 100 patients with AGC who received second-line chemotherapy. Results: Median overall survival (OS) since the initiation of second-line chemotherapy was 6.0 months (95% confidence interval [CI], 4.8 to 8.0 months), and median progression-free survival (PFS) was 2.7 months (95% CI, 2.1 to 3.4 months). In a multivariate analysis of PFS, a 3435 CC polymorphism (n = 45) was significantly associated with longer PFS compared with the CT/TT type polymorphism (n = 55), with borderline significance (PFS of 3.2 months vs. 2.2 months, respectively; HR 1.50; 95% CI, 0.98-2.30; P = 0.061). ABCB1 3435 C>T polymorphisms were not associated with OS. No interaction was seen between ABCB1 polymorphisms and treatment regimens. Conclusion: Genetic polymorphisms of ABCB1 3435C>T might have a possible impact on clinical outcomes of second-line chemotherapy in AGC. Further prospective evaluation using a larger sample size is required.

Keywords: gastric cancer - ABCB1 polymorphisms - chemotherapy

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Introduction

P-glycoprotein (Pgp) is a plasma membrane protein that works as an efflux pump to transport natural products or toxins (Fromm et al., 2004). Pgp is expressed in normal cells, such as peripheral blood mononuclear cells, intestinal cells, renal cells, hepatic cells, and cells of the blood-brain barrier. Pgp protects cells and organs from toxic substrates. Pgp is comprised of two hydrophobic transmembrane domains that dimerize and form a pore. Several hydrophobic chemotherapeutic agents, such as paclitaxel, docetaxel and irinotecan, are known to be substrates of Pgp (Kolesar et al., 2009). Therefore, tumor cells that overexpress Pgp may be resistant to these anticancer agents due to altered pharmacokinetics and reduced intracellular concentrations.

Pgp is encoded by the ATP binding cassette gene B1 (ABCB1). More than 50 single nucleotide polymorphisms (SNPs) are identified for ABCB1, and their effects on Pgp expression and substrate distribution have been evaluated (Fromm, 2002; Kolesar et al., 2009). Although several reports have investigated the clinical impact of these polymorphisms on clinical outcomes after chemotherapy in several types of cancer (Green et al., 2006; Marsh et al., 2007; Johnatty et al., 2008; Pan et al., 2008; Sissung et al., 2008; Chang et al., 2009), to our knowledge, there is only one report that analyzed small number of patients with advanced gastric cancer (AGC) treated with paclitaxel (Chang et al., 2010).

Key chemotherapeutic agents for gastric cancer

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are fluorouracil/fluoropyrimidine, platinum, taxanes (paclitaxel and docetaxel) and irinotecan (NCCN Clinical Practice Guidelines in Oncology). Among them, the combination of fluorouracil/fluoropyrimidine and platinum is commonly used as first-line chemotherapy in Japan (Koizumi et al., 2008), while taxanes or irinotecan are frequently used in the second-line setting. Since taxanes and irinotecan are known to be substrates of Pgp, we hypothesized that genetic polymorphisms in ABCB1 may have an effect on clinical outcomes in patients with gastric cancer who received second-line chemotherapy in Japan.

To address this issue, we carried out a retrospective cohort study using data from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC), Japan.

Methods

Patients

Cases were selected from the database of the HERPACC, conducted at Aichi Cancer Center Hospital (ACCH). Details of the HERPACC have been described elsewhere (Tajima et al., 2000; Hamajima et al., 2001). In brief, 23,408 HERPACC-enrolled, first-visit outpatients treated between January 2001 and November 2005 were asked to provide blood samples in addition to information on lifestyle factors. Of those who participated, 22,727 (97.1%) completed the questionnaire satisfactorily and were enrolled in the HERPACC. The study was approved by the Institutional Ethical Committee of ACCH.

In the present study, cases of patients with newly diagnosed AGC who participated in the HERPACC with the following criteria were included: (1) presence of histologically or cytologically proven, inoperable gastric cancer (2) performance status according to the Eastern Cooperative Oncology Group criteria of 0-2 (3) treatment with second-line chemotherapy after failure of first-line chemotherapy (4) available blood samples.
A total of 100 patients with AGC were included in this study. Detailed patient characteristics prior to initiation of second-line chemotherapy were acquired from the hospital's patient records.

