PharmacoEconomics - Open
https://doi.org/10.1007/s41669-020-00219-6

ORIGINAL RESEARCH ARTICLE

Treatment-Related Healthcare Costs of Metastatic Castration-Resistant Prostate Cancer in Germany: A Claims Data Study

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Abstract

Purpose Treatments for patients with metastatic castration-resistant prostate cancer (mCRPC) have expanded rapidly. They include the chemotherapies docetaxel and cabazitaxel, hormonal drugs abiraterone and enzalutamide, and best supportive care (BSC). Cabazitaxel has proven to be the last life-prolonging option, associated with a significant risk of serious adverse events. Given the lack of real-world evidence, we aimed to compare healthcare resource utilization (HRU) and costs in patients with mCRPC treated with cabazitaxel, docetaxel, abiraterone, enzalutamide, and BSC.

Methods We used 2014–2017 claims data from a large German statutory health insurance fund, the Techniker Krankenkasse, to identify patients with mCRPC. Patient allocation to individual therapy regimens was based on clinical knowledge and included therapy cycles, duration of therapy, and continuous treatment. The study period lasted from the first claim until death, the end of data availability, a drug switch, or discontinuation of therapy, whichever came first. Multivariate regression models were used to compare monthly all-cause and mCRPC-related HRU and costs across cohorts by adjusting for baseline covariates (including age and comorbidities).

Results The 3944 identified patients with mCRPC initiated treatment with cabazitaxel ($n = 240$), docetaxel ($n = 539$), abiraterone ($n = 486$), enzalutamide ($n = 351$), or BSC ($n = 2328$). In most domains, HRU was highest in the cabazitaxel cohort and lowest in the BSC group. Accordingly, the highest all-cause and mCRPC-related costs per month, respectively, were observed in patients receiving cabazitaxel (€7631/€6343), followed by abiraterone (€5226/€4579), enzalutamide (€5079/€4416), docetaxel (€2392/€1580), and BSC (€959/€438). Cost variations were mostly attributable to drugs, inpatient treatment, and sick leave payments.

Conclusion mCRPC treatment imposes a high economic burden on statutory health insurance. Cabazitaxel is associated with substantially higher expenses, resulting from higher drug costs and a greater need for inpatient treatment. As mCRPC continues to be incurable, decision makers and clinician leaders should carefully evaluate public access to innovative agents and optimal treatment strategies.

Key Points for Decision Makers

Patients with metastatic castration-resistant prostate cancer (mCRPC) treated with cabazitaxel have more hospital admissions and substantially higher monthly treatment costs than patients treated with docetaxel, abiraterone, enzalutamide, and best supportive care.

In choosing a treatment, the clinical management of mCRPC should carefully weigh expected survival against potential adverse events and the financial burden resulting from healthcare resource utilization.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s41669-020-00219-6) contains supplementary material, which is available to authorized users.

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Published online: 30 May 2020

1 Introduction

Castration-resistant prostate cancer (CRPC) is an advanced form of cancer where the disease progresses despite medical or surgical treatments to lower androgens. Approximately 10–20% of patients with prostate cancer (PC) become hormone refractory within 5 years after diagnosis. At CRPC diagnosis, over 84% of patients have metastases. Of the remaining patients, one-third could expect metastasis diagnoses within 2 years [1, 2]. Although, in 2010, the median overall survival after metastatic CRPC (mCRPC) diagnosis was reported to be 9–13 months [1], new treatments have increased median survival to approximately 16–35 months, depending on the tumor burden [3]. In Germany, almost 14,000 men die every year from PC [4].

Although treatment for patients with mCRPC is limited to palliative care, several treatment options are available. Depending on clinical symptoms, performance status, pretreatment, and patient preferences, treatments include immunotherapy, hormonal therapy, chemotherapy, and supportive measures (best supportive care [BSC]) [5]. Treatment options improved with the introduction of docetaxel, which was the first drug to improve survival in patients with mCRPC and has been the standard first-line therapy since 2004 [6, 7]. Further life-prolonging drugs became available with the approval of cabazitaxel chemotherapy in 2010, followed by the hormonal drugs abiraterone and enzalutamide [5]. Cabazitaxel was designed to overcome docetaxel resistance. In the TROPIC phase III trial, cabazitaxel led to a significant increase in median overall survival compared with mitoxantrone (15.1 vs. 12.7 months) in patients pretreated with docetaxel [8]. Antineoplastic activity of cabazitaxel has also been shown in patients with progressing mCRPC pretreated with docetaxel and hormonal drugs (abiraterone or enzalutamide) [9]; however, as a first-line treatment, cabazitaxel did not demonstrate superiority over docetaxel in terms of overall and progression-free survival [10]. Cabazitaxel also raised some concerns as it induced a significantly higher risk of grade III/IV neutropenia compared with mitoxantrone (82 vs. 58%, respectively) [8]. Current German guidelines recommend cabazitaxel as second-line therapy for patients with mCRPC with disease progression during or after docetaxel treatment and a good performance status [11].

Although treatments have expanded rapidly, information on their financial impact is limited. In the EU, the total economic burden of PC was estimated to be €8.43 billion in 2009, of which €5.43 billion was attributable to direct healthcare costs. Germany has Europe's highest PC healthcare expenditure per person [12]. PC costs of illness (COI) in Germany were estimated at approximately €1.85 billion in 2015 [13]. Focusing on COI analyses in the field of mCRPC, a recently published worldwide review [14] reported a broad range of cancer-specific healthcare costs, depending on the characteristics of included patients. However, only few studies have stratified costs by treatment, with most focusing exclusively on selected treatments—for example, hormonal therapy [15–17]—only considering pharmacy costs [15, 18, 19], and/or estimating costs for a hypothetical patient population (literature-based cost analysis) [16, 20]. Since mCRPC healthcare costs have not previously been reported for Germany [14, 21] and the evidence for real-world outcomes of mCRPC stratified by contemporary treatment are limited, this study's purpose is to analyze the healthcare resource utilization (HRU) for patients with mCRPC and the costs of treatment with cabazitaxel, docetaxel, abiraterone, and enzalutamide in comparison with BSC. This can provide valuable information for decision makers and clinician leaders regarding public access to innovative treatments and optimal treatment decisions.

