Drug Design, Development and Therapy

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REVIEW

Preclinical profile of cabazitaxel

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
13 October 2014
Number of times this article has been viewed

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Abstract: First-generation taxanes have changed the treatment paradigm for a wide variety of cancers, but innate or acquired resistance frequently limits their use. Cabazitaxel is a novel second-generation taxane developed to overcome such resistance. In vitro, cabazitaxel showed similar antiproliferative activity to docetaxel in taxane-sensitive cell lines and markedly greater activity in cell lines resistant to taxanes. In vivo, cabazitaxel demonstrated excellent antitumor activity in a broad spectrum of docetaxel-sensitive tumor xenografts, including a castration-resistant prostate tumor xenograft, HID28, where cabazitaxel exhibited greater efficacy than docetaxel. Importantly, cabazitaxel was also active against tumors with innate or acquired resistance to docetaxel, suggesting therapeutic potential for patients progressing following taxane treatment and those with docetaxel-refractory tumors. In patients with tumors of the central nervous system (CNS), and in patients with pediatric tumors, therapeutic success with first-generation taxanes has been limited. Cabazitaxel demonstrated greater antitumor activity than docetaxel in xenograft models of CNS disease and pediatric tumors, suggesting potential clinical utility in these special patient populations. Based on therapeutic synergism observed in an in vivo tumor model, cabazitaxel is also being investigated clinically in combination with cisplatin. Nonclinical evaluation of the safety of cabazitaxel in a range of animal species showed largely reversible changes in the bone marrow, lymphoid system, gastrointestinal tract, and male reproductive system. Preclinical safety signals of cabazitaxel were consistent with the previously reported safety profiles of paclitaxel and docetaxel. Clinical observations with cabazitaxel were consistent with preclinical results, and cabazitaxel is indicated, in combination with prednisone, for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with docetaxel. In conclusion, the demonstrated activity of cabazitaxel in tumors with innate or acquired resistance to docetaxel, CNS tumors, and pediatric tumors made this agent a candidate for further clinical evaluation in a broader range of patient populations compared with first-generation taxanes.

Keywords: XRP6258, CNS tumors, mCRPC, pediatric tumor, taxane resistance, xenograft

Introduction

Since the initial approval of paclitaxel (Taxol®; Bristol-Myers Squibb, New York City, NY, USA) in 1992,[1,2] the first-generation taxanes paclitaxel and docetaxel (Taxotere®; Sanofi, Paris, France) have altered the treatment paradigm for a wide variety of solid tumors, including breast, lung, prostate, gastric, and ovarian cancers.[3,4] Despite demonstrating significant antitumor activity as monotherapy or in combination regimens, clinical use of first-generation taxanes is frequently limited by innate or acquired resistance.[5–7] In prostate cancer, the majority of patients will eventually acquire resistance to docetaxel therapy.[8]

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Cabazitaxel (Jevtana®, Sanofi) is a novel second-generation semisynthetic taxane that was identified through a preclinical screen of 450 molecules derived from 10-deacetylbaccatin-III, with the aim of identifying a compound with activity in both taxane-sensitive and taxane-resistant tumors.[9] In the pivotal Phase III TROPIC study (NCT00417079), cabazitaxel combined with prednisone significantly extended overall survival compared with mitoxantrone plus prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel-containing regimen.[10] This led to cabazitaxel's approval in 2010, in combination with prednisone, for the treatment of patients with hormone-refractory metastatic prostate cancer who have previously received docetaxel-based therapy.[11,12]

This review article presents an overview of the preclinical properties of cabazitaxel, including its development, mechanism of action, antitumor activity in a range of in vitro and in vivo tumor models, pharmacokinetics (PK), and metabolic and toxicity profiles, as well as a summary of its clinical development.

Taxanes' mechanism of action and resistance mechanisms

Mechanism of action

Taxanes are microtubule inhibitors that induce cellular apoptosis through the stabilization of microtubules.[7] Microtubules are major components of the cytoskeleton, with critical roles in a variety of cellular processes including maintenance of cell shape, intracellular transport, cell signaling, and cell division.[7,13–15] It is this pivotal role in mitosis that makes microtubules a key cellular target for anticancer therapeutics.[7]

Microtubules are highly dynamic polymers of tubulin, continually undergoing assembly and disassembly within the cell. Taxanes inhibit microtubule function by binding to tubulin molecules, promoting their polymerization, and stabilizing microtubules. Suppression of microtubule dynamics leads to a block in mitosis and, ultimately, tumor cell death.[7,13,14]

