Effects of Single Nucleotide Polymorphisms on Treatment Outcomes and Toxicity in Patients Treated with Sunitinib

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Abstract. *Background/Aim: We analyzed the efficacy and toxicity profile of sunitinib according to single nucleotide polymorphisms (SNPs) of vascular endothelial growth factor receptor (VEGFR) and Kinase insert domain receptor (KDR). Patients and Methods: We examined eight known SNPs of VEGFA and five SNPs of KDR among patients with gastric or biliary tract cancer who were treated with sunitinib. We retrospectively assessed clinical outcomes and their relationships to these SNPs. Results: A total of 63 patients were evaluable. Among candidate SNPs, rs2010963 and rs833068 of VEGFA, and rs1870377 of KDR were associated with poor time to treatment failure (TTF) (p=0.009, 0.002, and 0.029, respectively), while rs1870377 and rs7692791 of KDR were associated with poor overal survival (OS) (p=0.001 and 0.03, respectively). Multivariate analysis showed that only rs1870377 had significant effects on both TTF and OS. Toxicity evaluation indicated that rs1531289 of KDR was associated with grade 3-4 anemia. (p=0.021). Conclusion: Certain SNPs of KDR may affect treatment outcome and toxicity in patients treated with sunitinib.*

Sunitinib is an orally active inhibitor that targets tyrosine kinases such as the vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptors (PDGFRs), stem cell factor receptor (KIT), rearranged during transfection (RET), and FMS-like tyrosine kinase (FLT3). This drug has been widely used for treatment of patients with advanced renal cell carcinoma (RCC), imatinib-resistant gastrointestinal stromal tumor (GIST), and pancreatic neuroendocrine tumor (1-3). Beyond these, sunitinib has demonstrated a promising efficacy in many phase II trials against various other types of tumors, such as small cell lung cancer, sarcoma, and ovarian or biliary tract cancer, with or without combination of cytotoxic agents (4-7).

Toxicity is one of the major concerns for treatment with sunitinib. In a recent phase II trial that we conducted with sunitinib, 46% of the patients experienced grade 3 or higher toxicity, which led to treatment delay or dose reduction in 44.4% and 16.9% of the patients, respectively (7). In previous phase III studies, frequent dose modifications and treatment interruptions were needed for patients with RCC and GIST (8, 9).

VEGFs are ligands to cell surface receptor tyrosine kinases named VEGFRs. One member of the VEGFR family, VEGFR2, is expressed on vascular and lymphatic endothelial cells (10) and is encoded by the *KDR* gene. This receptor plays a key role in the angiogenesis that is the major target of sunitinib (10). VEGFA, encoded by the *VEGFA* gene, is the primary ligand for VEGFR2 and is the most abundant biologically active form of the VEGFs (10). *KDR* and *VEGFA* genes have multiple single nucleotide polymorphisms (SNPs) (11-14), which have been reported to be associated with the efficacy and toxicity of anti-VEGF treatments such as sunitinib (15, 16). Therefore, a search to find potential host factors that can contribute to sunitinib toxicity is worthwhile. Sunitinib is generally used as palliative treatment for advanced stages of cancer; therefore, careful selection of patients who may be susceptible to sunitinib

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toxicity is required. In this study, we analyzed the efficacy and toxicity of sunitinib according to the SNPs of *KDR* and *VEGFA* in patients who were treated with sunitinib.

Patients and Methods

Study population. We previously conducted two phase II studies to evaluate the efficacy of sunitinib in patients with unresectable biliary tract cancer and advanced gastric cancer (7, 17). We collected clinical data, including toxicity profiles, from the patients assigned to the sunitinib-containing arm. All inclusion and exclusion criteria were described previously in the relevant articles (7, 17). One study, which evaluated the efficacy and toxicity of sunitinib against biliary tract cancer, enrolled patients who had tumor histologically confirmed as unresectable or metastatic adenocarcinoma of the biliary tract (7). We also tested sunitinib as a second-line treatment for another patient group who had advanced gastric cancer, comparing randomized treatment arms comprised of docetaxel alone or docetaxel plus sunitinib (17). In both studies, the protocol was approved by the Institutional Review Board at the Samsung Medical Center and the trial was conducted in accordance with the Declaration of Helsinki. All patients were required to give written informed consent before enrolment. Each trial was registered at www.clinicaltrial.gov as #NCT01082809 (biliary tract cancer study) and #NCT01238055 (gastric cancer study).

