Potential for improvement of docetaxel-based chemotherapy: a pharmacological review

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Since the introduction of docetaxel, research has focused on various approaches to overcome treatment limitations and improve outcome. This review discusses the pharmacological attempts at treatment optimisation, which include reducing interindividual pharmacokinetic and pharmacodynamic variability, optimising schedule, route of administration, reversing drug resistance and the development of structurally related second-generation taxanes.

Keywords: docetaxel; taxotere; taxanes; pharmacology

The anticancer drug docetaxel (Taxotere®) is approved for the treatment of patients with locally advanced or metastatic breast or non-small-cell lung cancer and androgen-independent metastatic prostate cancer. The recommended dose ranges from 60 to 100 mg m⁻² given as a 1-h intravenous (i.v.) infusion once every 3 weeks. An important limitation associated with docetaxel use is the unpredictable interindividual variability in efficacy and toxicity. Since its clinical introduction, attempts to improve docetaxel treatment have covered various areas: reducing the interindividual pharmacokinetic (PK) and pharmacodynamic (PD) variability, optimising schedule, route of administration and drug formulation, and reversing drug resistance. This review will discuss pharmacological strategies aimed to overcome the limitations of docetaxel therapy.

ALTERNATIVE SCHEDULES

When treated at a dose of 100 mg m⁻² once every 3 weeks, grade 4 neutropenia and febrile neutropenia occur in 75%, respectively 11%, of patients; a dose of 75 mg m⁻² only moderately reduces this incidence (http://www.taxotere.com). For patients with a poor performance status (PS), multiple comorbidities, decreased haematological reserves, a history of extensive pretreatment and severe toxicity, elderly patients and for patients whom treatment is palliative, a less toxic schedule seemed desirable. Therefore, a schedule involving weekly administration was developed. Numerous trials have evaluated this schedule; however, due to considerably different study populations and small sample sizes, comparisons of weekly vs 3-weekly efficacy were difficult. Recent randomised trials although demonstrate, for the approved indications, that the efficacy of weekly docetaxel is comparable to 3-weekly treatment (Engels and Verweij, 2005), the toxicity profiles are, however, distinctly different. With weekly docetaxel, acute toxicities, in particular myelosuppression, are mild and never dose limiting. In contrast, cumulative side effects are much more prominent. The most common and dose-limiting toxicity is fatigue/asthenia. These side effects can only be managed by reducing the dose or by shortening the schedule to 2–3 consecutive weekly infusions, followed by a 1-week rest interval. Other cumulative toxicities include alopecia, excessive tearing and nail disorders. Although the latter two side effects are usually mild, they are persistent, can lead to treatment discontinuation and have a substantial negative impact on a patient’s quality of life. Given the similar efficacy observed for the two schedules and the remarks on toxicity, it is reasonable to conclude that, at this point, 3-weekly docetaxel is still the standard and most convenient schedule. Treatment with weekly docetaxel should only be considered as an alternative for specific patient populations.

PK OPTIMISATION

The PK of total docetaxel are linear and independent of schedule. Nonetheless, there is a large interpatient variability in exposure (AUC) and drug clearance (Bruno et al, 1998; Hirth et al, 2000; Rudek et al, 2004; Baker et al, 2005; ten Tije et al, 2005). In a large population, PK/PD analysis variability in efficacy and toxicity was associated with variability in PK (Bruno et al, 1998); a 50% decrease in docetaxel clearance increased the odds of developing grade 4 neutropenia and febrile neutropenia 4.3-fold, respectively 3.0-fold. Subsequent studies have therefore focused on identifying factors, which most affect PK variability. Ultimately, reducing interpatient exposure variability should improve the risk–benefit ratio of docetaxel therapy.

Initially, the main predictors of total docetaxel clearance (variability) were body surface area (BSA), α1-acid glycoprotein (AAG), hepatic function (elevated alkaline phosphatase (ALKPH)
and transaminases levels) and age (Bruno et al., 1996). More recently, hepatic, cytochrome P450 isozyme 3A4 (CYP3A4) activity was also included (Hirth et al., 2000). The relevance of all these predictors to docetaxel dose optimisation has been further (re-) evaluated.

