Original Article

Safety and survival of docetaxel and cabazitaxel in metastatic castration-resistant prostate cancer

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Objectives

To investigate real-world haematological toxicity, overall survival (OS) and the treatment characteristics of docetaxel and cabazitaxel chemotherapy in metastatic castration-resistant prostate cancer (mCRPC).

Patients and Methods

This retrospective claims data study followed patients with mCRPC receiving cabazitaxel or docetaxel from their first chemotherapy infusion. Haematological toxicities were measured using treatment codes and inpatient diagnoses. OS was estimated using the Kaplan–Meier method. A multivariable Cox regression analysis was used to identify OS predictors.

Results

Data from 539 patients administered docetaxel and 240 administered cabazitaxel were analysed. Regarding adverse events, within 8 months of treatment initiation, some kind of treatment for haematological toxicity was documented in 31% of patients given docetaxel and in 61% of patients given cabazitaxel. In the same period, hospitalization associated with haematological toxicity was documented in 11% of the patients in the docetaxel cohort and in 15% of the patients in the cabazitaxel cohort. In the docetaxel cohort, 9.9% of patients required reverse isolation and 13% were diagnosed with sepsis during hospitalization. In the cabazitaxel cohort, the cumulative incidence was 7.9% and 15%, respectively. The median OS was reached at 21.9 months in the docetaxel cohort and, because of a later line of therapy, at 11.3 months in the cabazitaxel cohort. A multivariate Cox regression revealed that indicators of locally advanced and metastatic disease, severe comorbidities, and prior hormonal/cytotoxic therapies were independent predictors of early death.

Conclusion

Cabazitaxel patients face an increased risk of haematological toxicities during treatment. Together with their short survival time, this calls for a strict indication when using cabazitaxel in patients with mCRPC.

Keywords

cabazitaxel, claims data, docetaxel, metastatic castration-resistant prostate cancer, survival, toxicity

Introduction

With the introduction of novel agents during the past two decades, the treatment landscape for patients with metastatic castration-resistant prostate cancer (mCRPC) has expanded rapidly. The breakthrough came in 2004, with the approval of the taxane docetaxel, which has become the standard of care in chemotherapy [1]. Since then, further agents designed to increase life expectancy have been introduced. These include abiraterone, which blocks androgen biosynthesis, enzalutamide, which inhibits the androgen receptor signalling pathway, and alpha emitter Radium-223, which targets bone metastases [2].

One of the last life-prolonging options, cabazitaxel, another taxane, was approved as a second-line chemotherapy agent in 2010, after achieving a survival benefit of 2.4 months over mitoxantrone in patients pretreated with a docetaxel-containing regimen in the TROPIC trial [3]. Cabazitaxel also retained antitumour activity in patients who progressed after treatment with androgen receptor signalling targeted inhibitors [4]. However, in comparison with docetaxel, cabazitaxel was not convincing as a first-line therapy when it came to overall survival (OS). Febrile neutropenia, neutropenic infection, diarrhoea, and haematuria occurred more frequently among patients who received cabazitaxel [5]. According to the current

German guidelines [6], cabazitaxel therapy can be offered to docetaxel-pretreated patients with a good performance status, but careful monitoring is required.

Despite a wide range of life-prolonging treatment options, the optimal therapeutic sequencing, timing, and combinations of treatments for mCRPC patients remain unclear [7]. This makes it important to consider the patient's health status and adverse events when selecting an appropriate drug. While hormone manipulation is well tolerated, chemotherapy places a significant burden on patients. In terms of safety, the greatest risks posed by cabazitaxel are its myelosuppressive effects, in particular, neutropenia. This may result in dose modifications, treatment delays, premature discontinuation of therapy, or even death due to severe infection [8]. In the pivotal study of cabazitaxel, 82% of patients developed grade ≥ 3 neutropenia, 8% developed febrile neutropenia, 11% developed grade ≥ 3 anaemia, and 5% died from complications [3]. Due to the increasing use of granulocyte colony-stimulating factor (G-CSF), newer clinical studies have shown a lower incidence of neutropenia, although their results vary considerably [8]. However, real-world studies have reported comparatively high rates of haematological toxicity [9,10]. Given the strict eligibility criteria in clinical trials, participating patients may not be representative of a real-world population, since patients differ with respect to baseline variables and treatment. In real-life care, mCRPC patients had less favourable baseline prognostic factors, including older age, more aggressive disease, and a higher comorbidity burden [11,12].

Decision makers and clinical leaders are increasingly demanding real-world data to advance knowledge of effectiveness and safety in routine practice. Since health insurance claims data are routinely collected for billing and reimbursement, they provide an almost complete picture of healthcare utilization, and may be less affected by patient selection bias. The main objective of the present study therefore, was to use claims data to enhance knowledge of real-world clinical care in mCRPC patients treated with docetaxel or cabazitaxel by assessing patient and treatment characteristics, haematological toxicity, and OS. Since the two agents are used in different lines of therapy (cabazitaxel is approved for docetaxel-pretreated patients), this study has not compared the clinical endpoints of these therapies.

Patients and Methods
Data Basis and Patient Selection

This was a retrospective, observational cohort study based on claims data from the Techniker Krankenkasse which is one of the largest health insurance funds in Germany. Data obtained for the period from 2014 to 2017 covered sociodemographic information, drug claims, outpatient and inpatient care, and updated information on OS up to 30 September 2020.

