Role of TDM-based dose adjustments for major taxane anticancer drugs

Marsilla Muth[1], Francis Ojara[2], Charlotte Kloft[2], and Markus Joerger[1]

[1]Kantonsspital Sankt Gallen
[2]Free University of Berlin

April 28, 2020

Abstract

Purpose: The classical taxanes (paclitaxel, docetaxel), the newer taxane cabazitaxel and the nanoparticle-bound nab-paclitaxel are among the most widely used anticancer drugs. Still, the optimal use and the value of pharmacological personalization of the taxanes is still controversial. Methods: We give an overview on the pharmacological properties of the taxanes, including metabolism, pharmacokinetics-pharmacodynamic relations and aspects in the clinical use of taxanes. The latter includes the ongoing debate on the most effective and safe regimen, the recommended initial dose, and pharmacological dosing individualization. Conclusions: The taxanes are among the most widely used anticancer drugs in patients with solid malignancies. Despite their longtime use in clinical routine, the optimal dosing strategy (weekly versus 3-weekly) or optimal average dose (cabazitaxel, nab-paclitaxel) has not been fully resolved, as it may differ per tumor entity and line of treatment. The value of pharmacological individualization of the taxanes (TDM, TCI) has partly been explored for 3-weekly paclitaxel and docetaxel, but remains mostly unexplored for cabazitaxel and nab-paclitaxel at present.

Article type: Invited review

Role of TDM-based dose adjustments for major taxane anticancer drugs

M. Muth[1], F.W. Ojara[2], C. Kloft[2], M. Joerger[1]

[1]Department of Oncology & Hematology, Cantonal Hospital, St. Gallen, Switzerland, Rorschacherstrasse 95, .Gallen, Switzerland

[2]Department of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germnay

Keywords:Therapeutic drug monitoring, Pharmcotherapy, Clinical Pharmacy, Chemotherapy, Toxicity

Introduction: The classical taxanes (paclitaxel, docetaxel), the newer taxane cabazitaxel and the nanoparticle-bound nab-paclitaxel are among the most widely used anticancer drugs. Despite years of research, the optimal dosing regimen (weekly versus 3-weekly) and optimal dose are still controversial, as is the value of pharmacological personalization of taxane dosing.

Areas covered: We give an overview on the pharmacological properties of the taxanes, including metabolism, pharmacokinetics-pharmacodynamic relations and aspects in the clinical use of taxanes. The latter includes the ongoing debate on the most effective and safe regimen (paclitaxel, docetaxel, nab-paclitaxel), the recommended initial dose (cabazitaxel), and pharmacological dosing individualization.

Expert opinion: The taxanes share the characteristics of extensive hepatic metabolism and biliary excretion, the need for dose adaptation in patients with liver dysfunction, and a substantial pharmacokinetic variability even after taking into account known patient chareacteristics. Data from clinical studies suggest that optimal scheduling of the taxanes is dependent not only on the specific taxane compound, but also on the tumor type and line of treatment. Finally, treating oncologists should be aware of the substantial risk for drug-drug interactions that is a direct consequence of the complex hepatic metabolism of the taxanes.

Introduction

The taxanes represent the backbone of many systemic anticancer treatment regimens for early and advanced solid tumors. Paclitaxel was the first compound of this class and was discovered as part of the U.S. National Cancer Institute program to detect new anticancer drugs. In 1963, a crude extract form the bark of the Pacific Yew, Taxus brevifolia, a scarce and slow-growing evergreen found in the forests of the Pacific Northwest, was found in preclinical studies to have cytotoxic activity against many tumors, and paclitaxel was identified as the active moiety in 1971. Docetaxel was detected somewhat later, is also synthesized from 10-deacetylbaccatin III, and represents a more water-soluble and potent taxane derivative. Cabazitaxel is a semi-synthetic 10-deacetylbaccatin-III derivative, selected for clinical testing due to its poor affinity for the ATP-dependent, resistance-related drug efflux pump P-glycoprotein (PgP, MDR1, ABCB1), and its improved blood-brain barrier penetration. The application of nanotechnology in oncology has enabled the development of nab-paclitaxel, a soluble form of paclitaxel that is linked to albumin nanoparticles. This has resulted in improved pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of nab-paclitaxel compared to cremophor-bound paclitaxel or polysorbate 80-bound docetaxel, neutralizing the taxane's inherent hydrophobicity. This review article will systematically approach pharmacological aspects including invidualized dosing and therapeutic drug monitoring (TDM) of these major taxane anticancer compounds.

Paclitaxel

Paclitaxel is an alkaloid ester consisting of a taxane ring system linked to a four-member oxetan ring at positions C-4 and C-5. The drug is approved for the treatment of solid tumor entities including non-small cell lung cancer (NSCLC), breast and ovarian cancer as well as upper gastrointestinal tumors.

Paclitaxel metabolism

Paclitaxel stabilizes microtubule polymerisation that results in mitotic arrest and apoptotic cell death in sensitive cancer cells. Resistance mechanisms to paclitaxel are complex and a result of different mechanisms, including efflux mediated by PgP (MDR1, ABCB1) and other ABC transporters (efflux systems), alteration of paclitaxel binding to tubulin (overexpression or mutations of tubulin), modifications of cellular apoptotic signals and paclitaxel detoxification by CYP3A4 and CYP2C8. Among mechanisms of resistance to taxanes, those related to microtubule-associated proteins (MAP) are of major importance (summarized in [1]).

