Influence of Drug Formulation on OATP1B-Mediated Transport of Paclitaxel

Annemieke J.M. Nieuweboer1, Shuiying Hu2, Chunshan Gui3, Bruno Hagenbuch3, Inge M. Ghobadi Moghaddam-Helmantel1, Alice A. Gibson2, Peter de Bruijn1, Ron H.J. Mathijssen1, and Alex Sparreboom1,2

Abstract

Taxane antineoplastic agents are extensively taken up into hepatocytes by OATP1B-type transporters before metabolism and excretion. Because the biodistributional properties imposed upon these agents by different solubilizers drive clinically important pharmacodynamic endpoints, we tested the hypothesis that the in vitro and in vivo interaction of taxanes with OATP1B transporters is affected by the choice of drug delivery system. Transport of paclitaxel, docetaxel, and cabazitaxel was studied in vitro using various cell lines transfected with OATP1B1, OATP1B3, or the rodent equivalent OATP1B2. Pharmacokinetic studies were done in wild-type and OATP1B2-knockout mice in the presence or absence of polysorbate 80 (PS80) or Kolliphor EL (formerly Cremophor EL; CrEL). Paclitaxel and docetaxel, but not cabazitaxel, were transported substrates of OATP1B1, OATP1B3, and OATP1B2, and these in vitro transport processes were strongly reduced in the presence of clinically relevant concentrations of PS80 and CrEL. When paclitaxel was administered without any solubilizers, deficiency of OATP1B2 in mice was associated with a significantly decreased systemic clearance because of a liver distribution defect (P = 0.000484). However, this genotype dependence of paclitaxel clearance was masked in the presence of PS80 or CrEL because of significant inhibition of OATP1B2-mediated hepatocellular uptake of the drug (P < 0.05). Our findings confirm the importance of OATP1B-type transporters in the hepatic elimination of taxanes and indicate that this process can be inhibited by PS80 and CrEL. These results suggest that the likelihood of drug–drug interactions mediated by these transporters is strongly dependent on the selected taxane solubilizer. Cancer Res; 74(11); 1–9. ©2014 AACR.

Introduction

The nonionic surfactants Kolliphor EL (formerly Cremophor EL; CrEL) and polysorbate 80 (Tween 80; PS80) are widely used to solubilize drugs, including the taxane-based antineoplastic agents paclitaxel (1), docetaxel (2), and cabazitaxel (3). A wealth of experimental data has indicated that these solubilizers are biologically and pharmacologically active compounds, and their use as drug formulation vehicles has been implicated in clinically important toxic side effects such as acute hypersensitivity reactions (4). CrEL and PS80 have also been found to influence the disposition of solubilized drugs administered intravenously (5). This is particularly striking in the case of paclitaxel formulated in CrEL, where the overall resulting effect is a highly increased systemic exposure to paclitaxel (6), which is dependent on the dose and time-varying blood concentrations of the solubilizer (7). Kinetic experiments (8,9) and model-based predictions (10,11) have revealed that paclitaxel undergoes reversible partitioning into a circulating surfactant microemulsion that acts as a nano-sink and reduces the fraction of free drug available for extravascular distribution.

In line with these predictions, it was demonstrated that CrEL can inhibit the hepatic elimination of paclitaxel in the isolated perfused rat liver, the main organ of elimination (12), by preventing the drug from reaching sites of metabolism and excretion (13). This process is believed to be primarily mediated by the organic anion-transporting polypeptides OATP1B3 (in humans; refs. 14 and 15) and OATP1B2 (in rodents; refs. 16 and 17), which are uptake transporters localized to the basolateral membrane of hepatocytes (18). To add further to the complexity of the carrier-mediated disposition properties of paclitaxel, CrEL was found to strongly inhibit the uptake of OATP1B3 substrates in vitro into cells overexpressing the transporter (19). However, the mechanistic basis underlying this observation, as well as its in vivo relevance, remains unclear.

Because the biodistributional properties imposed upon taxanes by different solubilizers drive clinically important pharmacodynamic endpoints that further depend, at least in part, on whether or not the pharmacokinetics of carrier-released...
(free) drug is formulation-dependent (10), we here tested the hypothesis that the in vitro and in vivo interaction of paclitaxel with OATP1B-type transporters is affected by the choice of a particular drug delivery system.