Normalisation of clearance for BSA reduces interindividual variability marginally (<2%), thus questioning the clinical relevance of BSA-based dosing (Rudek et al., 2004). Clearance was, however, significantly higher by 33% \( (P = 0.0029) \) for patients with BSA values \( >2.00 \text{ m}^2 \) compared to values \( <1.71 \text{ m}^2 \). Flat dosing, possibly differentiating for extremes of BSA \( (>2.00 \text{ m}^2) \), may be easier and just as precise and should be investigated prospectively.

In general, the unbound (i.e. free) fraction of any drug is phosphorylated in a dose-dependent manner. In contrast, doxorubicin and etoposide are metabolised by phase II enzymes (e.g. glutathione conjugation). Therefore, individualisation of docetaxel dosing (Rivory et al., 2005) is of importance, but also when selecting a suitable alternative drug. In addition to docetaxel, midazolam, erythromycin and dexamethasone are predictors of docetaxel clearance (Hirth et al., 2000; Goh et al., 2002; Puisset et al., 2004). As dexamethasone is routinely used as premedication, it may be more attractive as a probe drug than midazolam or erythromycin. Recently, individualised dosing based on the 24-h urinary metabolite of exogenous cortisol as phenotypic CYP3A probe was evaluated (Yamamoto et al., 2005). Individualised phenotypic dosing significantly reduced the interindividual PK variability compared to BSA-based dosing. Further larger studies, preferably comparing phenotyping strategies, are required to assess which probe is the best predictor of CYP3A activity. Nonetheless, phenotyping techniques have practical disadvantages (i.e. 24-h urine collection, radiotracer administration) that, may limit their applicability in common oncology practice.

The involvement of CYP3A in docetaxel elimination renders the drug potentially subject to a host of enzyme-mediated PK drug interactions with conventional drugs, complementary and alternative medicine and food constituents that interfere with CYP3A function or expression. Docetaxel has a narrow therapeutic window. Therefore, the risk of a PK interaction resulting in under- or overexposure, thereby modifying treatment outcome, is high. For several coadministered cytoxic agents, PK interactions with docetaxel are known and have led to dose or schedule recommendations. Interestingly, for the potent CYP3A inhibitor ketoconazole interaction data are inconsistent. Both trials observed large interindividual variability in the reduction of docetaxel clearance (Van Veldhuizen et al., 2003; Engels et al., 2004). Yet, in one trial was highly significant (Engels et al., 2004) whereas in the other, although docetaxel clearance decreased 2–4-fold in 25% of the patients, thus increasing the risk for severe neutropaenia, it was not (Van Veldhuizen et al., 2003). Efforts to reduce the interindividual PK variability through inhibition of CYP3A by ketoconazole have not been successful. No clinically relevant PK interaction has been observed between dexamethasone, a possible CYP3A inducer, and docetaxel (Hirth et al., 2000; Goh et al., 2002). Thus, there is no reason to abandon routine dexamethasone premedication. Clearly, the degree to which a PK interaction is clinically relevant, and requires an intervention depends upon the CYP3A-inducing or -inhibiting properties of the coadministered agent. Since specific dose adjustment recommendations are not available, concomitant administration of potent CYP3A-modulating comedication should generally be avoided.

Docetaxel is also a substrate for the ATP-binding cassette transmembrane transporter protein ABCB1 (P-glycoprotein (P-gp); MDR-1). ABCB1 is expressed in tumours and in normal tissues including the blood – brain – barrier (BBB), biliary tract and intestinal epithelium. Although ABCB1 plays a (major) role in the intestinal absorption and biliary excretion of orally administered substrates, its influence on the plasma PK of i.v. administered drugs, including docetaxel, is minimal to absent (van Zuylen et al., 2000). ABCB1 inhibition does, however, significantly influence the faecal disposition of docetaxel, reducing the amount of excreted unchanged drug (approximately 18-fold) without affecting plasma PK (van Zuylen et al., 2000), indicating that the effects of ABCB1
modulation on docetaxel PK cannot be evaluated when analysing only plasma. Monitoring plasma levels and PK-guided dose adjustments is referred to as therapeutic drug monitoring (TDM). At present, the use of TDM in oncology is limited. A prerequisite for TDM is that individual PK variability is less than interindividual PK variability, which is the case for docetaxel. For reasons of patient convenience and practicality, validated limited sampling strategies (LDS), requiring only two to four samples to characterise an individual PK profile (Bruno et al, 1996, 1998), should be used. LDS used in combination with a population PK model and Bayesian analysis allows individual PK parameters to be estimated with adequate precision while sampling and dosing times remain feasible and dosing decisions can be made without drug exposure. However, development of a suitable oral formulation has been impeded by low (≤10%) and highly variable oral bioavailability, due to the discussed extensive CYP3A-mediated first-pass metabolism and, to a lesser degree, to affinity for outward-directed transport by ABCB1 in the gastrointestinal tract. Modulating these elimination routes has therefore been a focus of research.

