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CASE REPORT

Severe irinotecan-induced toxicity in a patient with *UGT1A1*28* and *UGT1A1*6* polymorphisms

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Abstract

Many studies have demonstrated the impact of UGT1A1 on toxicity of irinotecan. In particular, patients bearing UGT1A1*28 (TA 7/7) have a higher risk of severe neutropenia and diarrhea. Based on this, prescribers of irinotecan are advised that patients with UGT1A1*28 (TA 7/7) should start with a reduced dose of irinotecan, although a particular dose is not specified. Research in Asian countries has shown a lower incidence of UGT1A1*28 (TA 7/7), while UGT1A1*6 (A/A) is more often found and is associated with severe irinotecan-related neutropenia. We report here a case of a metastatic colorectal cancer patient who is heterozygous for the *UGT1A1*28* polymorphism (TA 6/7) as well as the *UGT1A1*6* polymorphism (G/A). The patient was treated with FOLFIRI for 9 cycles and underwent two irinotecan dose reductions according to pharmacokinetic data regarding exposure to the active metabolite, SN-38. Simultaneous heterozygous *UGT1A1*28* and *UGT1A1*6* polymorphisms may produce higher exposure to SN-38 and a higher risk of adverse effects related to irinotecan. Additional studies will be necessary to determine the optimal starting dose of irinotecan for patients with both *UGT1A1*28* and *UGT1A1*6* polymorphisms.

Key words: Irinotecan; Toxicity; *UGT1A1*28*; *UGT1A1*6*; Polymorphism

Core tip: This is the first reported case. This patient with heterozygous *UGT1A1*28* and *UGT1A1*6* polymorphisms experienced two dose reductions of irinotecan due to severe toxicity according to pharmacokinetic analyses of SN-38 and SN-38 glucuronide levels. It seems that this patient benefited from a longer treatment duration, suggesting that irinotecan dose individualization for mutant metastatic colorectal cancer patients with heterozygous *UGT1A1*28* or *UGT1A1*6* polymorphisms may be warranted.

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INTRODUCTION

The FOLFIRI regimen, which is composed of 5-fluorouracil (5-FU), leucovorin, and irinotecan, is a commonly

used treatment regimen for metastatic colorectal cancer. UGT1A polymorphisms have been the focus of irinotecan pharmacokinetics (PK) and toxicity research since UGT1A enzymes play a key role in the glucuronidation of the active metabolite of irinotecan, SN-38, to the inactive SN-38G[1-3]. There have been a number of studies to examine the associations of the *UGT1A1*, *UGT1A7*, and *UGT1A9* genotypes and severe irinotecan-induced toxicity, particularly diarrhea and neutropenia[4-7]. The data strongly suggest that the *UGT1A1*28* genotype is associated with severe irinotecan-induced diarrhea and neutropenia[7-9], which led to a change in the irinotecan United States label to recommend dose reduction in patients with lower UGT1A1 activity. The incidence rates of severe neutropenia and diarrhea (grade 3/4) in patients homozygous for UGT1A1*28 (TA 7/7) in Western and Eastern populations were > 30%[10,11]. Interestingly, there are no polymorphisms at the UGT1A1*6 locus reported in the Western population. However, studies in Asian countries indicated that there is a common (35.8%-38.9%) single nucleotide polymorphism at the UGT1A1*6 (G→A) locus that is associated with severe irinotecan-related neutropenia[12-14]. The effects of other *UGT1A7* and *UGT1A9* polymorphisms on irinotecan-related toxicity remain unclear[4,12]. To determine the optimal dose of irinotecan in the FOLFIRI regimen, we are conducting a prospective and multicenter clinical trial in which the dose of irinotecan is adjusted for the specific *UGT1A* genotypes in patients with metastatic colorectal cancer (NCT01523431).