Resistance mechanisms

Innate or acquired resistance to first-generation taxanes is frequently observed in different tumor types, resulting in treatment failure. Multiple potential mechanisms of taxane resistance have been identified in preclinical studies, and it is likely that several of these contribute to a resistant phenotype.[6,7,16–19]

Two mechanisms in particular have frequently been associated with the development of resistance to taxanes; however, it is worth noting that these are yet to be validated in patient samples, and their clinical relevance is not fully understood.[6,7] In preclinical studies, resistance commonly results from overexpression of members of the ATP-binding cassette family of transporters, of which P-glycoprotein, encoded by the multidrug resistance gene (ATP-binding cassette, sub-family B [MDR/TAP], member 1; *ABCB1*), is the best known.[20] Docetaxel and paclitaxel are substrates of P-glycoprotein, which acts as a drug efflux pump, decreasing intracellular drug levels and limiting cytotoxicity.[6,7,21,22] Resistance may also arise from spontaneously acquired mutations in tubulin, the cellular target of taxanes, resulting in changes to the tubulin binding site or altered microtubule dynamics.[6,7,23]

Clinical data suggest that additional mechanisms may contribute to taxane resistance in patients, including the altered expression of specific tubulin isotypes,[17] and expression or binding of microtubule-regulatory proteins,[18] loss of functional p53,[16] dysfunctional regulation of apoptotic and intracellular signaling (eg, HER2 overexpression),[19] and decreased tumor cell permeability.[24]

A number of potential predictive markers for taxane resistance have been identified, including the mitotic spindle checkpoint proteins Aurora A, BUBR1, MAD2, and synuclein-γ, and cell cycle proteins such as BRCA1;[18] however, conflicting results have been reported clinically.[24]

The development of alternative therapies able to overcome taxane resistance has been the focus of considerable attention.

Cabazitaxel development

Paclitaxel and docetaxel are semisynthetic derivatives of 10-deacetylbaccatin-III,[25,26] a natural paclitaxel precursor molecule that can be extracted easily and sustainably from the needles of the European yew tree (Figure 1).[26] In light of the clinical limitations that result from taxane resistance, a large-scale preclinical screening process was undertaken that aimed to identify a taxane derivative with equivalent efficacy to docetaxel in docetaxel-sensitive tumors, but greater activity than docetaxel in tumors that are docetaxel-resistant.[9]

In total, 450 candidate molecules were designed and generated for preclinical assessment, based on preclinical comparative structure–activity relationships of paclitaxel and docetaxel. Structural modifications initially focused on the side chain, as this was considered critical for potency, with subsequent modifications to other functional groups within the baccatin moiety.[9] The antitumor potential of the taxane derivatives was assessed over three stages: in vitro