In wild-type mice, exposure to orally administered docetaxel was six-fold lower compared to Abcb1a/b knockout mice (Bardelmeijer et al, 2002). More importantly, the relative bioavailability increased from 4 to 183% by coadministration of the potent CYP3A (and poor ABCB1) inhibitor ritonavir, increasing systemic exposure 50-fold. Subsequently, a small PK study, in which patients were given oral docetaxel (75 mg m⁻²) with or without the ABCB1 and CYP3A inhibitor CsA, confirmed the observation (Malingre et al, 2001). In the presence of CsA, systemic exposure increased approximately seven-fold (from 0.37 ± 0.33 to 2.71 ± 1.81 mg h⁻¹ l⁻¹). When given 100 mg m⁻² docetaxel i.v. (without CsA), the resulting systemic exposure was 4.27 ± 2.26 mg h⁻¹ l⁻¹. Adjusted for the difference in dose, exposure following oral administration with concomitant CsA does not greatly differ from exposure after i.v. administration without CsA. The investigators performed a phase II trial with weekly oral docetaxel (100 mg) in combination with CsA (Kruijtzer et al, 2001). Interpatient PK variability, haematological toxicity and antitumour activity seem to be in the same range as for intravenous docetaxel. Oral docetaxel (100 mg) was also combined with OC144-093, a potent and selective oral ABCB1 inhibitor, and compared to 100 mg i.v. docetaxel (Kuppens et al, 2005). The relative oral bioavailability of docetaxel was 26 ± 8%, lower than previously observed after CsA coadministration and systemic exposure after i.v. docetaxel was administered three-fold higher compared to the oral application, despite the ABCB1 modulation. This indicating that CYP3A-mediated (first-pass) metabolism is the crucial process involved in the poor oral bioavailability of docetaxel.

Notwithstanding the fact that the oral bioavailability of docetaxel can be increased through pharmacologic modulation, the development of second-generation oral taxanes is likely to prevail.

SECOND-GENERATION DOCETAXEL-BASED TAXANES

Lately, structure-activity relationship studies have focused on identifying novel structurally related docetaxel analogues with increased cytotoxicity in resistant tumours, increased penetration across the BBB, decreased toxicity, oral bioavailability and higher water solubility, the latter facilitating drug formulation. Chemical modification of the core structure of docetaxel has resulted in docetaxel-based second-generation taxanes, which are in different phases of clinical development (Table 1).

Docetaxel is synthesised from 10-deacetylbaccatin III, a noncytotoxic precursor derived from the European yew tree. Research initially focused on modifications of this compound and yielded XRP9881 (RPR109881A) and XRP6258 (RPR116258A or TXD258). Both agents have comparable mechanism of action to docetaxel, and in tumour models sensitive to docetaxel, cytotoxic activity was similar to docetaxel (http://www.AventisOncology.com). Importantly, in vitro these agents are characterised by potent growth inhibitory activity in moderately and highly docetaxel-resistant cell lines, most probably based upon a substantially lower affinity for ABCB1. Furthermore, glioblastoma
models proved to be sensitive to these agents, suggesting penetration of the BBB. Phase I trials and early phase II studies with XRP9881 in metastatic breast cancer patients suggest adequate adequacy (Kurata et al., 2000). A differentiating feature of XRP6258 is its antitumour activity following oral administration, yet initial development is as intravenous administration. Both agents demonstrate marked interpatient variability in drug clearance, similar to docetaxel. Short-lasting and manageable neutropenia, fatigue and diarrhoea are the dose-limiting toxicities.

