SUMMARY

Cabazitaxel is a new taxane characterized by convenient administration, a favorable pharmacokinetic and safety profile and a decreased propensity for P-glycoprotein (Pgp)-mediated drug resistance. In preclinical studies cabazitaxel inhibited cell growth in a wide range of human cancer cell lines, including tumor models expressing Pgp. Phase I clinical trials established that the cabazitaxel side effect profile is similar to that reported for taxanes, with neutropenia and neuropathy being the most commonly reported toxicities. Further clinical studies have revealed that cabazitaxel is clinically active in women with taxane-resistant metastatic breast cancer and in men with metastatic castration-resistant prostate cancer previously treated with docetaxel. The TROPIC phase III trial concluded that, compared to mitoxantrone/prednisone, the combination cabazitaxel/prednisone conferred a statistically significantly longer overall survival in patients after treatment with a docetaxel-containing regimen, providing the basis for its FDA approval in 2010.

INTRODUCTION

Microtubules constitute one of the major components of the cytoskeleton of eukaryotic cells and are involved in many essential processes, including cell division, cell motility and intracellular transport. The basic building block of the microtubule is tubulin, which assembles in a head to tail arrangement to form a linear protofilament (1). Soluble tubulin exists as a heterodimer of one mole-
cule of β-tubulin and one molecule of β-tubulin (2). The subsequent formation of lateral interactions between 13 protofilaments results in their assembly into the wall of the cylindrical microtubules. Microtubules are highly dynamic structures that alternate between periods of growth and shrinkage through the addition or removal of tubulin subunits at the end of each protofilament (3). Highly dynamic microtubules are required for the proper attachment of chromosomes to the mitotic spindle and for the complex movements of chromosomes, including their proper alignment during metaphase and chromosome separation during anaphase (4, 5).

As microtubules are essential for several cell functions, they have been used as a target for a variety of anticancer drugs. At appropriate concentrations, some of these anticancer agents depolymerize spindle microtubules. In this regard, vinca alkaloids (e.g., vinblastine, vincristine and vinorelbine) have been successfully used for the treatment of acute leukemia, lymphomas, Kaposi’s sarcoma and breast and lung cancer (6-8). More recently, eribulin mesilate, a synthetic analogue of the marine macrolide halichondrin B, has demonstrated antitumor activity and improvement of overall survival in extensively pretreated breast cancer patients, with a manageable tolerability profile (9). In contrast, other agents increase spindle microtubule mass by inducing tubulin polymerization (10). The taxanes are a family of antineoplastic drugs including the natural compound paclitaxel and the hemisynthetic docetaxel, which are remarkably potent against various cancers (11). Taxanes bind to β-tubulin, interfering with dynamic instability by stabilizing microtubules. Taxanes are commonly used for the treatment of adjuvant and advanced breast cancer, non-small cell lung carcinoma (NSCLC) and castration-resistant prostate cancer. The family of epothilones (A to F) comprises a new class of microtubule-stabilizing agents. These macrolides have a similar mechanism of action to taxanes but a decreased propensity for drug resistance (12, 13). Ixabepilone, the most widely studied epothilone to date, was recently approved in the U.S. for use as monotherapy or in combination with capcitabine for the treatment of anthracycline- and taxane-pretreated or refractory metastatic breast cancer (12-14).

Depolymerizing or polymerizing agents inhibit cell proliferation by inducing a sustained mitotic arrest at the metaphase to anaphase transition, leading to the appearance of “lagging chromosomes”, mitotic blockade and cell death. The effects of microtubule-binding drugs are not specific to cancer cells; one of the most significant side effects of these drugs is neurotoxicity caused by the interaction between microtubules and the axonemal transport in the central and peripheral nervous system (10).