Paclitaxel pharmacokinetics

Paclitaxel biotransformation is mediated by cytochrome P450 enzymes (CYP), most prominently CYP3A4 and CYP2C8. With a high affinity and metabolic rate, CYP2C8 is involved in a stereoselective hydroxylation of paclitaxel at the 6-position to the main metabolite 6α-hydroxy-paclitaxel (M5 metabolite). Additionally, paclitaxel undergoes hydroxylation at the C13 side-chain of the molecule to 3'-p-hydroxyphenyl-paclitaxel (M4). Hydroxylation of paclitaxel is highly influenced by potential induction or inhibition of CYP3A4.

Paclitaxel exhibits non-linear pharmacokinetics that becomes obvious when giving the drug at the conventional intravenous infusion over one or three hours (as compared to 24-hour infusions). Nonlinear PK of paclitaxel is caused by saturable transport [2], saturable binding [3] of the drug, but also by interaction with the micelle-forming solvent Cremophor EL (CrEL) [4]. CrEL has been suggested to inhibit PgP-mediated biliary secretion [5], cause lipoprotein dissociation that would alter protein binding [6], and alterations in the distribution of paclitaxel by entrapment in micelles [7]. As a consequence, the free fraction of paclitaxel decreases with increasing concentrations of CrEL [7].

Paclitaxel has been shown to bind to both albumin and α1-acid glycoprotein [8], resulting in a high distribution volume of paclitaxel of roughly 60 L/m^2. The terminal half-life of paclitaxel has been estimated to between 8 and 12 hours [9, 10], while it's maximum elimination capacity when given at a dose of 175mg/m^2 over a 3-hour infusion has been estimated to 36 μmol/L*h [11]. While drug *clearance* describes the body's capacity to eliminate a specific drug that exhibits linear pharmacokinetics, *maximum elimination capacity* is the preferred parameter for drugs with non-linear PK. Finally, paclitaxel undergoes biliary excretion, which is why patients with liver function impairment or liver metastases have a slower elimination of the drug and are at increased risk of toxicity [12, 13]. Accordingly, a 3-weekly paclitaxel dose of 135 mg/m^2 is recommended in patients with increased liver function tests (LFT), 115 mg/m^2 with a total bilirubin between 25 and 40 μmol/L and 100 mg/m^2 with a total bilirubin between 40 and 70μmol/L. Paclitaxel should not be used in patients with a total bilirubin >70 μmol/L [14].

2.3. Pharmacokinetics/pharmacodynamics relationships

The time above a paclitaxel plasma concentration of 0.05 μmol/L ($T_{C>0.05}$) emerged as a predictor of neutropenia [15-17] and chemotherapy-induced polyneuropathy (CIPN), as well as clinical outcome in some studies. Mielke and colleagues showed a significant association between paclitaxel $T_{C>0.05}$ and CIPN in 24 patients with advanced solid tumors [18]. Overall, there is a fairly consistent association between paclitaxel exposure and drug-associated toxicity, mainly haematological and neurological adverse events. Two studies found an association between exposure to paclitaxel and clinical outcome in advanced NSCLC [19] and ovarian cancer [20], respectively. In the study by Huizing and colleagues, patients with a paclitaxel $T_{C>0.10}$ [?]15 hours had a longer median survival as compared to patients with a paclitaxel $T_{C>0.10}$ <15 hours (8.2 versus 4.8 months, p = 0.06) [19]. In the study by Joerger and colleagues in ovarian cancer patients receiving 3-weekly paclitaxel and carboplatin for ovarian cancer after cytoreductive surgery, a paclitaxel $T_{C>0.05}$ >61 hours had an improved time to disease progression as compared to patients with a paclitaxel $T_{C>0.05}$ <61 hours (85.2 versus 63.3 weeks; P = 0.05) [20].

2.4. Paclitaxel therapeutic drug monitoring and target concentration intervention

Major paclitaxel-associated toxicities include bone marrow suppression (neutropenia, anemia, thrombopenia), acute or chronic neurotoxicity resulting in either arthralgia and myalgia or cumulative peripheral paresthesias or hypesthesias, respectively, and less frequent but potentially severe acute CrEL-associated hypersensitivity reactions [21]. Weekly instead of 3-weekly scheduling of paclitaxel has become popular in some clinics due to its relative ease, shorter infusion times, convenient monitoring, favourable clinical activity and potential for reduced toxicity [22]. For the treatment of advanced NSCLC, carboplatin in combination with weekly paclitaxel 100 mg/m^2 has been shown to be equally effective as 3-weekly dosing at 200 or 225 mg/m^2. In NSCLC, lower incidences of CIPN were reported with weekly paclitaxel 100 mg/m2 compared to 3-weekly paclitaxel at 200 and 225 mg/m^2, however contrary findings have been shown in breast cancer patients with higher incidences of CIPN with paclitaxel 80 mg/m^{2}weekly dosing compared to 175 mg/m^2 3-weekly dosing [23-25]. For breast cancer, weekly regimens are superior in terms of efficacy to 3-weekly paclitaxel schedules in both the adjuvant [25] and metastatic setting [24]. In ovarian cancer, weekly paclitaxel has become of particular interest since the publication of the JGOG 3016 data [26].