Materials and Methods

In vitro transport studies

Xenopus laevis oocytes injected with OATP1B1, OATP1B3, or rat OATP1B2 cRNA along with water-injected controls were obtained from BD Biosciences. The transporter nomenclature used throughout is based on recent recommendations proposed by Hagenbuch and Stieger (20). The transporter-expressing oocytes were functionally characterized by assessing the uptake of estrone-3-sulfate (2 μmol/L) by OATP1B1 and OATP1B2, and of estradiol-17β-o-glucuronide (2 μmol/L) by OATP1B3. Human embryonal kidney (HEK293) cells overexpressing OATP1B1, OATP1B3, or OATP1B2 have been described previously (21). The Chinese hamster ovary (CHO) cells expressing OATP1B1 or OATP1B3 were generated as follows. The open reading frames of the two transporters (22) were PCR amplified in order to introduce a 6-His tag at the C-terminal end. The amplicons were ligated into pcDNAs/FRT, and after verifying the sequences, Flp-In-CHO cells were transfected with the plasmids in the presence of pOG44 ed in order to introduce a 6-His tag at the C-terminal end. The amplicons were ligated into pcDNAs/FRT, and after verifying the sequences, Flp-In-CHO cells were transfected with the plasmids in the presence of pOG44 following the manufacturer’s protocols (Life Technologies). Cells were selected with hygromycin B (600 μg/mL) and single clones were isolated by limited dilution. Overexpression of transporters was confirmed using TaqMan probes (Applied Biosystems). The cell culture conditions and details of accumulation experiments for [3H]paclitaxel (specific activity, 25.6 Ci/mmol; Vitrax) and [3H]docetaxel (specific activity, 60.0 Ci/mmol; American RadioChemicals) were described earlier (21). Radioactivity was quantified by liquid scintillation counting using an LS 6500 Counter (Beckman).

Intracellular concentrations of cabazitaxel were measured by liquid chromatography/tandem mass spectrometry (LC/MS-MS), as described (23). Total protein was measured using a Pierce BCA Protein Assay Kit (Thermo Scientific) and quantified using a Biotek microplate spectrophotometer. Drug uptake results were normalized to total protein content and then to data obtained in cells carrying an empty vector plasmid, which was set to 100%.

Animal experiments

Wild-type and OATP1B2 knockout [OATP1B2(−/−)] mice, both on a DBA/1lac background, between 8 and 12 weeks of age, were housed in a temperature-controlled environment with a 12-hour light cycle. Experiments were approved by the Institutional Animal Care and Use Committee of St. Jude Children’s Research Hospital. All mice received a standard diet and water ad libitum and were fasted 3 hours before drug administration. Paclitaxel was formulated in CrEL-ethanol (1:1, v/v; Taxol; Bristol-Myers Squibb), PS80-ethanol (1:1, v/v), or as an albumin-bound nanoparticle (nab-paclitaxel; ABI-007; Abraxane; Celgene) without either CrEL or PS80. These solutions were diluted in normal saline and administered by intravenous bolus in the tail vain at a dose of 10 mg/kg. Docetaxel (Taxotere; Sanofi-Aventis) and cabazitaxel (Jevtana; Sanofi-Aventis) were formulated in PS80-ethanol (1:1, v/v), diluted in normal saline (docetaxel) or 5% dextrose in water (cabazitaxel), and then administered by tail vein injection at a dose of 10 mg/kg.