SNP analysis. We analyzed eight known SNPs in the *VEGFA* gene and five in the *KDR* gene to determine if these SNPs had any impact on disease progression, survival, or sunitinib-related toxicity. The eight SNPs in *VEGFA* were the following: rs2010963 (C>G), rs3025039 (C>T), rs1570360 (C>T), rs3025033 (A>G), rs833068 (G>A), rs833061 (C>T), rs2146323 (C>A), and rs699947 (A>C). The five SNPs in *KDR* were: rs1870377 (T>A), rs2071559 (T>C), rs2305948 (C>T), rs7692791 (T>C), and rs1531289 (G>A).

Germline DNA was isolated from 1 ml of EDTA blood. DNA was extracted using the Puregene DNA Purification Kit (Gentra Systems Inc., Minneapolis, MN, USA) Genotyping was undertaken using the Sequenom® iPLEX platform™, according to the manufacturer's instructions (www.sequenom.com; Sequenom Inc., San Diego, CA, USA). The detection of SNPs was carried out by the analysis of primer extension products generated from previously amplified genomic DNA, using a Sequenom chip-based matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry platform. Multiplex SNP assays were designed using SpectroDesigner software (Sequenom). The polymerase chain reaction (PCR) amplification was performed in 96-well plates containing 2.5 ng DNA in each well, following the specifications of Sequenom Inc. Unincorporated nucleotides in the PCR product were deactivated using shrimp alkaline phosphatase. Allelic discrimination reactions were conducted by adding the extension primers, DNA polymerase, and a cocktail mixture of deoxynucleotide triphosphates and di-deoxynucleotide triphosphates to each well. MassExtend clean resin (Sequenom Inc.) was added to the mixture to remove extraneous salts that might interfere with the MALDI-TOF analysis. The primer extension products were then cleaned and spotted onto a SpectroChip (Sequenom Inc.). Genotypes were determined by spotting an aliquot of each sample onto a 384 SpectroChip, which was subsequently read by the MALDI-TOF mass spectrometer. Duplicate samples and negative controls were included to check genotyping quality.

Assessing clinical outcomes and toxicity. Sunitinib was administered orally at a daily dose of 37.5 mg according to the relevant protocol (7). The regulations for treatment delay and dose modification were described previously (7). Treatment responses were assessed according to RECIST v1.1 (18). We calculated the time-to-treatment failure (TTF) as the period from the date of starting sunitinib treatment to the date of objective tumor progression, unacceptable toxicity, or consent withdrawal. Overall survival (OS) was defined as the duration from the date of starting sunitinib treatment to the date of death or the last follow-up visit. Laboratory results, including hematological findings, were checked on day 1 of every cycle. Toxicities were reported on the basis of NCI-CTC AE v3.0 (http://ctep.cancer.gov/).

Statistics. The relationship between SNPs and degree of toxicities was evaluated using Pearson's Chi-square test, by dividing two categories for each SNP (major homozygosity *vs*. heterozygosity/ minor homozygosity, or major homozygosity/heterozygosity *vs*. minor homozygosity). We constructed Kaplan-Meier curves according to the SNPs, and compared these by log-rank tests to find which SNPs affected TTF or OS. When a statistically significant difference was found between the SNPs for TTF or OS, multivariate analysis using a Cox regression model was performed to determine if the significance remained valid after adjusting for the age, sex, ECOG and the SNPs with statistical significance in the univariate analysis.

Results

Patients. From December 2008 to February 2011, 163 patients were entered into the studies. The subjects of the present study were those who had been treated with sunitinib; this included 56 patients from the study of biliary tract cancer (7). A total of 105 patients with gastric cancer were enrolled; these patients had also been treated with docetaxel in addition to sunitinib as combination therapy. Out of these, 56 patients were assigned to the docetaxel-plus-sunitinib arm (17). Among the whole study population, we selected evaluable patients whose blood samples were available for genetic analysis. The total number of evaluable patients was 63; 34 patients with gastric cancer and 29 patients with biliary tract cancer. The median age of the patients was 54 years, with a range between 26 and 75 years. Among these, 46 were males and 17 were females (73% *vs*. 27%, respectively). The baseline characteristics are listed in Table I. The hematological profile prior to sunitinib treatment was within normal limits among the enrolled patients, except for a mild degree of anemia (10.9 g/dl). The genotypic frequencies for the 13 SNPs are summarized in Table II.