At least four prospective clinical studies explored paclitaxel therapeutic drug monitoring (TDM) and target concentration intervention (TCI) using Bayesian dose adjustments [table 1; 27-30]. In the study by Woo and colleagues, seven children with refractory acute leukemia were enrolled [28]. During a 24-hour paclitaxel

infusion, repeated PK-samples were drawn within the first eight hours, paclitaxel clearance was immediately calculated using a population model, and dose adjustment was performed 12 hours after the start of paclitaxel infusion to target a paclitaxel AUC of 31.5 45 μM*h. Target concentration intervention (TCI) resulted in significantly more courses being in the AUC target (71% versus 0%, p = 0.02), and TCI resulted in a decrease of PK variability [28]. In the study by de Jonge and colleagues, 25 patients with advanced NSCLC received paclitaxel 175 mg/m^2 over 3 hours and carboplatin AUC 6 every 3 weeks, and patients underwent repeated TDM and TCI [27]. Paclitaxel data were subjected to population modeling, and paclitaxel dose was calculated to target a paclitaxel $T_{C0.1}$ of [?]15 hours. Similarly to the study of Woo and colleagues, TDM and TCI resulted in decreased PK variability and an increased proportion of patients reaching the paclitaxel PK target (from 64% to 88%). A large prospective phase 3 clinical trial randomized patients with advanced NSCLC to receive first-line palliative 3-weekly paclitaxel 200 mg/m^2 in combination with carboplatin AUC 6 either adjusted on clinical symptoms or additionally receiving TDM and TCI to target paclitaxel $T_{C0.05}$ of between 26 and < 31 hours [29]. Among 365 patients randomly assigned patients, grade 4 neutropenia was only numerically decreased in the TDM versus non-TDM arm (19% versus 16%; p = 0.10), but CIPN grade [?]2 was significantly improved by using TDM and TCI (38% versus 23%, p < 0.001) as was CIPN grade [?]3 (9% versus 2%, p < 0.001). Paclitaxel TDM and TCI resulted in a significantly lower final paclitaxel dose (199 versus 150 mg/m^2, p < 0.001), but this did not result in worse clinical efficacy (radiological response was 31% versus 27%, overall survival 10.1 versus 9.5 months) [29]. A similar prospective phase 3 trial randomized Chinese patients with advanced NSCLC to receive first-line palliative 3-weekly paclitaxel 175 mg/m^2 in combination with carboplatin AUC 6 either adjusted on clinical symptoms or additionally receiving TDM and TCI to target paclitaxel $T_{C0.05}$ of between 26 and < 31 hours [30]. Among 275 patients randomly assigned patients, grade 4 neutropenia was significantly decreased in the TDM versus non-TDM arm (24% versus 15%; p = 0.009), while CIPN grade [?]2 was significantly improved by using TDM and TCI (21% versus 8%, p = 0.005). Similarly to the CEPAC-TDM trial, paclitaxel TDM and TCI resulted in a significantly lower final paclitaxel dose in the trial by Zhang and colleagues (161 versus 128 mg/m^2, p < 0.001), while clinical efficacy was numerically improved by using TDM and TCI (radiological response was 26% versus 32%, overall survival 21.0 versus 24.0 months); progression-free survival was significantly higher in the TDM plus TCI arm (4.17 versus 4.67 months, p = 0.026) [30]. Overall, current data suggest individual paclitaxel $T_{C>0.05}$ of 26 to <31 hours to be adequate. Paclitaxel $T_{C>0.05}$ data can be calculated with a single 24-hour PK sample of paclitaxel using readily available online tools [31]. Rigorous population modelling of the CEPAC-TDM trial data has enabled further characterisation of the relationship between paclitaxel/platinum drug exposure and the occurrence of key treatment-associated toxicities (neutropenia and CIPN). A physiologically-motivated PK-PD model was developed to characterise the time course of neutropenia after multiple cycles of chemotherapy. Applying this model enables long-term prediction of neutropenia for dose adaptation in patients undergoing paclitaxel/platinum drug combination chemotherapy [32]. Furthermore, a parametric time-to-event model was developed to characterise the time-course in risk of first occurrence of clincally relevant paclitaxel-associated peripheral neuropathy (NCI-CTC grade [?]2) and quantify the impact of time-dependent paclitaxel exposure and patient characteristcs (age, sex and smoking status) for better prediction of the individual patients' risk of peripheral neuropathy for different paclitaxel dosing schedules. In addition, population modelling should in future also be leveraged to characterise key efficacy end points such as overall survival, thus establishing a framework to jointly predict treatment response and associated toxicities a priori for different paclitaxel treatment schedules based on treatment exposure and patient characteristics.

Docetaxel

Docetaxel also has a four-member oxetan ring with minor modifications of the C13 side-chain. It is approved for the treatment of malignant tumors of the breast, lung, prostate, upper gastrointestinal tract and head and neck.

Docetaxel metabolism

Similar to paclitaxel, docetaxel undergoes extensive hepatic metabolism, biliary excretion and almost ex-

clusive fecal elimination. Biotransformation of docetaxel is different from paclitaxel, in that it undergoes CYP3A4/3A5-mediated hydroxylation of the tert-butyl group to form the M2 primary alcohol metabolite. Subsequently, docetaxel is undergoing ring closure via a putative aldehyde, resulting in two diastereoisomers M1 and M3. This is followed by oxidation to the M4 ketone metabolite. Similar to paclitaxel, the metabolites of docetaxel are substantially less active compared to the parent compound. Resistance mechanisms to docetaxel include cellular efflux through PgP (MDR1, ABCB1), ABCB4 and ABCC1, mutations in or altered expression of β-tubulin, overexpression of MAP or upregulation of anti-apoptotic cellular signaling. The most extensively studied mechanism of acquired or intrinsic resistance to taxanes is overexpression of ABCB1 (summarized in [1]).

