SHORT COMMUNICATION

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Inhibition of OATP1B1 by tyrosine kinase inhibitors: *in vitro–in vivo* correlations

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Background: Several tyrosine kinase inhibitors (TKIs) can decrease docetaxel clearance in patients by an unknown mechanism. We hypothesised that these interactions are mediated by the hepatic uptake transporter OATP1B1.

Methods: The influence of 16 approved TKIs on transport was studied *in vitro* using HEK293 cells expressing OATP1B1 or its mouse equivalent Oatp1b2. Pharmacokinetic studies were performed with Oatp1b2-knockout and OATP1B1-transgenic mice.

Results: All docetaxel-interacting TKIs, including sorafenib, were identified as potent inhibitors of OATP1B1 *in vitro*. Although Oatp1b2 deficiency *in vivo* was associated with increased docetaxel exposure, single- or multiple-dose sorafenib did not influence docetaxel pharmacokinetics.

Conclusion: These findings highlight the importance of identifying proper preclinical models for verifying and predicting TKI–chemotherapy interactions involving transporters.

Docetaxel is widely used for the treatment of multiple solid tumours, including cancers of the breast, lung, head and neck, stomach, and prostate. The interindividual pharmacokinetic variability seen with docetaxel treatment remains high, and this phenomenon may have important ramifications for the agent's clinical activity and toxicity (Baker *et al*, 2006). Docetaxel is mainly metabolised by the hepatic enzyme CYP3A4, and the importance of this pathway has been confirmed in mice with a deletion of the *Cyp3a* gene cluster (Van Herwaarden *et al*, 2007). We previously reported that differential expression of organic anion-transporting polypeptides of the OATP1B family in the human liver regulates the initial step in the elimination of docetaxel, before metabolism (De Graan *et al*, 2012). In view of the relevance of these uptake transporters in the pharmacokinetics of docetaxel, instances of idiosyncratic hypersensitivity to docetaxel could possibly be the result of currently unrecognised drug–drug interactions at the level of hepatocellular uptake mechanisms involving OATP1B1, the main OATP1B-family member expressed in the human liver (Konig *et al*, 2013).

In this context, it is worth noting that several tyrosine kinase inhibitors (TKIs) evaluated in combination regimens with docetaxel, including axitinib (Martin *et al*, 2012), pazopanib (Hamberg *et al*, 2012), and sorafenib (Awada *et al*, 2012), can increase the systemic exposure to docetaxel in cancer patients by a mechanism that is currently not understood (Table 1). In the current study, we tested the hypothesis that these TKIs can inhibit the function of OATP1B1 and its murine equivalent Oatp1b2 *in vitro*, and evaluated the contribution of this process to an interaction with docetaxel *in vivo* using mice that are knocked out for Oatp1b2 or knocked in for OATP1B1.

MATERIALS AND METHODS

Crizotinib, lapatinib, nilotinib, regorafenib, ruxolitinib, sorafenib and vemurafenib were purchased from Chemie Tek (Indianapolis, IN, USA); dasatinib, erlotinib, imatinib, pazopanib, and vandetanib from LC laboratories (Woburn, MA, USA); gefitinib and sunitinib from Toronto Research Chemicals (Toronto, ON, Canada); axitinib from Selleckchem (Houston, TX, USA); and bosutinib from Pfizer (New York, NY, USA). [^{3}H]Docetaxel (specific activity, 60 Ci mmol^{-1}; radiochemical purity, 99.0%) and [^{3}H]estradiol-17β-D-glucuronide (specific activity, 50.1 Ci mmol^{-1}; radiochemical purity, 99.0%) were purchased from American Radiolabeled Chemicals (St. Louis, MO, USA). Dimethyl sulfoxide (Sigma Aldrich, St. Louis, MO, USA) was used as a solvent for all TKIs, and ethanol for docetaxel.