Survival analysis. For the entire population, the median TTF and OS values were 2.8 (range 0.4-20.5) months and 7.1 (range 0.5-25.4) months, respectively. The median TTF of patients who harbored major homozygosities for rs2010963 (n=21), rs1870377 (n=17), or rs833068 (n=18) was 1.3 months. 95% confidential interval (CI) was 0.55-2.05, 0.63-1.97, and 0.68-1.92 months, respectively. These patients had

Table I. *Baseline characteristics of patients.*

	Value
Median age (range), years	(26-75) 54
Gender, n (%)	
Male	46 (73.0)
Female	17 (27.0)
ECOG* performance status score	
0	9 (14.3)
1	52 (82.5)
2	2 (3.2)
Primary tumor site, n (%)	
Stomach	34 (54.0)
Biliary tract	29 (46.0)
Chemotherapeutic regimen, n (%)	
Sunitinib with docetaxel	34 (54.0)
Sunitinib only	29 (46.0)
Median cycles of treatment (range), n	(1-10), 2
Hematological profile prior to sunitinib treatment, median (range)	
WBC (/μl)	6,325 (2,910-17,270)
Hemoglobin (g/dl)	10.9 (8.0-17.1)
Platelet (/μl)	170,000 (69,000-404,000)
Absolute neutrophil count(/μl)	3,710 (1,080-13,700)

ECOG: Eastern Cooperative Oncology Group; WBC: white blood cell.

statistically shorter TTFs than those who were heterozygous/minor homozygous (GC/CC, AT/TT, GA/AA, respectively) for each SNP (Figure 1 and Table II, p=0.009, 0.002, 0.029, respectively).

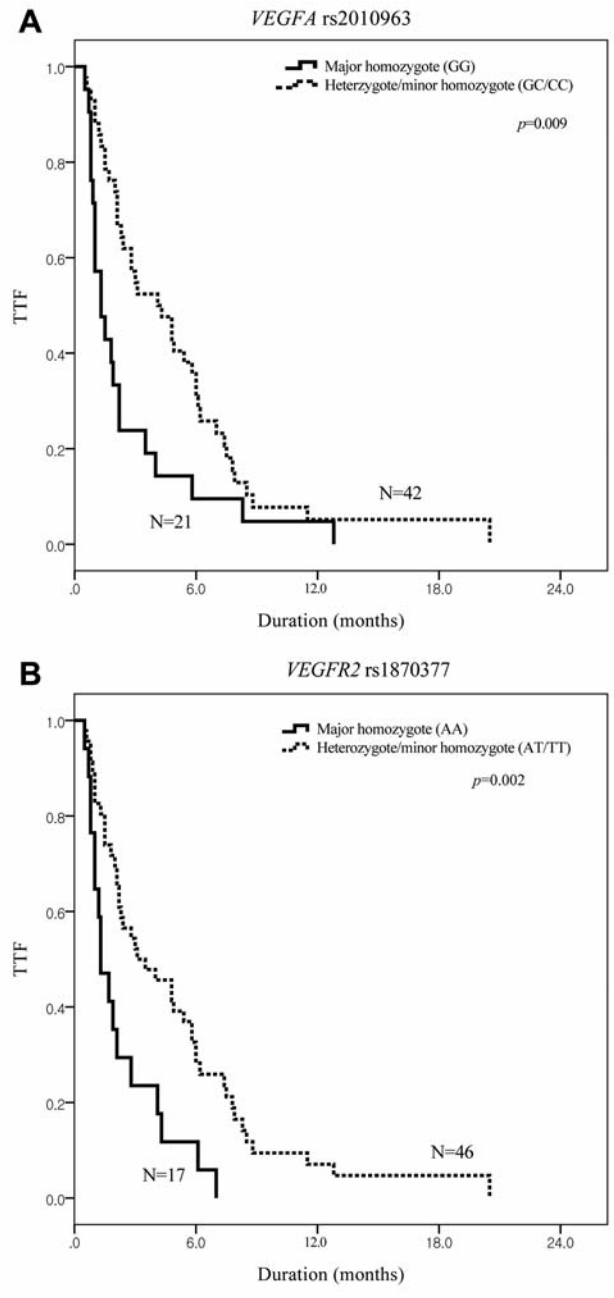
Major homozygosity for rs1870377 (AA) (n=17) and minor homozygosity for rs7692791 (n=6) were shown to have negative effects on OS. The median OS of patients with rs1870377 and rs7692791 were 4.1 and 3.4 months, with 95% CI of 3.43-4.77 and 1.00-5.80 months, respectively. Comparison of the heterozygous or minor homozygous rs1870377 (AT/TT) with the major homozygous AA, and comparison of the major homozygous or heterozygous rs7692791 with minor homozygous GG showed there to be statistically significant differences in the OS rate (Figure 2, p=0.001 and 0.03, respectively). Multivariate analysis revealed that the primary site of cancer significantly affected the survival outcome. The major homozygous rs1870377 SNP was the only SNP that significantly affected both TTF and OS (Table IV, p=0.011 and 0.003, respectively).

