Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial

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Summary

Background **Cabazitaxel is a novel tubulin-binding taxane drug with antitumour activity in docetaxel-resistant cancers. We aimed to compare the efficacy and safety of cabazitaxel plus prednisone with those of mitoxantrone plus prednisone in men with metastatic castration-resistant prostate cancer with progressive disease after docetaxel-based treatment.**

Methods **We undertook an open-label randomised phase 3 trial in men with metastatic castration-resistant prostate cancer who had received previous hormone therapy, but whose disease had progressed during or after treatment with a docetaxel-containing regimen. Participants were treated with 10 mg oral prednisone daily, and were randomly assigned to receive either 12 mg/m² mitoxantrone intravenously over 15–30 min or 25 mg/m² cabazitaxel intravenously over 1 h every 3 weeks. The random allocation schedule was computer-generated; patients and treating physicians were not masked to treatment allocation, but the study team was masked to the data analysis. The primary endpoint was overall survival. Secondary endpoints included progression-free survival and safety. Analysis was by intention to treat. This study is registered at ClinicalTrials.gov, NCT00417079.**

Findings **755 men were allocated to treatment groups (377 mitoxantrone, 378 cabazitaxel) and were included in the intention-to-treat analysis. At the cutoff for the final analysis (Sept 25, 2009), median survival was 15·1 months (95% CI 14·1–16·3) in the cabazitaxel group and 12·7 months (11·6–13·7) in the mitoxantrone group. The hazard ratio for death of men treated with cabazitaxel compared with those taking mitoxantrone was 0·70 (95% CI 0·59–0·83, p<0·0001). Median progression-free survival was 2·8 months (95% CI 2·4–3·0) in the cabazitaxel group and 1·4 months (1·4–1·7) in the mitoxantrone group (HR 0·74, 0·64–0·86, p<0·0001). The most common clinically significant grade 3 or higher adverse events were neutropenia (cabazitaxel, 303 [82%] patients *vs* mitoxantrone, 215 [58%]) and diarrhoea (23 [6%] *vs* one [<1%]). 28 (8%) patients in the cabazitaxel group and five (1%) in the mitoxantrone group had febrile neutropenia.**

Interpretation **Treatment with cabazitaxel plus prednisone has important clinical antitumour activity, improving overall survival in patients with metastatic castration-resistant prostate cancer whose disease has progressed during or after docetaxel-based therapy.**

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See Editorial page 1117

See Comment page 1119

See Perspectives page 1137

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Introduction

Prostate cancer is the second most common cause of cancer death in men in the USA[1] and the third most common cause of death in developed countries.[2] For patients with metastatic prostate cancer, androgen deprivation therapy improves symptoms, but patients invariably develop progressive disease.[3] On the basis of an improvement in survival compared with mitoxantrone plus prednisone in patients with metastatic castration-resistant prostate cancer,[4–6] docetaxel in combination with prednisone is standard first-line chemotherapy in this setting. No treatment has been approved by the US Food and Drug Administration, however, for patients whose disease progresses after docetaxel treatment. Mitoxantrone is often administered because of its favourable effects on quality-of-life outcomes.[7,8] However, no intervention improves survival in this disease setting.

Cabazitaxel (XRP6258; TXD258; RPR116258A) is a tubulin-binding taxane drug as potent as docetaxel in cell lines.[9] Additionally, the drug has antitumour activity in models resistant to paclitaxel and docetaxel.[10,11] Phase 1 and 2 clinical studies have shown that neutropenia is the primary dose-limiting toxicity, and the recommended phase 2 doses were 20 and 25 mg/m², with antitumour activity in solid tumours including docetaxel-refractory metastatic castration-resistant prostate cancer.[12,13] We undertook a randomised, multicentre, multinational, phase 3 trial (EFC6193; TROPIC) with the aim of assessing whether cabazitaxel plus prednisone improves overall survival compared with mitoxantrone plus prednisone in men with metastatic castration-resistant prostate cancer who had progressed after docetaxel-based chemotherapy.

