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Review

Taxanes: Old drugs, new oral formulations

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ABSTRACT

Oral administration of anticancer drugs is most often preferred over intravenous administration, as it is convenient for patients, prevents hospitalisation and reduces costs of the therapy. However, the oral route is often hampered by low oral bioavailability, for instance of the taxanes paclitaxel and docetaxel. Limited oral bioavailability can be due to pharmaceutical as well as pharmacological reasons. Taxanes are poorly water-soluble drugs and do not sufficiently dissolve when administered in their crystalline form. Furthermore, affinity for drug transporters highly expressed in the epithelial layer of the gastro-intestinal tract, such as the drug efflux pump P-glycoprotein (P-gp, *ABCB1*), and presystemic elimination by the cytochrome P450 (CYP) metabolic enzymes, especially CYP3A4, present in liver and gut wall, further hamper oral application of these important anticancer drugs. Preclinical studies with knockout mice lacking functional Pgp and CYP3A4 metabolic enzymes show a significant increase in the bioavailability of orally applied taxanes. Enhancement of oral bioavailability of both taxanes was shown also in wild-type mice using P-gp and CYP3A4 blockers such as cyclosporine A (CsA) and ritonavir (RTV). Subsequently, in clinical studies enhancement of the oral bioavailability of paclitaxel and docetaxel was established when administered orally in combination with CsA or ritonavir. Initially, in preclinical and clinical studies drinking solutions based on the intravenous formulations were applied for oral administration of taxanes. Because these solutions had several disadvantages, solid pharmaceutical formulations of paclitaxel and docetaxel were developed. Clinical studies with these novel formulations in combination with ritonavir are currently ongoing at our Institute.

Contents

1. Introduction

The taxanes paclitaxel and docetaxel are widely used anticancer agents with proven activity against malignancies such as; ovarian, gastric, head and neck, non-small cell lung, prostate and breast cancer. They have shown clinical activity by producing single agent response rates in breast cancer up to 60% of untreated patients with metastatic disease. In non-small cell lung cancer when compared to best

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supportive care taxanes have shown improved survival (Crown and O'Leary, 2002; Rowinsky, 1997). Unfortunately resistance of taxanes is often observed in cancer patients limiting the benefit of the therapy due to a variety of mechanisms possibly including P-gp-mediated-resistance. Currently taxanes are administered i.v. at different infusion schedules and dosages. Due to the extensive use and the occurrence of adverse effects related to the i.v. administration of taxanes, an increasing interest towards oral administration is seen. Advantages of oral treatment are the improvement in patient convenience and practicality, flexibility in dosing schedules, prevention of hospitalisation and thereby reducing the use of medical staff. Oral administration also avoids the discomfort of the injection and possibly related infections or extravasations. Another argument in favour of oral therapy is that it can be applied as chronic treatment of anticancer drugs. This is mainly important for cell specific agents and agents with a predominantly cytostatic effect such as angiogenesis and signal transduction inhibitors. Oral formulations of known anticancer drugs are for example topotecan, vinorelbine, idarubicin and capecitabine (5-fluoro-uracil). However, low oral bioavailability often hampers the development of oral formulations of anticancer drugs. Bioavailability defines the extent to which a drug, unchanged, is absorbed into the systemic circulation (Malingré et al., 2001a). Important factors that limit the oral bioavailability are aqueous solubility and dissolution, structural instability in the gastro-intestinal tract and affinity for cytochrome P450 (Cyp) metabolic enzymes and P-gp. Also oral therapy can be hampered by interpatient variability in pharmacokinetics, patient inability to comply with adequate drug intake and the medical condition such as obstructive disorders of the gastro-intestinal tract (Schellens et al., 2000). The development of mice lacking P-gp (*M*dr1a/1b) and/or Cyp3a provided excellent models to investigate the restricting roles of P-gp and Cyp3a on the availability on orally applied drugs (Schinkel et al., 1994; Schinkel et al., 1997). Moreover, preclinical studies demonstrated that the oral availability of taxanes could be greatly enhanced by the use of inhibitors of P-gp and/or CYP3A4 (Bardelmeijer et al., 2002;Bardelmeijer et al., 2004). These results from preclinical studies have been successfully translated to clinical phase I/II studies, which proved the principle of enhancing the oral availability of taxanes by co-administering inhibitors of P-gp or CYP3A4 (Malingré et al., 2001a; Meerum Terwogt et al., 1999; Oostendorp et al., 2009). Initially, oral ingestion of taxanes in preclinical and clinical studies was done as a drinking solution, based on the intravenous formulations. However, these pharmaceutical formulations had an unstable structure, bad taste and were unsafe for medical staff because the risk of exposure. Therefore, solid dispersion formulations (capsules and tablets) were developed for paclitaxel and docetaxel in order to ease oral administration for patients and to eliminate unsatisfactory solutions previously used (Moes et al., 2011). The novel solid dispersion formulations are currently being investigated in clinical phase I studies at our Institute.