In all experiments, at select time points after drug administration, blood samples (30 μL each) were taken from individual mice at 3.5, 7.5, and 15 minutes from the submandibular vein using a lancet, and at 30 and 60 minutes from the retro-orbital venous plexus using a capillary. A final blood draw was obtained at 120 minutes by a cardiac puncture using a syringe and needle. Isoflurane was used as an anesthetic. The total blood volume collected during the procedure from each mouse was 150 μL. All blood samples were centrifuged at 1,500 × g for 5 minutes, and plasma was separated and stored at –80°C until analysis. Livers, kidneys, and small intestines were collected from the same animals at 120 minutes. The lumen of small intestines were purged using saline to remove remaining content. A separate group of mice was euthanized by CO2 asphyxiation at 5 minutes and the same tissues were immediately collected and flash-frozen on dry ice. To prevent continuing metabolic activity, liver tissues were snap-frozen using liquid nitrogen. All tissue specimens were stored at –80°C until further processing, as described (21). Samples were analyzed by LC/MS-MS (see Supplementary Methods for details; ref. 24), and noncompartmental parameters were calculated using WinNonlin 6.2 software (Pharsight). Concentrations in tissue were corrected for contaminating plasma (25).

Statistical considerations

All data are presented as mean ± SD. Statistical analyses were done using SPSS version 20 (SPSS), and P < 0.05 was regarded as statistically significant. Student t test (2 groups) or one-way ANOVA (>2 groups) was used for statistical analysis on in vitro uptake data, plasma pharmacokinetic parameters, and tissue concentrations.

Results

Paclitaxel transport in vitro

Although previous in vitro studies have consistently identified paclitaxel as a potent inhibitor of OATP1B1 (22, 26) and OATP1B3-mediated transport (22, 27, 28), the actual transport of paclitaxel itself by these transporters remains controversial (14, 28–30). The presented methodologic details were selected on the basis of existing literature in order to clarify the reported discrepancies in taxane transport by OATPs. In line with these conflicting data, we found that the interaction of paclitaxel with human OATP1B1 and OATP1B3 was dependent on cell context, with both proteins being able to take up paclitaxel when expressed in HEK293 cells or CHO cells, but no noticeable transport occurring by OATP1B1 expressed in Xenopus laevis OATP1B1 or OATP1B3 was found to be transported into cells expressing mouse OATP1B1 or OATP1B3 (Fig. 1B), as predicted from previous studies done in isolated rat hepatocytes (31).

In the absence of solubilizers, the transport of paclitaxel into CHO cells transfected with OATP1B1 or OATP1B3 was found to be time-dependent and saturable (Supplementary Fig. S1) with a Michaelis–Menten constant (Km) of 0.408 ± 0.190 μmol/L.
and 2.36 ± 1.40 μmol/L, respectively, and a maximum velocity ($V_{max}$) of 22.1 ± 3.20 pmol/mg/min and 14.2 ± 5.26 pmol/mg/min, respectively, values that are similar to those reported previously for docetaxel (21).

Next, we evaluated the ability of CrEL and PS80 to inhibit the intracellular accumulation of paclitaxel into CHO cells overexpressing human OATP1B1, human OATP1B3, or mouse OATP1B2. Recently, it was reported that the effect of CrEL on the uptake of several substrates by OATP1B2, OATP1B1, or OATP1B3 was dose dependent (19). Similar to these findings, we found that PS80 also inhibited paclitaxel uptake in a concentration-dependent manner (Fig. 1C), which is in line with our observation that PS80 also affects the transporter-mediated uptake of docetaxel (21). The mechanism by which CrEL and PS80 inhibit OATP1B-type transporters is unclear and requires additional investigation. After correcting for nonspecific inhibition of paclitaxel uptake occurring in cells transfected with an empty expression plasmid because of drug trapping in solubilizer micelles (Supplementary Fig. S2), CrEL directly inhibited the transporters in decreasing order of potency OATP1B3 > OATP1B2 > OATP1B1, whereas PS80 inhibited all transporters to a similar extent (Fig. 1D).

**Paclitaxel tissue distribution studies in vivo**

We next evaluated the possible importance of these transporters for paclitaxel disposition in mice with a genetic deletion of OATP1B2 [OATP1B2(−/−) mice]. Early after administration (5 minutes) of paclitaxel as a nanoparticle suspension (nab-paclitaxel) in the absence of a solubilizer, uptake into the liver was dramatically decreased in OATP1B2(−/−) mice (Fig. 2A). This finding suggests that immediately after infusion paclitaxel uptake into the liver is mainly transporter-mediated, and is consistent with the notion that the amorphous nab-paclitaxel nanoparticles rapidly dissolve into soluble albumin-paclitaxel complexes with a size similar to that of native albumin, with no nanoparticles detected at any time point postinfusion (32). Therefore, phagocytosis-based uptake mechanisms in the liver involving the reticulo-endothelial system, which are relevant to the biodistribution of paclitaxel.
nanoparticles that remain stable in the circulation (33), are not contributing in the case of nab-paclitaxel.