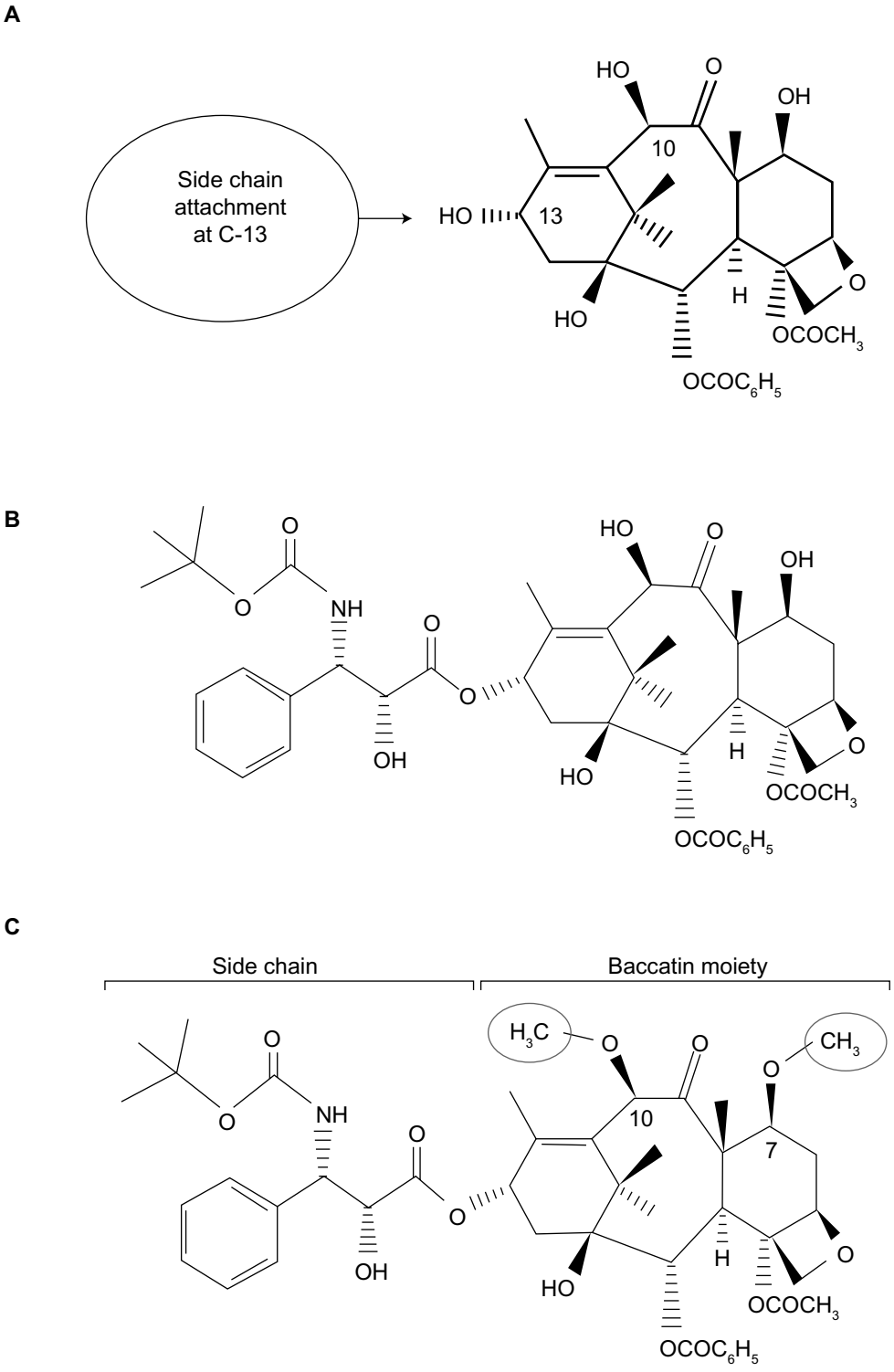

Figure 1 Chemical structure of 10-deacetylbaccatin III, docetaxel, and cabazitaxel.
Notes: (**A**) 10-deacetylbaccatin III. (**B**) Docetaxel. (**C**) Cabazitaxel.

activity against microtubules; in vitro activity in resistant cell lines; and in vivo activity in a tumor model.[24] The in vivo assessments included evaluation in a B16/TXT melanoma resistance model, which was developed through repeat exposure to docetaxel in mice bearing the docetaxel-sensitive B16 tumor, to allow evaluation of the taxane derivatives in a clinically relevant setting. This model mimics the clinical development of docetaxel resistance, where tumors initially respond to treatment, but develop resistance progressively over time.[24]

Initial attempts to modify the C-3′N–Boc and C-3′ phenyl groups within the side chain of docetaxel resulted in derivatives demonstrating either reduced in vitro potency or failure to improve activity in docetaxel-resistant cell lines (Figure S1).[9,27] Alterations to the C-2/C-4 and oxetane ring regions of the baccatin moiety were also evaluated, but failed to increase activity in the in vitro and/or in vivo resistance models.[9]

Cabazitaxel is a dimethyl derivative of docetaxel, bearing methoxy groups in place of hydroxyl groups at positions C-7 and C-10 (Figure 1).[9] In both docetaxel-sensitive and docetaxel-resistant cell lines, these structural alterations resulted in the greatest increase in in vitro potency, without significantly increasing toxicity at the maximum tolerated dose, in contrast to other C-7/C-10 modifications (Figure S1).[9] These modifications confer two advantages on cabazitaxel over docetaxel. Firstly, cabazitaxel, which is a P-glycoprotein substrate, has a higher lipophilicity than docetaxel (logP 3.9 versus 3.2),[9,28] resulting from the conversion of two secondary alcohols to more lipophilic ethers. This may result in increased cell penetration through passive influx, consequently leading to better activity in resistant cell lines where permeability of the plasma membrane may be altered.[24,28–30] This hypothesis was recently confirmed in an experiment in which drug uptake into MCF7 breast adenocarcinoma cells, which do not overexpress P-glycoprotein, was faster for cabazitaxel than for docetaxel.[31] Secondly, cabazitaxel has an improved ability to cross the blood–brain barrier (BBB) compared with docetaxel, offering potential benefit in patients with tumors of the central nervous system (CNS).[9,29,32,33]