Evaluation of genetic polymorphisms

DNA of each subject was extracted from the buffy coat fraction with the DNA Blood mini Kit (Qiagen K.K., Tokyo, Japan). Genotyping for the ABCB1 ABCB1 3435T>C (dbSNP ID: rs1045642) was based upon TaqMan Assays (Applied Biosystems, Foster City, CA). Five percent of the samples were examined in duplicate to ensure consistency.

Evaluation of treatment and statistical methods

The primary purpose of this study was to evaluate the association between genetic polymorphisms of ABCB1 and progression-free survival (PFS) or overall survival (OS). PFS associated with second-line chemotherapy was measured from the beginning of treatment to the date of disease progression, which was evaluated by each physician. PFS with first-line chemotherapy was also measured from the beginning of treatment to the date of disease progression. OS was defined as the interval between the date of initiation of second-line chemotherapy to the date of death or last follow-up using the Kaplan-Meier method. Vital status or disease status was confirmed by checking of medical record at the last date of follow-up visit. In the case of lost to follow-up, vital status was confirmed by census registration conducted annually.

To evaluate the effect of genetic polymorphisms on PFS and OS, univariate and multivariate Cox proportional hazards modeling was applied. Therefore, a measure of association in this study was the hazard ratio (HR) along with a 95% confidence interval (95% CI). Forward and backward stepwise methods were used for model building using threshold P values of 0.10 for inclusion and 0.20 for exclusion. Distribution of subject characteristics was assessed by the chi-square test or the Fisher exact test, as appropriate. Statistical analyses were performed using STATA ver. 10 (StataCorp LP, College Station, TX, USA). All tests were 2-sided, and P values less than 0.05 were considered statistically significant.

Results

Patient characteristics and survival

Detailed characteristics of the 100 patients analyzed are shown in Table 1. All patients received fluorouracil/fluoropyrimidine with or without cisplatin as first-line chemotherapy, with a median PFS of 5.6 months (95% CI: 4.5-6.6 months). Among the 100 patients, 61 patients (61%) received taxane-based, second-line chemotherapy (paclitaxel monotherapy in 46 patients and docetaxel

Table 1. Patient Characteristics and Genetic Polymorphisms

Characteristics		All n=100(%) n=61(%)	Taxane based n=39(%)	Irinotecan based
Age	Median (range)	60 (31-80)	58 (31-80)	62(33-74)
Gender	Male	66 (66)	39(64)	27 (69)
	Female	34 (34)	22(36)	12 (31)
EOCG PS	0 or 1	65(65)	36(59)	29(74)
	2	35 (35)	25(41)	10(26)
Disease status	Advanced	70(70)	40(66)	30(76)
	Recurrent	30 (30)	21(34)	9(24)
Pathological type	Diffuse	78 (78)	51(83)	27(69)
	Intestinal	22 (22)	10(17)	12(31)
Prior gastrectomy	Yes	49 (49)	34(55)	15(38)
	No	51 (51)	27(45)	24(62)
Adjuvant	Yes	9 (9)	5(8)	4(10)
	No	91 (91)	56(92)	35(90)
Metastatic places	1	56 (56)	37(43)	19(49)
	≥2	44 (44)	24(57)	20(51)
Ascites	Yes	25 (25)	18(30)	7(18)
	No	75 (75)	43(70)	32(82)
PFS (median) of 1st-line	<5.6 months	50 (50)	30(49)	20(51)
	>5.5 months	50 (50)	31(51)	19(49)
ABCB1 C3435T	C/C	45 (45)	28(46)	17(44)
	C/T	38 (38)	24(39)	14(36)
	T/T	17 (17)	9(15)	8(20)

ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival

Table 2. Univariate and Multivariate Analysis of PFS

Variant	Classification	n	Univariate analysis			Multivariate analysis		
			HR	95% CI	P value	HR	95% CI	P value
ABCB1 C3435T	C/C	45	1.00			1.00		
	C/T or T/T	55	1.41	0.93-2.13	0.10	1.50	0.98-2.30	0.061
ECOG PS	0 or 1	65	1.00			1.00		
	2	35	2.89	1.86-4.48	<0.001	2.95	1.86-4.67	<0.001
Metastatic place	1	56	1.00			1.00		
	2 or more	44	1.34	0.89-2.01	0.16	1.45	0.93-2.24	0.098
PFS of 1stline	<5.6 months	50	1.00			1.00		
	>5.6 months	50	0.58	0.39-0.88	<0.001	0.67	0.44-1.02	0.067

Adjusted by age, gender, disease status, pathology, prior gastrectomy, adjuvant, ascites, regimens; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; PFS, progression-free survival.

Table 3. Univariate and Multivariate Analysis of OS

Variant	Classification	n	Univariate analysis			Multivariate analysis		
			HR	95% CI	P value	HR	95% CI	P value
ABCB1 C3435T	C/C	45	1.00			1.00		
	C/T or T/T	55	1.15	0.81-1.63	0.43	0.93	0.60-1.43	0.72
ECOG PS	0 or 1	65	1.00			1.00		
	2	35	3.91	1.80-4.05	<0.001	3.94	2.34-6.05	<0.001
Metastatic place	1	56	1.00			1.00		
	2 or more	44	1.64	1.16-2.31	0.01	1.58	1.11-2.32	0.01
Pathology	Diffuse	78	1.00			1.00		
	Intestinal	22	0.63	0.41-0.96	0.035	0.61	0.37-1.03	0.063
PFS of 1stline	<5.6 months	50	1.00			1.00		
	>5.6 months	50	0.48	0.34-0.68	<0.001	0.43	0.26-0.69	<0.001

Adjusted by age, gender, disease status, prior gastrectomy, adjuvant, ascites, regimens; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PFS, progression-free survival

monotherapy in 15 patients), while the other 39 patients (39%) received irinotecan-based chemotherapy (irinotecan monotherapy in 26 patients and irinotecan plus cisplatin in 13 patients). The treatment schedules were similar to those of previous Japanese phase II trials (Futatsuki et al., 1994; Taguchi et al., 1998; Sato et al., 2001; Kodera et al., 2007). Median OS since initiation of second-line chemotherapy was 6.0 months (95% CI, 4.8 to 8.0 months), and median PFS was 2.7 months (95% CI, 2.1 to 3.3 months). Among the 100 patients, 48 patients (48%) received third-line chemotherapy. The frequencies of ABCB1 polymorphisms were as follows: C/C in 45 patients, C/T in 38 patients and T/T in 17 patients.

PFS according to genetic polymorphisms of ABCB1

Table 2 demonstrates univariate and multivariate analyses of ABCB1 polymorphisms and other clinical factors as prognostic factors for better PFS. In the multivariate analysis, CC type polymorphisms (n = 45) were associated with longer PFS than C/T or TT type polymorphisms, with borderline statistical significance (n = 55; 3.2 vs. 2.2 months; HR 1.50; 95% CI 0.98-2.30; P = 0.061, Figure 1a). Only a performance status of 0-1 was significant (P < 0.05); other predictive factors with borderline significance were PFS with first-line chemotherapy and number of metastatic sites.

OS according to genomic polymorphisms of ABCB1

Table 3 shows univariate and multivariate analyses of OS. In the multivariate analysis, no significant difference was observed between ABCB1 3435 CC type vs. C/T or TT type polymorphisms (OS 5.6 vs. 6.1 months, respectively; HR 0.93; 95% CI 0.60-1.43; p = 0.72, Figure 1b). Significant predictive factors for OS were