As predicted based on the in vitro inhibition data, the differences in uptake of paclitaxel into the liver between wild-type and OATP1B2(−/−) mice were much less pronounced in the presence of PS80 or CrEL. In particular, the liver uptake in wild-type mice receiving paclitaxel formulated in PS80 was similar to that observed in OATP1B2(−/−) mice receiving the drug without solubilizers, whereas uptake was further reduced by about two-fold in the presence of CrEL (Fig. 2A). Over time, the formulation-dependent differences in liver uptake normalized to control levels for the PS80 group (Fig. 2B), but remained noticeably reduced in the presence of CrEL. This is consistent with the fact that PS80 is very rapidly cleared, with plasma levels becoming undetectable within 15 minutes after intravenous administration (34), whereas the half-life of CrEL amounts to >17 hours (6).

Interestingly, a similar solubilizer-, time-, and genotype-dependent distribution of paclitaxel was observed for uptake into kidney (Fig. 2C and D) and intestine (Fig. 2E and F). The significant reduction of paclitaxel administered without a solubilizer (i.e., nab-paclitaxel) in the kidneys of OATP1B2(−/−) mice at 5 minutes after drug administration is possibly the result of low expression of OATP1B2 in renal cells of mice (35), and a similar phenotype has been reported previously for the OATP1B2 substrate, hydroxyurea (36). The concentrations of paclitaxel in the intestine after the administration of nab-paclitaxel were not dependent on OATP1B2 genotype at the

Figure 2. Influence of paclitaxel formulation and OATP1B2-deficiency on paclitaxel distribution. Paclitaxel was formulated as nab-paclitaxel in the absence of PS80 or CrEL, in PS80, or in CrEL (see Materials and Methods for details), and total paclitaxel levels were determined in wild-type and OATP1B2(−/−) mice at 5 minutes and 2 hours after intravenous injection in liver (A and B), kidney (C and D), and intestine (E and F). Tissue levels were normalized to the corresponding plasma concentration (5 minute data) or the AUC from time 0 to 2 hours (2 hour data). Data are presented as the mean (bars) of four observations per condition per time point, along with SD (error bars). *, a statistically significant difference compared with the corresponding wild-type group (P < 0.05); **, a statistically significant difference compared with the other formulations (P < 0.05).
early time point, where appearance of the drug likely reflects
direct intestinal secretion (37). At the 2-hour time point, the
higher levels in the intestine are presumably the result of
hepatobiliary secretion becoming an increasingly dominant
contributor to the elimination of paclitaxel.

Effects of formulation and transport on taxane clearance
in vivo

As anticipated from the tissue distribution findings, the
plasma concentration–time profiles of paclitaxel were inversely
related to corresponding drug levels in liver, and concentra-
tions in plasma were consistently higher by 5- to 7-fold for the
CrEL-containing formulation compared with the other groups
(Fig. 3A and B). The notion that the slow clearance of paclitaxel
administered in CrEL is because of a distribution defect rather
than an event occurring in the terminal elimination phase is
also consistent with the observed terminal half-lives of pacli-
taxel that were not significantly dependent on the formulation
or genotype (Supplementary Table S1).

