Aim: Our previous clinical study revealed that total plasma concentration of SN-38 was higher in cancer patients with SRF than those with normal kidney (NK), although SN-38 is mainly eliminated in the liver. Because SN-38 can bind to plasma protein, we hypothesized the possible increase in unbound fraction of SN-38 and area under the unbound plasma concentration-time curve (AUCu) caused by inhibition of plasma protein binding by uremic toxin(s) in patients with SRF.

Methods: Total and unbound plasma concentrations of SN-38 in the cancer patients treated with 100 mg/m² irinotecan alone were examined at 1 h after the end of irinotecan infusion to obtain unbound fraction of SN-38. Ex vivo analyses for SN-38 protein binding were performed with plasma samples obtained from 4 respective groups of patients (10-12 for each group) categorized by their renal function, estimated glomerular filtration (eGFR)<15, 15-30, 30-60 and >60 mL/min. The inhibition by 22 uremic toxins known to bind to plasma protein of SN-38 protein binding was also examined.

Results: Unbound fraction of SN-38 in 3 cancer patients with SRF (0.023 ± 0.0060) was significantly higher than that in 5 of those with NK (0.0089 ± 0.0043) (P = 0.0339). AUCu in patients with SRF and those with NK were 0.030 ± 0.015 and 0.0069 ± 0.0043 µM·h, respectively (P = 0.0253). Ex vivo experiments revealed that unbound fractions of SN-38 was inversely correlated with eGFR (Spearman’s rank correlation coefficient, -0.5207; P = 0.0003). The unbound fractions in patients with eGFR < 15 mL/min (3.1 ± 0.77) and 15-30 mL/min (2.7 ± 1.0) were significantly higher than those with NK (1.8 ± 1.2) (P = 0.0006 and 0.0409, respectively). An uremic toxin, 3-carboxy-4-methyl-5-propyl-2-furanpropionate (CMPF), potently inhibited the plasma protein binding of SN-38 at a clinically relevant concentration to significantly elevate the unbound fraction of SN-38 (0.051 ± 0.013 to 0.10 ± 0.014, P = 0.0000640).

Conclusions: Unbound concentrations of SN-38 were higher in patients with SRF than those with NK. The inhibition of SN-38 protein binding by CMPF is a possible mechanism.

Disclosure: All authors have declared no conflicts of interest.