The present analysis is based on a study population that was originally designed to evaluate the economic burden of treatment with docetaxel, cabazitaxel, abiraterone, enzalutamide, and best supportive care in mCRPC patients. Figure S1 summarizes the main inclusion criteria, applied stepwise. Details of the sample selection criteria can be derived from Kreis et al. [13]. As the present study analyses severe toxicities, we have restricted the population to patients treated with docetaxel and cabazitaxel.

The study population consisted of male insured persons with at least one inpatient and/or confirmed outpatient diagnosis of prostate cancer and (including metastases) at least one other diagnosis in the area of secondary malignant neoplasms, documented between 2014 and 2016. Analogous to the first-line therapy (in accordance with the guidelines valid at the time of the intervention) [14], patients identified by drug claims as having classic androgen deprivation therapy (ADT) were selected. Since claims data do not include clinical information, patients with mCRPC were allocated to further lines of therapy, based on the number of cycles, the duration of the therapy, and continuous treatment, as defined by clinical experts.

Study Design and Outcomes

Given its clinical importance, safety was assessed based on haematological toxicity. Adverse events were recorded while the patients were on chemotherapy. The patients were followed from the first administration of docetaxel/cabazitaxel (index date) until the earliest occurrence of one of the following events: therapy discontinuation, death, a drug switch during active treatment, or data cut-off (31 December 2017). In the first case, the end of the observation period was set to 21 days after the final drug administration. Given the lack of clinical information, haematological toxicity was operationalized by means of outpatient drug prescriptions (anatomical therapeutic chemical [ATC] codes) and operation and procedure (OPS) codes indicating treatment for haematological toxicity. OPS codes are part of the remuneration system for inpatient and outpatient treatment in Germany. All claim codes have been defined by medical experts; they are listed in Table S1. The time to each event was defined as the number of days from the index date to the earliest administration of G-CSF for the prophylaxis of neutropenia, blood transfusions for treating anaemia, or platelet concentrates for treating thrombocytopenia, as well as generally for any kind of haematological treatment. Using the same methodological approach, we also recorded hospitalizations with main or secondary diagnoses indicating medical complications that may arise from chemotherapy; the International Classification of Diseases (ICD) codes are listed

in Table S2. To explore whether the occurrence and treatment of haematological toxicities depends on the previous therapy, as a sensitivity analysis, within the cabazitaxel cohort we compared patients who received docetaxel during the previous 12 months with those who received it earlier in the course of treatment or never.

Treatment effectiveness was assessed in terms of OS, with the information on deaths updated until the end of September 2020. OS was measured as the period between the index date and death from any cause (German claims data do not include information on the cause of death).

We collected patient and treatment characteristics at the index date, during treatment follow-up, and in the case of death. Baseline patient characteristics included age, further malignancies, and general comorbidities, measured during the year prior to treatment initiation. Comorbidities were assessed using pharmacy-based metrics (PBMs) [15], which included 32 binary classes of chronic diseases, measured using drug claims. The advantage of a drug-based measurement over documented ICD codes is its likelihood of capturing conditions for which there is an actual need for treatment. Treatment characteristics included treatment history, the number of cycles, and information on the administration of cytotoxic drugs within the last 14 or 30 days before death. Regarding treatment history, the administration of the hormonal drugs abiraterone (ATC L02BX03, OPS 6-006.2) and enzalutamide (ATC L02BB04, OPS 6-007.6), and the cytotoxic agents docetaxel (ATC L01CD02, OPS 6-002.h) and cabazitaxel (ATC L01CD04, OPS 6-006.1) were recorded during the year prior to the index date.

Statistical Considerations

Descriptive analyses were carried out to summarize patient demographics and treatment characteristics. As docetaxel and cabazitaxel are administered in different lines of therapy, the treatments are not directly comparable. However, with regard to patient characteristics, we conducted chi-squared tests or Fisher's exact tests (count <5) for categorical variables and Mann–Whitney U-tests for continuous variables, in order to make valid statements about baseline conditions.

We assessed OS by the treatment cohort using the Kaplan–Meier method. Living patients were considered censored at the time of the last observation. An additional multivariable Cox regression model was used to identify predictors of OS. The following baseline covariates entered the regression model: age, further malignancies documented in mCRPC patients, comorbidities according to PBMs, and pre-treatment. All variables apart from age (metric, squared) were entered into the model as binary indicators. In the case of PBM-based comorbidities, we excluded the redundant group of malignancies (Group 9) from our analysis to avoid overadjustment. We tested the proportionality assumption; in case of a violation, we included the interaction of the covariate with time into the regression model [16]. Estimates were reported as hazard ratios (HRs) with 95% CIs, and the corresponding P values (P values ≤ 0.05 were taken to indicate statistical significance).