After the administration of nab-paclitaxel, the peak plasma
concentration of paclitaxel was significantly increased in
OATP1B2(−/−) mice, and this genotype dependence was
nullified in the presence of PS80 or CrEL (Fig. 3C). Based on
total area under the curve (AUC), a significant but blunted
influence of genotype was still noted for PS80-based formula-
tion, but not for CrEL (Fig. 3D). Because the same PS80
formulation is used in the clinical preparation of docetaxel
and cabazitaxel, we also evaluated the comparative plasma
pharmacokinetic properties of the two other approved taxanes
in the same mouse model. Studies performed in transfected
cells confirmed that, like paclitaxel, docetaxel is a transported
substrate of OATP1B2 (21), but this was not noted under the
experimental conditions applied for cabazitaxel (Fig. 4A). The
lack of transport of cabazitaxel by OATP1B2 is somewhat
surprising considering its structural similarity with docetaxel,
both having a 10-deacetyl baccatin III backbone (3), and
because cabazitaxel has been reported to inhibit OATP1B1
and OATP1B3, albeit at relatively high concentrations (Jevtana
prescribing information, see http://products.sanofi.us/jevtana/jevtana.pdf). As expected based on the in vitro studies,
the AUC (Fig. 4B) and plasma levels at the time points
evaluated were significantly increased in the absence of
OATP1B2 for paclitaxel (formulated in PS80; Fig. 4C) and
docetaxel (Fig. 4D), but not for cabazitaxel (Fig. 4E).

Discussion

This study adds to a growing body of knowledge that solute
carriers belonging to the OATP1B family can have a dramatic
impact on the hepatocellular accumulation and systemic
clearance of structurally diverse anticancer drugs. Using
an array of in vitro transport assays, including intracellular

Figure 3. Influence of formulation
and OATP1B2-deficiency on
paclitaxel plasma
pharmacokinetics. Paclitaxel was
formulated as nab-paclitaxel in the
absence of PS80 or CrEL, in PS80,
or in CrEL (see Materials and
Methods for details), and total
paclitaxel levels were determined
in wild-type (A) and OATP1B2(−/−)
mice (B) in plasma samples taken at
serial time points after dosing
(5–120 minutes). The resulting
collection–time profiles were
used to derive peak plasma
concentrations ($C_{\text{max}}$) (C) and
AUC (D). Data are presented as the
mean (symbols or bars) of four
observations per condition per
time point, along with SD (error
bars). *, a statistically significant
difference compared with the
controlled wild-type group
($P < 0.05$); **, a statistically
significant difference compared
with the other formulations
($P < 0.05$).
accumulation studies in multiple-transfected model systems, paclitaxel was confirmed to be a high-affinity substrate for both OATP1B1 and OATP1B3. We found that the interaction of paclitaxel with OATP1B1 and OATP1B3 was strongly dependent on cell context, and this has obvious implications for future screening strategies aimed at identifying novel substrates for these transporters. The relatively low $K_m$ observed for paclitaxel transport by OATP1B1 suggests that this route of entry into hepatocytes may be saturated first, and this is consistent with results obtained in humanized transgenic mice indicating that OATP1B1 does not substantially contribute to paclitaxel transport in vivo (15), when administered at an intravenous dose of 10 mg/kg. Indeed, the $K_m$ for OATP1B1 of 0.408 μmol/L is substantially lower than the peak plasma concentration of unbound paclitaxel in patients receiving nab-paclitaxel at the recommended dose of 260 mg/m² (on average, 1.50 μmol/L; ref. 38). This suggests that the contribution of OATP1B1 to the disposition of paclitaxel in patients is likely to be dependent on the prescribed product, in addition to the total dose and duration of infusion.

Our in vitro studies also confirmed that paclitaxel and docetaxel, but not cabazitaxel, are transported substrates of mouse OATP1B2 and, for paclitaxel, rat OATP1B2, the amino acid sequence of which is 81% identical to that of the murine transporter. Moreover, the rodent OATP1B2 transporters share more than 60% amino acid sequence homology to the two human isoforms, and on the basis of their shared basolateral localization in hepatocytes and overlapping substrate specificity (39), it is possible that, in the context of paclitaxel, the rodent OATP1B2 fulfills the same function in the liver as OATP1B1 and OATP1B3 in humans. Based on this premise, we evaluated the pharmacokinetic properties of paclitaxel in a mouse model with a genetic deletion of OATP1B2. One possible limitation of this model is the fact that, unlike in humans, mouse hepatocytes express multiple members of OATP1A subfamily, related transporters that can potentially provide compensatory restoration of function when OATP1B2 is lost (40). Despite this limitation, compared with wild-type mice, the systemic exposure to nab-paclitaxel, administered without PS80 or CrEL, in the OATP1B2(−/−) mice was increased by 2.5-fold. Our previously reported gene expression profiling and