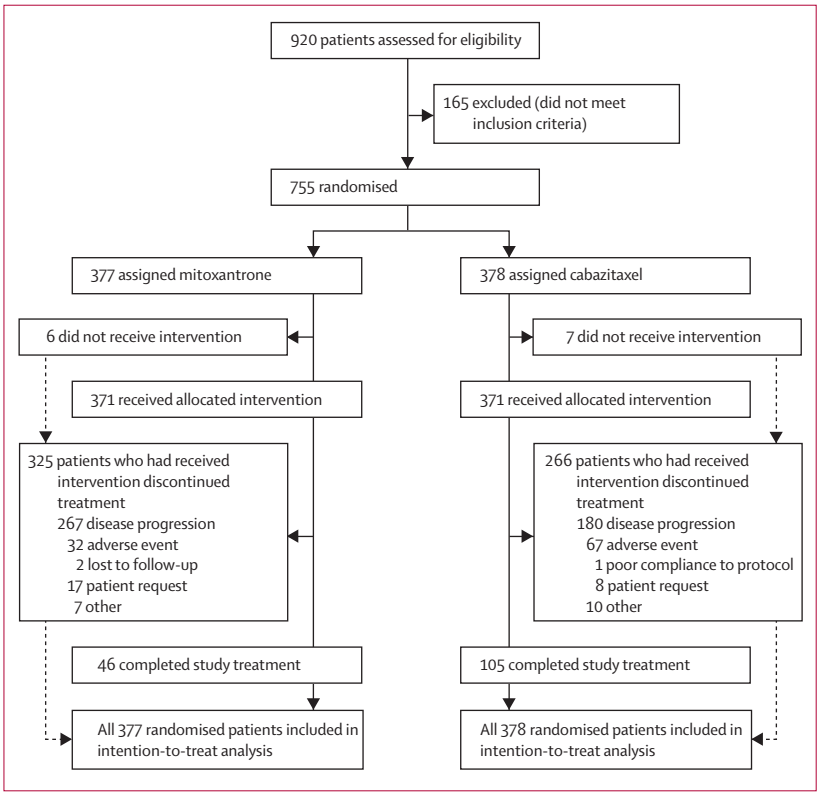


Figure 1: **Trial profile**

	Mitoxantrone (n=377)	Cabazitaxel (n=378)
Age		
Median (years)	67 (61–72)	68 (62–73)
≥75 years	70 (19%)	69 (18%)
Ethnic origin		
White	314 (83%)	317 (84%)
Asian	32 (8%)	26 (7%)
Black	20 (5%)	20 (5%)
Other	11 (3%)	15 (4%)
ECOG performance status 0 or 1	344 (91%)	350 (93%)
Extent of disease		
Metastatic	356 (94%)	364 (96%)
Bone metastases	328 (87%)	303 (80%)
Visceral metastases	94 (25%)	94 (25%)
Locoregional recurrence	20 (5%)	14 (4%)
Unknown	1 (<1%)	0
Median serum PSA concentration (μg/L)*	127·5 (44·0–419·0)	143·9 (51·1–416·0)
Serum PSA concentration ≥20 μg/L	325 (86%)	329 (87%)
Measurable disease	204 (54%)	201 (53%)
Pain at baseline†	168 (45%)	174 (46%)
Previous therapy		
Hormonal‡	375 (99%)	375 (99%)
Number of chemotherapy regimens		
1	268 (71%)	260 (69%)
2	79 (21%)	94 (25%)
>2	30 (8%)	24 (6%)
Radiation	222 (59%)	232 (61%)
Surgery	205 (54%)	198 (52%)
Biological agent	36 (10%)	26 (7%)
Number of previous docetaxel regimens		
1	327 (87%)	316 (84%)
2	43 (11%)	53 (14%)
>2	7 (2%)	9 (2%)
Total previous docetaxel dose (mg/m²)	529·2 (380·9–787·2)	576·6 (408·4–761·2)
Disease progression relative to docetaxel administration		
During treatment	104 (28%)	115 (30%)
<3 months from last dose	181 (48%)	158 (42%)
≥3 months from last dose	90 (24%)	102 (27%)
Unknown	2 (1%)	3 (1%)
Median time from last docetaxel dose to disease progression (months)	0·7 (0·0–2·9)	0·8 (0·0–3·1)

Data are number of patients (%) or median (IQR). *Serum PSA concentrations were available for 370 mitoxantrone and 371 cabazitaxel patients. †Pain was assessed with the McGill-Melzack present pain intensity scale[15] and analgesic score was derived from analgesic consumption (morphine equivalents). ‡Two patients in the cabazitaxel group did not receive previous orchiectomy or hormone therapy. ECOG=Eastern Cooperative Oncology Group. PSA=prostate-specific antigen.

Table 1: **Baseline characteristics and treatment history of patients in the intention-to-treat population**

Methods

Patients

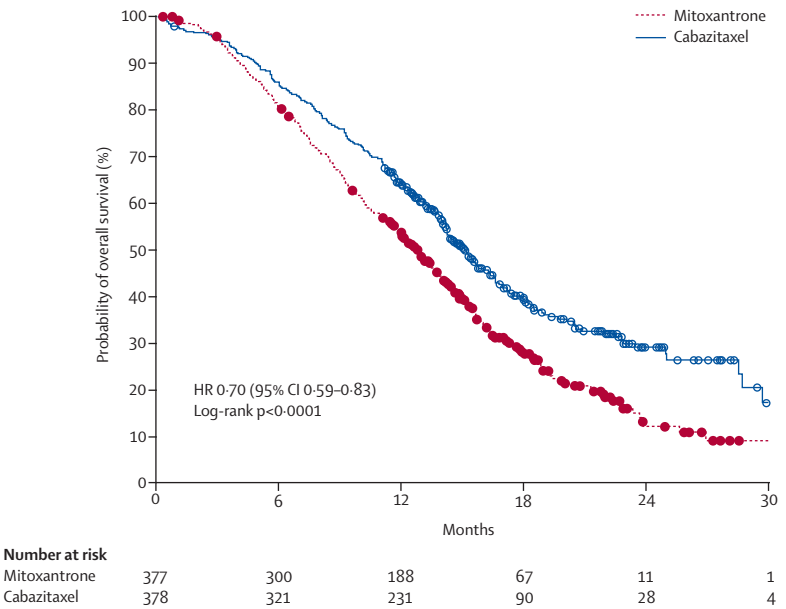
This randomised open-label phase 3 study was undertaken at 146 centres in 26 countries. Patients had pathologically proven prostate cancer with documented disease progression during or after completion of docetaxel treatment. Eligible patients were aged at least 18 years, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients who had previous mitoxantrone therapy, radiotherapy to 40% or more of the bone marrow, or cancer therapy (other than luteinising-hormone-releasing hormone [LHRH] analogues) within 4 weeks before enrolment were excluded. Patients with measurable disease were required to have documented disease progression by Response Evaluation Criteria in Solid Tumors (RECIST)[14] with at least one visceral or soft-tissue metastatic lesion. Patients with non-measurable disease were required to have rising serum prostate-specific antigen (PSA) concentrations (at least two consecutive increases relative to a reference value measured at least a week apart) or the appearance of at least one new demonstrable radiographic lesion.

