Cabazitaxel: More Than a New Taxane for Metastatic Castrate-Resistant Prostate Cancer?

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Abstract

The taxanes are recognized as a major class of chemotherapeutic agents; however, mechanisms of innate and acquired resistance can limit their usefulness. Cabazitaxel, a novel taxane with microtubule-stabilizing potency similar to docetaxel, exhibits activity against tumor cell lines resistant to paclitaxel and docetaxel. Cabazitaxel showed linear pharmacokinetics and a terminal elimination half-life comparable with that of docetaxel, findings which support dosing as a single infusion in three-week treatment cycles. Dose-ranging studies recommended doses of 20 or 25 mg/m^2 every three weeks. Antitumor activity was shown in patients with advanced cancer and chemotherapy failure (including taxane failure). Other early studies investigated the efficacy of cabazitaxel in pretreated metastatic breast cancer, either as a single agent or in combination with capecitabine. Objective antitumor response rates of up to 24% and sustained tumor stabilizations were also observed. The TROPIC phase III study, conducted in patients with metastatic castrate-resistant prostate cancer previously treated with docetaxel, established cabazitaxel as the first chemotherapeutic agent to offer a survival advantage in this patient population. Across these studies, the dose-limiting hematologic toxicity was neutropenia (including febrile neutropenia), usually controllable with colony-stimulating factor/granulocyte-colony stimulating factor support. *Clin Cancer Res; 18(24); 6574–9. ©2012 AACR.*

Introduction

Cabazitaxel [Jevtana, (Sanofi-Aventis); formerly XRP6258, RPR 116258A, and TXD258] is a taxane that recently received both U.S. Food and Drug Administration (FDA) and European Medicines Agency approval as a therapy for patients with metastatic hormone-resistant prostate cancer (mHRPC) previously treated with a docetaxel-containing regimen [package insert, Jevtana (Sanofi-Aventis)]. Like other taxanes, cabazitaxel exerts its cytotoxic effect through mitotic arrest at the metaphase–anaphase transition, leading ultimately to cell death (1–3). The most widely used taxanes, paclitaxel and docetaxel, have a documented affinity for MDR proteins, which counts as a major mechanism of either innate (primary) or acquired resistance (3, 4). A further disadvantage is their limited ability to cross the blood–brain barrier (BBB), with the central nervous system (CNS) consequently acting as a potential sanctuary for recurrence (5). In contrast, cabazitaxel showed poor recognition by MDR proteins, as well as penetration of the BBB and, therefore, may offer the potential for more durable responses and a wider antitumor spectrum.

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Preclinical Studies

Cabazitaxel was identified from a screen for taxanes with improved pharmacologic properties, including a low affinity for MDR proteins (6, 7). Structurally, it is a dimethoxy derivative of docetaxel. Cabazitaxel showed potent *in vitro* and *in vivo* activity against a range of docetaxel-sensitive and -resistant tumor cell lines, with IC_{50} ranging from 0.003 to 0.029 µmol/L (6, 8, 9). Notably, cabazitaxel was significantly more potent than docetaxel in cancer cell lines with MDR-mediated acquired resistance to docetaxel (9). In preclinical studies, intermittent dosing was superior to daily or split dosing for both antitumor activity and toxicity profile (6, 8–10). A feature that distinguishes cabazitaxel from other taxanes is its ability to penetrate the BBB in rodents and may also be due to its low affinity for MDR proteins (11, 12). Moreover, cabazitaxel showed antitumor activity in mice bearing orthotopic glioblastoma xenografts (13).

Early Pharmacokinetic and Dose-Ranging Studies

In the first dose-finding and pharmacokinetic study, 25 patients received cabazitaxel administered as a 1-hour infusion every 3 weeks (9, 14). Doses were escalated from 10 to 25 mg/m^2 on the basis of toxicities observed, but also, in part, on the basis of pharmacokinetic parameters. At the 25 mg/m^2 dose, grade 4 neutropenia was experienced by 2 patients and febrile neutropenia by 1 patient (9). In addition, 1 patient developed grade 3 diarrhea, the most severe nonhematologic toxicity in this study. The