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Table 1. Evaluation of pharmacokinetic interactions between TKIs and docetaxel in patients

TKI	Docetaxel dose (mg m^{-2})	Observation	Reference
Axitinib	100	AUC ~55% increased	Martin *et al*, 2012
Bosutinib		NA	
Crizotinib		NA	
Dasatinib	75	No change	Araujo *et al*, 2012
Erlotinib	25	No change	Chiorean *et al*, 2008
Gefitinib	75	No change	Manegold *et al*, 2005
Imatinib	20–25	No change	Connolly *et al*, 2011
Lapatinib	75	No change	LoRusso *et al*, 2008
Nilotinib		NA	
Pazopanib	50–60	AUC ~57% increased	Hamberg *et al*, 2012
Regorafenib		NA	
Ruxolitinib		NA	
Sorafenib	75–100	AUC ~36–80% increased	Awada *et al*, 2012
Sunitinib	75	No change	Bergh *et al*, 2012
Vandetanib		NA	
Vemurafenib		NA	

Abbreviation: NA = no data available.

Flp-In T-Rex293 cells transfected with OATP1B1*1A (wild type) and HEK293 cells overexpressing Oatp1b2 were created from a commercial *Slco1b2* cDNA cloned into a pDream2.1/MCS vector (GenScript, Piscataway, NJ, USA), as described (De Graan *et al*, 2012). Inhibition of OATP1B1- or Oatp1b2-mediated transport was determined by assessing the effect of TKIs on the intracellular accumulation of estradiol-17β-D-glucuronide or docetaxel according to established procedures (De Graan *et al*, 2012; Zimmerman *et al*, 2013).

Adult Oatp1b2 knockout mice and age-matched wild-type mice, both on a DBA/1LacJ background, were bred in-house. Adult knockout mice for entire Oatp1a and Oatp1b loci and age-matched transgenic mice with liver-specific expression of OATP1B1, both on an FVB background, were obtained from Taconic (Hudson, NY, USA). Mice were housed in a temperature-controlled environment with a 12-h light cycle and given a standard diet and water. All experiments were approved by the Institutional Animal Care and Use Committee of St. Jude Children's Research Hospital.

Docetaxel was formulated in polysorbate 80 and diluted in normal saline (final polysorbate 80 concentration, 5%), whereas sorafenib was formulated in 50% Cremophor EL (Sigma Aldrich) and 50% ethanol and diluted to 1 : 4 (vol/vol) with deionized water immediately before administration. Single or multiple doses of sorafenib (60 mg kg^{-1}) were administered by oral gavage, followed 1.5 h later by a tail vein injection of docetaxel (10 mg kg^{-1}). The selected doses of sorafenib and docetaxel in these murine experiments are associated with plasma concentrations that are similar to those observed in patients receiving sorafenib at 400 mg b.i.d. (Hu *et al*, 2011) or docetaxel at 100 mg m^{-2} (Van Tellingen *et al*, 1999). Previous *in vitro* studies have demonstrated that the drug vehicles employed in the mouse study may affect the function of hepatic transporters. In particular, Cremophor EL has been identified as a potent inhibitor of OATP1B3, OATP1A2 and OATP2B1 (Engel *et al*, 2012). However, Cremophor EL is not absorbed after oral administration (Malingré *et al*, 2000) and therefore will not be able to influence the function of hepatic transporters of relevance to the current investigation.

Plasma from each mouse was collected at 5, 15, 30, 60, 120, and 240 min after docetaxel administration, and samples were analysed by a validated method based on liquid chromatography with tandem mass-spectrometric detection (De Graan *et al*, 2012). Pharmacokinetic parameters were calculated using non-compartmental methods in the WinNonlin 6.2 software (Pharsight, St Louis, MO, USA). All data are presented as mean ± s.d. Statistical analyses were based on a two-tailed, non-parametric *t*-test (GraphPad Prism v5.0, La Jolla, CA, USA), and $P<0.05$ was considered statistically significant.

RESULTS

Inhibition of OATP1B1 by TKIs *in vitro*. We initially determined whether FDA-approved TKIs can inhibit OATP1B1 function in mammalian cells that overexpress the transporter, using estradiol-17β-D-glucuronide as a prototypical substrate (Konig *et al*, 2000). Of the 16 TKIs evaluated, axitinib, nilotinib, pazopanib, and sorafenib were identified as potent inhibitors of OATP1B1 (>90% inhibition; Figure 1A). As a representative of this class of TKIs, sorafenib was further evaluated and found to also potently inhibit the OATP1B1-mediated transport of docetaxel with a half-inhibitory maximum concentration of 6.96 nM (Figure 1B), and almost completely inhibit the function of human OATP1B1 (Figure 1C) and mouse Oatp1b2 (Figure 1D) at 10 μM, a concentration achievable in humans and mice (Hu *et al*, 2011).