Additional inclusion criteria were: previous and ongoing castration by orchiectomy or LHRH agonists, or both; antiandrogen withdrawal followed by progression had to have taken place at least 4 weeks (6 weeks for bicalutamide) before enrolment; adequate haematological, hepatic, renal, and cardiac function; and a left-ventricular ejection fraction of more than 50% assessed by multi-gated radionuclide angiography or echocardiogram.

	Mitoxantrone (n=377)	Cabazitaxel (n=378)
Patients receiving study treatment	371 (98%)	371 (98%)
Patients completing planned ten cycles of study treatment	46 (12%)	105 (28%)
Discontinuation of study treatment	325 (86%)	266 (70%)
Reasons for discontinuation of study treatment		
Disease progression	267 (71%)	180 (48%)
Adverse event	32 (8%)	67 (18%)
Non-compliance with protocol	0	1 (<1%)
Lost to follow-up	2 (1%)	0
Patient request	17 (5%)	8 (2%)
Other	7 (2%)	10 (3%)
Median number of treatment cycles*	4 (2–7)	6 (3–10)
Median relative dose intensity (%)*	97·3% (92·0–99·3)	96·1% (90·1–98·9)
Treatment delays, number of cycles†		
≤9 days	110 (6%)	157 (7%)
>9 days	28 (2%)	51 (2%)
Dose reductions, number of cycles†	88 (5%)	221 (10%)

Data are number of patients or cycles (%) or median (IQR). *Assessed in patients who received study treatment. †Percentages are of total number of treatment cycles (1736 for mitoxantrone and 2251 for cabazitaxel).

Table 2: **Treatment received and reasons for discontinuation in the intention-to-treat population***



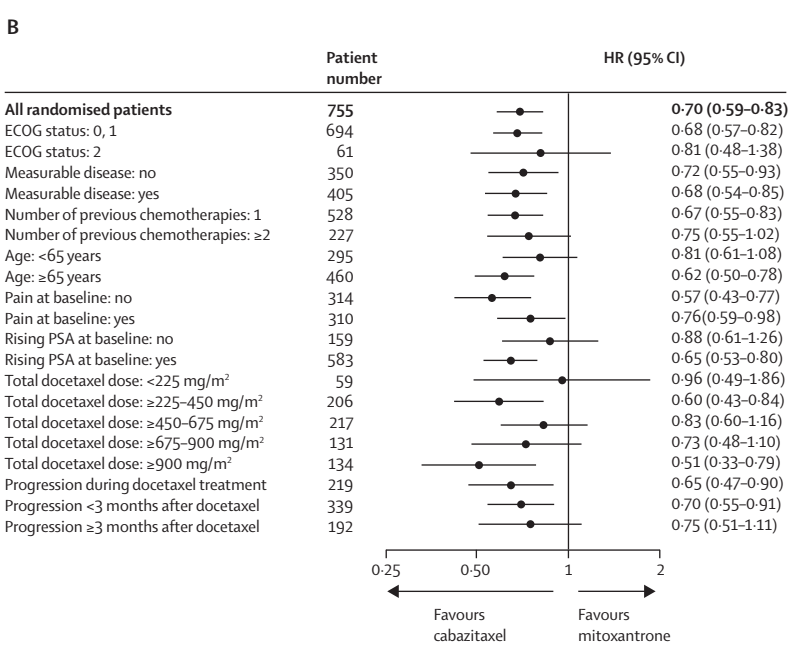


Figure 2: **Overall survival**
(A) Kaplan-Meier estimates of the probability of survival in patients in all patients randomly assigned to treatment with cabazitaxel plus prednisone or mitoxantrone plus prednisone. The points on the curves show censored observations. (B) Intention-to-treat analysis of overall survival in subgroups of patients defined by baseline characteristics. Hazard ratios (HRs) lower than 1 favour the cabazitaxel group and greater than 1 favour the mitoxantrone group.

