Differences in trial and real world populations in the Dutch castration-resistant prostate cancer registry (CAPRI).

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Abstract

Background
Trials in castration-resistant prostate cancer (CRPC) treatment have shown improved outcomes including survival. However, trial populations are selected and therefore results may not be representative for the real world population.

Objective
To assess the differences in a real world CRPC population between patients treated in a clinical trial versus standard care during the course of CRPC.

Design, setting and participants
A population based sample is registered in the observational, retrospective CAPRI registry. CRPC patients from 20 hospitals in the Netherlands have been included from 2010 to 2013.

Outcome measurements and statistical analysis
Baseline characteristics, systemic treatment and overall survival (OS) were the main outcomes. Descriptive statistics, multivariate Cox regression and multiple imputation by Monte Carlo Markov Chain method were used.

Results and limitation
Of the total 1,524 patients, 203 patients had been enrolled in trials at any time during a median follow up period of 23 months. Patients in the trial subgroup were significantly younger and had less comorbidity. Docetaxel treatment was more frequent in trial patients (85% vs 40%). Despite an observed unadjusted median OS difference of 35 versus 24 months between the trial and standard care subgroup, this difference was not retained after adjustment for baseline differences and treatment effect.

Conclusions
At CRPC diagnosis, baseline characteristics of patients who are enrolled in trials notably differ from patients who receive standard treatment options only. The survival difference between the trial and standard care subgroup could be explained by baseline differences and treatment effect. These results indicate that trial results cannot easily be translated to real world practice.

Patient summary
We observed that patients treated in clinical trials differ from patients who are not. We conclude that this may lead to differential treatment and survival. This warrants caution when comparing real world outcomes to trial results.

Introduction

Prostate cancer is a common cause of cancer in men[1]. The incidence and mortality in the Netherlands in 2010 were 104 and 25 per 100,000 (European Standardized Rate), respectively [2]. Relative survival for patients with prostate cancer in the Netherlands and Europe is comparable [3].

The first palliative treatment in metastatic prostate cancer is androgen deprivation therapy (ADT) by either medical or surgical castration. The addition of chemotherapy in hormone sensitive metastatic prostate cancer was not applicable in the study period. Once progression on ADT occurs the condition is known as castration-resistant prostate cancer (CRPC). Key items in the definition of CRPC are a castration level of testosterone and a rising PSA (biochemical progression) and/or radiologic progression [4-7].

Treatment recommendations depend mainly on the presence of metastases and the presence of symptoms, and include (year of introduction in the Netherlands in brackets): secondary hormonal manipulations (including abiraterone (post-docetaxel 2012, chemotherapy naïve 2013) and enzalutamide (post-docetaxel 2013, chemotherapy naïve 2014)), chemotherapy (including docetaxel (2005) and cabazitaxel (2011)), bone directed therapy (including radium-223 (2014)), immune therapy (sipuleucel-T, not available in the Netherlands during the study period) and treatment in clinical trials [4-7].

Trial outcomes form the basis of guidelines and treatment decisions in daily practice. However, trial populations are selected and therefore results may not be representative for the real world population [8]. Moreover, new treatment options in CRPC have changed treatment practice and thus influence baseline and post treatment characteristics. Real world data on CRPC patient characteristics, treatment and outcomes are scarce, and reports are often outdated [9]. Therefore we have initiated the CAPRI registry to investigate the clinical outcomes, treatment patterns and economic outcomes of CRPC treatment in daily practice.

In this paper we report the first results of the CAPRI registry. The aim of this analysis is to assess differences in baseline characteristics at CRPC diagnosis, systemic treatment and survival in patients treated in trials versus standard care during the course of CRPC.

Methods

Study design and setting

CAPRI (CAstration-resistant Prostate cancer RegIstry) is an investigator-initiated, observational multi-center cohort study in 20 hospitals in the Netherlands. Before the start of the study, 20 hospitals were selected on the basis of geographical spread, as well as by type of hospital (both general and academic hospitals) and accepted the invitation. Data collection started after approval by the local medical ethics committee and hospital board. Patients were retrospective included from January 1st, 2010 and data has been regularly updated for all patients from 2013 to 2015. The study population is an estimated 20% sample of all CRPC patients in the Netherlands in the study period. The study is registered in the Dutch Trial Registry as NTR3591.

Objective

To assess the differences in a real world CRPC population between patients treated in a clinical trial ("trial") versus standard care during the course of CRPC.

