Recent pharmacogenomics studies have made novel contributions in identifying genetic markers which are useful for personalized medicine. One of the examples is Irinotecan. Irinotecan (Camptosar), a topoisomerase I inhibitor, is widely used as the first-line treatment for a multiplicity of carcinomas, including colorectal and lung cancers. Unpredictable, severe, potentially fatal adverse reactions, neutropenia or diarrhea, have been reported to be associated with the use of Irinotecan. Irinotecan is a produg that is converted by carboxylesterase to its active SN-38. The SN-38 is further detoxified by uridine 5'-diphospho-glucuronosyl-transferase (UGT) 1A1 to an inactive metabolite. Recent multiple pharmacogenomics studies have revealed that genetic polymorphisms of UGT 1A1 are essential determinants of the individual variation in susceptibility to irinotecan-related toxicity. Since the first report by Ando et al. stating that a variant in the UGT1A1*28 gene is associated with slowing of irinotecan metabolism and increasing the risk of severe irinotecan toxicity (Grade 4 leukopenia and grade 3/worse diarrhea) [1], many pharmacogenomics studies have focused on the relationship between UGT1A1*28 and severe neutropenia associated with the use of irinotecan. Based on the cumulative results on these studies, in 2004, the US Food and Drug Administration (the US-FDA) advised revision of the irinotecan labeling to indicate the warning of the elevated risk of neutropenia for patients known to be homozygous for the UGT1A1*28 allele and to recommend a reduced starting dose for such patients [2]. A diagnostic test for the UGT1A1*28 genotype was approved by the US-FDA in 2005. Also in Japan in 2008, the Ministry of Health, Labour and Welfare Japan advised revision of the irinotecan labeling to indicate the role of UGT1A1*6 and UGT1A1*28 polymorphism and to recommend that careful attention is paid to patients who are homozygous or heterozygous for the polymorphism; in 2009 the Ministry approved a diagnostic test for the UGT1A1*28 and *6 [3].

The ethnic differences in the types and frequencies of variants of UGT1A1 have been also revealed by recent pharmacogenomics studies, UGT1A1*27, *6, *36 and *37 as well as *28. To date, few pharmacogenomics studies have targeted the association between irinotecan’s toxicity and these other variants, except for UGT1A1*28; this may be because the most common polymorphism in the Caucasian population is UGT1A1*28 [4]. Uncertainties in the relationship between these other polymorphisms and irinotecan toxicity still remain. Another issue is individual variation in susceptibility to severe diarrhea. Since most studies have targeted neutropenia, the association between another severe adverse drug reaction of irinotecan, diarrhea, and UGT1A1 polymorphisms has not enough studied.

The presence of variant types and frequencies of UGT1A1 polymorphisms varies depending on ethnic groups [4-6]. The allele frequency of UGT1A1*28, seven TA repeats in the promoter region of each UGT1A1 allele, is 33.4-36.5% [4,7] in the Caucasian population and 39.0-40.4% in Africans [4,8], which is the most common polymorphism in both ethnic groups. Whereas, in Asians, the allele frequency of UGT1A1*28 is lower (13.9%); another polymorphism of UGT 1A1, UGT1A1*6, a G→A transition at codon 71 (G71R), is higher (13.0%) compared to that in Caucasian or African-Americans [4]. Also In Asians, UGT1A1*28, a C→A transition at codon 229 (P229Q), is identified in 2.3% [4]. In Africans, UGT1A1*36, 5 TA repeats, and UGT1A1*37, 8 TA repeats, have been identified in 5.8-6.3% and 3.0-4.3%, respectively [4,8,9]. These ethnic differences suggest that the association between genetic polymorphisms of UGT1A1 and irinotecan toxicity could vary depending on ethnic groups. However, UGT1A1*28 has been the focus of most studies to date and studies on polymorphisms which are more commonly found in other ethnic groups have been more limited.

In particular, UGT1A1*6, which is one of the common polymorphisms in the Asian population, is the issue here. UGT1A1*28 and *6 are present on a mutually exclusive chromosome, and they are thought to exert an additive effect on irinotecan toxicity [10]. The frequency of severe neutropenia (Grade 3 and worse) among patients who are homozygous for *28 or *6 (*28/*28, *28/*6, *6/*6) is 50-100% [11-15], among patients who are heterozygous for *28 or *6 (*28/*1, *6/*1), 7.1-100% [11-17], and among wild type patients (*1/*1), 5-33.3% or 57.1% [11-16]. Though not enough studies are available to perform a meta-analysis to consolidate the evidence on the association between the polymorphisms for *28/*6 and the irinotecan toxicity, there is a trend towards an increased risk of severe neutropenia among patients homozygous for *28 or *6 compared to heterozygous and wild type patients. However, there are many limitations and controversial results in these studies. The regimen including dose and co-administered drugs used in the studies were widely varied. Some of the studies recommended dose adjustments even in the low dose therapy (<150 mg/m²) [18], others did not recommend dose adjustments [19,20]. Recommendations of an appropriate dose adjustment for particular regimens are still unclear. Some of the studies independently analyzed the patients with *28 and *6. Also, some of the studies failed to show the association between UGT1A1 polymorphisms and the risk of neutropenia due to a small sample size. To explore an additive effect of *28 and *6 on irinotecan toxicity, an analysis of a combined number of patients with *28 and *6 should be performed. Therefore, further studies are needed to consolidate the evidence and determine a recommendation of dose adjustments, according to particular regimens, for patients who are homozygous or heterozygous for *28 or *6.

