Association of ABCG2 polymorphism with clinical efficacy of imatinib in patients with gastrointestinal stromal tumor (GIST)

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Background

1) Imatinib is a substrate of drug metabolizing enzymes, including those of the cytochrome P450 (CYP) system, and of several drug transporters.

2) Differences in imatinib pharmacokinetics among individual patients may be influenced by genetic polymorphisms and be associated with clinical imatinib efficacy.

3) This study evaluated the correlation of genetic polymorphisms with trough imatinib levels and clinical efficacy in GIST patients.

Materials & Methods

1) 284 patients with GIST were enrolled in the present study
- who received imatinib for therapy at the Asan Medical Center (Seoul, Korea) from Oct 2010 to Nov 2011,
- histologically documented GIST accompanied by KIT overexpression, or *KIT* or *PDGFRA* mutation; age ≥ 18 years; and good treatment compliance

2) Genotyping
- Genotyping for the CYP3A5*3C 6986A>G (rs776746), ABCB1 1236C>T (rs1128503), ABCB1 2677 G>A>T (rs2032582), ABCB1 3435C>T (rs1045642), ABCG2 34G>A (rs2231137), and ABCG2 421C>A alleles (rs2231142) was carried out using the SNaPshot® method in accordance with the manufacturer's protocol. Analyses were performed with GeneMapper (ver. 3.7) software. Hardy–Weinberg equilibrium was confirmed for all of the analyzed SNP data.

3) Determination of plasma imatinib Level
- At any time period at steady-state, blood samples (at least 4 mL) were collected before the morning dose of imatinib, usually 22 to 26 hours after the previous dose. Imatinib plasma levels were measured by liquid chromatography–tandem mass spectrometry at Seoul Clinical Laboratories (Seoul, Korea).

Results

Patients Characteristics (N=209)

Characteristics		N (%)
Sex	Male	122 (58.4%)
Age	Median, range	54.7 (26-81)
Primary site	Gastric	94 (45.0%)
	Small bowel/others	115 (55.0%)
Gastrectomy	Total/Partial	32 (15.3%)
	Not done	177 (84.7%)
Purpose of imatinb therapy	Palliative	145 (69.4%)
	Adjuvant	50 (23.9%)
	Neoadjuvant	14 (6.7%)
Mutation status (N=196)	*KIT* exon 11	144 (73.5%)
	KIT exon 9	23 (11.7%)
	Wild type	20 (10.2%)
	Other	9 (4.6%)

Genotype frequencies of CYP3A5, ABCB1 and ABCG2 genes among patients with GIST

Genotype		No. of patients (%)			P-value*
		Wild type	Hetero	Variant	
CYP3A5	6986A>G	13 (6.2%)	68 (32.5%)	128 (61.2%)	0.444
ABCB1	1236C>T	35 (16.7%)	94 (45.0%)	80 (38.3%)	0.499
	2677G>A/T	41 (19.6%)	135 (64.6%)	33 (15.8%)	0.149
	3435C>T	81 (38.8%)	98 (46.9%)	30 (14.4%)	0.915
ABCG2	34G>A	119 (56.9%)	75 (35.9%)	15 (7.2%)	0.629
	421C>A	103 (49.3%)	88 (42.1%)	18 (8.6%)	0.972

* Hardy-Weinberg equilibrium p-value

Imatinib plasma trough level according to genotype

Genotype (N)			Imatinib trough level (ng/mL)		P-value*	P-value†	P-value†
			Mean	SD			
CYP3A5	6986A>G	AA (13)	1342.8	450.3	0.918	0.764	0.656
		AG (68)	1375.6	633.3			
		GG (128)	1415.8	711.7			
ABCB1	1236C>T	CC (35)	1346.3	673.9	0.205	0.573	0.092
		CT (94)	1347.2	678.3			
		TT (80)	1480.7	662.1			
	2677G>A/T	GG (41)	1477.4	774.9	0.394	0.315	0.447
		Hetero (135)	1350.2	620.5			
		TT (33)	1495.8	734.3			
	3435C>T	CC (81)	1454.9	672.1	0.338	0.258	0.239
		CT (98)	1343.4	708.1			
		TT (30)	1423.9	538.1			

(cont'd)