Pharmacokinetic studies *in vivo*. To test whether sorafenib inhibits OATP1B-type transporters *in vivo*, we determined the pharmacokinetic profile of docetaxel in a DBA/1LacJ strain of mice deficient in Oatp1b2 (Oatp1b2(−/−) mice). In the absence of the TKI, Oatp1b2 deficiency was associated with a significantly increased exposure to docetaxel, as measured by peak plasma concentration ($P=0.00033$; Figure 2A) and area under the curve (AUC) ($P<0.0001$; Figure 2B). Unexpectedly, coadministration of a single oral dose of sorafenib did not result in a significantly altered AUC of docetaxel in either wild-type ($P=0.97$) or Oatp1b2(−/−) mice ($P=0.75$). The lack of a pharmacokinetic interaction was also noted when sorafenib was given twice daily for 4 consecutive days before docetaxel administration to wild-type ($P=0.14$) or Oatp1b2(−/−) mice ($P=0.29$; Figure 2B).

As hepatocytes of the Oatp1b2(−/−) mice express multiple members of Oatp1a, a related subfamily of transporters that can potentially provide compensatory restoration of function when Oatp1b2 is inhibited (Iusuf *et al*, 2012), we next determined the pharmacokinetics of docetaxel in mice on an FVB strain deficient in both the *Oatp1a* and *Oatp1b* gene loci (Oatp1a/1b(−/−) mice), either with or without liver-specific expression of OATP1B1 (OATP1B1(tg)). The AUC of docetaxel was similar in Oatp1a/1b(−/−) and Oatp1b2(−/−) mice ($P=0.73$; Figure 2B), and was significantly reduced in OATP1B1(tg) mice ($P=0.0052$), supporting a direct role of OATP1B1 in the elimination of this agent. However, despite the ability of sorafenib to inhibit the OATP1B1-mediated transport of docetaxel *in vitro*, sorafenib did not influence the AUC of docetaxel in this mouse model ($P=0.15$; Figure 2B).

DISCUSSION

In this study, we demonstrate that several TKIs, including axitinib, pazopanib, nilotinib, and sorafenib, can inhibit the activity of the human OATP1B1 transporter by more than 90%. The results for pazopanib are consistent with a previous report using a similar model (Xu *et al*, 2010). Interestingly, among TKIs that have been evaluated clinically in combination with docetaxel, only those