Concomitant use of bisphosphonates was allowed if the dose had been stable for 12 weeks before enrolment. Patients receiving LHRH agonists were mandated to continue this treatment during the study. Additional exclusion criteria were active grade 2 or higher peripheral neuropathy or stomatitis, other serious illness (including secondary cancer), or a history of hypersensitivity to polysorbate 80-containing drugs or prednisone.

On the basis of emerging guidelines recommending the delivery of 12 weeks of treatment before adjustment of therapy for metastatic castration-resistant prostate cancer, an amendment was made to the trial protocol after 59 patients had been enrolled to exclude patients previously receiving a cumulative docetaxel dose lower than 225 mg/m². The study was undertaken in accordance with principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and with local ethics committee approval. Written informed consent was obtained from all participants.

Procedures

All patients received oral prednisone 10 mg daily (or similar doses of prednisolone where prednisone was unavailable). Patients were centrally randomly assigned to receive cabazitaxel 25 mg/m² intravenously over 1 h or mitoxantrone 12 mg/m² intravenously over 15–30 min on day 1 of each 21-day cycle, and were stratified for disease measurability (measurable *vs* non-measurable) and ECOG performance status (0–1 *vs* 2). A contract research organisation was responsible for randomising patients using an interactive voice response system and for the computer-generated random allocation schedule, but had no other involvement in the trial. A dynamic allocation method was used to avoid treatment assignment imbalances within a centre. Patients and

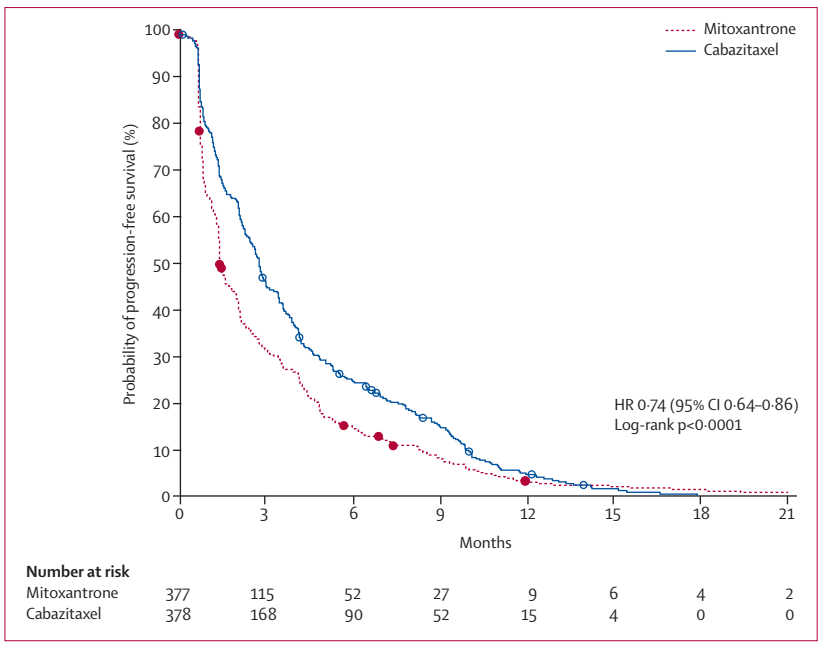


***Figure 3*: Progression-free survival**
Kaplan-Meier estimates of the probability of progression-free survival in all patients randomly assigned to treatment with cabazitaxel plus prednisone or mitoxantrone plus prednisone. The points on the curves show censored observations. Progression-free survival was established from the date of randomisation to whichever event occurred first—prostate-specific antigen progression, radiological progression, symptomatic progression, or death. HR=hazard ratio.

treating physicians were not masked to treatment allocation, but the study team was masked to the data analysis. Premedication, consisting of single intravenous doses of an antihistamine, corticosteroid (dexamethasone 8 mg or equivalent), and histamine H_2-antagonist (except cimetidine), was administered 30 min or more before cabazitaxel. Antiemetic prophylaxis was given at physicians' discretion.

Treatment was continued for a maximum of ten cycles to minimise risk of mitoxantrone-induced cardiac toxicity, while allowing for comparable exposure to the study treatment and a similar schedule of evaluation. Patients were followed up until the cutoff date for analysis or until death (whichever occurred first). Treatment delays of up to 2 weeks were allowed, with one dose reduction (cabazitaxel 20 mg/m² or mitoxantrone 10 mg/m²) per patient. Prophylactic granulocyte colony-stimulating factor was not allowed during the first cycle, but was allowed (at physicians' discretion) after first occurrence of either neutropenia lasting 7 days or more or neutropenia complicated by fever or infection.

Pretreatment evaluations included a medical history, ECOG performance status, physical examination, laboratory screening, serum PSA concentration, CT, bone scan, electrocardiography, and assessment of left-ventricular ejection fraction. Pain and analgesic consumption were assessed at baseline. Pain was assessed with the McGill-Melzack present pain intensity (PPI) scale[15] and analgesic use was derived from consumption normalised to morphine equivalents.[8]

Physical examinations and blood tests were repeated before each infusion of study drug and at the end of treatment. Complete blood counts were taken on days 1, 8, and 15 of each treatment cycle and repeated when clinically indicated. Patients who progressed or started another anticancer therapy were followed up every 3 months; patients who withdrew before documented disease progression were followed up every 6 weeks for the first 6 months and thereafter every 3 months.