Accordingly, during the screening of taxane derivatives and subsequent preclinical evaluation, cabazitaxel has demonstrated equivalent efficacy to docetaxel for stabilizing microtubules in vitro, greater potency than docetaxel in cell lines resistant to taxanes and other chemotherapeutics, activity superior to docetaxel in in vivo CNS disease models, broad-spectrum antitumor activity against a range of murine and human tumors, and in vivo activity in tumor models that are not sensitive, or are poorly sensitive, to docetaxel.[9,24,33]

In vitro activity

Microtubule stabilization

Cabazitaxel has shown equivalent potency to docetaxel for stabilization of microtubules in vitro. Both cabazitaxel and docetaxel induced a similar reduction in lag time for tubulin assembly (lag time to 50% aggregation 0–0.1 μmol/L) and stabilization of microtubules against cold-induced depolymerization (concentration producing 50% cell killing 0.1–0.25 μmol/L), indicating that cabazitaxel has a cytotoxic mechanism of action similar to that of docetaxel.[24]

Antiproliferative activity

In cell lines sensitive to chemotherapy, cabazitaxel had similar antiproliferative activity to docetaxel, achieving comparable 50% inhibitory concentration (IC_{50}) values across a range of murine and human cell types (0.004–0.041 μmol/L for cabazitaxel versus 0.008–0.079 μmol/L for docetaxel) (Table 1).[24]

In a panel of cell lines bearing acquired resistance to taxanes or to the chemotherapeutic agents doxorubicin, vincristine, or vinblastine, cabazitaxel showed markedly greater antiproliferative activity than docetaxel (IC_{50} ranged from 0.016–0.414 μmol/L for cabazitaxel versus 0.17–4.01 μmol/L for docetaxel).[24] Resistance factors, an indication of the difference in drug concentrations needed to inhibit resistant versus sensitive/parental cell lines, ranged from 2–10 for cabazitaxel and 5–59 for docetaxel in these P-glycoprotein-expressing cell lines (Table 1).[24]

In murine and human cell lines with resistance mechanisms other than P-glycoprotein overexpression, no cross-resistance to cabazitaxel was observed.[24]

In vivo activity

Plasma pharmacokinetics

The PK profile of cabazitaxel was evaluated in healthy and tumor-bearing mice, and healthy rats and dogs (Table 2) (Sanofi, data on file, 2010).

Absorption

Exposure to cabazitaxel increased with dose after single or repeated intravenous (IV) administration in all species. The increase in exposure was approximately dose-proportional in mice and more than dose-proportional in rats and dogs. No plasma accumulation was observed in mice, rats, or dogs after administration every 5 days, weekly, or every 3 weeks. No sex effect was observed in rats and dogs (Sanofi, data on file, 2010).

Distribution

Plasma protein binding of cabazitaxel was very high in mice (99.3%) and high in rats (95.5%), rabbits (91.4%), dogs (97.1%), and humans (91.9%) (Sanofi, data on file, 2010). Following a single IV administration, cabazitaxel exhibited a very large volume of distribution at steady state in both healthy (2.5–3.7 L/kg) and tumor-bearing mice (8.8 L/kg), in rats (22.7 L/kg), and in dogs (3.3–14.5 L/kg) (Sanofi, data on file, 2010).

Table 1 In vitro antiproliferative effects of cabazitaxel and docetaxel against sensitive and P-glycoprotein-expressing resistant cell lines

Cell line	Mean IC_{50}, µmol/L ± SD		Resistance factor[a]		*ABCB1* mRNA level[b]
	Docetaxel	Cabazitaxel	Docetaxel	Cabazitaxel	
P388 murine leukemia	0.079±0.004	0.041±0.017	–	–	–
P388/DOX	4.01±0.280	0.414±0.036	51	10	+++
P388 murine leukemia	0.039±0.012	0.013±0.005	–	–	–
P388/TXT	0.188±0.022	0.024±0.015	5	2	++
P388 murine leukemia	0.039±0.012	0.013±0.005	–	–	–
P388/VCR	0.227±0.038	0.024±0.003	6	2	++
HL60 human leukemia	0.031±0.004	0.022±0.010	–	–	–
HL60/TAX	0.250±0.110	0.060±0.029	8	3	++
Calc18 human breast adenocarcinoma	0.008±0.002	0.004±0.002	–	–	–
Calc18/TXT	0.170±0.040	0.016±0.004	21	4	++
KB human epidermoid carcinoma	0.042±0.021	0.035±0.026	–	–	–
KBV1	2.480±0.120	0.270±0.013	59	8	++++