Docetaxel pharmacokinetics and pharmacodynamics

Docetaxel exhibits linear PK, with a clearance being constant over a dose range between 20 and 115 mg/m^2. Docetaxel pharmaceutical formulations use polysorbate 80 instead of cremophor EL as the solvent. Docetaxel has a protein binding of roughly 95%, resulting in a high volume of distribution of 74L/m^{2}after a 100mg/m^2 dose [33]. Similar to paclitaxel, the free fraction of docetaxel decreases with increasing concentrations of polysorbate 80 [34]. Docetaxel has a terminal half-life of 12 hours and a clearance of 22 L/h/m^2 [33]. Docetaxel undergoes biliary excretion, which is why patients with liver function impairment or liver metastases have a slower elimination of the drug and are at increased risk of toxicity. Docetaxel clearance is 50% of normal in patients with LFT [?] 2.5-times ULN and 25% in patients with a total bilirubin [?] 1.5-times ULN. Docetaxel should be omitted in patients with a total bilirubin above ULN [35]. Docetaxel AUC is a significant predictor of febrile neutropenia, infection, severe mucositis, diarrhea or asthenia. In practical terms, the risk of severe toxicity doubles when docetaxel AUC increases from 4.2 to 6.5 µg*h/mL [36], and the the risk of febrile neutropenia triples when AUC doubles [37].

Docetaxel therapeutic drug monitoring and target concentration intervention

Major docetaxel-associated toxicities include (febrile) neutropenia, diarrhea, mucositis, alopecia, nail toxicity, cumulative CIPN and polysorbate 80-associated HSR. Weekly docetaxel has a more favourable toxicity profile compared to 3-weekly docetaxel, and is equally active in metastatic breast and lung cancer, but not in castration-resistant prostate cancer (CRPC) and early-stage breast cancer (summarized in [1]).

Crombag and colleagues studied docetaxel PK and clinical data from 157 patients, and found a significant impact of patient age on docetaxel clearance, with a reduction in clearance of 17% and 34% for a 10-year and 20-year increase of patient age [38]. According to a large meta-analysis in 1'150 cancer patients from 26 clinical trials, patients with CRPC have a significantly lower mean exposure (AUC) of docetaxel compared to patients with other solid tumors (fold change: 1.8, 1.5-2.2), and a 2.2-fold lower odds of developing severe neutropenia (odds ratio: 0.46, 0.31-0.90) [39]. This confirms older data from Franke and colleagues, and suggests castration-dependent PK of docetaxel [40]. At least one prospective, randomized clinical study explored TDM followed by TCI of docetaxel in 15 patients with advanced solid tumors using Bayesian dose adjustments compared to BSA-based dosing in another 15 patients [41]. All patients received docetaxel at an initial dose of 75 mg/m^2 at 3-weekly intervals, underwent limited docetaxel PK sampling and dose adaptation for the following cycle to achieve a docetaxel AUC of 4.9 mg/L*h (experimental arm) versus BSA-based dosing (standard arm). Docetaxel TDM and TCI resulted in a decrease of docetaxel PK variability by 39%, and a decrease of the variability of neutropenia by 50%. Hematological toxicity however was similar in the adjusted and the unadjusted dosing arm, suggesting no clear advantage of docetaxel TDM and TCI for clinical outcome in this small study [41]. While more research is required to evaluate docetaxel TDM and TCI, current data suggest that an individual AUC target of 5 mg/L*h should be adequate with standard dosing of 75 mg/m^2.

Cabazitaxel

Cabazitaxel is a semi-synthetic taxane from a single diastereoisomer of 10-deacetyl-baccatin-III. The drug is approved for the treatment of patients with CRPC progressing or relapsing after docetaxel. Cabazitaxel was selected for clinical development based on preclinical features such as activity in taxane-resistant models

and its ability to cross the blood-brain barrier.

Cabazitaxel metabolism

Cabazitaxel undergoes extensive hepatic metabolism, biliary excretion and mostly fecal elimination. Oxidative pathways include O-demethylation leading to 10-O-demethyl-cabazitaxel and 7-O-demethyl-cabazitaxel, followed by ring closure leading to an oxazolidine-like derivative. Cabazitaxel is mainly metabolized by CYP3A4 and CYP3A5 (the contribution of CYP3A estimated to be in the range of 80%–90%), and to a lesser extent by CYP2C8 [42]. Cabazitaxel is the major circulating compound. Cabazitaxel has been shown to be active in cell lines resistant to cytotoxic agents such as anthracyclines, vinca alkaloids and the older taxanes docetaxel and paclitaxel, probably due to its lower affinity for the P-glycoprotein efflux pump (ABCB1). Accordingly, cabazitaxel retains activity in some in vivo tumor models with innate or acquired resistance to taxanes and other chemotherapeutic agents [43].