Despite the clinical success of tubulin-binding agents, toxicity (neutropenia and neurotoxicity), complex galenic formulations (use of Cremophor EL) and limited oral bioavailability restrict the clinical use of these agents in cancer therapy (15). Moreover, several resistance mechanisms have been described in cell line studies, although their clinical relevance is not fully understood (16-19). Thus, new tubulin-targeting antimitotic agents with better tolerability and efficacy against late-stage resistant tumors are urgently needed.

Cabazitaxel (Fig. 1) is a new semisynthetic and potent taxane derivative with interesting pharmacological properties. Cabazitaxel is partially synthesized as a single diastereoisomer from 10-deacetylbaccatin III, the major natural taxoid derived from the needles of various Taxus species. It has a wide in vitro and in vivo spectrum of antitumor action, including activity against human glioblastoma cells implanted in the brain of mice (20, 21). Moreover, as the compound is a weak substrate for P-glycoprotein (Pgp), it is also active in tumor models overexpressing this efflux protein. Cabazitaxel is currently being evaluated in the clinic.

**PRECLINICAL PHARMACOLOGY**

In a tubulin polymerization assay, cabazitaxel promoted the assembly of tubulin in vitro and stabilized microtubules against cold-induced depolymerization (IC_{50} = 0.12 fM). The cytotoxicity of cabazitaxel was compared with docetaxel in several murine and human cell lines. In docetaxel-sensitive cell lines, including P388 (murine

![Figure 1. Chemical structure of cabazitaxel.](image-url)
leukemia), HL-60 (human leukemia), KB (human epidermoid carcinoma) and Calc18 (human breast carcinoma), cabazitaxel showed potent antitumor activity comparable to docetaxel, with 50% tumor-inhibitory concentrations \((IC_{50})\) ranging between 3 and 29 ng/mL. However, the compound was also active in cancer cell lines with acquired resistance to docetaxel, including P388/DOX, P388/TXT, P388/VCR, HL60/TAX, Calc18/TXT and KBVI (22). Resistance factor ratios ranged from 1.8 to 10 for cabazitaxel, whereas comparable values were 4.8-59 for docetaxel. Furthermore, cabazitaxel showed greater cytotoxicity compared to docetaxel against the human colon adenocarcinoma Caco-2 cell line, which exhibits primary resistance to taxanes (23). In contrast, cabazitaxel did not present cross-resistance with cytarabine (Ara-C), cyclophosphamide, cisplatin, 5-fluorouracil, methotrexate, vincristine, melphalan (24).

In vivo, cabazitaxel had a broad spectrum of antitumor activity against murine tumors such as B16 melanoma, colon C38 and pancreas P03 (20-22). Cabazitaxel also showed a high complete regression rate in eight of nine human tumor cell lines evaluated in human tumor xenograft models, with long-term survivors observed in hosts bearing colon carcinoma HCT 116, HCT-8 and HT-29, lung carcinoma A549 and NCI-H460, pancreatic carcinoma MIA PaCa-2, head and neck cancer SR475, kidney carcinoma Caki-1 and prostate carcinoma DU145 cancers (21, 22). Prominent antitumor activity was also documented in human glioblastoma SF295 and U251 in s.c. implantation or orthotopic models, suggesting that the drug is able to cross the blood–brain tumor barrier and/or the blood–brain barrier (20, 22).

In Pgp-overexpressing models, cabazitaxel proved active against B16/docetaxel-resistant melanoma but not against Calc18/TXT and P388/VCR. Both toxicity and antitumor activity profiles appeared to be optimal on an intermittent day 1 and 5 dosing schedule (58 mg/kg) compared with daily \(\times 5\) or split 12 mg/kg three times daily for 5 days dosing, as the observed maximum tolerated dose (MTD) was 4.8-fold higher on the first administration schedule compared to the second (22).