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Figure 1. Phase I cabazitaxel pharmacokinetic data (9). Representative plasma total cabazitaxel concentration-time profile of 1 patient treated with a 1-hour intravenous infusion at 20 mg/m^2 [○, observed value; —, fitted value (3-compartment model)]. Reprinted from Mita et al. (9).
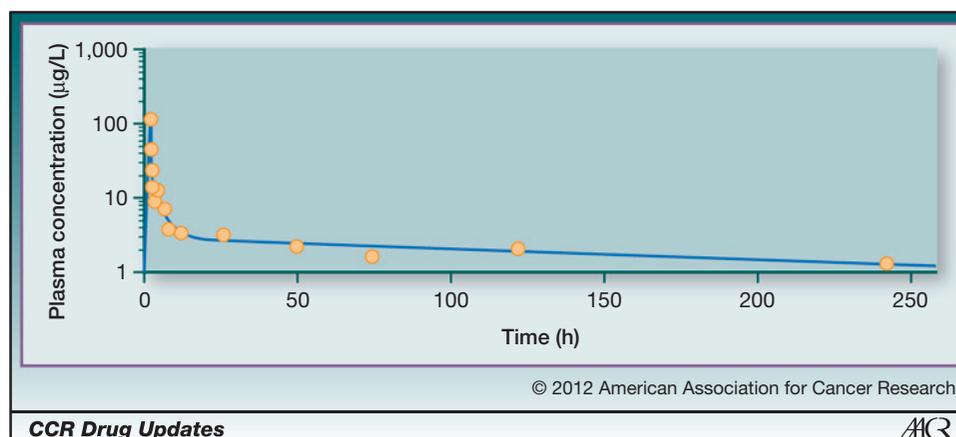
maximum-tolerated dose (MTD) was, therefore, established as 25 mg/m^2, and the recommended dose as 20 mg/m^2. Except for 1 episode each of grade 3 thrombocytopenia and grade 3 anemia, other hematologic toxicities were mild to moderate in severity. Nonhematologic toxicities including nausea, vomiting, diarrhea, neurotoxicity, and fatigue were also generally mild to moderate and manageable.

The pharmacokinetics of cabazitaxel showed dose-proportional drug exposure. Main pharmacokinetic parameters are shown in Table 1. The pharmacokinetic profile was best described by a triphasic model, with a rapid initial decline [mean half-life $(t_{1/2})_{\lambda 1} = 2.6 \pm 1.4$ minutes] followed by an intermediate phase (mean $t_{1/2\lambda 2} = 1.3 \pm 0.6$ hours) and a prolonged terminal phase (mean $t_{1/2\lambda 3} = 77.3 \pm 45.5$ hours; Fig. 1). Anticancer activity was seen in several patients, including 2 partial responses (PR) and 1 minor response in patients with mHRPC. Interestingly, 1 of the PRs occurred in a docetaxel-refractory mHRPC. One patient with bladder carcinoma experienced an unconfirmed PR, and 1 patient with osteosarcoma showed a minor response. In addition, 12 other patients (48%) had stable disease for 4 or more months (9).

Preliminary data from the first 16 patients enrolled in a second phase I study of cabazitaxel, with dosing every 3 weeks, conducted in France have also been reported (15). Cabazitaxel was administered as a 1-hour infusion every 3 weeks in an accelerated escalating-dose protocol (16). The MTD was identified as 30 mg/m^2 when 3 of 5 patients experienced dose-limiting toxicities (DLT) consisting of grade 4 neutropenia either exceeding 5 days (2 patients), or complicated by fever (1 patient). One patient at the 30 mg/m^2 dose died of neutropenic sepsis in cycle 3. A potential recommended dose of 25 mg/m^2 was to be confirmed by enrollment of additional patients, which was ongoing at the time of the report. Cabazitaxel pharmacokinetics were consistent with the findings of the earlier study. Preliminary efficacy data showed a minor response in 1 patient with non–small cell lung cancer (NSCLC), and stable disease in 3 patients with colorectal cancer.

Another phase I study investigated cabazitaxel administered as a weekly 1-hour infusion for 4 consecutive weeks on 5-week cycles (17). Patients were treated with cabazitaxel doses ranging from 1.5 to 12 mg/m^2. The MTD was 12 mg/m^2, at which 2 of 6 patients experienced DLTs in cycle 1, including 1 case of grade 3 diarrhea. Two confirmed PRs were seen in metastatic breast cancer patients with taxane-refractory disease, and 12 patients showed stable disease. Treatment duration ranged from 2 to 40 weeks. Pharmacokinetic results indicated dose proportionality

Table 1. Pharmacokinetic parameters across 4 studies that included pharmacokinetic determinations

