Science For A Better Life

Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Title	Second primary cancers in patients with castration resistant prostate cancer (BOCARP)
Keywords	Prostatic Neoplasms; Prostatic Neoplasms, Castration-Resistant; Neoplasms, Second Primary; Incidence; Bone Metastasis; Epidemiology
Rationale and background	Prostate cancer (PC) figures the most second common form of cancer in males with an estimated incidence of 65,800 cases in Germany in 2010. Usually, PC has a good prognosis with a relative survival rate of 93% within five years after the diagnosis. Yet once the patient has reached the symptomatic stage of PC, the prognosis worsens substantially and makes interventions necessary. At that time, 30% of patients present with a locally progressed tumor or metastases, decreasing the mean survival time below 3 years. The gold standard in treating symptomatic PC is hormone ablation with or without chemotherapy to stop or delay tumor progression by decreasing testosterone to castrate levels. Moreover, surgical castration is another option to decrease levels of testosterone in order to prevent tumors from growing. Patients, whose tumors still progress after castration, have developed the castrate-resistant form of prostate cancer (CRPC) which is frequently characterized by bone metastases (mCRPC) and a substantial decrease of life expectancy with 97% of patients dying within five years. This condition is not curable, and treatment primarily aims at symptom management. Recently, radium-223-dichloride (Xofigo®) has been approved in the US (May 2013) and Europe (November 2013) for the treatment of bone metastases in PC. It selectively targets bone metastases with high-energy, short-range alpha-particles. As this is a radiopharmaceutical agent, post-authorization monitoring of radiation associated second malignancies is necessary. Since for eligible patients the treatment with radium-223-dichloride cannot be denied due to ethical reasons, data from patients that might serve as control group to patients who are treated with radium-223-dichloride must be obtained from historical control groups.
Research question and objectives	The primary objective of this study was to estimate the incidence of any second primary malignancy (SPM, including myelodysplastic syndrome/acute myeloid leukaemia and osteosarcoma) among patients with PC and bone metastases (mPC), as well as among a subgroup of patients for whom the PC can be regarded as castration-resistant (mCRPC). The secondary objective of this study was the evaluation of the overall survival of mPC and mCRPC patients. Furthermore, the incidence of site-specific SPMs was evaluated.
Study Design	Observational retrospective cohort study
Setting	Data from January 1, 2004 to December 31, 2013 were used. The

	basic cohort included patients with PC and bone metastasis (mPC). For this, male subjects with a first bone metastases diagnosis (ICD-10 Code C79.5) after at least one year continuous observation period without the diagnosis (cohort entry) were enrolled from January 1, 2005 to December 31, 2011. Additionally, cohort members needed to have a diagnosis of PC (ICD-10 Code C61) not later than two months from cohort entry and should never have a claim for any radiopharmaceutical during the observation period. Among these mPC patients, a subcohort of patients was identified who were considered as being castrationresistant (mCRPC). For this, at least one of several algorithms needed to apply until up to 30 days from cohort entry. The algorithms were based on dispensed drugs and/or codes from inpatient procedures. Cohort exit was defined as the end of insurance coverage due to any reason (including death) or as the end of the study period (December 31, 2013).
Subjects and Study Size, including dropouts	A total of 6,442 patients with PC and bone metastases were identified (mPC). Among those, 2,360 met the additional inclusion criteria for castration resistance (mCRPC).
Variables and Data sources	The primary outcome was defined as any incident SPM (ICD-10 codes: C00-C76, C81-C96, D00- D09, D37-D48) during follow-up. To be considered incident, the respective ICD-10 code must not have occurred ever before cohort entry. In a sensitivity analysis, patients with a history of any abovementioned primary malignancies were excluded. The secondary outcome was the overall survival of mPC and mCRPC patients identified through the reason for the end of the insurance period and the reason for discharge from hospital. General characteristics of the study populations were described at cohort entry. Comorbidities, medication use, and operations were shown for different time periods. For the primary objective, the overall as well as the age-stratified incidence rate (IR) per 1,000 person years of SPMs was calculated separately for the mPC and mCRPC study populations. Further stratifications were done by treatments, comorbidities, and covariates. For the site-specific SPMs, IRs were calculated overall and age-stratified. For overall survival, Kaplan-Meier curves and survival rates were generated. This study was based on administrative data from two statutory health insurance providers (SHI) included in the German Pharmacoepidemiological Research Database (GePaRD).
Results	The mean age of subjects in the mPC cohort was 71.8 years (SD: 8.4) and 72.9 (SD: 7.8) years in the mCRPC subcohort, respectively; 60.9% of mPC patients were 70 years or older (mCRPC: 66.4%).