**PHARMACOKINETICS AND METABOLISM**

An initial study evaluated the pharmacokinetics and distribution of cabazitaxel administered i.v. at 40 mg/kg to CH3/HeN female mice bearing s.c. mammary adenocarcinoma MA16/C. This dosage corresponded to the highest nontoxic dose of cabazitaxel that produced 80% complete tumor regression after a single administration. Maximum plasma concentrations (24 fg/mL) were reached at the end of a 45-s infusion. The elimination profile was biphasic, with a short initial phase (half-life: 0.84 h) and a longer terminal phase (half-life: 26 h). The volume of distribution at steady state was large (8.8 L/kg), suggesting that cabazitaxel was extensively distributed in tissues. The plasma clearance was 1.7 L/h/kg. A maximum tumor concentration of 6.2 fg/g was reached 15 min after dosing, indicating rapid drug uptake. Cabazitaxel tumor concentrations decreased slowly thereafter, but remained higher than those in plasma (25, 26).

As Pgp is widely expressed in the blood–brain barrier, the amount of drug accumulating in the brain under a variety of conditions (dose and infusion time, species and plasma concentration) was investigated using conventional in vivo pharmacokinetic techniques and in situ brain perfusion. A conventional pharmacokinetic approach first evaluated the disposition of radiolabeled cabazitaxel in the plasma and brain of mice (infused with 15, 30, 45 and 90 mg/m² for 45 s or 1 h) and rats (infused with 15 and 60 mg/m² over 2.3 min) (27). The brain concentrations of cabazitaxel in mice and rats were maximal from 2 min to 1 h after infusion and radioactivity was still detectable after 168 h. While the plasma concentration of cabazitaxel increased linearly with the infused dose, the brain content increased more than proportionately. The influence of Pgp-mediated efflux across the blood–brain barrier on the nonlinear accumulation of cabazitaxel was later evaluated. Radiolabeled cabazitaxel was perfused in the brain of wild-type- and Pgp-deficient Mdr1⁻/⁻ mice and rats. The results showed that the concentration of cabazitaxel in the brain of Pgp-deficient mice was 3-fold higher than in the brains of wild-type mice, indicating that cabazitaxel is extruded across the blood–brain barrier by Pgp. The observed efflux of cabazitaxel in wild-type animals was confirmed by inhibiting Pgp activity with verapamil in both rats and mice, suggesting that the efflux is mainly due to Pgp activity at the blood–brain barrier. Altogether, these results demonstrated that the nonlinear accumulation of cabazitaxel in the brain appears to occur by saturation of the Pgp transport at the rodent blood–brain barrier. According to these results, the brain drug exposure could be increased as long as the plasma concentrations exceed the concentration needed to saturate the Pgp. Rapid or short infusions that raise the plasma peak concentration above this threshold helped to increase the AUC for brain cabazitaxel 7.5-fold compared to slow infusion. This could have several advantages, such as overcoming Pgp efflux and allowing cabazitaxel to work.
more effectively by increasing the amount of antitumor agent delivered to the brain tumor environment. On the other hand, this saturation could have some disadvantages, as the nonlinear pharmacokinetics could increase the risk of toxicity.

Similar results were observed in dogs (25). Blood plasma and brain radioactivity of cabazitaxel were analyzed after i.v. administrations to dogs at 15 mg/m² over 80 min. Brain concentrations attained the maximum between 2 min and 1 h after infusion and were still detectable up to 24 h. Cabazitaxel accounted for at least 80% of the total radioactivity in plasma and brain. Brain to blood or plasma ratios increased more than proportionately as the doses were increased, indicating a possible saturation of Pgp-mediated transport.