The primary endpoint of overall survival was calculated from date of randomisation to death. Secondary endpoints included a composite endpoint of progression-free survival, defined as the time between randomisation and the first date of progression as measured by PSA progression, tumour progression, pain progression, or death. Other secondary endpoints were PSA response (reduction in serum PSA concentration of ≥50% in patients with a baseline value of ≥20 µg/L); PSA progression (increase of ≥25% over nadir PSA concentration provided that the increase in the absolute PSA value was ≥5 µg/L for men with no PSA response, or ≥50% over nadir for PSA responders); objective tumour response for patients with measurable disease based on RECIST; pain response (for patients with median PPI score of ≥2 or mean analgesic score of ≥10 points at baseline, or both), which was defined as a reduction of 2 points or more from baseline median PPI score without increasing analgesic score, or decreases of more than 50% in analgesic use without an increase in pain, maintained for 3 or more weeks;[15] pain progression (increase in median PPI score of ≥1 point from the reference value or an increase of ≥25% in the mean analgesic score or requirement for palliative radiotherapy);[15] and time to tumour progression, defined as the number of months from randomisation until evidence of progressive disease (RECIST).

Adverse events, biochemistry, haematology, vital signs, and electrocardiograms were monitored throughout the study. Left-ventricular ejection fraction was monitored throughout the study in mitoxantrone-treated patients, but only if clinically indicated in those who received cabazitaxel. All adverse events were graded according to National Cancer Institute Common Terminology Criteria for adverse events (version 3.0).[16]

Statistical analysis

SAS (version 9.1.3) was used for all analyses. The study required an estimated sample size of 720 patients (360 per group) to detect a 25% reduction in the hazard ratio (HR) for death in the cabazitaxel group relative to the mitoxantrone group with 90% power, with a two-sided log-rank test at a significance level of 0·05 and on the assumption of 8 months median overall survival in the mitoxantrone group. We planned for the final analysis to take place when 511 deaths had occurred. Analysis of the primary endpoint was for the intention-to-treat population (all patients randomly assigned to treatment groups).

	Mitoxantrone	Cabazitaxel	Hazard ratio (95% CI)	p value for comparison
Tumour response rate*				
Number of evaluable patients	204	201	..	..
Response rate (%)	4·4% (1·6–7·2)	14·4% (9·6–19·3)	..	0·0005
PSA response rate†				
Number of evaluable patients	325	329	..	..
Response rate (%)	17·8% (13·7–22·0)	39·2% (33·9–44·5)	..	0·0002
Pain response rate‡				
Number of evaluable patients	168	174	..	..
Response rate (%)	7·7% (3·7–11·8)	9·2% (4·9–13·5)	..	0·63
Progression				
Number of patients in intention-to-treat analysis	377	378	..	..
Median time to tumour progression (months)	5·4 (2·3–10·0)	8·8 (3·9–12·0)	0·61 (0·49–0·76)	<0·0001
Median time to PSA progression (months)	3·1 (0·9–9·1)	6·4 (2·2–10·1)	0·75 (0·63–0·90)	0·001
Median time to pain progression (months)§	Not reached	11·1 (2·9–not reached)	0·91 (0·69–1·19)	0·52

*Tumour response was evaluated only for patients with measurable disease according to Response Evaluation Criteria in Solid Tumors.[14] †Prostate-specific antigen (PSA) response was defined as a 50% or more reduction in serum PSA concentration, established only for patients with a serum PSA concentration of 20 μg/L or more at baseline, confirmed by a repeat PSA measurement after at least 3 weeks. ‡Pain response was established only for patients with median present pain intensity (PPI) score of 2 or more or mean analgesic score (AS) of 10 points or more at baseline, or both, and was defined as a two-point or greater reduction from baseline median PPI score without an increased AS or a decrease of 50% or more in the AS without an increase in the PPI score, maintained for at least 3 weeks. §Data for 265 patients in the cabazitaxel group and 279 patients in the mitoxantrone group were censored as a result of more than two PPI or AS assessments, or both, being missed during the same week (unless a complete evaluation of ≥5 values showed pain progression).

Table 3: **Response to treatment and disease progression**

Safety analyses included patients who received at least part of one dose of study drug.

We analysed overall survival using the Kaplan-Meier method, with log-rank comparisons stratified according to disease measurability (measurable versus non-measureable) and ECOG performance status (0–1 versus 2). HRs and 95% CIs were calculated with a Cox proportional hazards model (for both primary and secondary analyses). Overall survival data were censored at the last date the patient was known to be alive or at the analysis cutoff date, whichever was earliest. Progression-free survival and progression of tumour, PSA, and pain were compared between treatments by log-rank testing.