Cabazitaxel pharmacokinetics and pharmacodynamics

Cabazitaxel exhibits linear PK with an average drug clearance of 26.4 L/h/m^2 and a long terminal half-life of 95 hours [44]. Cabazitaxel pharmaceutical formulations use polysorbate 80 as solvent. A pooled analysis of PK data from several cabazitaxel phase 1 studies showed cabazitaxel clearance to be significantly associated with body surface area (BSA) and tumor type. On the contrary, patient gender, weight, age, ethnicity, renal function and coadministration of CYP-inducing agents did not significantly impact cabazitaxel PK. Cabazitaxel is contraindicated in patients with severe hepatic impairment and should be dose-reduced in patients with moderate hepatic impairment [45]. Cabazitaxel can safely be administered in patients with mild to moderate renal impairment as this did not have meaningful effects on cabazitaxel PK [44].

Pharmacological aspects in the clinical use of cabazitaxel

Major cabazitaxel-associated toxicities include (febrile) neutropenia, diarrhea, mucositis, alopecia, cumulative CIPN and polysorbate 80-associated HSR. The PK-PD relationship between cabazitaxel exposure (AUC) and neutropenia follows a typical sigmoidal maximal effect (E_{max}) model, in which the value of AUC to obtain 50% of E_{max} was a cabazitaxel plasma concentration of 158 ng*h/mL for neutrophils and 143 ng*h/mL for leucozytes, which corresponds to a cabazitaxel relative dose of approximately 10 mg/m^2 [46, 47]. No significant association was found between cabazitaxel PK and overall survival in a small subset of 67 evaluable patients from the large randomized phase 3 *TROPIC* study in patients with metastatic CRPC [48]. In the *TROPIC* study, patients with metastatic CRPC progressing after docetaxel were randomized to receive either 3-weekly cabazitaxel 25 mg/m^2 or mitoxantrone 12 mg/m^2, both in combination with 10 mg oral prednisone daily. As a consequence of substantial toxicity in the TROPIC study, the approved dose of cabazitaxel 25 mg/m^2 was prospectively tested against cabazitaxel 20 mg/m^2 in 1'200 patients with metastatic CRPC *(PROSELICA)* [49]. Cabazitaxel at 20 mg/m^2 was confirmed non-inferior compared to cabazitaxel 25 mg/m^2, but the approved dose of cabazitaxel was numerically superior (overall survival 14.5 versus 13.4 months), and PSA response was significantly higher with the approved dose of 25 mg/m^2 versus 20 mg/m^2 (42.9% versus 29.5%, p<0.001). Most importantly, severe cabazitaxel-associated toxicity was less prominent in post-marketing clinical routine compared to the registration trial*(TROPIC)* , potentially as a consequence of improved toxicity management or less sensitive patient populations. A small prospective series of 10 patients with metastatic CRPC suggests metabolic phenotyping using midazolam to predict cabazitaxel PK [50], but there is no prospective data on cabazitaxel TDM/TCI or dose individualization published so far. A randomized phase-II trial assessed the impact of cabazitaxel TDM and TCI on the clinical outcome (toxicity and activity) in patients with metastatic CRPC *(EUDRACT 2013-005504-34) (CAINTA)* , and data are expected to be published in 2020.

Nab-paclitaxel

Nab-Paclitaxel has been developed in an attempt to reduce toxicity associated with conventional taxane formulations (caused by the use of cremophor EL and polysorbate 80, respectively), while potentially increasing antitumor activity. Cremophor EL and polysorbate 80 are associated with increased toxicity, most

importantly acute hypersensitivity reactions, that can be severe or even life-threatening, and requires the use of premedication with steroids and antihistamines. Conventional solvents may also hinder the ability of the circulating taxane molecules to cross the endothelial barrier and accumulate in tumors, reducing antitumor activity and increasing the risk of systemic toxicity. The first attempt to overcome the limitations imposed by the use of solvents was albumin-bound nab-paclitaxel.

Nab-paclitaxel metabolism

With nab-paclitaxel, reversible binding of albumin to paclitaxel permits exploitation of endogenous albumin pathways to enhance absorption, distribution and concentration of the drug at the tumor site. Albumin is a natural carrier of hydrophobic molecules and binds to the gp60 receptor on endothelial cells, resulting in the formation of vesicles (caveolae) in the membrane of target cells that carry the albumin complex across the endothelial membrane (transcytosis) and into surrounding tissues. The entry and retention of albumin complexes in tumor tissue are facilitated by the enhanced permeation and retention effect, i.e. the accumulation of albumin complexes and other macromolecules in the tumor interstitium via leaky tumor vasculature. Accumulation of albumin-bound paclitaxel is facilitated by the albumin-binding activity of secreted protein acidic and rich in cysteine (SPARC) in malignant tumors. The absence of cremophor EL or polysorbate 80 in the nanoparticle, albumin-bound formulation virtually eliminates the risk of acute, infusion-related hypersensitivity reactions without requiring steroid premedication that is mandatory with conventional taxane formulations. Additionally, the absence of a specific solvent in the nab-paclitaxel formulation allows rapid intravenous infusion of the drug in 30 minutes (versus 3 hour for 3-weekly paclitaxel and 60 minutes for weekly paclitaxel, docetaxel and cabazitaxel), and requires no special tubing or in-line filters. Nab-paclitaxel is approved for the treatment of tumors of the pancreas, breast and lung. The metabolism of and resistance mechanisms to nab-paclitaxel are very comparable to solvent-based paclitaxel.