Notes: Cells were incubated for 96 hours at 37°C in liquid medium with drugs at different concentrations. Viability was assessed by neutral red, with the mean of at least three results obtained. [a]Resistance factor = IC_{50} (resistant)/IC_{50} (parental) from the same experiment; [b]relative expression obtained from Northern blot experiments using the human *ABCB1* gene as probe. Reprinted by permission from the American Association for Cancer Research: Vrignaud P, Sémiond D, Lejeune P, et al. Preclinical antitumor activity of cabazitaxel, a semi-synthetic taxane active in taxane-resistant tumors. *Clin Cancer Res*. 2013;19:2973–2983, doi: 10.1158/1078-0432.CCR-12-3146.[24]
Abbreviations: *ABCB1*, *ATP-binding cassette, sub-family B, member 1*; Calc18/TXT, Calc18 human breast adenocarcinoma resistant to docetaxel; HL60/TAX, HL60 human leukemia resistant to paclitaxel; IC_{50}, 50% inhibitory concentration; KBV1, KB human epidermoid carcinoma resistant to vinblastine; P388/DOX, P388 murine leukemia resistant to doxorubicin; P388/TXT, P388 murine leukemia resistant to docetaxel; P388/VCR, P388 murine leukemia resistant to vincristine; SD, standard deviation.

The PK of cabazitaxel was also evaluated in mice bearing advanced-stage (>400 mm^3) mammary MA16/C adenocarcinomas.[24] Cabazitaxel was administered at the highest nontoxic dose (HNTD) of 40 mg/kg. Drug uptake into the tumor was both rapid and sustained, with maximum drug concentrations in tumor tissue reached within 15 minutes, and a 40-fold greater concentration of cabazitaxel within the tumor versus plasma after 48 hours (Figure 2).[24]

In this model, exposure to cabazitaxel was 1.6-times greater in the tumor compared with plasma during the 48 hours following treatment administration, and 2.9-times greater over the entire experimental period (168 hours). Concentrations of cabazitaxel above the cellular antiproliferative IC_{50} were sustained for 24 hours in the plasma and for 96 hours in tumor tissue.[24]

Brain distribution of cabazitaxel was assessed in mice, rats, and dogs. Cabazitaxel penetrated rapidly in the brain, with similar relative exposure between brain and blood across the different species.[33]

Metabolism

Cabazitaxel metabolism has been compared across multiple species. In vivo, cabazitaxel was the major circulating

Table 2 Pharmacokinetic parameters of cabazitaxel in normal and tumor-bearing mice, rats, and dogs

Species	Sex (M/F)	Dose (mg/kg)	Number of administrations	Infusion duration	C_{max} (ng/mL)	AUC (ng·h/mL)	CL (L/hr/kg)	Vss (L/kg)	$t_{1/2}$ (hr)
Normal mice	F	5	1	1 h	2,728	4,468	1.1	2.5	5.1
		10	1	1 h	4,805	11,211	0.9	2.7	7.4
		15	1	1 h	6,072	13,460	1.1	3.7	7.6
	F	5	5[a]	1 h	4,421	6,881	0.7	2.1	4.9
		10	5[a]	1 h	6,478	17,497	0.6	1.1	5.5
		15	5[a]	1 h	6,504	13,489	1.1	2.8	7.5
Tumor-bearing mouse	F	40	1	45 s	23,784	24,113	1.7	8.8	26.0
Rat	M	2.5	1	1 h	477	522	4.8	22.7	10.1
Dog	M	0.5	1	72–91 m	65	95	5.3	14.5	4.3
	F	0.5	1	72–91 m	97	101	5.2	12.8	3.2
	M	1	1	72–91 m	164	230	4.4	9.5	3.8
	F	1	1	72–91 m	360	417	2.5	3.3	3.0

Notes: [a]Every 3 weeks. Sanofi, data on file, 2013.
Abbreviations: AUC, area under the concentration–time curve; CL, clearance; C_{max}, maximum plasma concentration; F, female; M, male; $t_{1/2}$, half-life; Vss, steady-state volume of distribution.

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