A planned futility analysis of progression-free survival was done after 225 patients had a progression event. Additionally, an interim analysis of the primary efficacy endpoint of overall survival was planned after 307 events, but was actually done after 365 events with an adjusted significance level of 0·016, on the basis of the O'Brien-Fleming type 1 error spending function. A two-sided significance level of 0·0452 was used for the final analysis. Although the study team was masked to treatment allocation and patient outcomes throughout the trial, an independent contract statistician provided unmasked results to an independent data monitoring committee with the appropriate analyses for assessment.

This study is registered at ClinicalTrials.gov, NCT00417079.

Role of the funding source

The chief investigators (JSB and AOS) designed the trial protocol and analysed the data, with input from the sponsor, who funded the trial. The decision to submit the report for publication was made by the chief investigators, who drafted and then finalised the report with the help of a medical writer. The sponsor funded editorial assistance and reviewed the final draft before submission.

Results

Between Jan 2, 2007, and Oct 23, 2008, 755 patients were randomly assigned to treatment groups (378 cabazitaxel and 377 mitoxantrone; figure 1). The treatment groups were well balanced at baseline with respect to demographic and disease characteristics and previous treatments (table 1). Roughly 50% of patients had measurable soft-tissue disease and 25% had visceral (poor prognosis) disease. The median dose of docetaxel received before the study was 576·6 mg/m² (IQR 408·4–761·2) in the cabazitaxel group and 529·2 mg/m² (380·9–787·2) in the mitoxantrone group. Overall, 59 (8%) patients had received a cumulative dose of docetaxel less than 225 mg/m² and 482 (65%) received a cumulative dose of 450 mg/m² or more. About 70% of patients had progressive disease either during or within 3 months of completing docetaxel treatment, including about 30% of patients who had disease progression during docetaxel treatment (table 1). The median time from last docetaxel dose to disease progression, before trial participation, was 0·8 months (IQR 0·0–3·1) for the cabazitaxel group and 0·7 months (0·0–2·9) for the mitoxantrone group.

Patients in the cabazitaxel group were on study treatment longer—a median of six treatment cycles compared with four cycles—and were more likely to complete study treatment than were those in the

	Mitoxantrone (n=371)		Cabazitaxel (n=371)	
	All grades	Grade ≥3	All grades	Grade ≥3
Haematological†				
Neutropenia	325 (88%)	215 (58%)	347 (94%)	303 (82%)
Febrile neutropenia	..	5 (1%)	..	28 (8%)
Leukopenia	343 (92%)	157 (42%)	355 (96%)	253 (68%)
Anaemia	302 (81%)	18 (5%)	361 (97%)	39 (11%)
Thrombocytopenia	160 (43%)	6 (2%)	176 (47%)	15 (4%)
Non-haematological				
Diarrhoea	39 (11%)	1 (<1%)	173 (47%)	23 (6%)
Fatigue	102 (27%)	11 (3%)	136 (37%)	18 (5%)
Asthenia	46 (12%)	9 (2%)	76 (20%)	17 (5%)
Back pain	45 (12%)	11 (3%)	60 (16%)	14 (4%)
Nausea	85 (23%)	1 (<1%)	127 (34%)	7 (2%)
Vomiting	38 (10%)	0	84 (23%)	7 (2%)
Haematuria	14 (4%)	2 (1%)	62 (17%)	7 (2%)
Abdominal pain	13 (4%)	0	43 (12%)	7 (2%)
Pain in extremity	27 (7%)	4 (1%)	30 (8%)	6 (2%)
Dyspnoea	17 (5%)	3 (1%)	44 (12%)	5 (1%)
Constipation	57 (15%)	2 (1%)	76 (20%)	4 (1%)
Pyrexia	23 (6%)	1 (<1%)	45 (12%)	4 (1%)
Arthralgia	31 (8%)	4 (1%)	39 (11%)	4 (1%)
Urinary-tract infection	11 (3%)	3 (1%)	27 (7%)	4 (1%)
Pain	18 (5%)	7 (2%)	20 (5%)	4 (1%)
Bone pain	19 (5%)	9 (2%)	19 (5%)	3 (1%)

Data are number of patients (%). *Toxic effects were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0)[16] and summarised with the Medical Dictionary for Regulatory Activities terminology (version 12.0).[17] Events listed are those occurring at grade 3 or higher severity in ≥1% of patients in either treatment group. Grade 3 or higher events include those reported as leading to death (grade 5). †Data for haematogical adverse events were based on laboratory assessments.

Table 4: **Adverse events reported in patients who received at least one dose of study treatment***

mitoxantrone group (table 2). In the cabazitaxel group, 282 (76%) patients received more than 90% of the planned dose intensity, compared with 301 (81%) in the mitoxantrone group. The primary reason for treatment discontinuation in both groups was disease progression (table 2). Dose reductions were reported for 45 (12%) patients in the cabazitaxel group and 15 (4%) mitoxantrone-treated patients, and treatment delays occurred in 104 (28%) and 56 (15%) patients, respectively. Overall, 5% of mitoxantrone treatment courses were dose reduced compared with 10% of cabazitaxel treatment courses; delays to treatment were similar in both groups (table 2). Per protocol, crossover to cabazitaxel was not allowed for the mitoxantrone group, although 44 (12%) patients in this group received treatment with tubulin-binding drugs at progression.