Figure 4. Comparative effects of formulation and OATP1B2-deficiency on transport of paclitaxel, docetaxel, and cabazitaxel. A, the uptake of paclitaxel, docetaxel, and cabazitaxel by mouse OATP1B2 was evaluated in transfected HEK293 cells (0.1 μmol/L; 15 minutes). Data are presented as the mean percentage of uptake values in the VC cells (bars) for 4 to 11 observations per condition, along with SD (error bars). *a statistically significant difference compared with VC ($P < 0.05$). B, AUC of paclitaxel in wild-type and OATP1B2(−/−) mice following administration of paclitaxel, docetaxel, or cabazitaxel, all formulated in PS80 (see Materials and Methods for details), along with the corresponding plasma concentration–time profiles for paclitaxel (C), docetaxel (D), and cabazitaxel (E). Data are presented as the mean (bars or symbols) of four observations per condition per time point, along with SD (error bars). *a statistically significant difference compared with the corresponding wild-type group ($P < 0.05$); **a statistically significant difference compared with the other formulations ($P < 0.05$).
enzyme activity measurements in liver samples exclude alterations in alternate transport mechanisms or metabolic pathways as a likely cause of the delayed clearance phenotype in OATP1B2 (−/−) mice (20). Thus, these findings suggest that OATP1B2-mediated transport of paclitaxel is an important process in the elimination of this drug in mice, depending on the solubilizer used for drug formulation.

We previously reported that the presence of PS80, the pharmaceutical vehicle used to solubilize docetaxel in clinical preparations, even in relatively low amounts, can completely nullify the genotype-dependent transport of docetaxel by OATP1B1 (21), and similar findings have been reported for CrEL, used in one of the clinical preparations of paclitaxel (19). Based on our current in vitro and subsequent confirmatory in vivo studies, it seems that the interaction of paclitaxel with OATP1B2 is strongly diminished in the presence of PS80 and CrEL in a fashion that is consistent with the known disposition properties of these respective solubilizers. It is interesting to note that a previous study demonstrated that mice deficient in all Oatp1a and Oatp1b genes display a rather modest increase (<2-fold) in concentrations of paclitaxel in plasma following intravenous administration of a PS80-based formulation that is very similar to our present findings (17). These authors speculated that the lack of differences in plasma levels of paclitaxel early after its administration (up to 3.5 minutes) may be because of saturation of Oatp1a/Oatp1b-mediated liver uptake, and that this distribution process is predominantly dependent on other uptake mechanisms. Our current findings now provide an alternative explanation, where the initially high levels of PS80 in plasma can cause both temporary partitioning into a circulating PS80 microemulsion as well as directly inhibit the transporters required for hepatocellular uptake. These two mechanisms combined likely also explain the results obtained for paclitaxel in the presence of CrEL, although here the former mechanism clearly remains the dominant contributor to the overall disposition phenotypes.

The present observation that PS80 and CrEL can directly inhibit OATP1B-type transporters suggests that the pharmacokinetic profile of carrier-released (free) paclitaxel is not formulation independent. This finding contrasts previously made assumptions (10), and may have important ramification for a proper interpretation of the clinical pharmacology of paclitaxel. First, we previously found that several common, naturally occurring genetic variants in OATP1B3 with impaired function were not associated with the pharmacokinetics of paclitaxel in a cohort of 90 patients with cancer receiving the drug in a CrEL-based formulation (16). This somewhat unexpected observation is consistent with our current findings in that the interaction of paclitaxel with OATP1B3 may be masked by CrEL irrespective of an individual's genotypic constitution. It also suggests that the impact of reduced function variants of OATP1B1 and/or OATP1B3 on the clearance of paclitaxel may be much more pronounced for CrEL-free formulations of the drug, such as nab-paclitaxel.