At the clinical level, blood sampling for pharmacokinetic (PK) studies was done in 17 patients after administration of cabazitaxel (1.5-12 mg/m²) as a weekly 1-h infusion at the clinical level. Blood sampling for pharmacokinetic (PK) studies was done in 17 patients after administration of cabazitaxel (1.5-12 mg/m²) as a weekly 1-h infusion on days 1, 8, 15 and 22 every 5 weeks (28). Preliminary PK results indicated that AUC increased proportionately with the dose on day 1 at cycle 1. At 8.4 mg/m² the drug had a high total body clearance (50 L/h/m²), a very large volume of distribution (1424 L/m²) and a moderately long terminal half-life (31 h). There was a trend towards higher plasma levels at later sampling times on day 22 than on day 1 of cycle 1. However, no drug was detected at predose on day 22. A second phase I study analyzed the PK profile of cabazitaxel (dose levels of 10-25 mg/m²) administered as a 1-h infusion every 3 weeks (23). Cₘₐₓ and AUC₀₋₄₈ h values were estimated in 23 evaluable subjects. Compartmental PK modeling was done in 23 patients, with 9 and 2 patients having PK data from 2 and 3 consecutive courses, respectively. With this schedule, the plasma PK profile of cabazitaxel was similar to that of docetaxel and was characterized by dose proportionality in the dose range of the study and triphasic elimination in plasma. This was characterized by a rapid initial phase (mean t½ = 2.6 min), followed by an intermediate phase (t½ = 1.3 h) and a prolonged terminal phase (mean t½ = 77.3 h). Additional PK parameters indicated a high total body clearance (53.5 L/h/m²) and a large volume of distribution (2034 L/m²) compared to that of docetaxel. These parameters justified administration of cabazitaxel using an intermittent dosing schedule every 3 weeks. An analysis of PK data from individuals in whom plasma sampling was done during multiple courses showed no apparent changes in CL or AUC₀₋₄₈ h with repeated treatment.

SAFETY

When administered as a 1-h infusion during 4 consecutive weeks every 5 weeks (dose ranging from 1.5 to 12 mg/m²), the MTD was reached at 12 mg/m², at which level 2 of 6 patients experienced dose-limiting toxicities (DLTs) at cycle 1 (28). These DLTs consisted of grade 3 diarrhea. Other reported DLTs were grade 3 fatigue (two patients), grade 4 neutropenia lasting for more than 5 days (one patient) and febrile neutropenia (one patient). The main hematological toxicity was neutropenia, while nonhematological toxicities consisted of diarrhea, fatigue, mild hypersensitivity and neurosensory disturbances. No neurocentral toxicity was reported.

When administered as a 1-h infusion every 3 weeks, the principal DLT was neutropenia (23, 29). With this schedule, one patient experienced febrile neutropenia and two others showed prolonged grade 4 neutropenia at 25 mg/m². Moreover, at this dose level, grade 4 severe neutropenia was also observed in five other patients. In total, grade 4 events at 25 mg/m² occurred in 8 of 19 (42%) evaluable courses. Dose reduction due to hematological toxicity was done in four patients, with one patient requiring two dose reductions. The median time to absolute neutrophil count (ANC) nadir was 12 days. ANC recovery to grade 1 occurred in all patients by day 22. Thrombocytopenia occurred in only two patients (two courses, one grade 3 in course 5 and one grade 1 in course 1). There was only one single episode of grade 3 anemia. With this schedule, nonhematological toxicities included nausea, vomiting, diarrhea, neurotoxicity and fatigue (23). These toxicities were generally grade 1-2 in severity, except for a single patient who experienced grade 3 diarrhea in the first course at 15 mg/m². The event was short-lived and loperamide was administered for symptomatic management. Fatigue and neurosensory grade 1/2 symptoms were common at the 20 and 25 mg/m² dose levels. Neurosensory manifestations consisted principally of acral paresthesia and diminished deep tendon reflexes and discrimination of vibratory sensation. Cumulative neurotoxicity was not apparent in nine patients who received more than three courses at the two higher dose levels. Two patients experienced grade 1 hypersensitivity reactions, characterized by flushing, dizziness and chest tightness, which did not recur on retreatment in the absence of premedication. Alopecia was noted in two patients treated at the highest dose level. Neither onychodystrophy nor fluid retention was observed. The initiation of eight (8%) courses involving four patients was delayed due to unresolved nonhematological toxicities, specifically fatigue.
and fever in two patients, or at the patient’s request (two patients).