Study	Phase I ($N = 25$); Fumoleau and colleagues (17)	Phase I ($N = 16$); Lortholary and colleagues (15)	Phase I ($N = 25$); Mita and colleagues (9)	Phase I/II ($N = 33$); Villanueva and colleagues (19)
Locations	France, Spain	France	United States	Europe
Agent(s), target	Cabazitaxel, solid tumors	Cabazitaxel, solid tumors	Cabazitaxel, solid tumors	Cabazitaxel + capecitabine, breast cancer
Dose proportionality	No deviation within range 1.5–12 mg/m^2	Not reported	No deviation within range 10–30 mg/m^2	Not tested
Half-life, h	31	30–45	77	79
Plasma clearance, L/h/m^2	50	33–56	27	34
Volume of distribution, L/m^2	1,424	500–2,000	2,084	2,335

consistent with the findings of the 3-week administration schedules. The terminal $t_{1/2}$ was relatively long (31 hours), and there was a trend for higher plasma levels of the drug at late sampling times on day 22 of cycle 1 compared with day 1. The significance of this finding is unclear, as no drug was detected predose on day 22, but together with the long $t_{1/2}$ shown, it might be conducive to less frequent dosing.

A Phase III Study in mHRPC (TROPIC)

The TROPIC study was a registration trial conducted in patients with mHRPC whose disease progressed following docetaxel treatment (18). Interestingly, the study was initiated in the absence of a specific phase II study in patients with mHRPC, and was supported by robust preclinical and phase I data, as well as by the limited treatment options for the indication at that time. Patients were randomized to either cabazitaxel 25 mg/m^2 or mitoxantrone 12 mg/m^2, both plus prednisone 10 mg/d. In the intent-to-treat analysis, the median overall survival time was 15.1 months in the patients receiving cabazitaxel and 12.7 months in those receiving mitoxantrone. The hazard ratio of cabazitaxel treatment was 0.70 [95% confidence interval (CI), 0.59–0.83, $P < 0.0001$], translating to a 30% relative reduction in risk of death compared with the mitoxantrone regimen. Progression-free survival was double in the cabazitaxel arm compared with the mitoxantrone one (2.8 months vs. 1.4 months, $P < 0.0001$), and significantly more patients in the cabazitaxel group had prostate-specific antigen response (39.2% vs. 17.8%, $P = 0.0002$) and tumor response (14.4% vs. 4.4%, $P = 0.0005$; ref. 18).

In the TROPIC study, neutropenia, leukopenia, and anemia were the most common hematologic adverse events, each having more than 90% all-grade incidence in the cabazitaxel arm. Similarly, neutropenia (82%), leukopenia (68%), and anemia (11%) were the most frequent grade 3 or more hematologic adverse events. The most common grade 3 or more nonhematologic adverse events were diarrhea (6%), fatigue (5%), asthenia (5%), and back pain (4%; ref. 18).

Studies in Patients with Metastatic Breast Cancer

Two phase I–II/II trials of cabazitaxel in patients with metastatic breast cancer progressing after taxane and anthracycline-based therapies have been reported (19, 20). The first of these was a dose-escalation study of cabazitaxel 1-hour infusion on day 1 in combination with capecitabine dosed orally twice daily on days 1 to 14 (19). Thirty-three patients were enrolled at 3 dose levels: cabazitaxel/capecitabine 20/825 mg/m^2; 20/1,000 mg/m^2; and 25/1,000 mg/m^2, respectively. The 25/1,000 mg/m^2 dosing resulted in an excessively high level of grade 4 neutropenia. A dose level of cabazitaxel 20 mg/m^2 + capecitabine 1,000 mg/m^2 was established as the MTD. Twenty-one patients were treated in an expansion cohort at MTD for a range of 2 to 13 cycles (median 5 cycles). At this dose, the most frequent grade 3 or more toxicity was neutropenia (57.1% of patients). The most frequent grade 3 to 4 nonhematologic adverse events were asthenia/fatigue, hand-foot syndrome, and dyspnea (9.5% each). There was no elevated incidence of commonly observed toxicities of the 2 drugs, such as diarrhea or mucositis, as well as no novel toxicities that could be attributed to the combination of cabazitaxel and capecitabine.

The objective response rate (ORR) at the MTD was 23.8% (95% CI, 8.2–47.2%), including 1 complete remission (CR) and 4 PRs. Median duration of response was 3.1 months and median time to progression was 4.9 months (95% CI, 2.7–not reached). In addition, 52% of patients at this dose experienced stable disease.