	Patients of both groups were highly comorbid with hypertension, renal diseases and hyperlipidemia being prevalent in up to 72% of all patients during the follow-up period. Regarding the incidence of any SPM per 1,000 person-years, an estimated IR of 256.6 (95% CI: 246.9-266.5) was found for mPC patients (sensitivity analysis: 236.4, 95% CI: 222.8-250.6) and an IR of 274.9 (95% CI: 256.8-293.9) for mCRPC patients, respectively (sensitivity analysis: 260.3, 95% CI: 233.0-289.9). In both groups, the trajectories of incident SPMs were comparable, with 30% of patients having developed a SPM within the first year after cohort entry, and 50% of patients after two and half years, respectively. The proportion of patients who were free of SPM eight years after cohort entry was 25% (mPC), and 21% (mCRPC). For both groups, the IRs did not vary substantially across the age groups considered (log-rank test p-value=.343). For mPC patients, the IR for all SPM except skin cancer was 238.3 (95% CI: 229.0-248.0) and 106.91 (95% CI: 100.7- 113.4) for the category of solid tumors, with highest IRs for osteosarcoma (12.5, 95% CI: 10.4-14.8) and lung cancer (12.2, 95% CI: 10.1-14.5) and lowest rates for leukemia (1.9, 95% CI: 1.2-3.0) and myelodysplastic syndrome (0.97, 95% CI: 0.5-1.8). The IR for multiple SPM diagnoses was 10.9 (9.0-13.1). For mCRPC patients, the IR for all SPM except skin cancer was 260.8 (95% CI: 243.1-279.3) and 115.1 (95% CI: 103.5-127.7) for the category of solid tumors. Among those, highest IRs were found for bladder cancer (14.8, 95% CI: 10.8-19.7) and lung cancer (13.1, 95% CI: 9.4-17.8) and lowest IRs were found for leukemia (0.96, 95% CI: 0.2-1.8) and myelodysplastic syndrome (1.3, 95% CI: 0.3-3.3). The IR for multiple SPM diagnoses was 10.6 (95% CI: 7.3-14.9). For both patient groups site-specific IRs did not vary substantially in the sensitivity analysis. The median survival time for mPC and mCRPC patients was 635 days (95% CI: 603-667) and 475 days (95% CI: 442-503), respectively. Among mPC patients, 36% have died after one year, 64% after three years and 80% after seven years. Less than 18% were still alive more than 8 years after cohort entry. Among mCRPC patients, 42% have died within the first year after cohort entry, 63% have died after two years and, 75% after three years and less than 8% were still alive more than 8 years after the development of bone metastases. For both groups of patients a significant association between mortality and age was seen with lower survival rates for older patients at cohort entry than for younger patients ($p<0.001$).
Discussion	Our data underline the worse prognosis of PC once patients have

	reached the stage of bone metastases or bone metastases and castration-resistance. Moreover, our results suggest a substantial increased risk of further primary malignancies in patients with mPC/mCRPC. However, due to potential limitations concerning the validity of cancer diagnoses in this study, the high incidence rates for SPMs should generally be treated with caution. An overestimation of the rates seems likely but further investigations are necessary to make clearer statements about its magnitude.
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