The safety profile was confirmed in a subsequent phase II study of cabazitaxel (1-h infusion every 3 weeks at 20 mg/m²) in taxane-resistant metastatic breast cancer patients (30). The most common grade 3/4 adverse events were neutropenia (73%) and leukopenia (55%), with a low febrile neutropenia rate (3%). Grade 3/4 anemia and thrombocytopenia were rare. Treatment-emergent grade III/IV nonhematological adverse events related to study treatment were also rare, with the most common including hypersensitivity (4%), fatigue (3%) and hemorrhagic cystitis (3%). No severe nausea, vomiting, neuropathy sensory, myalgia and fluid retention was observed. A total of four patients were withdrawn from the study due to adverse events: three patients for grade 1/2 alteration of liver function tests and one for a grade 4 allergic reaction. Two deaths were reported, one related to cabazitaxel and one to an unknown cause.

A phase III trial evaluated the activity of cabazitaxel 25 mg/m² plus prednisone 10 mg/day in men with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel (31). The most frequent grade 3/4 toxicity for the combination was neutropenia, observed in 81.7% of patients, with rates of febrile neutropenia of 7.5%.

Three safety studies are currently under way. The first is assessing the potential effect on Q-TcF interval (Q-TcF Fridericia) of cabazitaxel in cancer patients (32). Cabazitaxel (25 mg/m² by 1-h infusion) is administered on a day 1 every 3 weeks schedule. The secondary objectives of the study are to assess the effects of cabazitaxel on heart rate, Q-T, Q-TcF-Bazett’s correction, and Q-TcF (population-specific correction) intervals. The main period of the study consists of a maximum of 21-day screening phase and then evaluation during the first 2 treatment cycles with cabazitaxel. The second study is evaluating the MTD and safety of cabazitaxel when administered to advanced solid tumor patients with varying degrees of hepatic impairment (33). Other endpoints are the determination of PK variables and their correlation with pharmacodynamic safety parameters in order to guide prescribers with regard to dosing in this patient population. The study consists of a screening phase (maximum length of 21 days) and a treatment phase with 21-day study treatment cycles. The cut off date is when the last patient treated has completed cycle 1 and the subsequent 30 days’ follow up. Finally, a phase I study of cabazitaxel in combination with gemcitabine every 3 weeks in patients with advanced solid malignancies is ongoing (34). The primary endpoints of the study are the determination of the MTD and the DLT of the combination and the antitumor activity of the combination in an additional extended cohort of patients with advanced solid malignancies treated with the defined MTD, as assessed by objective response rate (ORR) according to the revised guideline for Response Evaluation Criteria in Solid Tumours (RECIST 1.1 criteria). This study will also evaluate PK parameters.

**CLINICAL STUDIES**

The encouraging spectrum of antitumor activity of cabazitaxel in experimental tumor models served as a rationale to begin clinical evaluation (Table I). Weekly and every-3-week schedules of administration of cabazitaxel were tested in phase I trials (23, 28). In the first study, cabazitaxel (1.5-12 mg/m²) was given on a weekly schedule as a 1-h infusion on days 1, 8, 15 and 22 every 5 weeks (28). Twenty-five patients were included. Most of the patients presented advanced breast cancer. The MTD was reached at 12 mg/m². A total of 48 cycles were administered with treatment duration ranging from 2 to 40 weeks. Two confirmed responses in breast cancer patients after taxoid failure were reported at the dose levels of 8.4 and 12 mg/m² and 12 stable diseases were observed in different indications, such as breast, gastric, ovary, cholangiocarcinoma, carcinoid tumor and NSCLC patients. At the time of the report, a dose level of 10 mg/m² was being explored.