Toxicity. No differences were noted for non-hematological toxicities between patients according to SNPs. However, anemia and thrombocytopenia were noted in patients with the SNP rs1531289. The minor allele of rs1531289 was responsible for anemia greater than grade 3 (Table III, p=0.021).

Table II. *Incidence of single nucleotide polymorphism according to type of cancer.*

	Biliary tract cancer (n=29)	Gastric cancer (n=34)	Total (n=63)
VEGFA			
rs2010963 G>C			
GG (Major)	12	9	21
GC	8	20	28
CC	9	5	14
rs3025039 C>T			
CC (Major)	20	23	43
CT	8	10	18
TT	1	1	2
rs1570360 G>A			
GG (Major)	24	25	49
GA	5	9	14
AA	0	0	0
rs3025033 A>G			
AA (Major)	20	23	43
AG	8	10	18
GG	1	1	2
rs833068 G>A			
GG (Major)	11	7	18
GA	9	21	30
AA	8	6	14
(Missing data)	1	0	1
rs2146323 C>A			
CC (Major)	19	18	37
CA	8	16	24
AA	2	0	2
rs833061 T>C			
TT (Major)	18	17	35
TC	8	15	23
CC	2	2	4
(Missing data)	1	0	1
rs699947 C>A			
CC (Major)	18	16	34
CA	9	15	24
AA	2	2	4
(Missing data)	0	1	1
VEGFR2			
rs1870377 A>T			
AA (Major)	8	9	17
AT	17	17	34
TT	4	8	12
rs2071559 T>C			
TT (Major)	15	12	27
TC	13	14	27
CC	1	6	7
(Missing data)	0	2	2
rs2305948 G>A			
GG (Major)	21	24	45
GA	7	7	14
AA	1	3	4
rs7692791 A>G			
AA (Major)	9	15	24
AG	17	15	32
GG	3	3	6
(Missing data)	0	1	1
rs1531289 G>A			
GG (Major)	16	26	42
GA	10	8	18
AA	3	0	3

VEGFA: Vascular endothelial growth factor A; VEGFR2: Vascular endothelial growth factor receptor-2.