2 Methods

2.1 Perspective

This analysis was conducted to evaluate the economic burden of mCRPC in terms of statutory health insurance (SHI). Claims data were obtained from one of the largest sickness funds in Germany, the Techniker Krankenkasse, covering approximately 10 million individuals in 2017 [22]. The analysis includes HRU and pharmaceutical costs (ready-to-use drugs and cytostatic agents), outpatient and inpatient care, and sick leave payments. Copayments and out-of-pocket payments were not considered because costs were analyzed from an SHI perspective.

2.2 Study Population

Patient identification required documentation for at least one inpatient diagnosis, secured outpatient diagnosis, or hospital outpatient diagnosis for PC based on the *International Classification of Diseases, Tenth Revision, German Modification* (ICD-10-GM code C61) between 2014 and 2016. All male sample patients had to be continuously insured from 2014 to 2017 or until death (whichever came first). Identification of metastases was based on ICD codes C77, C78, and C79. To ensure the metastasis diagnosis was associated with PC (ICD codes do not include information on the primary tumor), patients were only included if ICD code C61 was documented in the same quarter. To ensure resources and costs were not influenced by additional cancer therapies, patients were excluded if further malignant neoplasms (ICD code 'C') were documented (in an inpatient or secured outpatient

diagnosis), with the exception of the following ICD codes: C20 (rectum), C41 (bone and articular cartilage of other and unspecified sites), C43/C44 (skin), C67 (bladder), C68 (other and unspecified urinary organs), C80 (malignancies without specification of side), and C85 (other and unspecified types of non-Hodgkin lymphoma). We allowed for malignancies that were judged by our clinical expert to be associated with locally advanced PC, for example malignant neoplasms of the bladder and rectum. Additionally, we did not exclude malignant neoplasms where the therapies did not compete with PC treatment (e.g., skin cancer).

Following current clinical practice guidelines for PC at the time of cohort selection [23–25], first-line therapy for maintaining castrate testosterone levels (androgen-deprivation therapy) was defined as at least one prescription of luteinizing hormone-releasing hormone (LHRH) agonists/antagonists identified through drug claims (L02AE01, L02AE02, L02AE03, L02AE04, L02BX01, L02BX02, and H01CA04). As regards second-line treatment, patients were categorized into five treatment groups: cabazitaxel, docetaxel, abiraterone, enzalutamide, and BSC. Patient allocation to cohorts was based on patients undergoing a first-line therapy who received either one of the second-line drugs or, for BSC, at least one of the selected outpatient/inpatient health services (e.g., pain therapy, radiotherapy, blood transfusion), as shown in Table 1 in the electronic supplementary material (ESM). As patients received multiple treatments (consecutively or in parallel), patient allocation to cohorts was based on clinical knowledge defining further criteria for continuous treatment. For inclusion in the cabazitaxel cohort, continuous treatment was defined as at least three cycles of chemotherapy within 90 days. For the docetaxel cohort, at least six cycles of chemotherapy were required, with three cycles given within 90 days. In the cabazitaxel and docetaxel cohorts, patients were excluded if they were not cabazitaxel naive and docetaxel naive, respectively, namely, if there was an initial drug prescription before the first-line index date. Reflecting clinical knowledge on the time period in which the first signs of resistance (i.e., prostate-specific antigen progression) can occur [26–28], in the abiraterone and enzalutamide cohorts, continuous treatment was defined as lasting at least 180 days, with at least six prescriptions within 180 days (with an average gap between pharmacy claims up to a maximum of 34 days). For the BSC cohort, we first restricted the potential pool of first-line therapy patients with mCRPC to those never having received cabazitaxel, docetaxel, abiraterone, or enzalutamide after first-line therapy. Inclusion in the BSC cohort required at least one BSC-specific healthcare service in addition to a PC diagnosis and an observation period of at least 180 days. In the hormonal cohorts and BSC, patients who received at least one cycle of chemotherapy (cabazitaxel or docetaxel) in the 3-month baseline period were excluded.

2.3 Study Design

The date of the first claim of chemotherapy/medication prescription or health service received (only in the BSC group) was defined as the index date. The study period spanned from that date until (1) death, (2) data cutoff (31 December 2017), (3) drug switch, or (4) discontinuation of therapy, whichever came first. In case (4), the observation period ended with the last claim plus 21 days (end of cycle) of cabazitaxel/docetaxel and plus 30/28 days (prescription length) in abiraterone/enzalutamide.

Complete claims data for patients meeting the eligibility criteria were extracted and the following baseline characteristics obtained: age at index date, duration of observation, and comorbidities. Patients' comorbidities were measured 1 year prior to the index date using the well-established pharmacy-based metrics (PBM) [29], which have been developed for risk adjustment in healthcare utilization. PBM include 32 binary indicators of chronic conditions identified by prescription claims data. Since diseases might not always be documented as ICD codes, filled prescriptions might reflect patients' perception of severe conditions that warrant treatment. To avoid overadjustment, PBM group 9 (including drug codes for malignancies) was discarded.

As the duration of observation differed between individuals, we calculated resource use and costs for the entire study period but reported them as monthly values. HRU was measured as the average number of drug prescriptions, outpatient visits, hospital outpatient visits, hospital admissions, hospital days, and days with sickness benefits. The number of outpatient visits was determined by adding up the number of invoiced services based on the uniform value scale per day and medical specialist [30].

