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PHARMACOKINETICS OF S-1 IN ELDERLY JAPANESE PATIENTS WITH CANCER
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Purpose: S-1 is an oral anticancer agent that combines tegafur with 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate. Tegafur is a pro-drug of 5-fluorouracil (5-FU). CDHP prevents degradation of 5-FU by inhibiting dihydropyrimidine dehydrogenase. We examined the effects of aging on the pharmacokinetics of the components of S-1.

Methods: The pharmacokinetics of the tegafur, 5-FU and CDHP seen in S-1 treated patients with age of 75 years or older were compared with those in patients younger than 75 years.

Results and Discussion: The median area under the concentration-time curve (AUC) of the active 5-FU did not significantly differ between 10 patients 75 years or older and 53 patients younger than 75 years (P=0.598, Mann-Whitney U). Interestingly, the median oral clearance of tegafur in patients 75 years or older was significantly lower than that in patients younger than 75 years (P=0.011). Furthermore, the median AUC of CDHP was significantly higher in patients 75 years or older than in those younger than 75 years (P=0.004). This was caused by reduced renal function in elderly, since CDHP is excreted in the urine by glomerular filtration. The opposing effects of aging on the oral clearance of tegafur and the AUC of CDHP may offset each other, leading to unchanged systemic exposure of 5-FU.

Conclusion: We found no significant difference in AUC of the active 5-FU between patients 75 years or older and those younger than 75 years.

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COMPREHENSIVE ANALYSIS FOR THE EXPRESSION OF DRUG TRANSPORTERS IN HEPATOCELLULAR CARCINOMA
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[Purpose] Drug transporters play crucial roles in hepatic uptake and excretion of many endogenous compounds and xenobiotics including anti-cancer drugs. In human liver, the expression of drug transporters are reported to be altered in various pathophysiological conditions such as hepatitis and cholestasis. However, limited data are available for liver cancer. In the present study, we carried out comprehensive analysis for the expression profile of hepatic drug transporters in human hepatocellular carcinoma (HCC) and to identify transporter(s) specifically regulated in HCC.

[Methods] The mRNA levels of 9 solute carrier (SLC) transporters (OAT2, OAT7, OATP1B1, OATP1B3, OATP2B1, OCT1, OCTN2, MATE1 and PEPT1) and 8 ATP-binding cassette (ABC) transporters (MDR1, MRP1-6 and BCRP) were determined by real-time RT-PCR in cancerous and non-cancerous liver tissues from 57 patients with HCC. Protein expression was evaluated by Western blot analysis.

[Results and Discussion] The mRNA levels of 11 transporters (OAT7, OCTN2, MATE1, PEPT1, MDR1, MRP1-6) were significantly increased in HCC compared with non-cancerous liver tissues, while only OCT1 mRNA was significantly decreased (0.65-fold, p=0.0004). Notably, the mRNA level of MRP4 showed the highest increase in HCC (7.4-fold, p<0.0001), which was consistent with the marked augmentation in the protein level.

[Conclusions] We demonstrated that most hepatic drug transporters were elevated in HCC tissues, and that MRP4 was remarkably up-regulated.