As when investigating haematological toxicities, multiple causes of failure were possible; we therefore performed competing-risk analyses. Our primary predictor was the type of chemotherapy, the failure event was the first occurrence of an adverse event, and the competing event was death. For all types of treatment with a sufficient number of events during the observation period, the time to the first adverse event was analysed using the cumulative incidence function. Statistical analyses were conducted using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

Patient and Treatment Characteristics

Given the inclusion criteria for continuous treatment (Figure S1), there were 539 and 240 patients in the docetaxel and cabazitaxel cohorts, respectively. As shown in Table 1, the patients had a median age of 72 years at baseline, and more than one-third of patients were 75 or more years old. In accordance with the course of the disease, patients in the docetaxel cohort had a significantly lower comorbidity burden than patients in the cabazitaxel cohort (four vs five PBM-based comorbidities; $P < 0.001$). Within the 12-month pre-index period, significant differences between docetaxel and cabazitaxel patients were visible in the following chronic conditions (in descending order): rheumatic conditions (78% vs 95%), acid peptic disease (52% vs 71%), congestive heart failure/hypertension (55% vs 63%), pain (25% vs 39%), epilepsy (7.1 vs 18%), anxiety and tension (4.5 vs 8.8%), and end-stage renal disease (1.1 vs 4.2%). Respiratory illness was more common among the docetaxel cohort (12% vs 6.7%). Table S3 provides a complete overview of all recorded comorbidities (online Supporting Information).

With regard to treatment characteristics, patients in the docetaxel cohort were followed up for a median of 4.5 months and received a median of eight cycles. Hormonal therapy during the previous year included abiraterone (26%) and/or enzalutamide (17%). During the 4.2 months of follow-up, patients in the cabazitaxel cohort received a median of six cycles of chemotherapy. As for their treatment history during the previous year, almost half of the patients received abiraterone (46%) and/or enzalutamide (45%) treatment. According to sequential therapy, 59% of patients in the cabazitaxel cohort had been treated with docetaxel during the previous 12 months.

TABLE 1 Patient and treatment characteristics by cohort.

	Docetaxel (N = 539)	Cabazitaxel (N = 240)	P *
Treatment follow-up, months	4.5 (4.2–6.1)	4.2 (2.8–5.4)	
Survival follow-up, months	21.9 (11.1–44.1)	11.3 (6.2–19.4)	
Patient characteristics			
Age at treatment initiation	72 (65–76)	72 (66–76)	0.7
Age group, n (%)			
< 65 years	122 (23)	48 (20)	0.16
65–69 years	108 (20)	40 (17)	
70–74 years	126 (23)	62 (26)	
75–79 years	121 (23)	70 (29)	
≥ 80 years	62 (12)	20 (8.3)	
Age at death¶	74 (68–78)	73 (67–77)	0.088
Comorbidities†	4 (3–6)	5 (4–7)	<0.001
Selected comorbidity† groups, n (%)			
Epilepsy	38 (7.1)	42 (18)	<0.001
Rheumatic conditions‡	418 (78)	228 (95)	<0.001
End-stage renal disease	6 (1.1)	10 (4.2)	0.006
Congestive heart failure / hypertension	296 (55)	151 (63)	0.037
Acid peptic disease	278 (52)	171 (71)	<0.001
Respiratory illness / asthma	63 (12)	16 (6.7)	0.032
Pain	134 (25)	93 (39)	<0.001
Anxiety and tension	24 (4.5)	21 (8.8)	0.018
Treatment characteristics			
Treatment cycles	8 (6–11)	6 (4–7)	–
Treatment cycle groups, n (%)			
3–5 cycles	–	104 (43)	
6–8 cycles	305 (57)	101 (42)	
9–11 cycles	115 (21)	18 (7.5)	
> 11 cycles	119 (22)	17 (7.1)	
Treatment history (1 year), n (%)			
Abiraterone	142 (26)	111 (46)	
Enzalutamide	89 (17)	109 (45)	
Docetaxel	12 (2.2)§	141 (59)	
Cabazitaxel	4 (0.7)	14 (5.8)§	
Chemotherapy before death¶, n (%)			
14 days before death	5 (1.2)	10 (4.4)	
30 days before death	20 (4.9)	23 (10)	