See Online for webappendix

The median follow-up for both treatment groups combined was 12·8 months (IQR 7·8–16·9). At the cutoff date for the final analysis (Sept 25, 2009), 234 deaths had occurred in the cabazitaxel group and 279 in the mitoxantrone group. The Kaplan-Meier analysis showed an overall survival benefit in favour of cabazitaxel (figure 2). Median overall survival was 15·1 months (95% CI 14·1–16·3) versus 12·7 months (11·6–13·7). This result corresponds to a 30% reduction in relative risk of death (HR 0·70, 95% CI 0·59–0·83, p<0·0001). Subgroup analyses of survival consistently favoured cabazitaxel (figure 2), with no significant interactions between prognostic factors and treatment response.

Median progression-free survival (a composite endpoint) was 2·8 months (95% CI 2·4–3·0) in the cabazitaxel group and 1·4 months (1·4–1·7) in the mitoxantrone group (figure 3; HR 0·74, 95% CI 0·64–0·86, p<0·0001). Patients treated with cabazitaxel had significantly higher rates of tumour response and PSA response than did those who received mitoxantrone (table 3). Significant improvements in time to tumour progression and time to PSA progression were also noted in the cabazitaxel group (table 3). Pain response rates were similar in the two groups; there was no significant difference between the treatment groups in time to pain progression. Similar proportions of patients in each group had either reductions or increases in pain (data not shown).

The most common toxic effects of cabazitaxel were haematological; the most frequent haematological grade 3 or higher adverse events were neutropenia, leukopenia, and anaemia (table 4). The most common non-haematological grade 3 or higher adverse event was diarrhoea, which was managed expectantly. Grade 3 peripheral neuropathy was uncommon (reported in three [1%] patients in each group). Overall, peripheral neuropathy (all grades) was reported during the study in 52 (14%) patients in the cabazitaxel group and 12 (3%) in the mitoxantrone group. Peripheral oedema (all grades) occurred in 34 (9%) patients in each group.

18 (5%) patients treated with cabazitaxel and nine (2%) treated with mitoxantrone died within 30 days of the last infusion. Table 5 summarises causes of death in patients who received at least one dose of study drug (the safety population). The most frequent cause of death in the cabazitaxel group was neutropenia and its clinical consequences. Analysis of the incidence of neutropenia and diarrhoea by subgroups suggested differences in rates of adverse events by age, previous radiotherapy, and geographical region (webappendix p 1).

Discussion

Cabazitaxel is the first drug to improve survival in patients with metastatic castration-resistant prostate cancer with progressive disease after docetaxel-based treatment, resulting in a 30% reduction in the risk of death and an improved median overall survival compared with mitoxantrone (panel). Currently, these patients have few therapeutic options, with no treatment able to prolong survival in this setting. The analysis of survival in subgroups defined by prognostic factors supports the robustness of the primary endpoint, favouring cabazitaxel over mitoxantrone, even in patients with disease progression during docetaxel treatment and in those who received high cumulative doses of docetaxel. Cabazitaxel

treatment also improved median progression-free survival and time to tumour progression and resulted in higher rates of tumour and PSA response than did mitoxantrone. Further studies are now planned to evaluate the effect of cabazitaxel on quality of life in men with castration-resistant prostate cancer. Nevertheless, these data have led to the approval of cabazitaxel by the US Food and Drug Administration for second-line treatment of metastatic castration-resistant prostate cancer. Importantly, in this trial addressing an unmet medical need, patients had poor prognosis disease, with 25% having visceral metastases and about 50% having measurable disease. These factors, as well as infiltration of bone marrow by tumour and previous treatment, could account for the high rates of neutropenia and febrile neutropenia in the control group of this trial. By way of historical comparison, with the same dose and schedule of mitoxantrone, but in a first-line setting, the incidence of grade 3–4 neutropenia was 22% in the TAX327 study[4] compared with 58% grade 3 or higher in our trial. Nonetheless, despite the compromised bone-marrow reserve of this patient population, more than 75% of patients received more than 90% of the planned dose intensity.

Cabazitaxel-treated patients had a higher risk of death within 30 days of the last drug dose than did mitoxantrone-treated patients, and three times as many patients on cabazitaxel had a dose reduction. Moreover, the rate of febrile neutropenia in the cabazitaxel group was 8%, suggesting that cabazitaxel treatment requires careful monitoring and management of emerging symptoms. Dose modifications (delay or reductions) as well as prophylactic treatment with granulocyte colony-stimulating factor in high-risk selected patients are potential risk-mitigation strategies that could be considered to manage these toxic effects (webappendix p 2). Pharmacogenomic studies correlating the presence of key single nucleotide polymorphisms associated with slow cabazitaxel clearance (in genes such as *CYP3A4* and *CYP3A5*) and drug toxicity are also warranted and could allow prospective patient identification.[9] Nevertheless, although dose reduction to 20 mg/m² might decrease myelotoxicity, this change could also decrease benefit from cabazitaxel. To elucidate this possibility, future studies would need to evaluate the non-inferiority and safety of 20 mg/m² of cabazitaxel compared with 25 mg/m². Moreover, cumulative neurotoxicity was not reported. Cabazitaxel hypersensitivity reactions were prevented by use of the prescribed prophylactic regimen; further studies to assess whether cabazitaxel can be safely administered with lower doses of steroids or anti-histamines are nonetheless warranted.