CASE REPORT

A 72-year-old male patient with an adenocarcinoma at the hepatic flexure of the colon underwent right hemicolectomy. Several mo later, the patient developed metastases in the liver, bilateral lungs and mediastinal lymph nodes. Liver biopsy confirmed metastatic disease from colon cancer. Routine genotyping showed that the patient was heterozygous for the *UGT1A1*28* polymorphism (TA 6/7) as well as the *UGT1A1*6* polymorphism (G/A). The patients had normal liver function and renal function. He was treated with the standard FOLFIRI regimen: a 90-min intravenous (*iv*) infusion of irinotecan (Camptosar, Pfizer) (180 mg/m^2); an *iv* infusion of leucovorin (400 mg/m^2); followed by 5-FU by *iv* bolus (400 mg/m^2) and continuous *iv* infusion (2400 mg/m^2) over 46 h; this regimen was repeated every 2 wk. Concurrently, a 5-mL heparinized blood sample was collected before irinotecan administration, at 1 and 1.5 h during the infusion and at 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 36, and 48 h after the termination of the drug infusion. After the first treatment cycle, the patient suffered grade 4 neutropenia, grade 3 diarrhea, grade 2 fatigue, and grade 2 mucositis. The area under the curve (AUC) of SN-38, the active metabolite of irinotecan, was 929 ng/mL per hour (Figure 1), which was 4-fold that of the mean AUC for wild-type patients treated with the standard FOLFIRI regimen

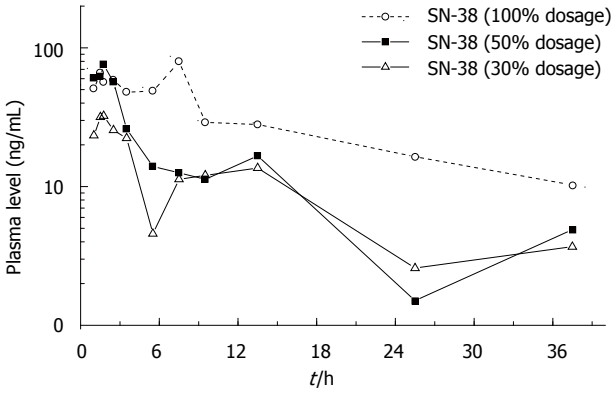

Figure 1 Plasma concentration-time profiles of SN-38 in different dose levels of irinotecan.

Table 1 Area under the curve of irinotecan, SN-38 and SN-38G for this patient at various doses of irinotecan, compared with a group of patients with wild type UGT1A1 at the standard dose of irinotecan

Irinotecan dose (mg/m^2)	AUC$_{irinotecan}$ (ng/mL per hour)	AUC$_{SN-38}$ (ng/mL per hour)	AUC$_{SN-38G}$ (ng/mL per hour)	AUC$_{SN-38G}$/AUC$_{SN38}$
180	26838	929	3000	3.2
90	12790	476	2014	4.2
54	9488	328	2096	3.4
		UGT1A1 wild type patients[1]		
180	6321 ± 3993	234 ± 185	645 ± 353	3.3 ± 2.1

[1]Treated with standard FOLFIRI regimen at our cancer center (n = 38, mean ± SD). AUC: Area under the curve.

at our cancer center. The AUC ratio of glucuronidated SN-38G/SN-38 was 3.23, which was similar to that of wild-type patients (Table 1). Therefore, we reduced the irinotecan dose by 50% (to 90 mg/m^2) but maintained the doses of 5-FU and leucovorin in subsequent cycles. The second round of pharmacokinetic analysis showed that the AUC of SN-38 was 476 ng/mL per hour, which was more than 2-fold that of the mean AUC for wild-type patients. After the second cycle, there was no neutropenia and only grade 1 diarrhea. Moreover, computerized tomography (CT) and magnetic resonance imaging scans showed a partial response in the lung and liver metastases, respectively, and the response was confirmed after two additional cycles (Figure 2). However, after the fifth cycle, the patient developed recurrent neutropenia and additional doses of irinotecan were held. His Eastern Cooperative Oncology Group performance status had worsened from 0 to 1. He received two cycles of capecitabine (2000 mg/m^2 divided *bid* for 2 wk on, 1 wk off) as maintenance therapy, and his CT showed stable disease (SD). However, the patient discontinued therapy for 1 mo because of grade 3 mucositis and grade 3 diarrhea. A few mo later, he experienced disease progression in the liver and lung and his weight had decreased from 54.5 to 47 kg over 3 mo. We decided to reinitiate the FOLFIRI regimen. The irinotecan dose was reduced by