A second study was carried out with cabazitaxel administered as a 1-h treatment every 3 weeks (dose levels ranging from 10 to 25 mg/m²). The study also sought to determine the MTD and the recommended dose and to seek preliminary evidence of anticancer activity. Twenty-five patients with advanced solid malignancies were treated with 102 courses of cabazitaxel across the 4 dose levels. These treatments were provided for subsequent courses, if clinically indicated. The median number of courses administered per patient was four (range: one to nine). Twenty-two (88%) patients had previously received chemotherapy, with 8 patients having received prior taxane-based therapy. All 25 patients (100%) were evaluable for safety and 24 patients (96%) were evaluable for efficacy. Because drug-related toxicities that exceeded grade 1 were not encountered at the first dose level, dose escalation proceeded to 15 mg/m² (23). At this dose level, one patient experienced grade 3 diarrhea.
during the first course and the cohort was then expanded to a total of six patients, with no additional DLT. At the next higher dose level (20 mg/m²), DLT was not observed in the initial three patients enrolled. However, at 25 mg/m², three of seven subjects experienced DLT, including protracted (> 5 days) grade 4 neutropenia and febrile neutropenia. Therefore, the rate of DLT exceeded the predefined limits of tolerability at the 25 mg/m² dose level. Objective antitumor activity included partial responses in two patients with metastatic prostate carcinoma, one unconfirmed partial response in a patient with a transitional cell carcinoma of the bladder and two minor responses in one patient each with prostate cancer and osteosarcoma. Twelve (48%) patients had stable disease as their best response for > 4 months. The study recommended a phase II dose of cabazitaxel on this schedule of 20 mg/m².

A multicenter phase II study assessed the activity of cabazitaxel in the treatment of taxane-resistant metastatic breast cancer (30). Originally, this study was designed as a three-arm trial comparing the relative efficacy and safety of cabazitaxel and larotaxel. However, due to a low recruitment during the first 6 months, the protocol was amended to a single-arm phase II study exploring the activity of cabazitaxel. Cabazitaxel was administered as a 1-h infusion on day 1 every 3 weeks at 20 mg/m². Intrapatient dose escalation to 25 mg/m² was permitted in patients who did not experience a significant adverse event during cycle 1. The primary endpoint was the ORR assessed according to RECIST guidelines. Of the enrolled and treated patients (N = 71; median age: 53 years) 4 were ineligible for the study, 2 were considered not to be resistant to taxanes, 1 did not have a histologically confirmed initial breast cancer and 1 had only one target lesion in a previously irradiated area. Six patients were not assessable for response due to the administration of concurrent treatments or early discontinuation due to adverse events or death. The per-protocol population therefore comprised 61 patients. In total, 345 cycles were administered, with a median of 4 cycles (range: 1-25 cycles). The median relative dose intensity was 0.98 (range: 0.60-1.14). The ORR was 14% (two complete and eight partial responses) with a median response duration of 7.6 months (range: 2.6-18.7 months). In addition, 18 patients (25%) had stable disease of more than 3 months’ duration. At a median follow-up of 20 months, the median time to progression was 2.7 months and the median overall survival was 12.3 months. The study concluded that cabazitaxel appeared to be active and well tolerated in this

<table>
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<th>Effect studied</th>
<th>Experimental model</th>
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<tr>
<td>Safety and tolerability</td>
<td>Phase I trial in advanced carcinoma patients</td>
<td>Cabazitaxel was given as a 1-h infusion during 4 consecutive weeks every 5 weeks. Administration was well tolerated with peripheral sensory neuropathy, neutropenia and diarrhea as the most common adverse events. The MTD was 12 mg/m²</td>
<td>28</td>
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<td>23, 29</td>
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<td>Efficacy</td>
<td>Phase II trial in patients with taxane-resistant metastatic breast cancer</td>
<td>Of 61 reported patients, responses were observed in 10 (2 CR and 8 PR)</td>
<td>30</td>
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<tr>
<td>Efficacy</td>
<td>Phase III trial in men with metastatic castration-resistant prostate cancer previously treated with docetaxel</td>
<td>Patients receiving cabazitaxel and prednisone demonstrated longer overall survival compared to those receiving mitoxantrone and prednisone (15.1 months vs. 12.7 months, respectively; hazard ratio [HR]: 0.70; 95% confidence interval [CI]: 0.59-0.83; P &lt; 0.0001)</td>
<td>31, 35</td>
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MTD, maximum tolerated dose; CR, complete response; PR, partial response.
group of taxane-resistant metastatic breast cancer patients.

