Concurrence of UGT1A polymorphism and end-stage renal disease leads to severe toxicities of irinotecan in a patient with metastatic colon cancer

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ABSTRACT

Aims and background. Colorectal cancer is one of the most common malignancies in the world, and irinotecan (CPT-11) is useful in its treatment. However, the safety and pharmacokinetics of irinotecan in dialysis patients with metastatic colorectal cancer are unclear.

Case report. We report the case of a 74-year-old man receiving chronic hemodialysis who had metastatic colorectal cancer. Palliative chemotherapy with irinotecan (80 mg/m2 weekly) was administered after hemodialysis. Blood samples were collected before and 1.5, 3, 6, 9, and 15 hours after administration of irinotecan. The peak serum concentrations (Cmax) of irinotecan and SN-38 in this patient were 1,480 and 17.8 ng/mL, respectively, which were similar to the reported values in patients with normal renal function after a similar dose of irinotecan (75 mg/m2). The area under the serum concentration-time curve (AUC0–∞) was 8,240 ng×h/mL for irinotecan and 619 ng×h/mL for SN-38. The AUC0–∞ for SN-38 was markedly higher than that for patients with normal renal function. Sequencing analysis of the UGT1A genes found that the patient had variant alleles of UGT1A1*28, UGT1A1*60 and UGT1A9*22, which may lead to decreased glucuronidation and excretion of SN-38, and may account for increased irinotecan-related toxicity. The patient developed febrile grade 4 neutropenia on day 7 after chemotherapy and died of septic shock on day 14.

Conclusions. UGT1A polymorphisms and renal failure may lead to accumulation of SN-38, which may have played a role in the death of this patient. Irinotecan should be used cautiously in dialysis patients with metastatic colorectal cancer and screening for UGT1A polymorphisms may help in identifying patients with lower SN-38 glucuronidation rates and greater susceptibility to irinotecan-induced toxicity.