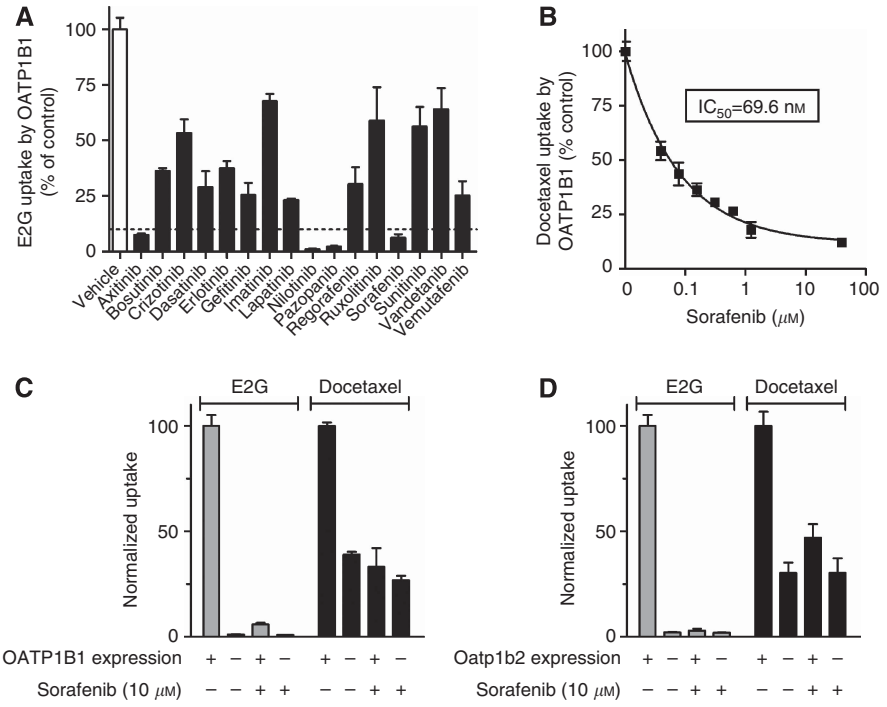

Figure 1. Inhibition of OATP1B-type transporters by TKIs. (**A**) Influence of 16 different TKIs (10 μM; 15-min pre-incubation) on the activity of OATP1B1, expressed in Flp-In T-Rex293 cells, as determined by the intracellular accumulation of [^{3}H]estradiol-17β-D-glucuronide (E2G) (0.1 μM; 5-min incubation). (**B**) Influence of sorafenib (0.040–40 μM; 15-min pre-incubation) on the activity of OATP1B1, expressed in HEK293 cells, as determined by intracellular accumulation of [^{3}H]docetaxel (0.1 μM; 5-min incubation). The curve was obtained by fitting the Hill equation to the data. (**C**, **D**) Influence of sorafenib (10 μM; 15-min pre-incubation) on the intracellular accumulation of [^{3}H]estradiol-17β-D-glucuronide (E2G) (0.1 μM; 5-min incubation) or [^{3}H]docetaxel (0.1 μM; 5-min incubation) in HEK293 cells with or without expression of OATP1B1 (**C**) or Oatp1b2 (**D**). All data represent the mean (bar) ± s.d. (error bar) of two experiments performed in triplicate ($n = 6$).

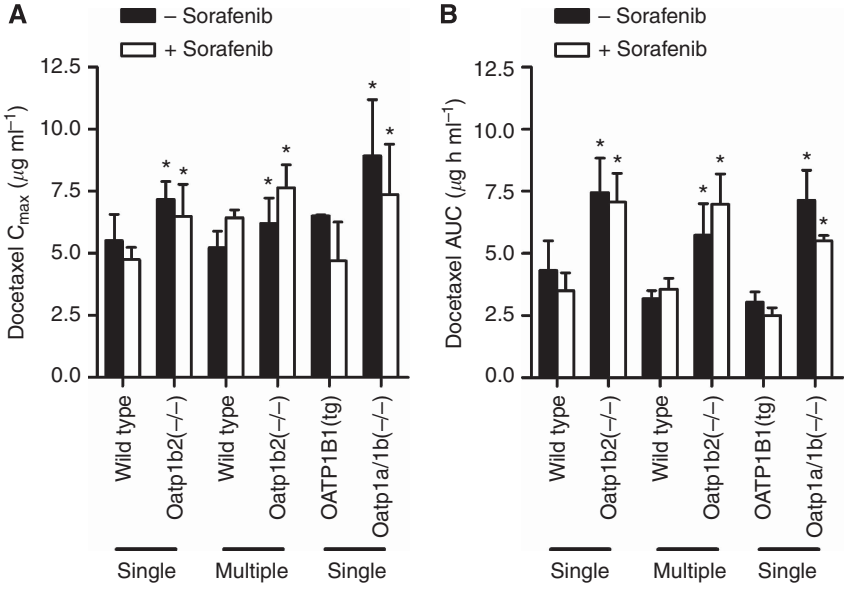

Figure 2. Influence of Oatp1b2 deficiency and sorafenib on docetaxel pharmacokinetics. Wild-type, Oatp1b2(−/−), Oatp1a/1b(−/−), or OATP1B1(tg) mice ($n = 3$–11 per group) were given oral vehicle or oral sorafenib (60 mg kg^{-1}) as a single oral dose (denoted 'single') or twice daily for 4 days (denoted 'multiple') before i.v. docetaxel (10 mg kg^{-1}). Results represent the mean (symbol) ± s.d. (error bar) for the observed peak plasma concentrations (C_{max}) in panel (**A**) or the area under the curve extrapolated to infinity (AUC) in panel (**B**). The corresponding plasma–concentration time profiles and kinetic parameter estimates are provided in Supplementary Figure S1 and Supplementary Table S1, respectively. *$P < 0.05$ compared with the reference group (wild type or OATP1B1(tg)).