Estimates were given as median (interquartile range) or frequeny (percentage). *Due to the fact that docetaxel and cabazitaxel are administered in different lines of therapy, the therapies are not directly comparable. The P value is given in order to make statements about the baseline conditions. P values were calculated using Mann–Whitney U-tests for continuous and chi-squared tests for categorial variables. †Comorbidities were assessed using a pharmacy-based metric (PBM) with 32 classes. The group of malignancies (Group 9) was excluded due to redundancies. For clarity, this table includes only PBM groups with significant differences between cohorts. ‡According to PBMs, corticosteroids for systemic use are part of the anatomical therapeutic chemical codes for the identification of rheumatic conditions. §As allocation to treatment cohort required continuous treatment with a minimum number of cycles, some individuals had received single doses before. ¶At cut off-date, death had occurred in 411 patients in the docetaxel cohort and in 229 patients in the cabazitaxel cohort.
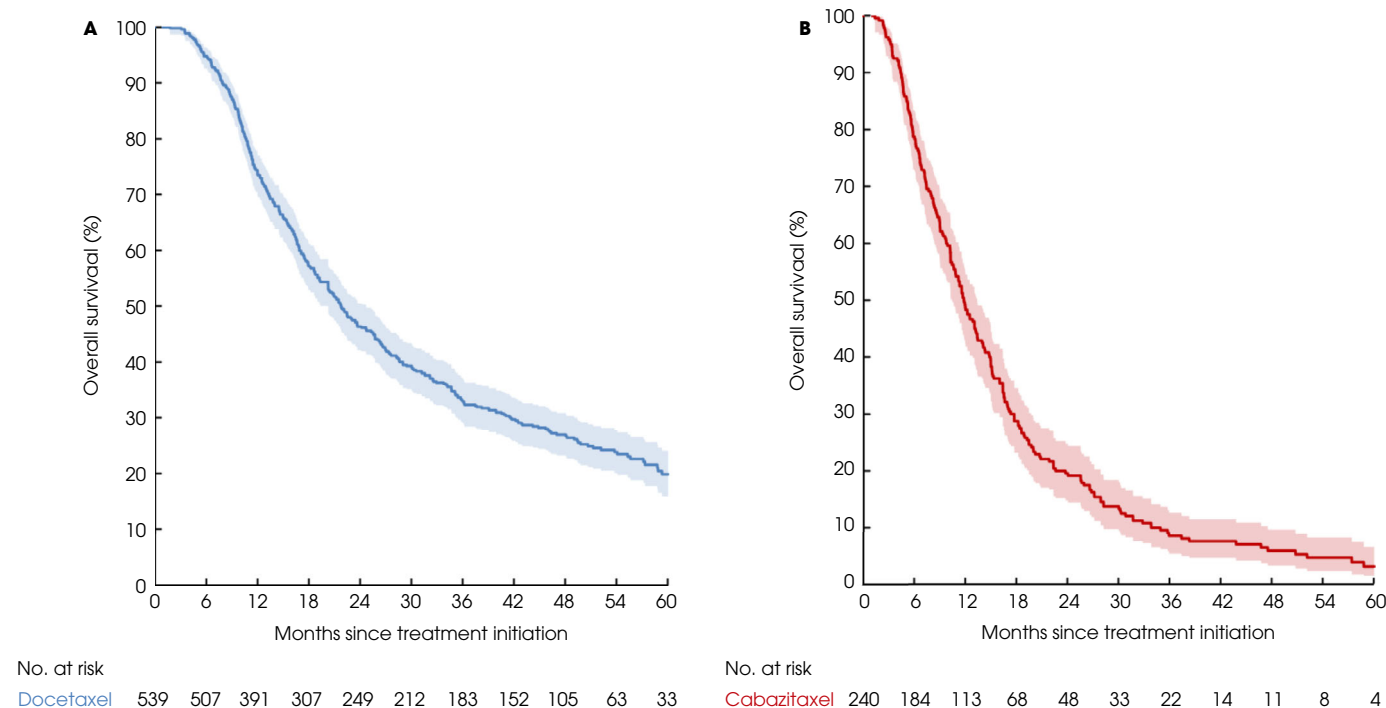
Overall Survival

At the cut-off date, death had occurred in 76% (*n* = 411) of the patients in the docetaxel cohort and in 95% (*n* = 229) of the patients in the cabazitaxel cohort (Table 1). Analogous to the therapy lines, patients in the cabazitaxel cohort were more likely to have received chemotherapy within a few weeks of death. Within 30 and 14 days of death, cytotoxic drugs were administered to 4.9% and 1.2%, respectively, of patients in the docetaxel cohort, and to 10% and 4.4%, respectively, of patients in the cabazitaxel cohort.

The Kaplan–Meier estimates are shown in Fig. 1. Patients in the docetaxel cohort had a median OS of 21.9 months. For cabazitaxel patients who had more progressed disease and were treated later, OS was 11.3 months. The 1-year, 2-year and 3-year survival rates were 73%, 46% and 35%, respectively, in the docetaxel cohort, and 48%, 15% and 6.3%, respectively, in the cabazitaxel cohort.

We also identified the predictors of OS (Fig. 2). The multivariate Cox regression showed that malignant neoplasms of the rectum (HR 2.01, 95% CI 1.05–4.14; *P* = 0.035) and bladder (HR 1.73, 95% CI 1.15–2.62; *P* = 0.009) were associated with diminished OS, while the presence of 'other malignant neoplasms of the skin' (ICD C44) was associated with a lower risk of all-cause death (HR 0.65, 95% CI 0.48–0.89; *P* = 0.007). Further comorbidities that increased mortality risk were end-stage renal disease (HR 1.83, 95% CI 1.05–3.18; *P* = 0.032), liver failure (HR 1.68, 95% CI 1.06–2.65; *P* = 0.027), acid peptic disease (HR 1.23, 95% CI 1.03–1.47; *P* = 0.026), and pain (HR 2.43, 95% CI 1.77–3.45;

FIG. 1 Overall survival (OS) in patients treated with A, docetaxel and B, cabazitaxel. Based on the criteria for continuous treatment, OS includes a minimum observation period of 49 days in the docetaxel cohort and a minimum of 39 days in the cabazitaxel cohort. As docetaxel and cabazitaxel are administered in different lines of therapy, the survival curves are presented separately and cannot be compared directly.