Healthcare costs (€) were also extracted, but no adjustments were made to a common year of valuation. To identify cost drivers, costs were analyzed by type. For each inpatient stay and sick leave period, costs were divided by the length of stay/duration and calculated according to the start and end of observation. For inpatient stays where the discharge day occurred after the end of observation, only costs within the follow-up period were considered. To obtain outpatient care costs, we calculated average costs per quarter day [30] and multiplied them by the number of days under observation in that quarter. Moreover, overall healthcare costs were calculated as the sum of costs from all domains. Whenever possible, HRU and costs were reported separately for all mCRPC-related events (defined as mCRPC-related medication or claims with a PC diagnosis) and regardless of underlying medical reasons (all-cause HRU and costs).

2.4 Statistical Analyses

To compare baseline characteristics, we reported absolute and relative frequencies for categorical variables and summarized continuous variables using the mean, standard deviation, and median. Differences between cohorts regarding patient characteristics and outcomes were analyzed using Chi-squared tests or Fisher's exact tests (count <5) for categorical variables and Mann–Whitney *U* tests (two groups) and Kruskal–Wallis tests (more than two groups) for continuous variables. Significance was determined at the level of ≤ 0.05.

We conducted unadjusted and adjusted comparisons. The HRU and cost outcomes of patients treated with cabazitaxel, docetaxel, abiraterone, and enzalutamide were compared with those of the patients in the BSC cohort. Adjustments were made for the following covariates: age groups, further malignancies documented in patients with mCRPC, and comorbidities according to PBM. For adjusted comparisons of HRU, incidence rate ratios (IRRs) were estimated using Poisson-specified regression models with or without zero inflation (depending on the model fit). To address uncertainties, we applied bootstrap analysis with 1000 samples per model for calculating the confidence intervals (CIs). For cost prediction, we estimated two-part models for all cost categories where the dependent variable was zero for at least one observation. Thus, we split the analysis into two parts, i.e., first fitting the probability of observing a positive versus zero outcome and then analyzing positive costs using linear regression based on ordinary least squares or generalized linear models with a gamma distribution, and identity link function, depending on the model fit. While the cohort estimates are provided exclusively in the following tables and figures, the entire output for all-cause healthcare costs is provided in Table 4 in the ESM (as a check for robustness).

To compare our results with those from other studies, we converted costs to € using the average exchange rate of a given year as listed in Eurostat [31] and reported them as monthly costs. Data management and statistical analyses were performed with SAS 9.4 for Windows, SAS Institute Inc., Cary, NC, USA.

3 Results

3.1 Study Population

We identified 92,712 patients (see Fig. 1) with a PC diagnosis in 2014–2016 who were continuously enrolled until the end of 2017 or to death, whichever came first. Of the 8525 patients with metastases, 5771 received first-line treatment with LHRH agonists or antagonists. Using the study inclusion criteria concerning the number of prescriptions, continuous treatment, and pretreatment, patients were treated as follows: cabazitaxel ($n = 240$), docetaxel ($n = 539$), abiraterone ($n = 486$), enzalutamide ($n = 351$), and BSC ($n = 2328$).

Table 1 presents patient demographics and baseline characteristics. With an average age of 71 years, patients receiving cabazitaxel and docetaxel were significantly ($p < 0.0001$) younger (by approximately 3 years) than patients starting hormonal therapy or BSC. In the cabazitaxel and docetaxel cohorts, there was a larger proportion of individuals aged < 70 years and a smaller share of individuals in the oldest age group (≥ 80 years). The median duration of observation ranged between 4 months in the cabazitaxel cohort and 24 months in the BSC cohort. When considering comorbidities at baseline, patients in the cabazitaxel cohort had the highest mean number of PBM groups, and BSC patients had the lowest. As shown in supplementary Table 2, 16 of 31 PBM groups differed significantly between cohorts. Cardiovascular diseases, rheumatic conditions, acid peptic diseases, and pain/inflammation were the most frequent chronic conditions documented in the 12 months preceding the index date.

3.2 Healthcare Resource Use

In most types of all-cause healthcare consumption, average unadjusted and adjusted utilization rates were highest for the cabazitaxel and lowest in the BSC group (Fig. 2). Adjusted analyses show that patients in the cabazitaxel, docetaxel, abiraterone, and enzalutamide cohorts had significantly more all-cause drug prescriptions, outpatient visits, and hospital outpatient visits than those in the BSC cohort (reference category). Cabazitaxel treatment was associated with a significantly higher number of all-cause inpatient admissions per month (IRR 2.34; 95% CI 1.77–2.93), even in comparison with all other cohorts. Moreover, patients in the chemotherapy cohorts spent significantly more days in hospital per month (cabazitaxel: IRR 2.57 [95% CI 1.65–3.77]; docetaxel: IRR 1.71 [95% CI 1.09–2.32]), whereas IRRs in the antihormone cohorts did not differ significantly from those receiving BSC. No significant differences existed in adjusted HRU between abiraterone and enzalutamide groups.

With the exception of inpatient admissions, a similar trend was observed in mCRPC-related HRU (Fig. 1 in the ESM). After adjusting for baseline covariates, all treatment cohorts showed a significantly higher number of mCRPC-related inpatient admissions compared with the BSC cohort. The adjusted IRRs (95% CIs) were 3.02 (2.14–4.02) for cabazitaxel, 1.48 (1.14–1.92) for docetaxel, 1.40 (1.11–1.76) for abiraterone, and 1.34 (1.06–1.68) for enzalutamide.