Nab-paclitaxel pharmacokinetics and pharmacodynamics

Nab-paclitaxel at a dose of up to 300 mg/m^2 is characterized by a linear, biphasic PK profile with a direct relationship between drug exposure and toxicity. Average total clearance of nab-paclitaxel is 15 L/h/m^2, with a terminal half-life of roughly 27 hours. The mean volume of distribution is large (roughly 630 L/m^2), indicating extensive extravascular distribution and/or tissue binding of paclitaxel. When comparing the population PK of 150 patients from several clinical studies receiving a 30-minutes infusion of nab-paclitaxel at a dose between 80 and 375mg/m^2 with previous data from solvent-based paclitaxel given over mainly 3 hours, nab-paclitaxel PK is characterized by fast transport-driven distribution to peripheral compartments, rapid disappearance of the parent compound from systemic circulation, high distribution volume and a maximum elimination rate that is roughly 25% of solvent-based paclitaxel (8.1 versus 31.9 mg/L) [15, 51]. The fraction of free paclitaxel is significantly higher with nab-paclitaxel (6.2%) as compared to solvent-based paclitaxel (2.3%), resulting in significantly higher exposure to unbound paclitaxel with nab-paclitaxel compared with solvent-based paclitaxel, even with total exposure being comparable. The clearance of nab-paclitaxel decreases with liver dysfunction, and the recocmmended 3-weekly dose for nab-paclitaxel is 260 mg/m^2 in patients with a total bilirubin > ULN to [?] 1.25-times ULN, 200 mg/m^2 for patients with a total bilirubin between 1.26 and 2-times ULN and 130 mg/m^2 for patients with a total bilirubin between 2 and 5-times ULN [52]. No dose adjustment is needed in patients with mild to moderate renal impairment [51].

Pharmacological aspects in the clinical use of nab-paclitaxel

Major toxicities with nab-paclitaxel include (febrile) neutropenia, alopecia, cumulative CIPN, but virtually no cases of acute, infusion-related HSR. Chen and colleagues found a significant association nab-paclitaxel exposure and neutropenia in 150 solid tumor patients, with the probability of experiencing a [?] 50% reduction in neutrophils being highly associated with the time above a nab-paclitaxel plasma concentration of > 720 ng/ml (0.84 μmol/L) [51]. The simulated duration above 720 ng/mL per cycle was reduced by 31% with weekly dosing at 100 mg/m^2 versus 3-weekly dosing at 300 mg/m^2. Nab-paclitaxel-associated neutropenia was positively correlated with advanced age, but was not significantly influenced by hepatic function, tumor type, patient gender or dosing schedule. In advanced breast cancer as well as NSCLC,

randomized data suggest weekly nab-paclitaxel to be the preferred regimen due to an improved safety-activity profile compared to 3-weekly regimens of nab-paclitaxel [53, 54]. Still, there are different dosing regimens approved from the different authorities for malignant tumors of the breast, pancreas and lung. Prospective studies exploring nab-paclitaxel TDM and TCI would be highly desirable.

Conclusion

The taxanes are among the most widely used anticancer drugs in patients with solid malignancies. Despite their longtime use in clinical routine, the optimal dosing strategy (weekly versus 3-weekly) or optimal average dose (cabazitaxel, nab-paclitaxel) has not been fully resolved, as it may differ per tumor entity and line of treatment. The value of pharmacological individualization of the taxanes (TDM, TCI) has partly been explored for 3-weekly paclitaxel and docetaxel, but remains mostly unexplored for cabazitaxel and nab-paclitaxel at present.

Declaration of interest

The authors have no relevant affiliations or financiel involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

TABLE(S)

REFERENCES

1. Joerger M. Metabolism of the taxanes including nab-paclitaxel. Expert Opin Drug Metab Toxicol 2015; 11: 691-702.

2. Sonnichsen DS, Hurwitz CA, Pratt CB et al. Saturable pharmacokinetics and paclitaxel pharmacodynamics in children with solid tumors. J Clin Oncol 1994; 12: 532-538.

3. Karlsson MO, Molnar V, Freijs A et al. Pharmacokinetic models for the saturable distribution of paclitaxel. Drug Metab Dispos 1999; 27: 1220-1223.

4. van Tellingen O, Huizing MT, Panday VR et al. Cremophor EL causes (pseudo-) non-linear pharmacokinetics of paclitaxel in patients. Br J Cancer 1999; 81: 330-335.

5. Gianni L, Kearns CM, Giani A et al. Nonlinear pharmacokinetics and metabolism of paclitaxel and its pharmacokinetic/pharmacodynamic relationships in humans. J Clin Oncol 1995; 13: 180-190.

6. Sykes E, Woodburn K, Decker D, Kessel D. Effects of Cremophor EL on distribution of Taxol to serum lipoproteins. Br J Cancer 1994; 70: 401-404.

7. Sparreboom A, van Zuylen L, Brouwer E et al. Cremophor EL-mediated alteration of paclitaxel distribution in human blood: clinical pharmacokinetic implications. Cancer Res 1999; 59: 1454-1457.

8. Kumar GN, Walle UK, Bhalla KN, Walle T. Binding of taxol to human plasma, albumin and alpha 1-acid glycoprotein. Res Commun Chem Pathol Pharmacol 1993; 80: 337-344.