2. Barriers for taxanes

CYP3A4 is a member of the cytochrome P450 family of enzymes. CYP3A4 enzymes function as oxidative metabolizers of a wide range of drugs currently used, including paclitaxel and docetaxel. They can be found predominantly in the liver and small intestine. Of a variety of enzymes which have been identified, CYP3A4 is probably most relevant for the first-pass metabolism of several drugs (van Herwaarden et al., 2009). Drugs metabolised by CYP3A4 are often also substrates of P-gp (Schellens et al., 2000). Cyp3a knockout mice have been generated and used to examine oral bioavailability of taxanes (van Herwaarden et al., 2007). Docetaxel was administered to wild-type and Cyp3a-/- mice orally and intravenously at a dose of 10 mg/kg. Results showed that the area under the plasma concentration-time curve (AUC) for docetaxel was 7-fold higher when administered intravenously compared to wild-type mice. Orally administered docetaxel even showed an 18-fold increase in AUC in Cyp3a-/- mice. The AUC_{oral} for Cyp3a-/- mice was higher than the $AUC_{i.v}$ for wild-type mice with the same dose for both administration routes. These results showed that Cyp3a seriously limits the oral docetaxel exposure. Additionally, transgenic Cyp3a-/- mice were generated with human CYP3A4 expression in the liver (Cyp3a-/-V mice), intestines (Cyp3a-/-A mice) or in both tissues (Cyp3a-/-AV mice). These humanised mouse models were used to gain insight into relative contribution of hepatic versus intestinal metabolism of docetaxel (Fig. 1) (van Herwaarden et al., 2007). CYP3A4 expression in the intestine of Cyp3a-/- mice completely decreased the oral exposure of docetaxel to similar levels as observed in wild-type mice. In contrast, CYP3A4 expression in the liver of Cyp3a-/- mice only partly decreases the systemic exposure of oral docetaxel.

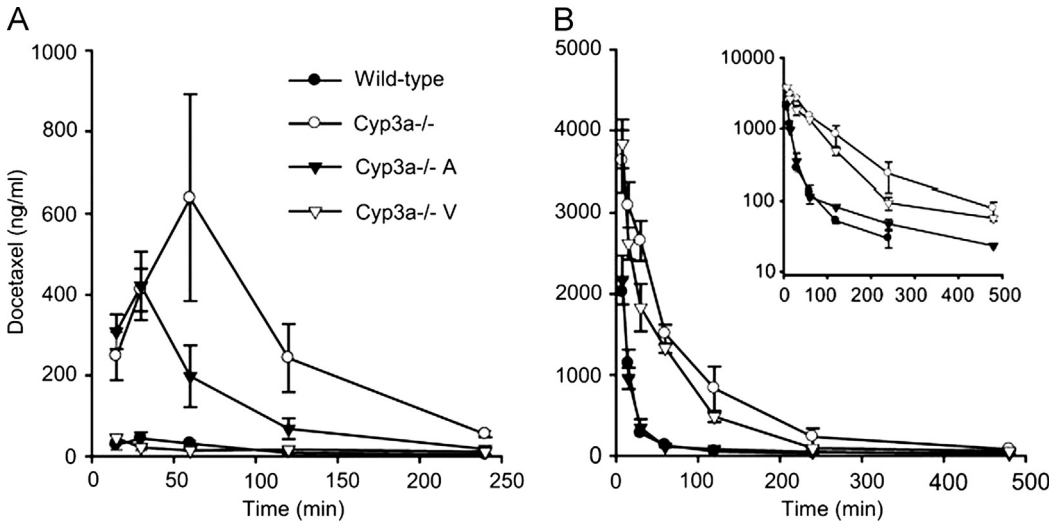

Fig. 1. Cyp3a limits docetaxel exposure. Expression of CYP3A4 in intestine virtually blocks docetaxel entry upon oral administration, whereas liver CYP3A4 expression predominantly limits systemic exposure. Plasma concentration versus time curve of docetaxel after oral (A) or i.v. (B) docetaxel administration (10 mg/kg) in wild-type, $Cyp3a^{-/-}$, $Cyp3a^{-/-}$A, and $Cyp3a^{-/-}$V mice. $n=4$ for each time point. Note differences in time and concentration scales between A and B. Differences between wild-type and $Cyp3a^{-/-}$ ($P<0.01$) and $Cyp3a^{-/-}$A and $Cyp3a^{-/-}$V ($P<0.05$) were significant for all time points after i.v. and oral administration. Inset in B shows the semi-log plot of the data. [Figure taken from (van Herwaarden, Wagenaar, van der Kruijssen, van Waterschoot, Smit, Song, van der Valk, van, van der Hoorn, Rosing, Beijnen, and Schinkel, 2007)].