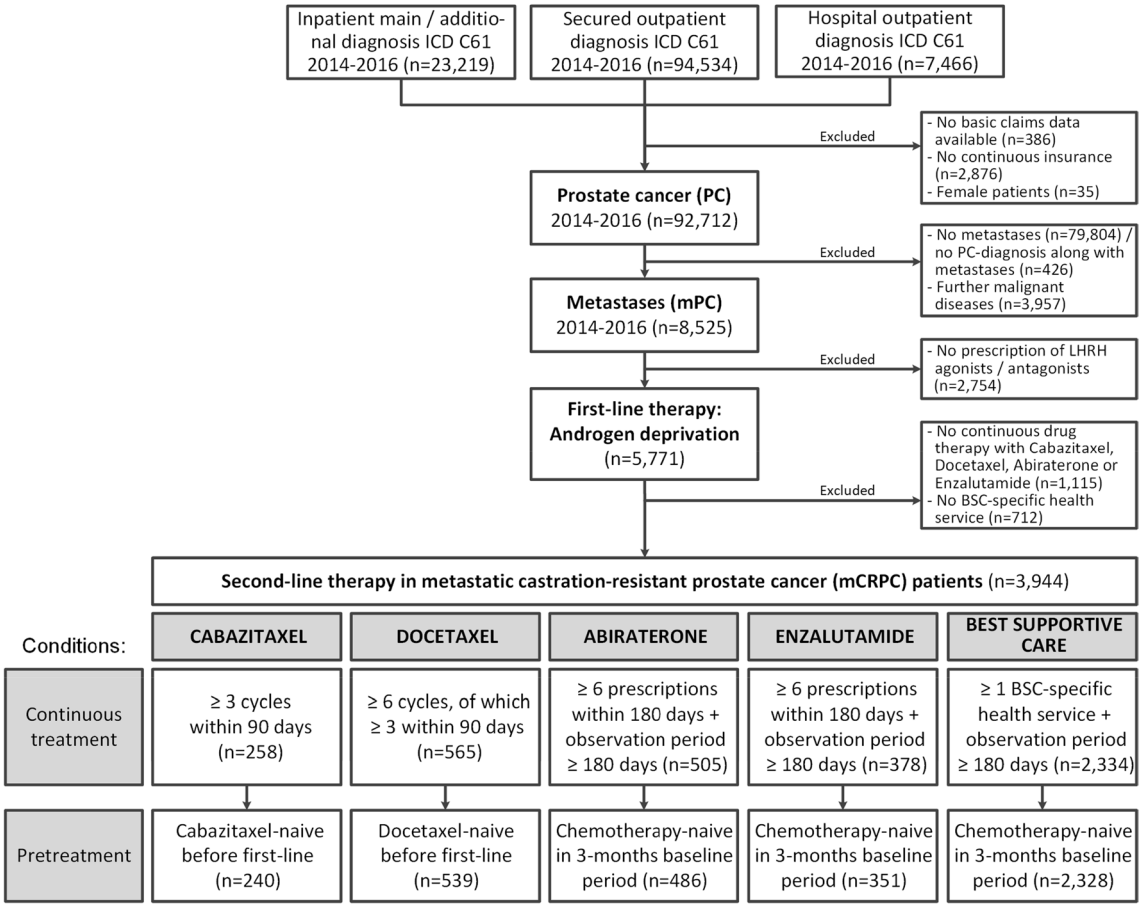

Fig. 1 Cohort selection. *BSC* best supportive care, *ICD* International Classification of Diseases, *LHRH* luteinizing hormone-releasing hormone, *mCRPC* metastatic castration-resistant prostate cancer, *mPC* metastatic prostate cancer, *PC* prostate cancer

3.3 Healthcare Costs

Adjusted monthly all-cause healthcare costs per patient (Fig. 3) totaled €7631 for cabazitaxel and were approximately three times higher than for docetaxel (€2392), 1.5 times higher than for abiraterone (€5226) and enzalutamide (€5079), and eight times higher than for BSC (€959). mCRPC-related healthcare costs accounted for 46–88% of monthly all-cause costs.

Except for hospital outpatient care, unadjusted cost analyses showed significant differences in healthcare costs among all cohorts (Table 3 in the ESM) and in most cost domains when considering cost differences compared with BSC (Table 2). Controlling for baseline covariates in mCRPC-related cost regression, Table 2 revealed that the probability of getting treatment did not differ significantly in all domains compared with BSC. However, if treatment occurred, costs associated with cabazitaxel or docetaxel treatment were significantly higher in almost all cost domains. Regarding cost distribution, variations were most prominent for pharmaceutical treatment, followed by inpatient care and sick leave payments. Compared with BSC, the adjusted differences (95% CI) in mCRPC-related monthly prescriptions and inpatient treatment were €4318 (4066–4428) and €417 (267–578), respectively, for cabazitaxel and €984 (914–1016) and €101 (38–170), respectively, for docetaxel. Thus, cabazitaxel-treated patients had significantly higher monthly drug and inpatient care costs when directly compared with those for patients receiving docetaxel. With respect to antihormonal therapy, the monthly burden of hospitalization in the abiraterone cohort was similar to that in the BSC cohort, and enzalutamide-treated patients did not differ with respect to hospital outpatient care and sick leave payments.

With regard to all-cause healthcare costs, adjusted differences showed a similar trend with drug prescription accounting for by far the majority of all-cause costs. No significant cost differences existed between abiraterone- and enzalutamide-treated patients in adjusted regression models.