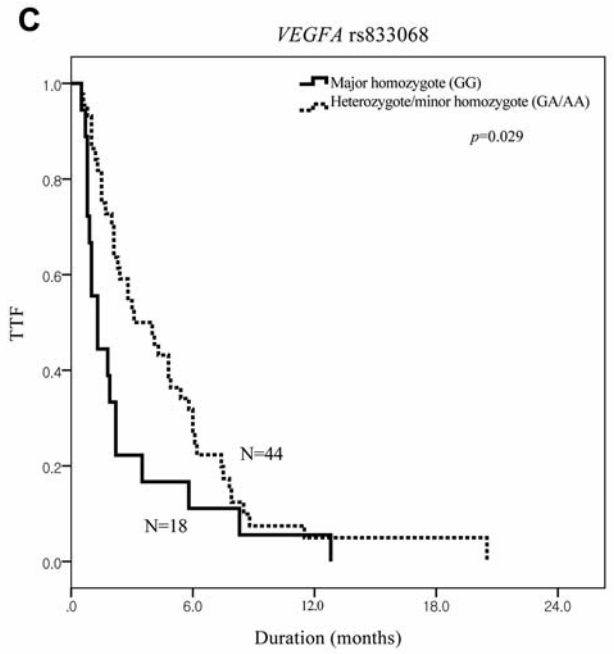


Figure 1. *Statistically significant single nucleotide polymorphisms affecting time-to-treatment failure (TTF). Univariate analysis of VEGFA rs2010963 and rs833068, and VEGFR2 rs1870377, and rs833068 SNPs revealed different TTFs according to their genotypes. The major homozygous (GG) rs2010963, major homozygous (AA) rs1870377, and major homozygous (GG) rs833068 genotypes had negative effects on TTF.*

Discussion

Genetic variation of VEGFR is thought to be responsible for the efficacy and toxicity of sunitinib, although conflicting data have been presented. Recently, several reports have arisen concerning patients who were administered sunitinib for treatment of metastatic renal cell carcinoma and gastrointestinal stromal tumor (12, 16, 19). Notably, even though these studies differed substantially from one another, all of the SNPs were statistically associated with efficacy or toxicity.

Two of these studies focused on sunitinib-related hypertension or hypothyroidism (12, 19). No study has yet investigated the association of sunitinib-related efficacy or toxicity in patients diagnosed with biliary tract cancer or gastric cancer, which are the target diseases of the present study. In this study, we found new SNPs that can affect patient survival or drug toxicity. Multivariate analysis showed that the major homozygous rs1870377 genotype of VEGFR2 had negative effects on both TTF and OS, when compared to the effects of the heterozygous or minor homozygous genotypes. No clear mechanism can yet explain why a specific SNP can have a different effect on patient outcome. Since sunitinib targets VEGFR, the individual variability of the targeted receptors can be assumed to result in a change in the level of binding of the drug and consequently alter its efficacy. In terms of GIST, the main target is thought to be the PDGFR rather than VEGFR.

The ECOG performance status was not a significant factor in patient survival in this study population. As mentioned earlier, we initially enrolled patients who had a relatively good performance for these phase II clinical trials. The type of cancer that the patients had (*i.e.* biliary tract cancer or gastric cancer) also had a statistically significant effect on survival by multivariate analysis. This is thought to be due to the different prognoses of the two types of tumors.

Sunitinib-related toxicity has been found to be due to drug metabolism (15, 16). Integration of the two trials that we conducted revealed that the toxicity profile was generally tolerable and manageable. As reported in previous studies, sunitinib-related adverse events are mainly related to cytochrome *P450* (CYP450), which is the key enzyme for metabolizing this drug (15, 16). Some SNPs of the gene coding for CYP450 were associated with the toxicity of sunitinib. Study of SNPs of the *CYP450* gene were not a planned component of our study.

The minor homozygous genotype of rs1531289 of VEGFR2 (AA) was a statistically associated with more severe adverse events. Anemia greater than grade 3 was more common in patients harboring the AA form of rs1531289 than in those with the GG/GA form. Setting apart the drug metabolism associated with the genetic variant of CYP450, the effect of sunitinib on hematological toxicity can be explained by the SNPs of VEGFR2 itself. VEGFR is expressed in vascular endothelial or tumor cells, as well as in hematopoietic stem cells (20, 21). The germline SNP of VEGFR can affect the susceptibility of its ligand, sunitinib. The effect of sunitinib on hematopoietic cells can be affected and might cause more aggressive anemia or thrombocytopenia according to specific SNPs. No association was found between non-hematological toxicities and SNPs.

Interestingly, a few patients suffered from secondary hypertension due to sunitinib. Hypertension is a known adverse event of sunitinib, occurring to different degrees ranging from 15-45% (22, 23). The incidence of sunitinib-related hypertension was found to be even more common than previously reported when the patients were monitored by 24-h ambulatory blood pressure monitoring (24). However, these reports mainly studied patients with RCC. In our study population, where we enrolled patients with biliary tract or gastric cancer, there were four patients (6.3%) from the biliary tract cancer population with grade 2 or 3 hypertension (two patients each, respectively). Newly, developed hypertension during sunitinib administration has been established as a positive prognostic marker in patients with RCC (25).