No. at risk

Docetaxel	539	507	391	307	249	212	183	152	105	63	33

Cabazitaxel	240	184	113	68	48	33	22	14	11	8	4

$P < 0.001$). Moreover, prior treatment with the hormonal agent abiraterone (HR 1.8, 95% CI 1.49–2.17; $P < 0.001$), and the cytotoxic agent docetaxel (HR 1.61, 95% CI 1.25–2.08; $P < 0.001$) and cabazitaxel (HR 1.94, 95% CI 1.16–3.25; $P = 0.012$) remained significantly associated with higher mortality risk.
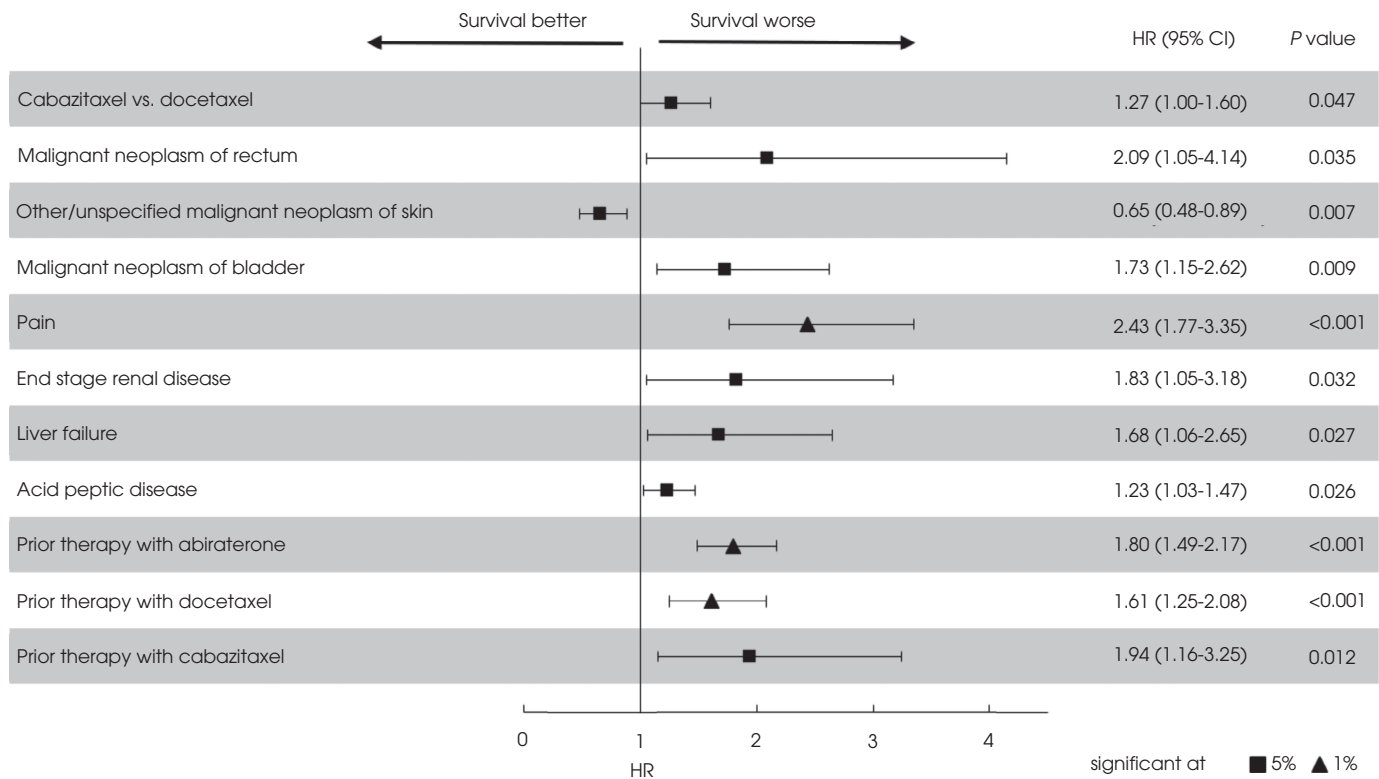
Haematological Toxicity

Within 8 months of treatment initiation, some kind of treatment for haematological toxicity, including neutropenia, anaemia, and thrombocytopenia, was documented in 31% of docetaxel-treated patients (Fig. 3A) and in 61% of cabazitaxel-treated patients (Fig. 3B). The most common drug administration occurred to prevent neutropenia, followed by the treatment of anaemia, while thrombocytopenia therapy played a minor role (not shown; numbers were too small to perform specific analyses).

Cumulative incidence plots showed that the time to the first event was shorter in patients treated with cabazitaxel. Regarding neutropenia, within 1 and 3 months of treatment initiation, 10% and 15% of the patients in the docetaxel cohort (Fig. 3C), and 25% and 32%, respectively, of patients in the cabazitaxel cohort (Fig. 3D) had received at least one administration of G-CSF. The incidence curve of the cabazitaxel patients showed a sharp increase approximately 3

and 6 weeks after therapy initiation and stabilized after approximately 3 months of therapy. Although treatment-emergent anaemia developed more slowly, a similar trend was evident between the treatment groups. Within 3 and 8 months after the index date, 8.2% and 17% of patients in the docetaxel cohort experienced treatment-emergent anaemia (Fig. 3E). In the cabazitaxel cohort, 16% and 33% of patients, respectively, experienced treatment-emergent anaemia (Fig. 3F). Regarding thrombocytopenia (not shown), within 8 months, treatment had occurred in only <1% of patients receiving docetaxel and in 3.4% of patients receiving cabazitaxel. Sensitivity analyses showed that, within the cabazitaxel cohort, the extent and treatment of haematological toxicities did not differ significantly according to whether patients had received docetaxel in the previous year or not.