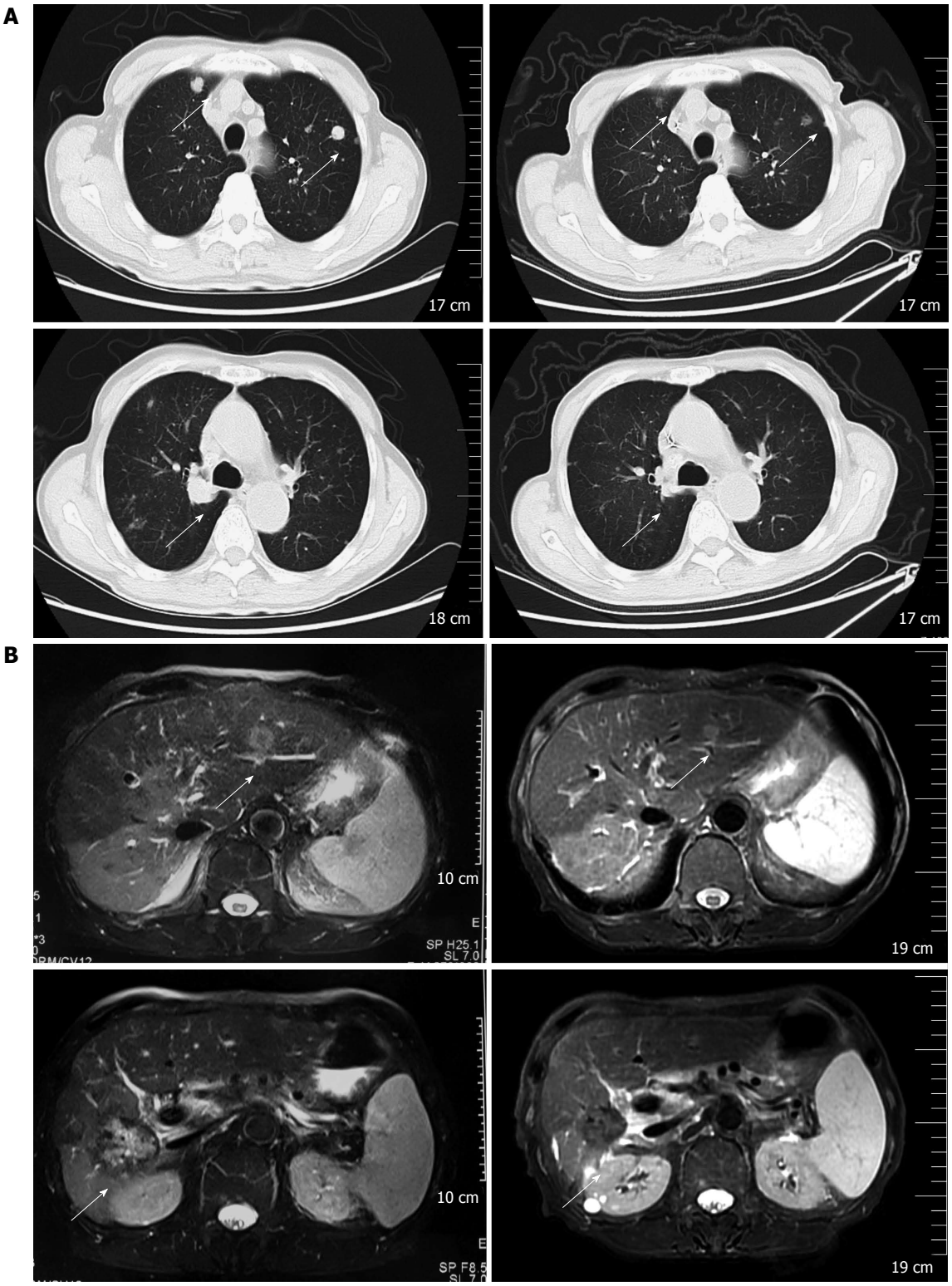

Figure 2 Computerized tomography scan (A) and magnetic resonance imaging (B). Before treatment (left figure) and after treatment (right figure) of the lung and the liver metastases, respectively; the response was confirmed after two additional cycles.