found here to be potent OATP1B1 inhibitors cause clinical drug–drug interactions, resulting in increases in the systemic exposure to docetaxel of up to 80%. Of these TKIs, pazopanib is a known weak inhibitor of CYP3A4 and can moderately increase exposure to other CYP3A4 substrates such as midazolam (Goh *et al*, 2010) and paclitaxel (Tan *et al*, 2010). This suggests that the mechanism by

which pazopanib affects the pharmacokinetic profile of docetaxel may involve both metabolism and transport. However, unlike pazopanib, axitinib does not inhibit CYP3A4 (Chen *et al*, 2013), and although sorafenib competitively inhibits recombinant CYP3A4 *in vitro* (Sugiyama *et al*, 2011) it has no influence on the pharmacokinetics of midazolam (Flaherty *et al*, 2011) or paclitaxel (Flaherty *et al*, 2008; Okamoto *et al*, 2010). The previous demonstration that axitinib (Reyner *et al*, 2013) and sorafenib (Zimmerman *et al*, 2013) are themselves substrates of OATP1B1 supports the possibility that the reported pharmacokinetic interactions of these TKIs with docetaxel in patients are the result of a competitive inhibitory mechanism at the level of docetaxel entry into hepatocytes mediated by OATP1B1. This would be consistent with the notion that, unlike for docetaxel, the pharmacokinetics of neither midazolam (Ziesenitz *et al*, 2013) nor paclitaxel (Van De Steeg *et al*, 2013) is affected by OATP1B1.

The human and rodent OATP1B-type transporters share a high degree of sequence homology, similarity in basolateral membrane localisation, and have largely overlapping substrate and inhibitor specificity (Roth *et al*, 2012). Our current *in vitro* data are in line with that prior knowledge in that sorafenib was found to be an inhibitor for both human OATP1B1 and mouse Oatp1b2. Moreover, our *in vivo* studies confirmed the significant influence of Oatp1b2 deficiency in mice on the pharmacokinetics of docetaxel (De Graan *et al*, 2012), and demonstrated that this defect can be fully restored by introducing OATP1B1 in the hepatocytes of these animals without involvement of the related Oatp1a-type transporters.

Surprisingly, the reported clinical pharmacokinetic interaction between sorafenib and docetaxel (Awada *et al*, 2012) could not be replicated in mice. We previously demonstrated that Oatp1b2 deficiency in mice is not associated with any pronounced compensatory alterations in expression of hepatic transporters that can explain these findings (Lancaster *et al*, 2012). Moreover, there are no changes in the functional expression of Cyp3a isoforms, the key enzymes associated with docetaxel metabolism in these transporter knockout mice (Lancaster *et al*, 2012). In our current study, we found no substantial differences in pharmacokinetic parameters of docetaxel when comparing results in Oatp1b2(−/−) mice to those in Oatp1a/1b(−/−) mice. This eliminates the possibility that the lack of a change in docetaxel plasma levels in the presence of sorafenib was due to compensatory effects involving Oatp1a-type transporters. The discrepancy between the clinical observations and those observed here in mice supports the possibility that additional uptake transporters for docetaxel may exist in mice that are insensitive to inhibition by sorafenib. Such demonstration of inherent interspecies differences in drug–drug interactions is not unprecedented, although this phenomenon is usually associated with differential affinity of inhibitors for human compared with rodent transporters (Shirasaka *et al*, 2010). Studies are ongoing to evaluate the potential utility of mice with a humanised liver (Chen *et al*, 2011) as a tool to predict interactions between TKIs and chemotherapy.

Overall, our findings support a direct contribution of OATP1B1 in previously recorded pharmacokinetic interactions between TKIs and docetaxel, which can be predicted from a simple *in vitro* experiment. Although the present investigation involved *in vivo* studies with only one TKI, our failure to reproduce an established interaction of sorafenib with docetaxel in mice suggests that caution is warranted when attempting to extrapolate *in vivo* findings to a clinical scenario.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DISCLAIMER

The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

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