9. Huizing MT, Vermorken JB, Rosing H et al. Pharmacokinetics of paclitaxel and three major metabolites in patients with advanced breast carcinoma refractory to anthracycline therapy treated with a 3-hour paclitaxel infusion: a European Cancer Centre (ECC) trial. Ann Oncol 1995; 6: 699-704.

10. Wiernik PH, Schwartz EL, Strauman JJ et al. Phase I clinical and pharmacokinetic study of taxol. Cancer Res 1987; 47: 2486-2493.

11. Joerger M, Kraff S, Huitema AD et al. Evaluation of a pharmacology-driven dosing algorithm of 3-weekly paclitaxel using therapeutic drug monitoring: a pharmacokinetic-pharmacodynamic simulation study. Clin Pharmacokinet 2012; 51: 607-617.

12. Joerger M, Huitema AD, Huizing MT et al. Safety and pharmacology of paclitaxel in patients with impaired liver function: a population pharmacokinetic-pharmacodynamic study. Br J Clin Pharmacol 2007;

64: 622-633.

13. Venook AP, Egorin MJ, Rosner GL et al. Phase I and pharmacokinetic trial of paclitaxel in patients with hepatic dysfunction: Cancer and Leukemia Group B 9264. J Clin Oncol 1998; 16: 1811-1819.

14. Joerger M, Beumer JH. Cancer Treatment in Patients with Hepatic Dysfunction. In: Cancer Treatments in Special Clinical Situations 2013; ESMO Handbook Series.

15. Joerger M, Huitema AD, van den Bongard DH et al. Quantitative effect of gender, age, liver function, and body size on the population pharmacokinetics of Paclitaxel in patients with solid tumors. Clin Cancer Res 2006; 12: 2150-2157.

16. Miller AA, Rosner GL, Egorin MJ et al. Prospective evaluation of body surface area as a determinant of paclitaxel pharmacokinetics and pharmacodynamics in women with solid tumors: Cancer and Leukemia Group B Study 9763. Clin Cancer Res 2004; 10: 8325-8331.

17. Mould DR, Fleming GF, Darcy KM, Spriggs D. Population analysis of a 24-h paclitaxel infusion in advanced endometrial cancer: a gynaecological oncology group study. Br J Clin Pharmacol 2006; 62: 56-70.

18. Mielke S, Sparreboom A, Steinberg SM et al. Association of Paclitaxel pharmacokinetics with the development of peripheral neuropathy in patients with advanced cancer. Clin Cancer Res 2005; 11: 4843-4850.

19. Huizing MT, Giaccone G, van Warmerdam LJ et al. Pharmacokinetics of paclitaxel and carboplatin in a dose-escalating and dose-sequencing study in patients with non-small-cell lung cancer. The European Cancer Centre. J Clin Oncol 1997; 15: 317-329.

20. Joerger M, Huitema AD, Richel DJ et al. Population pharmacokinetics and pharmacodynamics of paclitaxel and carboplatin in ovarian cancer patients: a study by the European organization for research and treatment of cancer-pharmacology and molecular mechanisms group and new drug development group. Clin Cancer Res 2007; 13: 6410-6418.

21. Joerger M. Prevention and handling of acute allergic and infusion reactions in oncology. Ann Oncol 2012; 23 Suppl 10: x313-319.

22. Huang TC, Campbell TC. Comparison of weekly versus every 3 weeks paclitaxel in the treatment of advanced solid tumors: a meta-analysis. Cancer Treat Rev 2012; 38: 613-617.

23. Fountzilas G, Dafni U, Dimopoulos MA et al. A randomized phase III study comparing three anthracycline-free taxane-based regimens, as first line chemotherapy, in metastatic breast cancer: a Hellenic Cooperative Oncology Group study. Breast Cancer Res Treat 2009; 115: 87-99.

24. Seidman AD, Berry D, Cirrincione C et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol 2008; 26: 1642-1649.

25. Sparano JA, Wang M, Martino S et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 2008; 358: 1663-1671.

26. Katsumata N, Yasuda M, Isonishi S et al. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. Lancet Oncol 2013; 14: 1020-1026.

27. de Jonge ME, van den Bongard HJ, Huitema AD et al. Bayesian pharmacokinetically guided dosing of paclitaxel in patients with non-small cell lung cancer. Clin Cancer Res 2004; 10: 2237-2244.

28. Woo MH, Relling MV, Sonnichsen DS et al. Phase I targeted systemic exposure study of paclitaxel in children with refractory acute leukemias. Clin Cancer Res 1999; 5: 543-549.

29. Joerger M, von Pawel J, Kraff S et al. Open-label, randomized study of individualized, pharmacokinetically (PK)-guided dosing of paclitaxel combined with carboplatin or cisplatin in patients with advanced non-small-cell lung cancer (NSCLC). Ann Oncol 2016; 27: 1895-1902.

30. Zhang J, Zhou F, Qi H et al. Randomized study of individualized pharmacokinetically-guided dosing of paclitaxel compared with body-surface area dosing in Chinese patients with advanced non-small cell lung cancer. Br J Clin Pharmacol 2019; 85: 2292-2301.

31. Joerger M, Kraff S, Jaehde U et al. Validation of a Commercial Assay and Decision Support Tool for Routine Paclitaxel Therapeutic Drug Monitoring (TDM). Ther Drug Monit 2017; 39: 617-624.