Table 2 shows the cumulative incidence of patients with inpatient treatment associated with a medical complication. Within 8 months of treatment initiation, hospitalization associated with any kind of haematological toxicity was documented in 11% of patients in the docetaxel cohort and in 15% of patients in the cabazitaxel cohort. During the same period, reverse isolation was indicated in 9.9% of patients given docetaxel and in 7.9% of patients given cabazitaxel. Sepsis occurred in 13% of docetaxel-treated patients and in 15% of cabazitaxel-treated patients. Other common non-

FIG. 2 Significant predictors of overall survival in patients treated with docetaxel and cabazitaxel. The direct comparison of cabazitaxel and docetaxel was included to reflect the fact that both therapies are used in different lines of therapy. HR, hazard ratio.

	HR (95% CI)	P value
Cabazitaxel vs. docetaxel	1.27 (1.00–1.60)	0.047
Malignant neoplasm of rectum	2.09 (1.05–4.14)	0.035
Other/unspecified malignant neoplasm of skin	0.65 (0.48–0.89)	0.007
Malignant neoplasm of bladder	1.73 (1.15–2.62)	0.009
Pain	2.43 (1.77–3.35)	<0.001
End stage renal disease	1.83 (1.05–3.18)	0.032
Liver failure	1.68 (1.06–2.65)	0.027
Acid peptic disease	1.23 (1.03–1.47)	0.026
Prior therapy with abiraterone	1.80 (1.49–2.17)	<0.001
Prior therapy with docetaxel	1.61 (1.25–2.08)	<0.001
Prior therapy with cabazitaxel	1.94 (1.16–3.25)	0.012

haematological toxicities included fatigue (10% and 14%, respectively).

Discussion

Given the increasing treatment options for mCRPC, the use of different agents must be carefully considered. This is particularly true for chemotherapies, where a short life extension may be associated with serious treatment-emergent health risks. To date, these issues have often been addressed using clinical trial data, in which participants may not fully represent real-life cancer care. To our knowledge, this is the first claims data study to assess haematological toxicity and OS in mCRPC patients treated with docetaxel and cabazitaxel. As one of the last treatment options, cabazitaxel is administered only when there is an advanced stage of disease in which other therapeutics are no longer effective.

At 11.3 months in the cabazitaxel cohort, the median OS of our patients was shorter than that in most clinical studies [8,12], but within the range of observational studies [10,12,17–19]. It ranged from 13.4 to 15.1 months in clinical trials [8,12], and from 9.6 to 12.9 months in routine clinical practice [10,12,17–19]. This may reflect the differing composition and prognostic baseline parameters of patients within and outside controlled clinical trials [11,12]. For

example, our study population exhibited a high number of baseline comorbidities, and we did not exclude patients with end-stage liver or kidney disease. Regarding predictors of early death, the Cox regression showed that baseline indicators of locally advanced and metastatic prostate cancer (including pain), end-stage liver and kidney disease, and prior hormonal and cytotoxic therapy were associated with diminished survival. The inverse influence of life-extending pre-treatments may have reflected the fact that these patients had further progressed to cancer. Thus, they may be older, in a later stage and have a greater tumour load.

Even if the primary goal of chemotherapy is to prolong survival, treatment decisions must account for symptom improvement and good tolerability. Haematological toxicities are particularly important, as the risk of serious complications, including bleeding, neutropenic fever, and life-threatening infections, increases during phases with the lowest concentrations of erythrocytes, leukocytes and platelets. The results of the present study suggest that patients who receive cabazitaxel chemotherapy have an increased risk of needing treatment for haematological toxicities, including inpatient care.

According to the treatment guidelines [6,14], the prophylactic administration of G-CSF is not recommended during the first

