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Inter-patient variability in docetaxel pharmacokinetics: A review

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ABSTRACT

Docetaxel is a frequently used chemotherapeutic agent in the treatment of solid cancers. Because of the large inter-individual variability (IIV) in the pharmacokinetics (PK) of docetaxel, it is challenging to determine the optimal dose in individual patients in order to achieve optimal efficacy and acceptable toxicity. Despite the established correlation between systemic docetaxel exposure and efficacy, the precise factors influencing docetaxel PK are not yet completely understood. This review article highlights currently known factors that influence docetaxel PK, and focusses on those that are clinically relevant. For example, liver impairment should be taken into account when calculating docetaxel dosages as this may decrease docetaxel clearance. In addition, drug–drug interactions may be of distinct clinical importance when using docetaxel. Particularly, drugs strongly inhibiting CYP3A4 such as ketoconazole should not be concurrently administered without dose modification, as they may decrease the clearance of docetaxel. Gender, castration status, and menopausal status might be of importance as potential factors influencing docetaxel PK. The role of pharmacogenetics in predicting docetaxel PK is still limited, since no polymorphisms of clinical importance have yet been established.

Introduction

Docetaxel is approved for the treatment of several solid malignancies, including non-small cell lung cancer (NSCLC), metastatic castration resistant prostate cancer (mCRPC), breast cancer and head and neck cancer [1,2]. Most of these cancers typically occur in elderly people, who may have comorbidities, organ dysfunction and are using various medications. The pharmacokinetics (PK) of docetaxel are highly variable, ranging from 30% to 45% [3]. Therefore, it is challenging to predict toxicity and antitumor activity of docetaxel in individual patients. Ideally, patients would be individually dosed to prevent toxicity and improve the efficacy of docetaxel.

It is believed that the systemic exposure to a drug like docetaxel is related to its efficacy [4]. This was also shown by Bruno et al. who found that the area under the plasma-concentration time curve (AUC) of the initial course of docetaxel was a predictor of time to progression in NSCLC patients [5]. Also, a decreased clearance (CL) increased the risk of grade 4 neutropenia and febrile neutropenia [6]. Knowledge of factors that are of importance for PK variability could therefore lead to the optimization of docetaxel therapy.

Several studies have focused on determining factors that may influence docetaxel PK, aiming for better prediction of toxicity and exposure to docetaxel (see Fig. 1). This excessive sum of studies makes it difficult to extract clinically relevant findings for usage in daily clinical practice. Hence, no label changes for docetaxel dosing have been made in the last decade although the current dosing strategy using body surface area (BSA) has been criticized, as this dosing strategy does not reduce the inter-individual variability (IIV) in docetaxel PK to an absolute minimum, since it does not account for other factors influencing docetaxel PK. This review article gives a comprehensive summary on the currently available and clinically relevant factors influencing docetaxel PK that can aid in individualizing docetaxel therapy in current clinical practice.

Drug transporters involved in docetaxel pharmacology

Drug transporters and docetaxel pharmacokinetics

The activity of docetaxel-transporters could be altered due to drug–drug interactions, which potentially influence the PK of docetaxel. The largest family of drug transporters consists out of passive transporters: the solute carriers (SLCs), which cover 48% of the