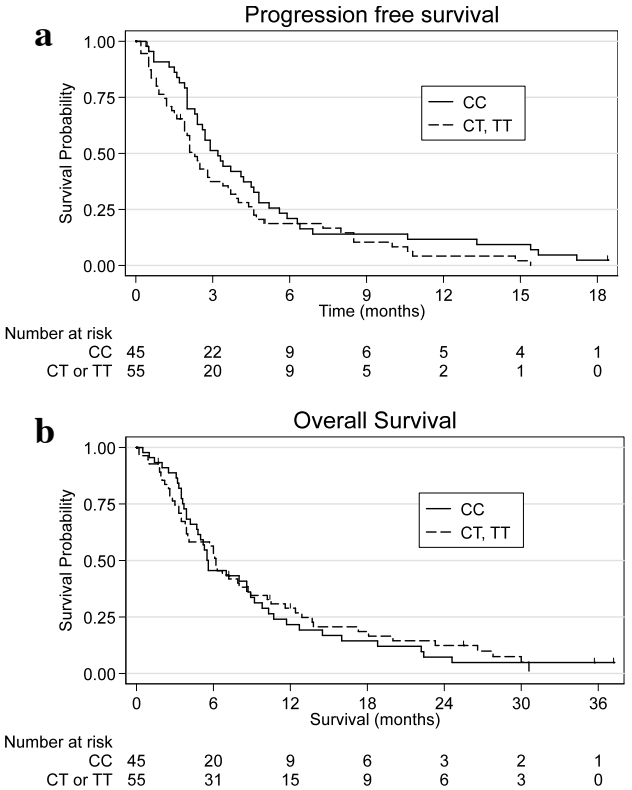

Figure 1. Kaplan-Meier Survival Curves for Progression Free (a) and Overall (b) Survival

Table 4. Association of Genotype and Survival Stratification by Regimens

	Genotype ABCB1 C3435T	n	Analysis for PFS HR	95% CI	P*	Analysis for OS HR	95% CI	P*
Taxane based	C/C	28	1.00			1.00		
(n = 61)	C/T or T/T	33	1.56	0.91-2.69		0.83	0.47-1.48	
Irinotecan based	C/C	17	1.00		**0.63**	1.00		**0.74**
(n = 39)	C/T or T/T	22	1.02	0.43-2.22		0.60	0.22-1.68	

Adjusted by age, gender, PS, pathological type, disease status, prior gastrectomy, adjuvant, metastatic site, ascites, PFS with first-line therapy; *P for interaction; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival

performance status, number of metastatic sites, and PFS with first-line chemotherapy.

Interaction of genetic polymorphisms and treatment regimens

The interaction of ABCB1 genotypes and treatment regimens (taxanes or irinotecan) with PFS or OS is shown in Table 4. The impact of this polymorphism on PFS seemed to be stronger in taxane-treated patients than in irinotecan-treated patients, although no significant interaction between genotype and regimens was observed either PFS or OS.

Discussion

In this study, we observed that genetic polymorphisms in ABCB1 3435C>T were associated with better PFS with borderline significance in patients with AGC treated with second-line chemotherapy. This observation was similar to the past report by Chang et al, which also showed longer PFS in patients with ABCB1 3435CC type (Chang et al., 2010). These results suggest that genetic polymorphisms of ABCB1 have some predictive value for second-line chemotherapy in AGC.

The influence of ABCB1 polymorphisms has been evaluated in patients with several types of cancers treated with chemotherapy. Among the chemotherapeutic agents used, taxanes have been most commonly studied (Gre´en et al., 2006; Marsh et al., 2007; Johnatty et al., 2008; Sissung et al., 2008; Chang et al., 2009). Although taxanes are commonly used as chemotherapeutic agent for AGC, only one report (Chang et al., 2010) evaluated ABCB1 polymorphisms with small number of patients (n=43), and no reports was seen from Japan. Additionally, an in vitro study suggested that ethnic differences influenced paclitaxel sensitivity in cancer cells, based on diff erent gene expression patterns in patients of Asian and Western ethnicity (Kwon et al., 2009). Therefore we conduct this study to evaluate Japanese patients with gastric cancer, for whom taxanes are commonly used as second-line chemotherapy.