Pharmacokinetic parameters for cabazitaxel were generally similar to those of the other studies with cabazitaxel monotherapy (Table 1). The mean area under the curve (AUC) in the patients receiving cabazitaxel 20 mg/m^2 + capecitabine 1,000 mg/m^2 was 8,870 ng/h/mL for capecitabine and 495 ng/h/mL for its active metabolite, 5-fluorouracil (5-FU). Capecitabine exposure was somewhat higher than that previously described in the literature (21) due to 4 patients with particularly high AUC values. Mean AUC of 5-FU was consistent with previously reported values (22–24).

Cabazitaxel monotherapy has been studied in a multicenter phase II study in patients with metastatic breast cancer and prior failure of taxanes (20). Cabazitaxel was administered at 20 mg/m^2 every 3 weeks, with an option to increase the dose to 25 mg/m^2 if no severe toxicities occurred in cycle 1. Thus, 28% of the patients were able to receive the higher dose from cycle 2. The 67 eligible patients received between 1 and 25 cycles of cabazitaxel (median 4 cycles). Neutropenia was the most common grade 3 to 4 toxicity (73% of patients, including 49% of patients with grade 4). However, neutropenic infection and febrile neutropenia occurred only in 3% and 4% of patients, respectively. The most common nonhematologic adverse events were fatigue (35%), nausea (32%), diarrhea (30%), vomiting (18%), myalgia (17%), and sensory neuropathy (17%). The most common grade 3 to 4 nonhematologic adverse events were hypersensitivity, fatigue, and hemorrhagic cystitis in 4%, 3%, and 3% of patients, respectively.

The ORR with cabazitaxel was 14%, including 2 CRs. The median response duration was 7.6 months (range 2.6 to >18.7 months), and the time to progression was 2.7 months (95% CI, 1.45–4.07). An additional 38% of patients had stable disease for longer than 3 months.

Discussion

Following the initial enthusiasm generated by the clinical success of paclitaxel and docetaxel, their inherent shortcomings in terms of both toxicities and resistance to treatment quickly became apparent. This led to the development of a plethora of novel taxane analogs with the hope of overcoming the limitations of existing taxanes (25–30). Criteria for improvement compared with paclitaxel and docetaxel have been clearly defined and include more

prominent, well-documented antitumor activity in potentially sensitive neoplasms, compelling evidence of activity in paclitaxel and/or docetaxel-refractory malignancies, or improved toxicologic, pharmacologic, and/or pharmaceutical properties (31). To date, cabazitaxel is the only novel taxane to satisfy any of these criteria in a controlled trial by improving the survival in patients with mHRPC with docetaxel failure. Thus, cabazitaxel has established itself as a valuable new treatment option and may potentially have broader application than its current indication. A careful analysis of its safety, efficacy, and pharmacologic profiles emerging from the early and ongoing trials will be key in its further development.

The main DLT of cabazitaxel is neutropenia, which is manageable with early intervention and proactive patient monitoring. Indeed, most grade 3 to 4 neutropenia in the reported studies did not exceed 4 days in duration. Neutropenic infection and febrile neutropenia have been uncommon and their incidence is comparable with what is observed for docetaxel (package insert, Taxotere, Sanofi Aventis). However, one cannot overlook the risk of serious (and occasionally fatal) neutropenic complications consistently reported in the trials with cabazitaxel. Patient education and rapid access to specialized care remain critical for the management of neutropenic complications. Prophylactic treatment with granulocyte colony-stimulating factor (G-CSF) in high-risk patients should be thoroughly considered, as recommended by the American Society of Clinical Oncology (ASCO) guidelines and outlined in the prescribing information brochure. Lower doses of cabazitaxel (20 mg/m^2) seem to be associated with less hematologic toxicity, and may be considered in some patients. The incidence and severity of other hematologic toxicities seemed to be low and not of major clinical concern.

Nonhematologic side effects such as fatigue, nausea, and diarrhea have only rarely reached grade 3. The incidence of diarrhea following therapy is unique for cabazitaxel compared with other taxanes, and may be a consequence of enteric accumulation (32). Although diarrhea seemed manageable with loperamide, caution needs to be exercised as the combination of diarrhea and neutropenia is known to significantly increase treatment-related mortality (33). Importantly, the indicated dose of cabazitaxel has not been linked, to date, with any clinically worrisome cumulative toxicities, including neurotoxicity, which positions cabazitaxel favorably versus other taxanes.