In general, older age was associated with significantly lower all-cause monthly healthcare costs (Table 4 in the ESM). Compared with patients aged <65 years,

Table 1 Patient demographics and baseline characteristics

	Cabazitaxel	Docetaxel	Abiraterone	Enzalutamide	BSC
Age					
Years, mean ± SD	70.61 ± 7.7	70.46 ± 7.8	73.98 ± 7.7	74.72 ± 8.2	73.74 ± 8.6
Years, median	72	72	75	76	75
Age group, n (%)					
<65 years	48 (20.0)	122 (22.6)	63 (13.0)	43 (12.3)	317 (13.6)
65–69 years	40 (16.7)	108 (20.0)	53 (10.9)	43 (12.3)	314 (13.5)
70–74 years	62 (25.8)	126 (23.4)	121 (24.9)	72 (20.5)	528 (22.7)
75–79 years	70 (29.2)	121 (22.5)	132 (27.2)	94 (26.8)	616 (26.5)
≥80 years	20 (8.3)	62 (11.5)	117 (24.1)	99 (28.2)	553 (23.8)
Follow-up duration[a]					
Months, mean ± SD	4.5 ± 2.5	5.6 ± 2.9	16.2 ± 9.7	15.7 ± 7.9	26.3 ± 12.7
Months, median	4.2	4.5	12.7	13.4	24.2
Comorbidities[b]					
Mean ± SD	5.2 ± 2.3	4.6 ± 2.5	4.0 ± 2.4	4.4 ± 2.7	3.6 ± 2.5
Comorbidity classes[b], *n (%)*					
0	2 (0.8)	9 (1.7)	25 (5.1)	21 (6.0)	203 (8.7)
1–3	53 (22.1)	192 (35.6)	208 (42.8)	123 (35.0)	1028 (44.2)
4–6	123 (51.3)	219 (40.6)	182 (37.5)	128 (36.5)	806 (34.6)
7–9	51 (21.3)	103 (19.1)	64 (13.2)	67 (19.1)	247 (10.6)
≥10	11 (4.6)	16 (3.0)	7 (1.4)	12 (3.4)	44 (1.9)

Cohorts differ significantly ($p < 0.0001$) in all baseline characteristics. Differences were analyzed using Chi-squared tests for categorical variables and Kruskal–Wallis tests for continuous variables

BSC best supportive care, *SD* standard deviation

[a]Follow-up duration was measured as the time span from the index date until the end of observation (death, drug switch, discontinuation of therapy, or data cutoff, whichever came first)

[b]Comorbidities were assessed using a pharmacy-based metric with 32 classes. The redundant group of malignancies (group 9) was excluded

the gamma-specified regression model on all-cause costs showed a cost reduction of €316 for patients aged 65–69 years, €420 for patients aged 70–74 years, €329 for patients aged 75–79 years, and €286 for patients aged ≥80 years. The presence of the following chronic conditions significantly increased monthly all-cause costs (descending order): end-stage renal disease (€3633), HIV (€1003), pain (€458), anti-arrhythmics (€281), rheumatic conditions (€181), Parkinson's disease (€155), diabetes (€147), acid peptic disease (€101), and pain and inflammation (€88).

4 Discussion

This study provides insights into the HRU and costs of mCRPC for cabazitaxel, docetaxel, abiraterone, enzalutamide, and BSC in a real-world setting. It also contributes to an understanding of which factors drive costs. It highlights the high healthcare burden related to patients with mCRPC, especially those treated with cabazitaxel. Our analysis used claims data from one of the largest sickness funds in Germany, providing a greater sample size than most other COI studies on mCRPC [14, 32]. The participants' mean age (73 years) is similar to the previously reported mean age at CRPC diagnosis [1, 14]. Cabazitaxel- and docetaxel-treated patients were about 3 years younger than those in the other groups. At baseline, there were significant differences in the burden of disease across cohorts, with patients receiving cabazitaxel showing the highest mean number of comorbidities.

This study also revealed that HRU and costs highly depend on the treatment. Existing literature shows a wide range of healthcare costs in mCRPC [14, 32], but only few studies stratify costs by treatment. We found that, with few exceptions, adjusted IRRs were highest with cabazitaxel and lowest with BSC. Accordingly, cabazitaxel resulted in the highest healthcare costs by far, followed by abiraterone, enzalutamide, docetaxel, and BSC. Although we did not find any study analyzing healthcare costs by all the treatments used here, these cost proportions were also observed in studies comparing treatment with selected chemotherapies and hormonal therapies [18, 20, 33]. The higher economic burden with cabazitaxel was mainly due to higher drug costs and a greater need for inpatient treatment, even compared with docetaxel. As we detected large differences in CIs concerning hospitalization, further research should investigate