The ABCB1 3435 polymorphism is one of the most common polymorphisms of the ABCB1 gene. In vitro, the homozygous CC genotype in C3435T was reported to be associated with twofold higher Pgp protein expression levels compared with the TT genotype (Hoffmeyer et al., 2000; Cascorbi et al., 2001). Therefore, patients with the CC genotype would be expected to respond worse to chemotherapy, with higher drug efflux rates and lower tissue concentrations (Kolesar et al., 2009). However, in our study, the CC type tended to have better PFS than the TT or TC types with the borderline significance, which was compatible to the another report in patients with AGC (Chang et al., 2010).Other studies in breast cancer and non-small cell lung cancer also showed a better clinical outcome (disease control rate or response rate) in patients with the CC type (Pan et al., 2008; Chang et al., 2009). Although some studies showed no impact of this polymorphism (Gre´en H et al., 2006; Marsh et al., 2007; Johnatty et al., 2008), no reports have shown a worse outcome with the CC type. To support our result, Nakamura et al. showed higher MDR1 mRNA levels in healthy Japanese subjects carrying the ABCB1 3435T allele compared with subjects with the 3435C allele (Nakamura et al., 2001). Considering these controversial preclinical and clinical data, further study is necessary to investigate genetic polymorphisms, Pgp expression of normal organs and tumor cells and clinical outcomes of patients comprehensively.

In the subset analysis of each treatment group, the impact of this polymorphism on PFS seemed to be stronger in taxane-treated patients than in irinotecan-treated patients, although no significant interaction was observed. Some studies have evaluated the influence of ABCB1 polymorphisms on irinotecan pharmacokinetics (Kaniwa et al., 2003; Mathijssen et al., 2003; Han et al. , 2007). In a study of Japanese patients with colorectal cancer, an ABCB1 polymorphism of 3435TT was associated with reduced renal clearance of irinotecan and its metabolites (Kaniwa et al., 2003). In contrast, in patients with non-small cell lung cancer treated with irinotecan and cisplatin, 3435TT carriers showed a lower plasma AUC of SN-38G compared with 2677GG/3435CC carriers (Han et al., 2007).These controversial results were suggested to be based on the complex metabolic pathway of irinotecan, where ABCB1 makes a relatively smaller contribution than other enzymes, such as uridine diphosphate glucuronosyltransferase (UGT).

In our study, the ABCB1 3435 polymorphism had no impact on OS against the borderline significance on PFS. This observation was also similar to another report in AGC10.The cause of this inconsistency is unknown, but one possibility is that other factors such as PS or PFS of first-line chemotherapy were too strong for ABCB1 polymorphisms to show an impact on OS. Another possibility was that ABCB1 polymorphisms are related to patient prognosis itself independently of treatment effect since ABCB1 is reported to play a significant survival role in normal and cancer cells during tumor progression, and metastasis (Tahara et al., 2007; Chang et al., 2010).

In this point of view, further study might be important to comprehensively investigate genetic polymorphisms in both patients with cancers treated with or without chemotherapy and healthy subjects.

There are several methodological issues in this study. This study did not evaluate other ABCB1 polymorphisms, such as 2677G>T/A. There is some controversy regarding the effect of this polymorphism (2677G > T/A) on ABCB1 transport activity (Kaniwa et al., 2003; Yi et al., 2004; Lee et al., 2005; Han et al., 2007; Tahara et al., 2007). In addition, the minor 2677A allele, as well as the major 2677G allele, is strongly linked to the major 3435C allele (Cascorbi et al., 2001; Johne et al., 2002; Yi et al., 2004; Lee et al., 2005; Song et al., 2006). Therefore, we did not evaluate this polymorphism in this study, although it might contribute to the inconclusive results.

Additionally, the small sample size used may be a study limitation, which may contribute to lack of statistical power to show the statistically significant difference in PFS or significant interaction between outcome with each treatment regimens and genetic polymorphisms. Therefore further similar studies or meta-analysis study is required to duplicate this work in larger cohort.

In conclusion, our findings indicate that the genetic polymorphisms of ABCB1 have some predictive value for clinical outcome of AGC patients treated with second-line chemotherapy. Further prospective evaluation is required.

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