Finally, cabazitaxel was evaluated in the TROPIC trial. This phase III study was designed to evaluate the efficacy and safety of cabazitaxel in men with mCRPC previously treated with docetaxel (31, 35). In this study, 775 men progressing during or after docetaxel (cumulative dose $\geq 225$ mg/m$^2$) were randomized to receive 10 mg/day of prednisone orally with either mitoxantrone (infusion of 12 mg/m$^2$ every 3 weeks; $n = 377$) or cabazitaxel (infusion of 25 mg/m$^2$ every 3 weeks; $n = 378$). The primary endpoint was overall survival; secondary endpoints included progression-free survival, response rate, pain measures and safety. The study had 90% power to detect a 25% reduction in the hazard ratio (HR) for death (one-sided $\alpha = 0.05$) after 511 events occurred. Median follow-up was 12.8 months. Median number of treatment cycles was six for cabazitaxel/prednisone and four for mitoxantrone/prednisone. In the primary analysis, patients receiving cabazitaxel/prednisone demonstrated a statistically significantly longer overall survival compared to mitoxantrone/prednisone (15.1 months vs. 12.7 months, respectively; HR: 0.70; 95% confidence interval [CI]: 0.59-0.83; $P < 0.0001$). Progression-free survival (composite of tumor, prostate-specific antigen [PSA], or pain progression; or death) and response rates for tumor assessments by RECIST, PSA response and PSA progression were also statistically significantly in favor of the cabazitaxel-treated group. The investigator-assessed tumor response rate was 14.4% for patients in the cabazitaxel group compared with 4.4% for patients in the mitoxantrone group. The study concluded that, compared to mitoxantrone/prednisone, the combination of cabazitaxel with prednisone conferred a statistically significantly longer overall survival in patients with mCRPC progressing after treatment with a docetaxel-containing regimen.

CONCLUSIONS

The clinical success of taxanes in cancer treatment has stimulated the search for new analogues with a similar mode of action and higher activity. Cabazitaxel is a new semisynthetic and potent taxane derivative with interesting pharmacological properties. Cabazitaxel displays some different qualities compared to other taxanes. On one hand, the compound is a weak substrate for Pgp, and thus it is also active in tumor models overexpressing this efflux protein in vitro and in animal models. On the other hand, cabazitaxel may be able to cross the blood–brain barrier in humans, as it showed interesting activity in human glioblastoma cells implanted in the brain of mice. Finally, its solubility is similar to that of docetaxel, allowing a Cremophor-free formulation, and therefore premedication to avoid hypersensitivity reactions is not needed.

Due to its potency in preclinical studies in taxane-sensitive and -resistant models, cabazitaxel progressed to clinical trials. These clinical studies have established that the side-effect profile of cabazitaxel is similar to that reported for other taxanes, with neutropenia and neuropathy being the most commonly reported toxicities. In terms of clinical activity, the results observed in the phase III TROPIC trial, where the combination of cabazitaxel and prednisone conferred a significantly longer overall survival in patients with metastatic prostate cancer progressing after treatment with a docetaxel-containing regimen, indicated that cabazitaxel is an attractive candidate to benefit a number of patients presenting taxane-resistant cancer disease.

DISCLOSURES

Dr. Galmarini is presently an employee of PharmaMar. Dr. Bouchet states no conflicts of interest.

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