Recent pharmacogenomics studies on the association between UGT1A1 polymorphisms and irinotecan toxicity have mainly focused...
on neutropenia [4,20]. Regarding another severe toxicity of irinotecan, severe diarrhea, very few studies have been reported to identify a clear association between the polymorphisms for UGT1A1*28 or *6 and severe diarrhea [11,12,16,17,21,22]. Uncertainties in the relationship between UGT1A1 polymorphisms, including *28, and severe diarrhea still remain. Further studies are needed not only from the Asian population but also from other populations to determine an appropriate irinotecan therapy preventing severe diarrhea.

References
1. Ando Y, Saka H, Ando M, Sawa T, Muro K, et al. (2000) Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res 60: 6921-6926.
2. Label of Camprosar (irinotecan), Pharmaceutical and Medical Devices Agency (Japan).
3. Label of Camprosar (irinotecan), Pharmaceutical and Medical Devices Agency (Japan).
4. Palomaki GE, Bradley LA, Douglas MP, Kolor K, Dotson WD (2009) Can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? An evidence-based review. Genet Med 11: 21-34.
5. Liu JY, Qu K, Sferruzza AD, Bender RA (2007) Distribution of the UGT1A1*28 polymorphism in Caucasian and Asian populations in the US: a genomic analysis of 138 healthy individuals. Anticancer Drugs 18: 693-696.
6. Marques SC, Ikediobi ON (2010) The clinical application of UGT1A1 pharmacogenetic testing: gene-environment interactions. Hum Genomics 4: 239-248.
7. Borucki K, Weikert C, Fisher E, Jakubiczka S, Luley C, et al. (2009) Haplotype analysis of the UGT1A1 gene and its role as genetic determinants of bilirubin concentration in healthy German volunteers. Clin Biochem 42: 1635-1641.
8. Horsfall LJ, Zeiltn D, Tarekhegn A, Bekele E, Thomas MG, et al. (2011) Prevalence of clinically relevant UGT1A alleles and haplotypes in African populations. Ann Hum Genet 75: 236-246.
9. Hong AL, Huo D, Kim HJ, Niu Q, Fackenthal DL, et al. (2007) UDP-Glucuronosyltransferase 1A1 gene polymorphisms and total bilirubin levels in an ethnically diverse cohort of women. Drug Metab Dispos 35: 1254-1261.
10. Sai K, Saeki M, Saito Y, Ozaawa S, Katori N, et al. (2004) UGT1A1 haplotypes associated with reduced glucuronidation and increased serum bilirubin in irinotecan-administered Japanese patients with cancer. Clin Pharmacol Ther 75: 501-515.
11. Takano M, Kato M, Yoshikawa T, Sasaki N, Hirata J, et al. (2009) Clinical significance of UDP-glucuronosyltransferase 1A1*6 for toxicities of combination chemotherapy with irinotecan and cisplatin in gynecologic cancers: a prospective multi-institutional study. Oncology 76: 315-321.
12. Minami H, Sai K, Saeki M, Saito Y, Ozaawa S, et al. (2007) Irinotecan pharmacokinetics/pharmacodynamics and UGT1A1 genetic polymorphisms in Japanese: roles of UGT1A1*6 and *28. Pharmacogenet Genomics. 17: 497-504.
13. Okuyama Y, Hazama S, Nozawa H, Kobayashi M, Takahashi K, et al. (2011) Prospective phase II study of FOLFIRI for mCRC in Japan, including the analysis of UGT1A1 28/6 polymorphisms. Jpn J Clin Oncol 41: 477-482.
14. Sai K, Saito Y, Sakamoto H, Shira K, Kurose K, et al. (2008) Importance of UDP-glucuronosyltransferase 1A1*6 for irinotecan toxicities in Japanese cancer patients. Cancer Lett 261: 165-171.
15. Satoh T, Ura T, Yamada Y, Yamazaki K, Tsujinaka T, et al. (2011) Genotype-directed, dose-finding study of irinotecan in cancer patients with UGT1A1*28 and/or UGT1A1*6 polymorphisms. Cancer Sci 102: 1869-1873.
16. Hazama S, Nagashima A, Kondo H, Yoshida S, Shimizu R, et al. (2010) Phase I study of irinotecan and docetaxel for metastatic colorectal cancer focusing on the UGT1A1*28 polymorphism. Cancer Sci. 101: 722-727.
17. Sunakawa Y, Ishikawa Y, Fujita K, Nagashima F, Ishida H, et al. (2011) UGT1A1*1/*28 and *1/*6 genotypes have no effects on the efficacy and toxicity of FOLFIRI in Japanese patients with advanced colorectal cancer. Cancer Chemother Pharmacol 68: 279-284.
18. Hu ZY, Yu Q, Pei Q, Guo C (2010) Dose-dependent association between UGT1A1*28 genotype and irinotecan-induced neutropenia: low doses also increase risk. Clin Cancer Res 16:3832-3842.
19. Sugiyama T, Hirose T, Kosumoto S, Shira T, Yamaoka T, et al. (2010) The UGT1A1*28 genotype and the toxicity of low-dose irinotecan in patients with advanced lung cancer. Oncol Res. 18: 337-342.
20. Hoskins JM, Goldberg RM, Qu P, Ibrahim JG, McLeod HL (2007) UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters. J Natl Cancer Inst 99:1290-1295.
21. Marucello E, Altés A, Menoyo A, Del Rio E, Gómez-Pardo M, et al. (2004) UGT1A1 gene variations and irinotecan treatment in patients with metastatic colorectal cancer. Br J Cancer 91: 678-682.
22. Araki K, Fujita K, Ando Y, Nagashima F, Yamamoto W, et al. (2006) Pharmacogenetic impact of polymorphisms in the coding region of the UGT1A1 gene on SN-38 glucuronidation in Japanese patients with cancer. Cancer Sci 97: 1255-1259.