Genotype (N)			Imatinib trough level (ng/mL)		P-value*	P-value†	P-value†
			Mean	SD			
ABCG2	34G>A	GG (119)	1360.5	486.8	0.930	0.940	0.959
		GA (75)	1393.8	727.1			
		AA (15)	1405.7	659.2			
	421C>A	CC (103)	1339.3	655.3	0.216	0.477	0.201
		CA (88)	1477.4	693.5			
		AA (18)	1347.9	648.6			

- *P-value for log-transformed imatinib level
- †After adjusting for sex, age, BSA, Hb, Albumin, and CCr
- ‡Patients who received imatinib for metastatic or recurrent GIST (N=145)

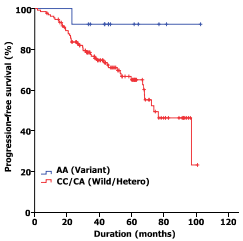
Progression-free survival according to genotype in patients with metastatic GIST (N=145)

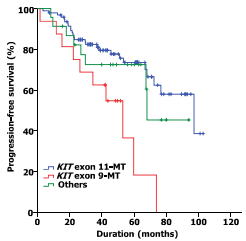
Genotype or characteristic (N)			Progression-free survival		P-value
			5Y-PFS (%)	95% CI	
CYP3A5	6986A>G	AA (8)	100.0	-	0.771
		AG (52)	62.6	49.4-75.8	
		GG (85)	67.3	57.3-77.3	
ABCB1	1236C>T	CC (26)	67.0	48.9-85.1	0.686
		CT (66)	71.0	60.0-81.9	
		TT (53)	63.4	50.4-76.4	
	2677G>A/T	GG (26)	76.4	60.0-72.7	0.943
		Hetero (95)	65.6	56.0-75.2	
		TT (24)	68.8	50.3-87.3	
	3435C>T	CC (56)	68.1	55.9-80.3	0.682
		CT (67)	69.9	58.9-80.9	
		TT (22)	52.7	31.8-73.6	
ABCG2	34G>A	GG (82)	65.4	55.1-75.7	0.673
		GA (53)	69.3	56.9-81.7	
		AA (10)	74.1	46.9-100.0	
	421C>A	CC (68)	67.1	55.9-78.3	0.139
		CA (64)	63.2	51.4-75.0	
		AA (13)	92.3	77.8-100.0	
	421C>A	CC/CA (132)	65.0	56.9-73.1	0.047
		AA (13)	92.3	77.8-100.0	

Progression-free survival according to clinical factors in patients with metastatic GIST (N=145)

Genotype or characteristic (N)		Progression-free survival		P-value
		5Y-PFS (%)	95% CI	
Sex	Male (85)	66.2	56.1-76.3	0.760
	Female (60)	67.5	55.6-79.4	
Age	≤ 65 years (115)	73.5	65.4-81.6	0.005
	> 65 years (30)	38.5	21.1-55.9	
Primary site	Gastric (62)	97.0	68.5-125.5	0.931
	Small bowel/others (83)	73.8	-	
Mutation status	*KIT* exon 11 (95)	73.5	64.6-82.4	0.007
	KIT exon 9 (16)	18.2	0.00-37.1	
	Others (23)	72.5	54.3-90.7	

Progression-free survival curves according to ABCG2 421C>A genotype, and mutation status





Multivariate Analysis for Progression-free survival

Factor		Hazard ratio	95% CI	P-value
Sex	Female	Reference		0.570
	Male	1.20	0.64-2.28	
Age	≤ 65 years	Reference		0.019
	> 65 years	2.29	1.14-4.57	
ABCG2, 421C>A	AA	Reference		0.158
	CA/CC	4.22	0.57-31.17	
Mutation status	*KIT* exon 11	Reference		0.033
	KIT exon 9	2.75	1.29-5.87	0.009
	Others	1.38	0.62-3.06	0.434

Conclusion

- We found that the transporter gene polymorphism in ABCG2, 421C>A, could influence the clinical efficacy of imatinib in patients with advanced GIST receiving imatinib 400 mg daily.
- Patients with AA variants of ABCG2 421C>A constituted about 9% of total patients, and exhibited significantly favorable PFS in advanced GIST.
- However, there was no significant difference found in imatinib plasma trough level according to genotype, including ABCG2 421C>A.

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