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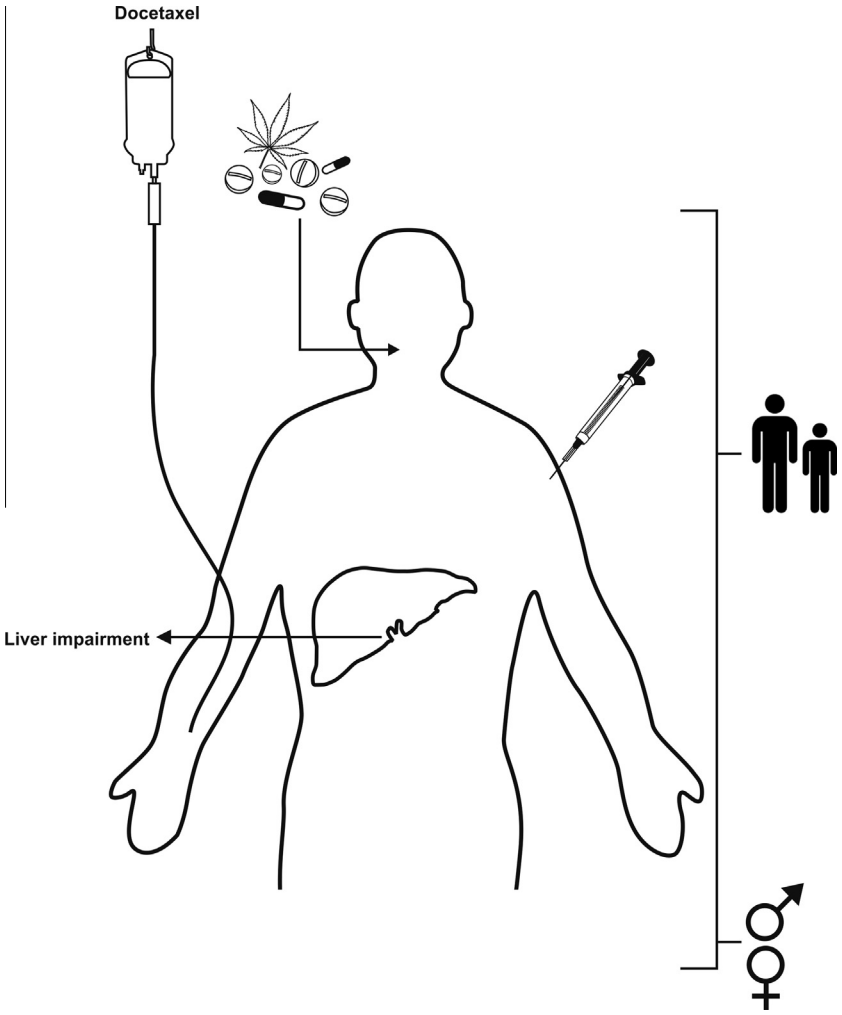

Fig. 1. Factors influencing docetaxel pharmacokinetics. Co-medication and the use of complementary alternative medicines (CAMs) impact docetaxel PK in a clinically relevant way and should be taken into account when optimizing docetaxel treatment. In addition, patient related factors such as liver impairment, gender and hormonal status could potentially influence docetaxel PK.

total amount of transporters. Docetaxel is a known substrate of SLC22A7 [7], SLCO1B1 [8], SLCO1B3 [9], SLC22A7 [7] and possibly SLCO1A2 [7,10]. Besides SLCs, members of the ATP-binding cassette (ABC) transporters are extensively studied with regard to multidrug resistance and the PK of several anticancer drugs. Docetaxel is known to be transported by ABCB1 (ATP-binding cassette transporter B1, p-glycoprotein (p-gp)) [11], ABCC2 (canalicular multispecific organic anion transporter 1 (*cMOAT*), MRP2) [12] and ABCC10 (multidrug resistance-associated protein 7 (MRP7)) [13].

Absorption

The gastro-intestinal absorption of docetaxel is limited. This is because ABCB1 directly excretes docetaxel into the intestinal lumen or bile [14]. Moreover, docetaxel' s bioavailability is greatly reduced by the liver's first pass effect [15]. Docetaxel is currently only being administered intravenously. As oral administrations of docetaxel could be more patient friendly, research is ongoing to improve the bioavailability of docetaxel [16,17].

Tissue distribution and accumulation

Over ninety percent of docetaxel is bound to plasma proteins [1]. Because of its lipophilic properties, docetaxel has a large distribution volume, indicating accumulation in several tissues [1]. Based on a bio-distribution study in cancer patients, a high uptake of [^{11}C]-docetaxel in the liver and gall bladder was seen, while there was fewer uptake in the small intestines, kidney, bone marrow, lungs and bladder [18]. Uptake of docetaxel in the brain was limited, resulting from an effective blood brain barrier containing efflux transporters like ABCB1 and ABCC2 [19].

Docetaxel metabolism and excretion

Hepatic uptake

Docetaxel is metabolized in the liver (Fig. 2). Uptake is facilitated via uptake transporters such as Organic Anion Transporting Peptides (OATP) 1B1 and OATP1B3, which belong to the SLC family. These transporters mediate the uptake of docetaxel from sinusoidal blood into the hepatocytes [8–10]. Iusuf and colleagues recently found that OATP1A2 was also involved in the ***in vivo*** uptake of docetaxel [10]. Animal studies with the OATP1B3/OATP1B1 orthologue OATP1B2 showed that the CL of docetaxel is substantially decreased in OATP1B2 knockout mice [8,10,20,21] in a manner that resembles drug phenotypes observed in mice with a deficiency of metabolic Cyp3a activity [22]. Therefore, co-medication that inhibits both OATP1B1 and 1B3 should only be used with caution in combination with docetaxel. Also, we previously found that docetaxel's formulation vehicle