FIG. 3 Treatment of haematological toxicities. Cumulative incidence function of time to first treatment of any haematological toxicity, first use of granulocyte colony-stimulating factor (G-CSF), and first blood transfusion since treatment initiation in patients treated with docetaxel (**A,C,E**) and cabazitaxel (**B,D,F**). As docetaxel and cabazitaxel are administered in different lines of therapy, the treatment curves are presented separately and cannot be compared directly.
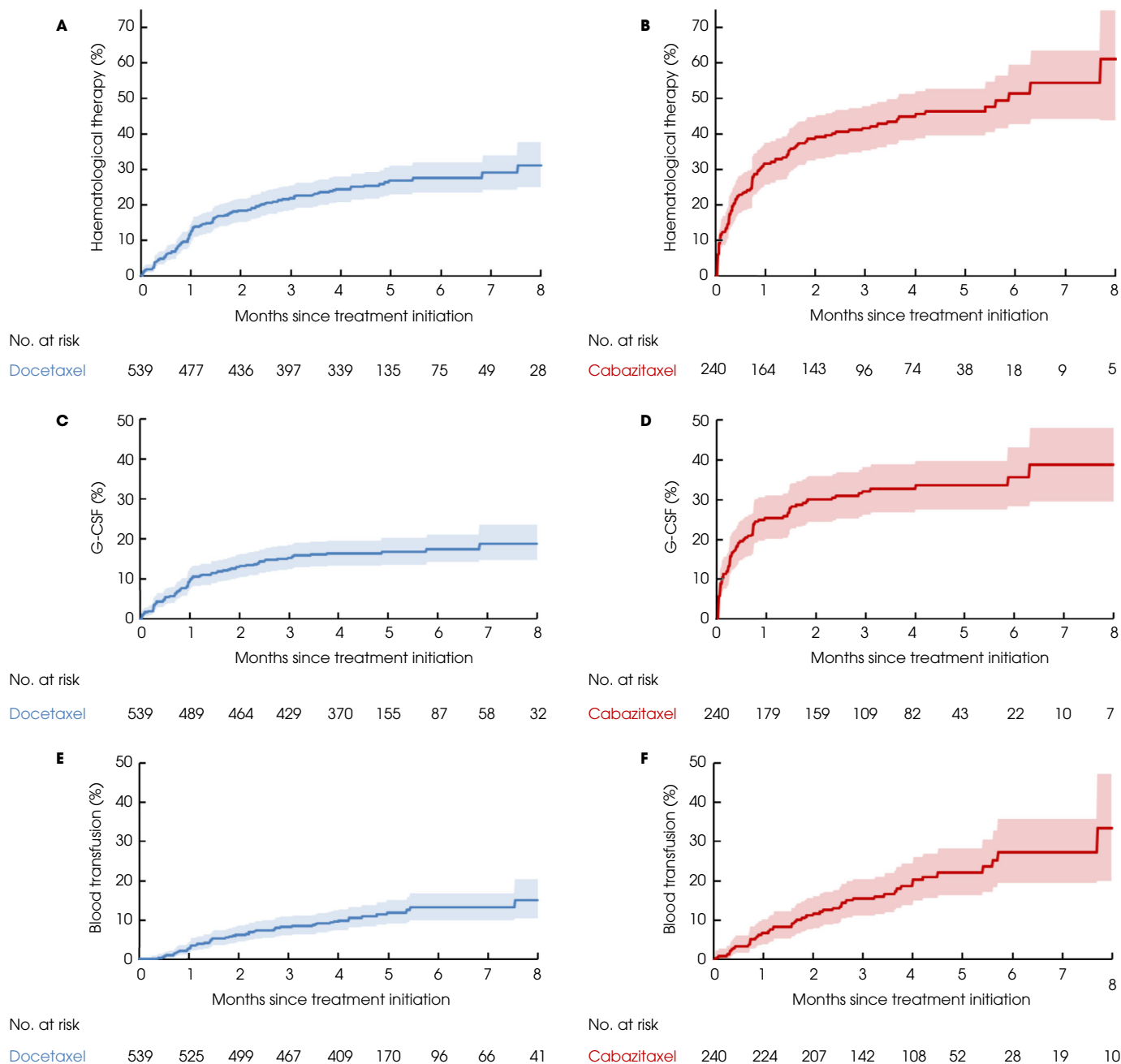
chemotherapy cycle with cabazitaxel or docetaxel; however, it is indicated as a prophylactic measure in the case of severe symptomatic neutropenia in subsequent cycles. In general, however, with respect to cabazitaxel [4], primary prophylaxis with G-CSF should be considered for patients with clinical high-risk factors for serious complications (e.g. age > 65 years, poor general condition, previous episodes of febrile

neutropenia). In the present study, sharp increases in the cumulative incidence plot of cabazitaxel-treated patients may reflect drug administration at the beginning of each conventional 3-week treatment cycle. Over the entire treatment period, administration rates of G-CSF (40%) were lower than those found in early access studies (≥ 60%) [9,20,21]; this may reflect greater risk avoidance through

TABLE 2 Inpatient stays associated with adverse events*.

Indication	Docetaxel			Cabazitaxel		
	1 month	3 months	8 months	1 month	3 months	8 months
Any kind of haematological toxicity	9 (1.7)	23 (4.3)	37 (11)	11 (5.0)	18 (8.4)	25 (15)
Neutopenia	5 (0.9)	15 (2.8)	24 (5.8)	7 (3.3)	11 (5.5)	16 (9.7)
Anaemia	4 (0.7)	9 (1.7)	16 (6.1)	4 (1.7)	8 (3.4)	12 (7.0)
Thrombocytopenia	0 (0)	1 (0.2)	2 (0.4)	2 (0.8)	4 (1.7)	8 (6.4)
Reverse isolation[†]	5 (0.9)	15 (2.8)	24 (9.9)	3 (1.7)	6 (3.2)	10 (7.9)
Sepsis	6 (1.1)	13 (2.4)	30 (13)	4 (1.7)	10 (4.4)	16 (15)
Fatigue	6 (1.1)	16 (3.0)	29 (10)	2 (1.3)	10 (4.8)	21 (14)
Nausea / vomiting	5 (1.1)	7 (1.5)	16 (7.1)	2 (0.8)	6 (2.6)	9 (4.7)
Diarrhoea /gastroenteritis	4 (0.7)	4 (0.7)	4 (0.7)	0 (0)	1 (0.4)	2 (5.8)

*Estimates are given as cumulative frequeny (cumulative percentage). *Cumulative incidence function of time to first admission with selected diagnoses (main or secondary diagnosis) within 1, 3 and 8 months after treatment initiation. [†]Admission to protect the individual from his surroundings.*

more intensive monitoring and early use in these studies. However, in line with other studies, the present study shows that, where treatment with G-CSF occurred, it was already in cycle 1 in half the cases [9,10,20,21]. By contrast, the administration of G-CSF in advanced cycles, as observed in the docetaxel cohort, may have been due to severe neutropenia in previous cycles.