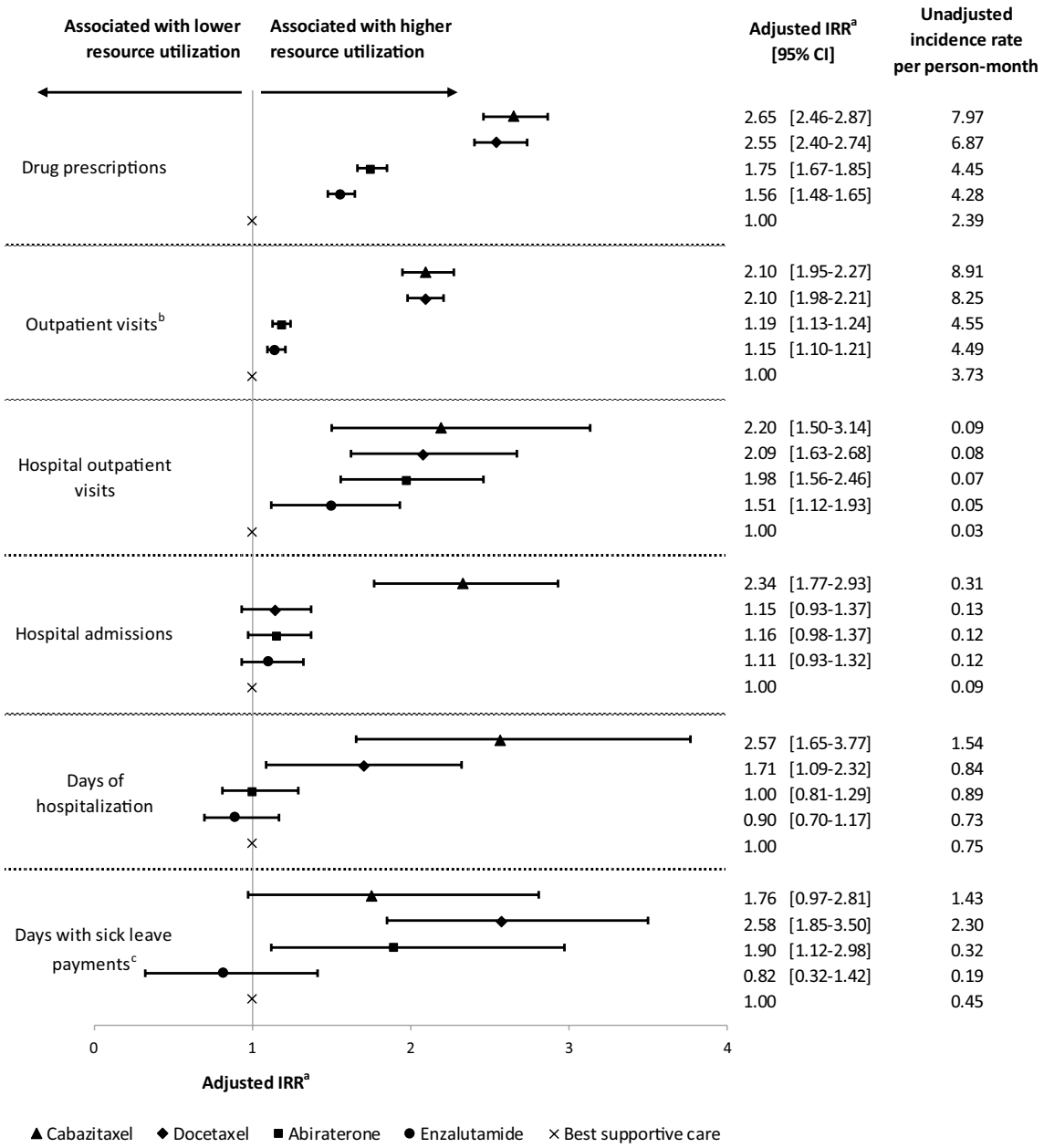

Fig. 2 Monthly all-cause health resource utilization by cohort. *CI* confidence interval, *IRR* incidence rate ratio. [a]IRRs were estimated using Poisson-specified regression models with or without zero inflation (depending on the model fit). Adjustments were made for the following baseline covariates: age groups, comorbidities (pharmacy-based classes), and further malignancies documented in patients with mCRPC. For calculation of CIs, a total of 1000 bootstrap samples were used. An estimate is statistically significant whenever the confidence interval does not include 1.0 (does not cross the vertical axis). [b]The unadjusted number of outpatient visits is underestimated. Flat-rate fees mean that not every outpatient consultation is documented in German claims data. [c]If an illness lasts longer than 6 weeks, the employee will receive sick leave payments from the health insurance covering 70% of the gross salary for up to 78 weeks

whether the increased number of hospital admissions might be due to planned hospitalizations to administer chemotherapy or the result of serious adverse events (e.g., febrile neutropenia) related to cabazitaxel. Controlling for baseline covariates, higher all-cause drug costs with cabazitaxel might stem from the fact that these patients are generally treated with more comedication to increase the safety and tolerability of chemotherapy than were the other mCRPC cohorts. Moreover, the higher sick leave payments in the chemotherapy cohorts might reflect the greater proportion of patients entitled to sickness allowance (employed individuals) combined with higher hospitalization rates.

Compared with existing literature on absolute cost values, our analysis revealed that, with €6343 for cabazitaxel and

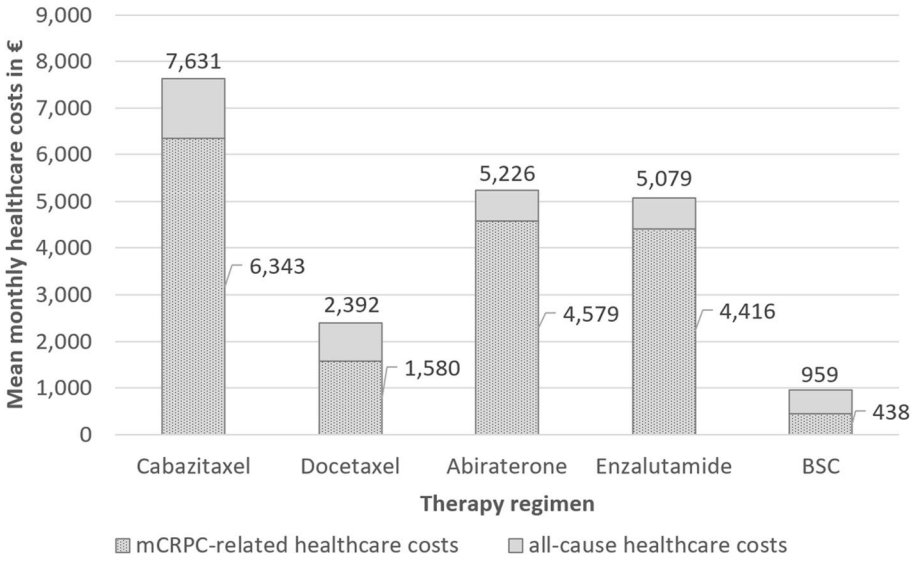

Fig. 3 Adjusted[a] mean monthly healthcare costs in patients with mCRPC by therapy. *BSC* best supportive care, mCRPC metastatic castration-resistant prostate cancer. [a]Adjusted models controlled for the following baseline covariates: age groups, comorbidities (pharmacy-based classes), and further malignancies documented in patients with mCRPC

€1580 for docetaxel, the monthly total mCRPC-related costs for chemotherapy seem to be slightly lower. In US/Canadian budget impact analyses/modelling approaches, monthly cabazitaxel treatment has been priced at €6182 (2013) for primary medication [18] and €9823–10,546 (2012) for drugs and administration [20]. The corresponding values for docetaxel were €566 (2013) for drugs [18]; €1310 (2014) for drugs, administration, concomitant medication, monitoring, and adverse events [33]; and €2817–3275 (2012) for docetaxel retreatment drug and administration [20]. However, variations might be explained by differences in healthcare system structure, reimbursement schemes, unit costs, and practice patterns [34].