32. Henrich A, Joerger M, Kraff S et al. Semimechanistic Bone Marrow Exhaustion Pharmacokinetic/Pharmacodynamic Model for Chemotherapy-Induced Cumulative Neutropenia. J Pharmacol Exp Ther 2017; 362: 347-358.

33. Clarke SJ, Rivory LP. Clinical pharmacokinetics of docetaxel. Clin Pharmacokinet 1999; 36: 99-114.

34. Loos WJ, Baker SD, Verweij J et al. Clinical pharmacokinetics of unbound docetaxel: role of polysorbate 80 and serum proteins. Clin Pharmacol Ther 2003; 74: 364-371.

35. Joerger M, Beumer JH. Cancer Treatment in Patients with Hepatic Dysfunction. In Cancer Treatments in Special Clinical Situations. ESMO Handbook Series 2013.

36. Bruno R, Olivares R, Berille J et al. Alpha-1-acid glycoprotein as an independent predictor for treatment effects and a prognostic factor of survival in patients with non-small cell lung cancer treated with docetaxel. Clin Cancer Res 2003; 9: 1077-1082.

37. Bruno R, Hille D, Riva A et al. Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. J Clin Oncol 1998; 16: 187-196.

38. Crombag MBS, Dorlo TPC, van der Pan E et al. Exposure to Docetaxel in the Elderly Patient Population: a Population Pharmacokinetic Study. Pharm Res 2019; 36: 181.

39. de Vries Schultink AHM, Crombag MBS, van Werkhoven E et al. Neutropenia and docetaxel exposure in metastatic castration-resistant prostate cancer patients: A meta-analysis and evaluation of a clinical cohort. Cancer Med 2019; 8: 1406-1415.

40. Franke RM, Carducci MA, Rudek MA et al. Castration-dependent pharmacokinetics of docetaxel in patients with prostate cancer. J Clin Oncol 2010; 28: 4562-4567.

41. Engels FK, Loos WJ, van der Bol JM et al. Therapeutic drug monitoring for the individualization of docetaxel dosing: a randomized pharmacokinetic study. Clin Cancer Res 2011; 17: 353-362.

42. Pean E, Demolis P, Moreau A et al. The European Medicines Agency review of cabazitaxel (Jevtana(R)) for the treatment of hormone-refractory metastatic prostate cancer: summary of the scientific assessment of the committee for medicinal products for human use. Oncologist 2012; 17: 543-549.

43. Vrignaud P, Semiond D, Lejeune P et al. Preclinical antitumor activity of cabazitaxel, a semisynthetic taxane active in taxane-resistant tumors. Clin Cancer Res 2013; 19: 2973-2983.

44. Ferron GM, Dai Y, Semiond D. Population pharmacokinetics of cabazitaxel in patients with advanced solid tumors. Cancer Chemother Pharmacol 2013; 71: 681-692.

45. Sarantopoulos J, Mita AC, He A et al. Safety and pharmacokinetics of cabazitaxel in patients with hepatic impairment: a phase I dose-escalation study. Cancer Chemother Pharmacol 2017; 79: 339-351.

46. Dieras V, Lortholary A, Laurence V et al. Cabazitaxel in patients with advanced solid tumours: results of a Phase I and pharmacokinetic study. Eur J Cancer 2013; 49: 25-34.

47. Mita AC, Denis LJ, Rowinsky EK et al. Phase I and pharmacokinetic study of XRP6258 (RPR 116258A), a novel taxane, administered as a 1-hour infusion every 3 weeks in patients with advanced solid tumors. Clin Cancer Res 2009; 15: 723-730.

48. de Bono JS, Oudard S, Ozguroglu M et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010; 376: 1147-1154.

49. Eisenberger M, Hardy-Bessard AC, Kim CS et al. Phase III Study Comparing a Reduced Dose of Cabazitaxel (20 mg/m(2)) and the Currently Approved Dose (25 mg/m(2)) in Postdocetaxel Patients With Metastatic Castration-Resistant Prostate Cancer-PROSELICA. J Clin Oncol 2017; 35: 3198-3206.

50. Janssen A, Verkleij CPM, van der Vlist A et al. Towards better dose individualisation: metabolic phenotyping to predict cabazitaxel pharmacokinetics in men with prostate cancer. Br J Cancer 2017; 116: 1312-1317.

51. Chen N, Li Y, Ye A et al. Population Pharmacokinetics (PK) and Exposure-Neutropenia Relationship of nab-Paclitaxel (nab-P) in Patients With Solid Tumors. J Clin Oncol 2014; Abstract 2559.

52. Biakhov MY, Kononova GV, Iglesias J et al. nab-Paclitaxel in patients with advanced solid tumors and hepatic dysfunction: a pilot study. Expert Opin Drug Saf 2010; 9: 515-523.

53. Gradishar WJ, Krasnojon D, Cheporov S et al. Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. J Clin Oncol 2009; 27: 3611-3619.

54. Socinski MA, Manikhas GM, Stroyakovsky DL et al. A dose finding study of weekly and every-3-week nab-Paclitaxel followed by carboplatin as first-line therapy in patients with advanced non-small cell lung cancer. J Thorac Oncol 2010; 5: 852-861.

Hosted file

`TABLE-1.xlsx` available at https://authorea.com/users/313871/articles/444272-role-of-tdm-based-dose-adjustments-for-major-taxane-anticancer-drugs