INVESTIGATION OF THE IMPORTANCE OF OATP1B3 AND MRP2 IN DOCETAXEL-INDUCED HEMATOPOIETIC TOXICITY

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[Purpose] In chemotherapy, neutropenia is one of the critical dose-limiting toxicities. Kiyotani et al. have demonstrated that the incidence of docetaxel-induced neutropenia was significantly associated with genetic polymorphisms of organic anion transporting polypeptide (OATP) 1B3 and multidrug resistance-associated protein 2 (MRP2) (Kiyotani K et al., Cancer Sci. 99(5):967–72 (2008)). The purpose of this study is to investigate how these transporters determine docetaxel-induced neutropenia.

[Methods] The uptake study with docetaxel using transporter expression systems was performed. To evaluate how much of its overall hepatic uptake is transporter-mediated, the saturable uptake into cultured rat hepatocytes was also evaluated. To investigate docetaxel-induced hematopoietic toxicity, colony forming assay with rat bone marrow cells was performed and the dose-dependent toxicity in vivo was examined in control rats and EHBRs (Mrp2-deficient rats).

[Results and Discussion] Significant uptake of docetaxel was observed only in OATP1B3-expressing cells and transporter-mediated uptake was predominant in rat hepatocytes. Docetaxel-induced toxicity was significantly increased in bone marrow cells from EHBRs, but no significant potentiation of docetaxel-induced toxicity by a lack of MRP2 was observed in vivo.

[Conclusions] OATP1B3 could be involved in the hepatic uptake of docetaxel in humans and a dysfunction of uptake transport could reduce its hepatic clearance. Mrp2 appears to be one of the determinants of docetaxel-induced hematopoietic toxicity, but no significant relationship between its toxicity and Mrp2 function could be confirmed in our in vivo system and further studies will be needed to optimize the experimental conditions.

PREDICTION OF INTESTINAL DRUG ABSORPTION AND DISPOSITION BY NON-INVASIVE METHOD USING PERIPHERAL BLOOD LYMPHOCYTES

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[Purpose] ATP binding cassette (ABC) transporters have a large impact on pharmacokinetic parameter of various drugs. Although it is important to know the expression of transporters in each patient, we can get the information only by biopsy. We focused on peripheral blood lymphocytes (PBL) which have various function such as immune response, to establish the non-invasive method that we can predict the pharmacokinetic parameters in each patient. We also focused on Pregnane X receptor (PXR) which is involved in induction of many ABC transporters.

[Methods] Five mg/kg LPS (from E.coli O111:B4) were intrapentoneally administered to Wistar/ST male rat by single dosing or multiple dosing (once a day, for 3 days or for 5 days). Eight hr after final dosing, ABC transporters function was investigated by in situ single pass perfusion method. The levels of mRNA and protein were analyzed by real time RT-PCR and Western blotting method, respectively.

[Results and Discussion] In ileum and liver, the mRNA levels of ABC transporters and PXR, and function of ABC transporters such as P-glycoprotein (P-gp) were significantly decreased at 8 hr after single injection of LPS. These down-regulations of mRNA and P-gp function were moderated by multiple injections of LPS. On the other hands, the mRNA levels of ABC transporters and PXR in PBL were increased by single injection of LPS, and returned to the control levels after multiple injections of LPS. The correlation between the mRNA level of PXR in PBL and the function of ABC transporters in ileum and liver is now under investigation.