Second, it can be postulated that intrinsic physiologic and environmental variables influencing OATP1B1- or OATP1B3-mediated uptake of paclitaxel into hepatocytes may have a more profound influence on drug clearance for formulations lacking solubilizers. For example, substrates of OATP1B1 and OATP1B3 for which the liver is the main organ of elimination are highly liable to drug interactions associated with these transporters (41, 42). Although formal drug interaction studies have not been performed to date with nab-paclitaxel, our present findings strongly suggest that interactions at the level of hepatocellular uptake mechanisms would be exacerbated with a formulation like nab-paclitaxel. Conversely, CrEL may act as a perpetrator in known pharmacokinetic interactions involving other OATP1B substrates coadministered with paclitaxel in phase I clinical trials (reviewed in ref. 4), such as etoposide (43), docetaxel (44), oxaliplatin (45), and SN-38 (46).

Third, OATP1B1 is expressed at relatively high levels in tumors of the colon, endometrium, esophagus, lung, prostate, stomach, testis, and bladder, and both OATP1B1 and OATP1B3 contribute to the in vitro cytotoxicity of paclitaxel in ovarian cancer cells (29). Although systemic exposure to free paclitaxel is believed to be the dominant driver of drug-induced cytotoxicity at tumor sites (10), it is conceivable that these transporters can contribute directly to tumoral uptake and that this process can be inhibited by solubilizers such as PS80 and CrEL, leading to diminished antitumor activity. This possibility would be consistent with available clinical data on the comparative efficacy of the various paclitaxel formulations (reviewed in ref. 10), and with preclinical findings suggesting that (i) the absorption rate constant of paclitaxel uptake into tumors is dramatically decreased in the presence of CrEL compared with nab-paclitaxel (47), and (ii) a tumor-delivery mechanism exists for nab-paclitaxel that is independent of SPARC (48), a matricellular glycoprotein produced by tumors and/or neighboring stroma that facilitates the intracellular accumulation of intact albumin nanoparticles (49).

Collectively, our findings demonstrate the importance of OATP1B-type solute carriers in the hepatic elimination of paclitaxel, and indicate that solubilizers used in clinical preparations of this agent can inhibit this process in a time-dependent fashion. These results offer a mechanistic basis for previously reported interrelationships of taxane disposition with PS80 and CrEL, and suggest that the likelihood of drug–drug interactions mediated by these transporters is strongly dependent on the selected paclitaxel formulation.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: A.J.M. Nieuweboer, A. Sparreboom
Development of methodology: A.J.M. Nieuweboer, S. Hu, A.A. Gibson
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.J.M. Nieuweboer, S. Hu, A.A. Gibson
Analysis and interpretation of data (e.g., statistical analysis, biosatistics, computational analysis): A.J.M. Nieuweboer, S. Hu, I.M. Ghobadi Moghaddam-Helmantel, A.A. Gibson, P. de Bruijn, R.H.J. Mathijssen, A. Sparreboom
Writing, review, and/or revision of the manuscript: A.J.M. Nieuweboer, S. Hu, A. Sparreboom
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.J.M. Nieuweboer, S. Hu, C. Gui
Study supervision: S. Hu, A. Sparreboom
Nieuweboer et al.

Acknowledgments

The authors thank R. Kim and J. Stock for providing the OATP1B2(+/−) mice, and C. Lancaster, A. Vasilyeva, A. Walker, and E. Zimmerman for their assistance with performing the animal experiments.

Grant Support

This study was supported in part by the American Lebanese Syrian Associated Charities (ALSAC), USPHS Cancer Center Support Grant P30CA021765, the NIH Grants RB021940 and GM077336, and by an Academic Internship Grant from the Dutch Cancer Society.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received December 27, 2013; revised March 4, 2014; accepted March 18, 2014; published OnlineFirst April 22, 2014.

References

OATP1B-Mediated Clearance of Paclitaxel


Influence of Drug Formulation on OATP1B-Mediated Transport of Paclitaxel


Cancer Res  Published OnlineFirst April 22, 2014.

Updated version  Access the most recent version of this article at: doi:10.1158/0008-5472.CAN-13-3634

Supplementary Material  Access the most recent supplemental material at: http://cancerres.aacrjournals.org/content/suppl/2014/04/22/0008-5472.CAN-13-3634.DC1

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.