70% (to 54 mg/m^2), while the 5-FU dose was reduced by 30%. The third round of pharmacokinetic analysis showed that the AUC of SN-38 was 328 ng/mL per hour, which is close to the mean AUC with a standard dose in wild-type patients. After two additional cycles, he had SD but experienced grade 3 neutropenia and grade 2 diarrhea. CT scan showed disease progression after two additional cycles of chemotherapy.

DISCUSSION

Recent studies in Asian countries have indicated that

the polymorphism in UGT1A1*6 has a similar effect as UGT1A1*28 on irinotecan-induced toxicity and PK[12,15,16]. However it is unclear whether simultaneous heterozygous *UGT1A1*28* and *UGT1A1*6* (TA 6/7 + G/A genotype) polymorphisms may have significantly more side effects and impact on PK of SN38. Irinotecan PK are determined by multiple metabolizing enzymes, whereas the saturation of enzymatic reactions is affected by other factors, such as age and creatinine clearance[17]. The patient in the present study, who carried both polymorphisms, experienced serious toxicity after one cycle of a standard irinotecan dose, which corresponded to an SN-38 exposure (AUC) that was 4-fold higher than in wild-type patients. It has been reported that low dose irinotecan-induced toxicity is not associated with *UGT1A1* polymorphisms[18]. In the present study, however, toxicity recurred even after reducing the irinotecan dose by 50%, and the AUC of SN-38 was still 2-fold higher than the mean in wild-type patients who received standard dose irinotecan. Even after a 70% dose reduction, the AUC of SN-38 was close to the mean in wild-type patients who received standard dose irinotecan. This observation suggests that the PK were still affected by the polymorphisms in the *UGT1A1* gene even at relatively low doses. Whether dosing and AUC may be associated with efficacy is still unclear; however, data from Toffoli *et al*[7] suggest that higher doses and higher AUC may be associated with higher efficacy in patients with mutant metastatic colorectal cancer.

When faced with intolerable toxicity, oncologists typically reduce the dose, delay treatment, or discontinue treatment, any or all of which may reduce the treatment duration and affect the progression-free survival and overall survival of patients. The patient in this report underwent two irinotecan dose reductions during the course of 9 treatment cycles with FOLFIRI, as well as 2 cycles of capecitabine as maintenance therapy. The duration of disease control, including breaks, was 7 mo, which suggests that the patient benefited from the dose reductions. The AUC ratio of SN-38G/SN-38 did not decrease with additional treatment cycles, suggesting that patients with UGT1A1 polymorphisms may not experience the irinotecan-induced inhibition of UGT1A1 and corresponding decrease in the AUC ratio of SN-38G/SN-38 that has been observed by Hirose *et al*[16] in wild-type patients. To our knowledge, the present case is the first report to adjust the irinotecan dose twice based on the patient's *UGT1A1* genotype and according to PK characteristics. Additional studies will be necessary to determine the optimal starting dose of irinotecan for patients with both *UGT1A1*28* and *UGT1A1*6* polymorphisms and to determine how this genotype may influence efficacy.

In summary, simultaneous heterozygous *UGT1A1*28* and *UGT1A1*6* polymorphisms may produce higher exposure to SN-38 and a higher risk of adverse effects related to irinotecan. Additional studies will be necessary to determine the optimal starting dose of irinotecan for patients with both *UGT1A1*28* and *UGT1A1*6* polymorphisms.

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