Regarding antihormonal therapy, our analysis revealed monthly mCRPC-related healthcare costs of €4579 for abiraterone and €4416 for enzalutamide. Although abiraterone treatment monthly pharmacy costs are similar to those previously reported in US studies, averaging approximately €4500 (2012/2014/2017) [15, 17, 20], monthly total mCRPC-related costs are reported to be higher in most US studies, ranging from €5727 (2014) to €9715 (2017) [16, 17, 33]. However, some of these studies included additional cost domains (e.g., post-progression treatments and end-of-life care). Comparing enzalutamide to abiraterone, some US studies [15, 17, 33] considered its pharmacy costs to be higher but costs beyond drug acquisition (e.g., monitoring, adverse events, and end-of-life care [16, 17]) to be lower. By contrast, a recent claims data analysis [17] failed to show significant differences in total mCRPC-related healthcare costs. Controlling for baseline covariates, we did not find any significant differences in HRU and healthcare costs between these groups.

With monthly costs of €438, by far the lowest HRU and costs in most domains were observed with BSC. As its aim is to minimize symptom burden and maintain quality of life without directly affecting tumor activity, drug costs remain relatively low. As BSC covers a wide range of services, relevant drugs (e.g., cortisone) might have been neglected, thus underestimating costs. Since some health services (e.g., drugs) are not documented with an ICD diagnosis in German claims data, non-indication-specific medication is difficult to allocate to the underlying disease. However, consulting a clinical expert, we defined key treatment options in patients receiving BSC, including disease surveillance, pain therapy, radiotherapy, and blood transfusion. Further research is necessary to describe the BSC population and capture all kinds of supportive services.

Irrespective of the treatment, like previous studies [14, 17, 21, 35–37], our analysis highlights the financial impact of medication, followed by that of inpatient care (and partly sick leave payments) as the most important cost drivers in mCRPC. Moreover, across all cohorts, the youngest patients were the costliest per month. Although the age gradient has been a controversy discussed in PC treatment [36, 38, 39], it might be explained as follows: depending on their performance status, older men might receive a smaller dose of chemotherapy and thus have a lower risk of developing serious adverse events requiring intensive treatment.

Some limitations must be mentioned, most of which are inherent in the database (for an overview, see Kreis et al. [40] and Neubauer et al. [41]). First, patient allocation to treatment cohorts was based exclusively on services reimbursed by SHI. As claims data are routinely collected for billing and reimbursement, information on clinical parameters, such as cancer stage or tumor type, were not available for patient selection or cost stratification. Moreover, as already stated [32], we did not find a completely validated algorithm identifying patients with mCRPC in the literature.

Table 2 Difference in monthly healthcare costs (in €) compared with best supportive care

	Unadjusted cost differences[a]								Adjusted cost differences[b]								Model[c]
	Cabazitaxel vs BSC		Docetaxel vs BSC		Abiraterone vs BSC		Enzalutamide vs BSC		Cabazitaxel vs BSC		Docetaxel vs BSC		Abiraterone vs BSC		Enzalutamide vs BSC		
	Diff	*p* value	Diff	*p* value	Diff	*p* value	Diff	*p* value	Diff	*p* value	Diff	*p* value	Diff	*p* value	Diff	*p* value	
All-cause costs																	
Drugs	6417	> 0.999	1420	> 0.999	4294	> 0.999	4160	> 0.999	6280	> 0.999	1336	> 0.999	4253	> 0.999	4107	> 0.999	Logit
		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001	Gamma[d]
Outpatient care	162	< 0.001	108	< 0.001	− 9	0.277	0	0.982	130	< 0.001	109	< 0.001	− 2	0.690	4	0.535	Gamma[e]
Hospital outpatient care	31	0.002	31	0.082	4	0.528	15	0.851	22	< 0.001	23	0.006	6	0.614	12	0.730	Logit
		< 0.001		< 0.001		0.064		< 0.001		0.001		< 0.001		0.003		0.002	Gamma[d]
Inpatient care	385	0.004	90	< 0.001	84	0.062	95	0.147	237	< 0.001	38	< 0.001	40	0.004	59	0.003	Logit
		< 0.001		< 0.001		< 0.001		0.001		< 0.001		0.040		0.137		0.048	Normal[f]
Sick leave payments[g]	530	0.127	845	< 0.001	184	0.002	23	0.022	289	0.794	775	0.208	153	0.001	− 31	0.020	Logit
		< 0.001		< 0.001		0.013		0.804		0.023		< 0.001		0.009		0.703	Normal[f]
Total costs	7128	< 0.001	1707	< 0.001	4360	< 0.001	4249	< 0.001	6672	< 0.001	1432	< 0.001	4267	< 0.001	4120	< 0.001	Gamma[e]
mCRPC-related costs[h]																	
Drugs	4538	0.041	994	0.003	4074	> 0.999	3909	> 0.999	4318	0.127	984	0.006	4071	0.999	3906	0.999	Logit
		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001	Gamma[d]
Hospital outpatient care	36	0.643	33	0.050	0	0.001	− 1	0.004	35	0.606	37	0.815	14	0.003	8	0.002	Logit
		0.006		< 0.001		0.912		0.881		< 0.001		< 0.001		0.002		0.064	Gamma[d]
Inpatient care	622	0.007	157	0.668	93	< 0.001	139	0.006	417	0.082	101	< 0.001	58	0.024	114	0.527	Logit
		< 0.001		< 0.001		0.040		0.006		< 0.001		0.004		0.172		0.013	Normal[f]
Sick leave payments[g]	540	0.145	862	< 0.001	197	0.004	58	0.018	277	0.720	783	0.145	169	0.002	− 4	0.014	Logit
		< 0.001		< 0.001		0.012		0.537		0.033		< 0.001		0.009		0.957	Normal[f]
Total costs	6116	> 0.999	1315	> 0.999	4192	> 0.999	4031	> 0.999	5904	> 0.999	1141	0.999	4141	0.999	3978	> 0.999	Logit
		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001	Gamma[d]

