**INTERACTION OF TYROSINE KINASE INHIBITORS WITH THE ORGANIC CATION TRANSPORTER MATE1**

*Zahra Talebi 1, Xiaolin Cheng2, Sharyn Baker1, Alex Sparreboom1*

*1Division of Pharmaceutics and Pharmacology, College of Pharmacy, The Ohio State University, Columbus, OH 43210, USA; 2Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, OH 43210, USA*

BACKGROUND

Membrane transporters regulate systemic and cellular drug levels and can influence both efficacy and toxicity of administrated drugs. We previously reported that the organic cation transporters OCT1 and OCT2 can be potently inhibited by drugs in the class of tyrosine kinase inhibitors (TKIs).1,2 Since the basolaterally localized OCT1 and OCT2 form a functional unit in the kidney and liver, respectively, with the apically expressed MATE1 transporter to regulate elimination of organic cation,3,4 we hypothesized that MATE1 might also be sensitive to inhibition by TKIs. As MATE1 substrates are frequently prescribed in cancer patients, this study can provide valuable clinical insights for prescribers to prevent drug-drug interactions.

METHODS

The effect of all FDA approved TKIs on uptake profile of the prototypical MATE1 substrate tetraethylammonium (TEA) was evaluated in HEK293 cells engineered to overexpress human MATE1 (hMATE1), followed by liquid scintillation counting. Typical studies involved a 15-min incubation cells with MATE1 media containing NH4Cl, a 15-min pre-incubation with inhibitor, and a 15-min co-incubation of inhibitor and radiolabeled substrate. Meformin was used as an alternative substrate to evaluate substrate dependency of observed inhibition profiles, and cimetidine was used as a positive control inhibitor. Different incubation times and conditions were used on select compounds to further understand the mechanism of the interaction between MATE1 and TKIs.

RESULTS

All 58 currently approved TKIs, except Alectinib inhibited MATE1 activity to some degree at a concentration of 10 µM, and 23 of these (~40%) inhibited MATE1 function by >90% compared with vehicle control conditions. We confirmed the MATE1-inhibitory potential of several TKIs, such as capmatinib, entrectinib, erfaditinib, gilteritinib, osimertinib, trametinib and upadacitinib, which are listed as MATE1 inhibitors in their prescribing information or in the published literature, such as imatinib and vandetanib. However, we identified several FDA-approved TKIs as previously unrecognized, potent inhibitors of MATE1, including ibrutinib and nilotinib. Subsequent examination demonstrated that the inhibitory potential of these agents is dependent on TKI concentration, but not dependent on the substrate used. Next, we found that ibrutinib and nilotinib influenced MATE1 function at concentrations that can be observed in patients (IC50, ~0.5-1.5 µM), and that the mechanism of inhibition is predominantly non-competitive, as indicated by kinetic analyses in a Dixon plot. Inhibition of MATE1 function was very slowly reversible, with recovery to about 50% of baseline activity after an 8-hour washout period following a single, short-term exposure to the TKI.

CONCLUSION

This study reports an unexpected interaction between multiple biologically and structurally-diverse TKIs and the transporter MATE1 that is more common than previously indicated and more extensive than anticipated based on similar prior screens against OCT1 and OCT2. We are currently exploring the *in vivo* significance of this inhibitory mechanism using recently developed analytical methods to trace endogenous biomarkers of MATE1 function in both wild-type and MATE1-deficient mice. In addition, studies are ongoing to employ computational modeling approaches to further elucidate the mechanism of this interaction and its potential clinical relevance.

1. Uddin ME, Garrison DA, Kim K, Jin Y, Eisenmann ED, Huang KM, Gibson AA, Hu Z, Sparreboom A, Hu S. Influence of YES1 Kinase and Tyrosine Phosphorylation on the Activity of OCT1. Frontiers in Pharmacology. 2021;12:291.
2. Sprowl JA, Ong SS, Gibson AA, Hu S, Du G, Lin W, Li L, Bharill S, Ness RA, Stecula A, Offer SM. A phosphotyrosine switch regulates organic cation transporters. Nature communications. 2016 Mar 16;7(1):1-1.
3. Otsuka, M., et al., A human transporter protein that mediates the final excretion step for toxic organic cations. Proc Natl Acad Sci U S A, 2005. 102(50): p. 17923-8.
4. Dresser, M.J., M.K. Leabman, and K.M. Giacomini, Transporters involved in the elimination of drugs in the kidney: organic anion transporters and organic cation transporters. J Pharm Sci, 2001. 90(4): p. 397-421.