Kobayashi and Satoh, J Pharmacogenom Pharmacoproteomics 2012, 3:2
DOI: 10.4172/2153-0645.1000e117

Journal of Pharmacogenomics & Pharmacoproteomics

Editorial Open Access

Clinical Applications of UGT1A1 Polymorphisms for Irinotecan Therapy

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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 prodrug 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 regimens 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/m^2) [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

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Received February 24, 2012; **Accepted** February 27, 2012; **Published** Ferbruary 29, 2012

Citation: Kobayashi E, Satoh N (2012) Clinical Applications of UGT1A1 Polymorphisms for Irinotecan Therapy. J Pharmacogenom Pharmacoproteomics 3:e117. doi:10.4172/2153-0645.1000e117

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.

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