Diff difference in monthly costs compared with BSC, *BSC* best supportive care, *mCRPC* metastatic castration-resistant prostate cancer

[a]Unadjusted models include therapy cohorts as explanatory variables

[b]Adjustments were made for the following baseline covariates: age groups, comorbidities (pharmacy-based classes), and further malignancies documented in patients with mCRPC

[c]Adjusted and unadjusted costs were estimated using two-part models for all categories where the dependent variable was zero for at least one observation. Positive costs were analyzed using linear regression based on ordinary least squares or generalized linear models with a gamma distribution, and identity link function, depending on the model fit. *p* values are shown for all parts of the models. As different regression models were used, adjusted cost differences cannot be summed up to total costs

[d]Two-part gamma model

[e]Gamma-specified model

[f]Two-part ordinary least squares model

[g]If an illness lasts longer than 6 weeks, the employee will receive sick leave payments from the health insurance, covering 70% of the gross salary for up to 78 weeks

[h]mCRPC-related drug costs were defined as any claim for cabazitaxel, docetaxel, abiraterone, enzalutamide and luteinizing hormone-releasing hormone. mCRPC-related hospital (outpatient) costs and sick leave payments were defined as any claim with a diagnosis of prostate cancer (*International Classification of Diseases* C61), including main/additional diagnosis in inpatient care

However, consulting a clinical expert, we developed an algorithm identifying patients with PC, metastasis, castration resistance, and second-line treatment, using a wide range of different classification systems for claims data. There is a strong likelihood that mCRPC in the final treatment cohorts was appropriately captured because inclusion required the prescription of (predominant) disease-specific drugs and evidence of continuous treatment.

Second, regarding HRU, the number of outpatient visits is underestimated. Flat-rate fees mean that not every outpatient consultation is documented in German claims data; for example, a patient may go to the doctor several times per quarter but be documented as a single treatment case [30]. Moreover, as only quarterly outpatient care cost data were available, costs might not have been assigned adequately depending on the varying treatment duration of drug groups. However, in a sensitivity analysis, we calculated costs by using the date of treatment in the database, confirming our main results. Third, similarly, mCRPC-related medication costs and consequently total mCRPC-related healthcare costs by treatment group are rather underestimated because the costs of comedication (e.g., antiemetics) and adverse events (e.g., nausea, stomatitis, and diarrhea) associated with the primary therapy were not considered in the analysis. Since drug claims are not linked with a diagnosis in German claims data, the assignment of costs from non-indication-specific drugs is challenging. However, we used a conservative approach to estimate mCRPC-related costs and calculated all-cause drug costs to report the maximum of healthcare costs.

Novel agents in the field of hormonal manipulation and chemotherapies are rapidly changing the available mCRPC treatments; therefore, patient allocation to cohorts represented a challenge, requiring further criteria for continuous treatment. To achieve the aims of palliative treatment, proper sequencing and effective combination of available agents becomes increasingly important for both clinicians and researchers. Although general guidelines on treatment options and algorithms exist [11, 23, 24], studies on the optimal choice, combination, and sequence of agents to maximize the clinical benefits (and minimize cross-resistance) [5, 42] or define thresholds for therapy changes are lacking.

5 Conclusion

This is the first study to assess all-cause and PC-related HRU and costs in patients with mCRPC stratified by five contemporary treatments reflective of real clinical practices. In Germany, mCRPC treatment represents a high economic burden for SHI. Our study observed substantial differences in age, HRU, and costs with cabazitaxel, docetaxel, abiraterone, enzalutamide, and BSC. Cabazitaxel- and docetaxel-treated patients were significantly younger than those receiving the other treatments. In most domains, cabazitaxel was associated with the highest HRU and healthcare costs because of the higher drug costs and inpatient care required. Future analyses should examine the reasons for this greater need for inpatient treatment and assess the financial impact with respect to survival time and adverse event rates. With expanding treatment options for patients with mCRPC resulting in an increased economic burden, public access to innovative agents and optimal therapeutic strategies should be carefully evaluated.

Author contributions All authors contributed to the study conception and design. Data validation, preparation, and analysis were performed by Kristine Kreis. Dirk Horenkamp-Sonntag and Udo Schneider offered access to claims data and were consulted on database specifics and statistical methods. Jan Zeidler provided expert oversight in the conception, implementation, and interpretation of the cost analysis and contributed throughout the manuscript. Lothar Weissbach initially developed the idea and provided clinical expertise during data analysis (by defining patient identification and cohort selection) and interpretation. Gerd Glaeske offered a drug-specific background in claims data-based healthcare research and focused on the structure of the paper. The first draft of the manuscript was written by Kristine Kreis, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability The data that support the findings of this study are available from the Techniker Krankenkasse, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Compliance with Ethical Standards

Funding No sources of funding were used to conduct this study or prepare this manuscript. The publication of this article was funded by the Open Access Fund of the Leibniz Universität Hannover.

Conflict of interest KK, DHS, US, JZ, GG, and LW have no conflicts of interest that are directly relevant to the content of this study.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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