Several cytotoxic analogues derived from 14-$\beta$-hydroxy-docetaxel, a natural compound closely related to the core structure of docetaxel, have been evaluated. The most interesting is ortataxel (IDN5109, BAY 59-8862). Ortataxel has a free hydroxyl group compared to docetaxel-sensitive cell lines and human xenografts. It is more potent (20–30-fold) in human breast and colon cancer cell lines. *Drug resistance in KBV1 cells: eight-fold lower for MAC-321. *More potent (40–50-fold) in PC-6/VCR29-1 cell lines. DAB = deacetyl baccatin III; wks = weeks; iv. = intravenous.

### Table 1 Second-generation taxanes, structurally related to docetaxel

| Drug       | Nature of derivative                  | Cytotoxicity | Cytotoxicity | Developmental phase | Administration route(s) and recommended dose | Firm                  |
|------------|---------------------------------------|--------------|--------------|---------------------|---------------------------------------------|-----------------------|
| XRP9881    | 10-DAB                                | Similar      | Superior     | Phase II            | iv. 90 mg m$^{-2}$, q 3 wks                  | Aventis Pharma        |
| XRP6258    | 10-DAB                                | Similar      | Superior     | Phase I             | iv. 30 mg m$^{-2}$, q 3 wks also orally active | Aventis Pharma        |
| Ormtaxel   | 14-$\beta$-hydroxy-DAB                | Similar      | Superior$^a$ | Phase II            | iv. 75 mg m$^{-2}$, q 3 wks also orally active | Bayer/Indena          |
| MAC-321    | 10-deacetyl-7-propanoyl baccatin      | Similar      | Superior$^d$ | Phase II            | Oral 60 mg m$^{-2}$, q 3 wks                 | Wyeth-Ayerst          |
| DJ-927     | 7-deoxy-9-$\beta$-dihydro-9,10,10'-acetal taxane | Similar     | Superior$^a$ | Phase I             | Oral 27 mg m$^{-2}$, q 3 wks                 | Daichi Pharmaceuticals |

$^a$ Compared to docetaxel-sensitive cell lines and human xenografts. $^b$ Compared to docetaxel (highly and moderately) resistant cell lines and human xenografts (over)expressing ABCB-1. $^c$ More potent (20–30-fold) in human breast and colon cancer cell lines. $^d$ Drug resistance in KBV1 cells: eight-fold lower for MAC-321. $^e$ More potent (40–50-fold) in PC-6/VCR29-1 cell lines. DAB = deacetyl baccatin III; wks = weeks; iv. = intravenous.

### Table 2 Investigated areas of improvement of docetaxel-based chemotherapy

| Area of improvement          | Outcome                                                                 |
|------------------------------|-------------------------------------------------------------------------|
| Weekly schedules             | Alternative for patients at high risk for myelotoxic complications       |
| PK                           | Interindividual variability can be decreased by phenotypic individualised dosing |
|                              | Most predictive phenotyping probe controversial                          |
|                              | Practical disadvantages of phenotyping in oncology practice              |
| Reversal of resistance       | ABCB1-modulating agents insufficiently reverse (multi)drug resistance due to multiple resistance mechanisms |
| Oral administration          | Oral administration feasible upon pharmacologic modulation               |
|                              | Second-generation oral taxanes likely to prevail                         |
| Second-generation taxanes    | In clinical phase III development; also oral drugs                       |
| Alternative formulations     | Alternative formulations in preclinical phase                            |
| Pharmacogenomics and pharmacogenetics | Introduction not foreseen in near future                                 |

PK = pharmacokinetics; TDM = therapeutic drug monitoring.

### Conclusion

Continued research has offered us new and complementary insights on various aspects of docetaxel treatment, and yet, dose and schedule are still based on initial recommendations. Although this may sound disappointing, important steps forward have been made (Table 2) and research is ongoing. Besides the discussed areas of treatment optimisation, future investigations will focus on further development of preclinically promising alternative formulations, on pharmacogenomic-based treatment optimisation and on pharmacogenetic-based dose individualisation strategies. However, given the large, ethnically diverse population studies required, introduction of the latter two strategies is not expected in the foreseeable future. On shorter term, it is likely that TDM will be explored as it provides a potential tool for rapidly achievable treatment optimisation.

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