To date, no evidence exists for sunitinib-induced hypertension as a prognostic factor other than for RCC, except for one recent study on GIST (19). Sunitinib can induce hypertension by blocking the VEGF signaling pathway (22). For this reason, the relatively low rate of hypertension in our population most likely translates into a different mechanism of sunitinib function against biliary tract or gastric cancer. While sunitinib mainly targets VEGFR in RCC, which leads to treatment-induced hypertension, another target other than VEGFR might contribute to the efficacy of sunitinib for other types of cancer. Whether hypertension is also associated with prognosis in patients with biliary tract or gastric cancer remains to be validated by an independent cohort study.

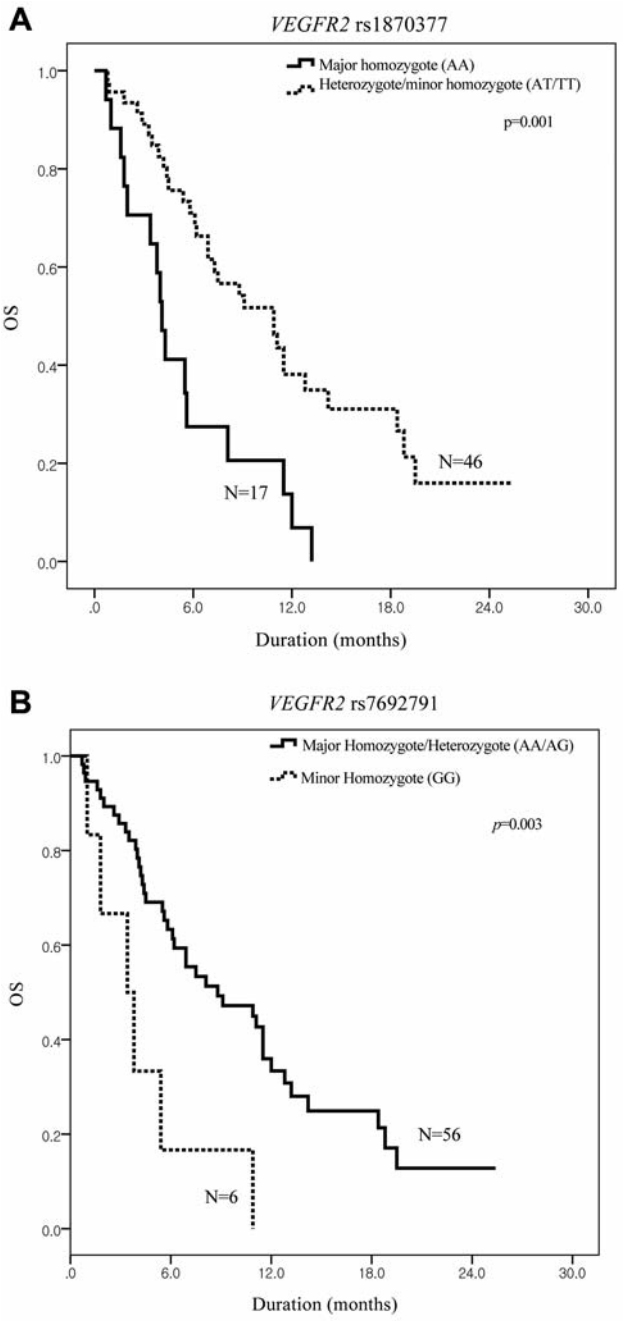


Figure 2. *Statistically significant single nucleotide polymorphisms affecting overall survival (OS). Univariate analysis of the major homozygous VEGFR2 (AA) rs1870377 and minor homozygous (GG) VEGFR2 rs7692791genotypes revealed they conferred shorter OS.*

The limitations of this study are worth describing. Firstly, in the patients with gastric cancer, we compared the primary outcome between a group treated with docetaxel-only and a group treated with docetaxel and sunitinib as a combination therapy. The treatment modality was not

Table III. *Correlation between the survival analysis/adverse events and single nucleotide polymorphism in vascular endothelial growth factor A (VEGFA) and vascular endothelial growth factor receptor-2 (VEGFR2).*