Crucially, the subgroup of patients in the intention-to-treat population (29%) who had progressive disease during docetaxel treatment before participating in this trial derived a significant overall survival benefit from cabazitaxel. Moreover, 45% of patients who had disease progression within 3 months of completing docetaxel treatment also had an overall survival benefit. These data suggest that cabazitaxel imparts a survival benefit to patients unlikely to benefit from further docetaxel treatment, in keeping with preclinical data showing that cabazitaxel has antitumour activity in docetaxel refractory models.

	Mitoxantrone (n=371)	Cabazitaxel (n=371)
Total deaths during the study	275 (74%)	227 (61%)
Deaths ≤30 days after last dose of study drug	9 (2%)	18 (5%)
Causes of death ≤30 days after last dose of study drug		
Disease progression	6 (2%)*	0
Adverse events		
Neutropenia and clinical consequences/sepsis	1 (<1%)	7 (2%)
Cardiac	0	5 (1%)
Dyspnoea†	1 (<1%)	0
Dehydration/electrolyte imbalance	0	1 (<1%)
Renal failure	0	3 (1%)
Cerebral haemorrhage	0	1 (<1%)
Unknown cause	0	1 (<1%)
Motor vehicle accident	1 (<1%)	0
Deaths >30 days after last dose of study drug	266 (72%)	209 (56%)

Data are number of patients (%). *Includes three patients whose death was reported as an adverse event coded as disease progression. †Dyspnoea was reported as the adverse event leading to death, but the investigator regarded the death as related to disease progression.

Table 5: **Deaths in patients who received at least one dose of study treatment**

Panel: **Research in context**

Systematic review

We obtained background evidence by searching Medline and Embase for English-language articles and conference abstracts using the search terms prostate cancer (metastatic, hormone-refractory, castration-resistant), mitoxantrone, docetaxel, and cabazitaxel (XRP6258, TXD258; RPR116258A).

Interpretation

Men with metastatic castration-resistant prostate cancer are typically treated with docetaxel plus prednisone. No treatments, however, have been approved for patients with disease progression after these treatments. Cabazitaxel is a taxane tubulin-binding drug with antitumour activity in docetaxel refractory models. In this phase 3 trial of cabazitaxel versus mitoxantrone, both administered with prednisone, we show a significant 2·4-month median overall survival advantage in favour of cabazitaxel and prednisone in men with metastatic castration-resistant prostate cancer with progressive disease after docetaxel and prednisone treatments. These data support regulatory approval of cabazitaxel in the USA. On the basis of these results, cabazitaxel will become a standard of care for treatment of prostate cancer in this setting. Neutropenia is a common toxic effect of this drug; in view of the risk of neutropenic sepsis this agent should be administered with appropriate caution and monitoring.

A limitation to studies of novel agents after docetaxel treatment is the absence of a standard definition for docetaxel resistance. Definition of disease progression for patients with metastatic castration-resistant prostate cancer remains challenging and is often based on combinations of measures such as rising serum PSA concentrations, new or enlarging radiological lesions, or appearance of symptoms.[18] Studies to evaluate the clinical use of novel analytically validated circulating biomarkers such as circulating tumour cells[19] or the caspase-cleaved cytokeratin product M30[20] are urgently needed to improve the early identification of disease progression and definitions of docetaxel-resistant disease.

In conclusion, we show that treatment with cabazitaxel plus prednisone has important clinical antitumour activity, improving overall survival in patients with metastatic castration-resistant prostate cancer progressing during or after docetaxel-based therapy. Cabazitaxel is the first treatment to prolong survival for metastatic castration-resistant prostate cancer in the post-docetaxel setting. We now envision that if patients with metastatic castration-resistant prostate cancer have progressive disease after 12 weeks of docetaxel treatment, as recommended by the amended Prostate Cancer Clinical Trials Working Group guidelines,[18] then cabazitaxel treatment will be the standard of care. Trials assessing cabazitaxel administration both in chemotherapy-naive patients and in patients with early evidence of tumour progression on docetaxel, for example with rising circulating tumour cell counts, are now warranted.

Contributors

JSB and AOS were the trial chief investigators and participated in trial design, patient accrual, and report drafting and completion. SO, MO, SH, J-PM, IK, GG, IB, and MJM contributed to patient accrual. LS and MR contributed to statistical analyses. SG contributed to trial design, conduct, and analyses.

Conflicts of interest

Sanofi-Aventis funded this clinical trial. JSB, AOS, SO, and SH have served as paid consultants for Sanofi-Aventis. LS, MR, and SG are employees of Sanofi-Aventis.

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