On the basis of the toxicities observed, some early trials recommended a cabazitaxel dose of 20 mg/m^2; nevertheless, there was some evidence of therapeutic advantages of the 25 mg/m^2 dose (as used in the TROPIC study). Therefore, it seems likely that the approved dose of 25 mg/m^2 is feasible in most patients, with additional precautions about the patients at higher risk for febrile neutropenia, especially if associated with diarrhea. Two ongoing phase III trials are designed to compare these 2 doses for safety and antitumor efficacy in mHRPC: FIRSTANA in chemotherapy-naïve patients, and PROSELICA in patients previously treated with docetaxel.

Cabazitaxel was shown to have linear pharmacokinetics over the studied doses range (9, 15, 17). In the population pharmacokinetic analysis, body surface area (BSA) was identified as a significant covariate, with plasma clearance of cabazitaxel directly correlated with BSA, which supports the adjustment of dose to BSA (Cabazitaxel Investigator Brochure, Sanofi-Aventis). The pharmacokinetic profile is consistent with a 3-compartment model characterized by rapid initial and intermediate phases (population $t_{1/2}$ 4.4 minutes and 1.6 hours, respectively) and a long terminal phase ($t_{1/2}$ 95.1 hours). The long $t_{1/2}$ supports the use of the every 3-week dosing regimen in further clinical studies. Cabazitaxel rapidly cleared from plasma and exhibited a very high volume of distribution, suggesting that it was rapidly taken up by normal tissues and tumors. Both the volume of distribution and terminal $t_{1/2}$ seemed greater than those previously reported for docetaxel (34). It is possible that the highly sensitive assay for cabazitaxel (lower limit of detection, 1 ng/mL) may have contributed to this difference. However, the elimination of cabazitaxel may be slower than that of other taxanes, potentially due to the presence of a deep compartment and/or other reasons to be further clarified. Although the variability between patients in pharmacokinetic parameters, most notably AUC, seemed to be moderate, significant variations could occur in patients with decreased activity of CYP3A4 and CYP3A5, leading to slow cabazitaxel clearance and potentially increased side effects. Studies aimed to reduce the toxicity risks, including pharmacogenomic studies of certain single-nucleotide polymorphisms of CYP3A4 and CYP3A5 genes, as well as drug–drug interaction studies of chemical compounds that could affect cabazitaxel clearance, are underway.

Cabazitaxel activity against a range of different tumors was apparent in phase I studies, and may justify further clinical development for paclitaxel- and docetaxel-refractory malignancies. The antitumor activity observed in the TROPIC trial is particularly encouraging, especially considering the numerous failed attempts in this indication with either cytotoxics and/or targeted therapies (35–37). On the basis of these results, cabazitaxel is currently being compared to docetaxel as a first-line therapy for mHRPC in the FIRSTANA trial. In patients with heavily pretreated breast cancer, with evidence of drug resistance (e.g., treatment progression on, or shortly after, previous therapy), the ORRs seen with cabazitaxel were comparable with those with other active agents used in this setting (38–43). Minor responses and prolonged stable disease occurred in more than half the patients, which may also be evidence of clinical benefit in these patient populations. Further trials exploring the role of cabazitaxel for the treatment of patients with breast cancer are either planned or ongoing. As of March 2012, there were 29 studies listed on ClinicalTrials.gov exploring cabazitaxel in a plethora of malignancies potentially sensitive to taxanes, including head and neck, urothelial, gastroesophageal, small cell, and NSCL carcinomas.

Finally, although cabazitaxel may penetrate the BBB, patients with active CNS metastases have been excluded from phase I, II, and III studies, and specific trials in primary CNS malignancies have not been conducted to date (11, 13). Therefore, additional trials will be needed to determine the clinical significance of the ability of cabazitaxel to cross the BBB.

Conclusion

Cabazitaxel showed manageable safety profile, objective responses, and evidence of clinical benefit in patients with malignancies resistant to other taxanes, including prostate and breast cancer. Early clinical studies and the phase III TROPIC trial showed the importance of cabazitaxel in mHRPC. The data from phase I to II studies in patients with solid tumors support the design of further studies to define the antitumor spectrum of cabazitaxel.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: A.C. Mita, R. Figlin, M.M. Mita
Development of methodology: A.C. Mita, R. Figlin
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.C. Mita, R. Figlin
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.C. Mita, R. Figlin, M.M. Mita
Writing, review, and/or revision of the manuscript: A.C. Mita, R. Figlin, M.M. Mita

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