Variable	Associated SNP	Genotype	Duration or frequency	*p*-Value
Survival analysis			Duration (months)	
TTF	*VEGFA* rs2010963	GG *vs*. GC/CC	1.3 *vs*. 4.1	0.009
	rs833068	GG *vs*. GA/AA	1.3 *vs*. 3.1	0.029
	VEGFR2 rs1870377	AA *vs*. AT/TT	1.3 *vs*. 3.1	0.002
OS	*VEGFR2* rs1870377	AA *vs*. AT/TT	4.1 *vs*. 10.9	0.001
	rs7692791	AA/AG *vs*. GG	8.8 *vs*. 3.4	0.030
Adverse events			Frequency	
Anemia ≥ grade 3*	*VEGFR2* rs1531289	GG/GA *vs*. AA	1/26 *vs*. 2/3	0.03

TTF: Time-to-treatment failure; OS: overall survival. *Analysis of relationship between anemia ≥grade 3 and SNP was performed among patients with biliary tract cancer who were treated by sunitinib alone.

Table IV. *Multivariate analysis of time-to-treatment failure (TTF) and overall survival (OS) according to variables*

		p-Value	Hazard ratio	95% CI
TTF	Age (<60 *vs*. ≥60)	0.083	1.004	0.98-1.03
	Gender (male *vs*. female)	0.726	0.893	0.48-1.68
	Primary site (gastric *vs*. biliary)	0.006	0.409	0.22-0.78
	ECOG (0-1 *vs*. 2)	0.176	0.302	0.05-1.69
	VEGFA rs2010963 GG *vs*. GC/CC	0.126	2.681	0.76-9.48
	rs833068 GG *vs*. GA/AA	0.497	0.634	0.17-2.36
	VEGFR2 rs1870377 AA *vs*. AT/TT	0.001	3.309	1.68-6.50
OS	Age (<60 *vs*. ≥60)	0.670	0.994	0.97-1.02
	Sex (male *vs*. female)	0.734	0.894	0.47-1.71
	Primary sites (gastric *vs*. biliary)	0.012	0.440	0.23-0.84
	ECOG (0-1 *vs*. 2)	0.157	0.301	0.05-1.68
	VEGFR2 rs1870377 AA *vs*. AT/TT	0.020	2.271	1.14-4.53
	rs7692791 AA/AG *vs*. GG	0.403	0.659	0.25-1.76

ECOG : Eastern Cooperative Oncology Group.

uniformly the same as that used for the patients with biliary tract cancer, who received only sunitinib. This discrepancy may result in bias, especially when analyzing toxicity. We used multivariate analysis using a Cox regression model to eliminate and adjust the bias of different tumor types and treatment. As seen in Table IV, we analyzed variables including the primary site ie. gastric *vs*. biliary tract cancer. In terms of different treatment (docetaxel plus sunitnib, or sunitnib alone), each treatment corresponds to each tumor type. That is, all patients with gastric cancer analyzed in this study were treated with docetaxel and sunitnib, while all those with biliary tract cancer were treated by sunitinib alone. As a result, the treatment variable (docetaxel plus sunitnib, or sunitnib alone) is exactly the same with the primary site variable. The multivariate analysis showed the effect of both primary site and SNP (rs1870377 AA *vs*. AT/TT) to be statistically significant. Understandably it is reasonable that the primary site has a significant effect on TTF and OS since the nature and prognosis of gastric cancer and biliary tract cancer are different. Considering the effect of primary site, another variable, SNP rs1870377 AA, still has statistical significance. In order to exclude the possible interaction between the primary site and SNP (VEGFR2 rs1870377 AA *vs*. AT/TT), we performed an interaction analysis using the product of each variable and found that the primary site and the VEGFR2 SNP rs1870377 retained their significance. Secondly, as described earlier, the true factors affecting sunitinib metabolism and related toxicity are readily-reflected in genetic variability of CYP450, but we analyzed only the SNPs of the *VEGFA* and *VEGFR2* genes.

In conclusion, specific SNPs can affect treatment outcomes and the degree of toxicity among patients treated with sunitinib (VEGFR2 rs1870377 for TTF and OS, and VEGFR2 rs1531289 for hematological toxicity). Many different types of SNPs have been reported as relevant

biomarkers in sunitinib treatment; therefore, these SNPs need to be validated in an independent population. In the future, personalized genotyping for screening the SNPs of VEGFR might be adopted to optimize treatment with sunitinib.

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