Annals of Oncology 19: 2089–2094, 2008

Genetic testing for *UGT1A1*28* and **6* in Japanese patients who receive irinotecan chemotherapy

Polymorphisms of the *UDP-glucuronosyltransferase* (*UGT*) *1A1* gene, such as *UGT1A1*28* and *UGT1A1*6*, can cause severe neutropenia and diarrhea in patients who receive irinotecan [1, 2]. Homozygosity for *UGT1A1*28* is associated with less efficient glucuronidation of SN-38, the active metabolite of irinotecan, resulting in increased plasma SN-38 concentrations. Four pharmacogenetic trials have demonstrated an association between *UGT1A1*28* genotype and irinotecan-induced hematologic toxicity, diarrhea, or both [3]. In response to these findings, the United States Food and Drug Administration has approved genetic testing for *UGT1A1*28* and recommends that the initial dose of irinotecan is reduced by at least one level in patients who are homozygous for *UGT1A1*28*, albeit the effectiveness of such testing remains to be confirmed prospectively. *UGT1A1*6* is also associated with severe irinotecan-related toxicity [4]. Given that the area under the time versus concentration curve ratio (SN-38 glucuronide/SN-38) seen in patients homozygous for *UGT1A1*28* and **6* are almost equal [4], the impact of these variants on glucuronidation capacity of UGT1A1 for SN-38 is almost the same. The distribution of genotypes associated with these polymorphisms varies considerably among ethnic groups. *UGT1A1*28* is found in Japanese and whites, but the allele frequency in Japanese is lower than that in whites [2, 4]. *UGT1A1*6* is found in Japanese, but not in whites [4]. Homozygosity for *UGT1A1*28* or *UGT1A1*6* and heterozygosity for both *UGT1A1*6* and *UGT1A1*28* are associated with severe irinotecan-related neutropenia in Japanese patients [1, 4]. The Ministry of Health, Labour and Welfare in Japan has therefore recently approved genetic testing for *UGT1A1*28* and **6*.

The value of genetic testing for *UGT1A1* depends on genotype frequency and the association of genetic variants with irinotecan-induced toxicity. The higher the frequency of toxicity-related polymorphisms, the greater is the number of patients who would benefit from genetic testing. Large prospective studies are needed to accurately estimate the distribution of *UGT1A1* polymorphisms in a given population. We have carried out the largest prospective study to date, examining the distributions of *UGT1A1*28* and *UGT1A1*6* genotypes in 300 Japanese patients (male/female, 172 of 128) with various solid tumors (200 colorectal, 43 gastric, 15 ovarian, 14 breast, 10 lung, and 18 others).

All patients gave written informed consent, and the study protocol was approved by the Institutional Review Board of Saitama Medical University. Genotyping was carried out as described elsewhere [5].

*UGT1A1*28* and *UGT1A1*6* were in Hardy–Weinberg equilibrium ($P > 0.05$). Only 2 of 300 patients were *UGT1A1*28* homozygotes (0.7%) (Table 1). The frequency of homozygosity for *UGT1A1*28* was much lower than that in other prospective studies in Japan (2.3%, 4 of 176) [4]. The frequency of *UGT1A1*6* homozygosity was 5.7% (Table 1), higher than that reported previously (2.8%) [4]. Eleven patients were both heterozygous for *UGT1A1*6* and *UGT1A1*28* (3.7%). The combined frequency of patients with two 'risk alleles' (i.e. **28/*28*, **6/*6*, and **6/*28*) was 10.1% (95% confidence interval, 6.8% to 14.0%). Such patients might be at increased risk for irinotecan-related neutropenia. Given the genotype frequencies of *UGT1A1*28* and *UGT1A1*6*, genetic testing for *UGT1A1* might not be essential for identifying homozygotes for *UGT1A1*28*, but useful for identifying homozygotes for *UGT1A1*6* as well as heterozygotes for *UGT1A1*6* and *UGT1A1*28*, thereby avoiding severe irinotecan-induced toxicity in Japanese patients. The present results and considerations are likely to have application across East Asia. Prospective evaluations of genetic testing for *UGT1A1* polymorphisms, encompassing both medical aspects and cost effectiveness, appear to be warranted, especially in East Asian countries including Japan.

funding

Grant-in-Aid for Cancer Research (17-8) to YS; Health and Labour Sciences Research Grant from the Ministry of Health, Labour and Welfare of Japan (2005-Clinical Cancer Research-008) to YS; Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (A-16200038) to YS; Japan Research Foundation for Clinical Pharmacology to KF.

Table 1. Genotype frequencies of *UGT1A1*28* and *UGT1A1*6* in Japanese

Genotype	*n* (%)	95% confidence interval (%)
*UGT1A1*1/*1*[a]	135 (45.0)	39.3–50.8
*UGT1A1*1/*28*	47 (15.7)	11.7–20.3
*UGT1A1*1/*6*	88 (29.3)	24.1–34.8
*UGT1A1*28/*28*	2 (0.7)	0.1–2.4
*UGT1A1*6/*6*	17 (5.7)	3.3–8.9
*UGT1A1*6/*28*	11 (3.7)	1.8–6.5

[a]*UGT1A1* allele without **28* or **6* was defined as **1*.

Y. Akiyama[1,2], K. Fujita[1,2], F. Nagashima[1,2], W. Yamamoto[1], H. Endo[1], Y. Sunakawa[1], K. Yamashita[1], H. Ishida[1], K. Mizuno[1], K. Araki[1], W. Ichikawa[1], T. Miya[1], M. Narabayashi[1], K. Kawara[1], M. Sugiyama[1], T. Hirose[1], Y. Ando[1] & Y. Sasaki[1,2]*

[1]Department of Medical Oncology, Saitama International Medical Center-Comprehensive Cancer Center, Saitama Medical University, [2]Project Research Laboratory, Research Center for Genomic Medicine, Saitama Medical University, Saitama, Japan
(*E-mail ysasaki@saitama-med.ac.jp)

references

1. Ando Y, Saka H, Ando M et al. Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res 2000; 60: 6921–6926.
2. Innocenti F, Undevia SD, Iyer L et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 2004; 22: 1382–1388.
3. Hoskins JM, Goldberg RM, Qu P et al. UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters. J Natl Cancer Inst 2007; 99: 1290–1295.
4. Minami H, Sai K, Saeki M et al. Irinotecan pharmacokinetics/pharmacodynamics and UGT1A genetic polymorphisms in Japanese: roles of UGT1A1*6 and *28. Pharmacogenet Genomics 2007; 17: 497–504.
5. Araki K, Fujita K, Ando Y et al. Pharmacogenetic impact of polymorphisms in the coding region of the UGT1A1 gene on SN-38 glucuronidation in Japanese patients with cancer. Cancer Sci 2006; 97: 1255–1259.

doi:10.1093/annonc/mdn645
Published online 26 October 2008