A similar risk profile has emerged in the treatment of anaemia. According to the treatment guidelines [6,14], the administration of erythropoiesis-stimulating substances is only recommended for symptomatic anaemia, after careful consideration of the risks. The present study found that one-third of patients given cabazitaxel experienced treatment-emergent anaemia. Our results suggest that, under real-life conditions, crude rates of severe anaemia during treatment with cabazitaxel are higher than the rates of grade ≥ 3 anaemia reported in clinical studies, which were less than 12% [3,5,22]. Real-world studies [9,10,19,21,23] showed a much wider range, with a maximum of up to 27% [18].

To enhance the tolerability of cabazitaxel, several clinical trials have investigated different combinations of dose modifications and administration schedules [24]. When considering treatment-emergent adverse events, even in patients receiving low-dose cabazitaxel, the authors of an editorial [25] have explicitly pointed out the dangers of overtreatment, and called for precise patient selection, based on a comprehensive geriatric assessment (e.g. a G8 questionnaire). According to the guidelines developed for patients with prostate cancer aged > 70 years [26], treatment decisions should not depend primarily on age, but rather on patient health status, which affects both survival and the ability to tolerate adverse events. Aggressive treatment should only be administered to patients with reversible impairments (e.g. malnutrition). In this study, a substantial number of patients had severe underlying diseases, such as cardiovascular diseases or end-stage renal or liver failure.

Timing should also be considered when choosing an end-of-life therapy. Even if the patient's remaining life expectancy is difficult to predict and cabazitaxel represents one of the last options for tumour control, patients in the terminal phase can only benefit from chemotherapy when there is a genuine possibility of prolonging life or palliating symptoms. In the present study, one in 10 deceased patients in the cabazitaxel cohort received cytotoxic drugs in the last month of life. In the docetaxel cohort, only one in 20 patients received such drugs. In general, it has been demonstrated that cancer patients who receive tumour therapy very close to the end of life tend to have a higher symptom burden and poorer quality of life [27,28] than those who receive palliative care alone; the former often end their lives in acute care hospitals, [29] rather than entering hospices to receive appropriate palliative care. Regardless of the timing of therapy, a recent real-world study [13] has shown that, during active treatment, patients receiving cabazitaxel generally have a higher need for inpatient care than those receiving docetaxel (which is administered during earlier lines of therapy). Together with higher pharmaceutical costs, the monthly economic healthcare burden is three to four times higher for patients treated with cabazitaxel than for those receiving docetaxel.

The present study has some limitations. Because no ICD code for mCRPC exists, patients were identified using a combination of different classification systems (e.g. ICD and drug codes); however, as the purpose of treatment administration is not reported, some drugs may also be prescribed in a different setting. For example, in a clinical trial published in August 2015, the superiority of concomitant treatment with ADT plus docetaxel over ADT alone was demonstrated in terms of OS in patients with hormone-sensitive disease [30]. Depending on how quickly docetaxel was introduced into the therapeutic landscape, there might be a risk that patients with hormone-sensitive prostate cancer have been included. However, one-third of the patients in the docetaxel cohort had already started therapy before August

2015 and guideline implementation was only carried out in December 2016 [14].

Unfortunately, no information on the administered dosages was available in the claims data. In relation to adverse events, the number of patients with haematological toxicities was underestimated for two reasons: first, given the lack of clinical information in German claims data, patients were allocated to a treatment cohort based on a minimum number of therapy cycles, the duration of therapy, and continuous treatment. For example, patients who discontinued therapy after one or two cycles of cabazitaxel were excluded during patient selection, even though adverse effects or a poor response may have been of particular concern for these patients. Second, we were unable to differentiate between laboratory abnormalities and grade ≥3 adverse events. Nevertheless, drug code identification enabled us to record toxicities that were treatment-related in routine clinical settings. When reporting medical complications using inpatient diagnoses, it should be noted that these do not allow any conclusions to be drawn about the primary cause of hospitalization and that the causal relationship with prostate cancer or chemotherapy cannot be proven. However, as these are typical adverse events and competing oncological diseases were largely excluded in the course of patient selection [13], the probability of a correlation is high.

In conclusion, under real-life conditions, patients treated with cabazitaxel face an increased risk of haematological toxicities requiring treatment; in addition, their remaining lives are likely to be shorter than those reported in clinical studies. In some cases, cabazitaxel is administered shortly before death. With docetaxel as a reference, the treatment costs of cabazitaxel are also significantly higher, mainly due to higher drug costs and a greater need for inpatient treatment. In light of these findings, better guidelines are needed to establish criteria for the indication and timing of aggressive treatment at the end of life. Treatment choice requires a physician–patient discussion of the prognosis, which carefully considers the options for prolonging life, existing comorbidities, risks and the tolerability of adverse events and their treatment, as well as the patient's preferences for his remaining lifetime.

Conflicts of Interests

None declared.

Data Availability Statement

Claims data from the Techniker Krankenkasse were used under licence for the present study, and so are not publicly available.

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Abbreviations: ADT, androgen deprivation therapy; ATC, anatomical therapeutic chemical; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; ICD, International Classification of Diseases; mCRPC, metastatic castration-resistant prostate cancer; OPS, operation and procedure; OS, overall survival; PBM, pharmacy-based metric.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Sample selection flow chart.
Table S1. Claim codes indicating treatment for haematological toxicity.
Table S2. ICD codes for the identification of medical complications.
Table S3. Baseline comorbidities by cohort.