Abstract

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Title of diploma thesis: Interaction of gilteritinib with OCT1 and OCT2 transporters; relation to conventional therapy of acute myeloid leukemia.

Gilteritinib is one of the recently approved drugs which is primarily used in the treatment of relapsed/refractory acute myeloid leukemia (AML) with mutated FMS-like tyrosine kinase 3 (FLT3) receptor. In this project, gilteritinib was investigated in terms of its ability to interact with solute carrier (SLC) membrane transporters, namely with OCT1 and OCT2. These membrane proteins play a role in uptake of endogenous compounds and also drugs into the cells of main elimination organs (liver, kidney), but also to cancer cells. In particular, we wanted to examine potential interaction with daunorubicin and mitoxantrone, drugs traditionally used in AML therapy.

First, we performed accumulation study and evaluated, whether gilteritinib is potential inhibitor of OCT1 and OCT2 studying differential uptake of daunorubicin and mitoxantrone into MDCKII-OCT1 and MDCKII-OCT2 cells based on OCT1 and OCT2 inhibition by gilteritinib. Secondly, the study evaluating the transfer of gilteritinib across the monolayers of MDCKII-OCT1 and control MDCKII-VK cell lines was conducted to test gilteritinib as a potential substrate of this transporter.

The obtained data showed that gilteritinib has ability to inhibit the OCT1-mediated transport of daunorubicin into the MDCKII-OCT1 cells. This effect was not observed neither in control cell line, nor MDCKII-OCT2 cells. We further observed enhanced basolateral-to-apical transport of gilteritinib across monolayers of MDCKII-OCT1 and MDCKII-OCT2 cells compared to MDCKII-VK cells. This difference was abolished in the presence of OCT1 inhibitor, suggesting that gilteritinib is a substrate of OCT1.

Results obtained in our study indicate that gilteritinib might be prone to OCT1-mediated pharmacokinetic drug-drug interactions. The hypothesis that combinatory treatment of AML

with gilteritinib and daunorubicin could result in decreasing availability of the drugs to the leukemia cells leading to lower efficacy of the treatment should be verified.