Participants

Patients were screened for inclusion in both the urology and medical oncology departments of each hospital, and were identified by the diagnosis code prostate cancer from the hospital information systems based on encoded "Diagnosis Treatment Combinations", a nationwide coding and reimbursement system providing information about the type of care, diagnosis and all treatment modalities. Eligible patients had to be diagnosed with prostate cancer (defined as histologic confirmation of prostate cancer or as concluded by the treating doctor based on elevated PSA and metastatic pattern), and had disease progression despite ADT. Disease progression was defined as in the EAU CRPC definition [6], or as progression according to the treating doctor. Anti-androgen therapy following progression on ADT was considered first line systemic therapy for CRPC. In addition, patients had to be diagnosed with CRPC in years 2010, 2011 or 2012 and have more than two outpatient clinic visits. Eligible patients treated in more than 1 hospital were included only once.

If a patient was enrolled in a phase 1, 2 or 3 trial during the follow up period, the patient was assigned to the "trial" subgroup, otherwise the patient was assigned to the "standard care" subgroup.

Follow up and data collection

Predefined and readily available data from medical records were retrospectively collected by trained data managers. Database cut-off was set on March 1st, 2015. See Appendix 1 for full overview of data variables.

Study size

Here we report the first analysis after registration of the first 1,524 consecutive patients.

Statistics

Descriptive statistics were used. Differences in subgroups were tested for significance by either Chi-square test (categorical variables) or Mann-Whitney U (continuous variables). Survival analyses were done by Kaplan-Meier methods and Cox regression analyses. Differences were considered of statistical significance at a p-value of 0.05 or less.
For imputation of missing baseline characteristics, multiple imputation by Monte Carlo Markov Chain method was used as described before [10]. For statistical analyses, IBM SPSS

Statistics version 22 was used.

Results

At the time of this analysis (March 2015), 29,565 prostate cancer patients were identified in 20 hospitals (11 large teaching hospitals, 5 general hospitals and 4 academic hospitals). A flow diagram of the screened population, exclusion and inclusion of patients is shown in Figure 1.

1,524 CRPC patients were included, diagnosed with CRPC in 2010 (30%), 2011 (37%) or 2012 (33%). Of all patients, 203 (13%) had been treated in at least one trial (range 1-4; 48 patients participated in more than 1 trial) during the course of disease (trial subgroup). The remaining 87% patients had not been treated in a trial (standard care subgroup). The most common trials are shown in supplementary Table S4. Life prolonging drugs have been given to patients in the trial subgroup in both trials and as standard care: docetaxel 46/173 (27%) in trials, cabazitaxel 69/94 (73%) in trials, abiraterone 3/114 (3%) in trials, enzalutamide 0/46 (0%) in trials and radium-223 4/7 (57%) in trials. Life-prolonging drugs have been given as study drug in randomized placebo-controlled trials in a minority of cases (abiraterone/placebo n=5, enzalutamide/placebo n=18).

The median follow up period from CRPC diagnosis was 23 months (Inter quartile range (IQR) 11 to 34 months). At the time of the database cutoff, 983 deaths (65%) had occurred, 180 patients (12%) were lost to follow up and 361 patients (24%) were still in follow up with a median follow up period of 39 months (range 26 – 62 months).

Baseline characteristics

Baseline characteristics of the patients at CRPC diagnosis, and differences between the two subgroups, are shown in Table 1. Distribution of CRPC criteria are provided in supplementary Table S5. The population includes 6% of patients without a histologic diagnosis of prostate cancer and 4% with unknown histologic status, thus included on the basis of PSA and clinical characteristics alone. Testosterone was not measured in 51% at baseline, however in 10% of patients testosterone was measured later in the course of CRPC. Patients in the trial subgroup were significantly younger (67 vs 76 years, $p<0.001$) and had less comorbidity (No comorbidity 76% vs 54%, $p<0.001$). At CRPC diagnosis, patients in the trial subgroup had higher hemoglobin (8.4 vs. 8.0 mmol/L, $p<0.001$), lower LDH (215 vs 228 U/L, $p=0.033$), and better clinical performance score (ECOG $\geq$2 2% vs 7%, $p=0.015$).

Treatment

All systemic treatments until end of follow up are summarized in Table 2.

During the follow up period, 46% of all patients had been treated with docetaxel. In the trial subgroup, 85% of patients were treated with docetaxel as compared to 40% of patients in the standard care subgroup ($p<0.001$). In the trial subgroup, cabazitaxel (46% vs 7%, $p<0.001$), abiraterone post-docetaxel (50% vs 22%, $p<0.001$), enzalutamide post-docetaxel (20% vs 15%, $p<0.001$), enzalutamide chemo-naïve (5% vs 1%, $p<0.001$) and radium-223 post-docetaxel (3% vs 1%, $p=0.003$) were initiated more often, whereas prescription of abiraterone (6% vs 8%, $p=0.419$)and radium-223 (0% vs <1%, $p=0.377$) in chemotherapy-naïve patients was more equally spread.

Survival

Median overall survival (OS) of all patients was 26 months (IQR 12 – 48 months). Median OS was 35 months (IQR 21 –60 months) for the trial subgroup, as compared to 24 months

(IQR 12 – 48 months) for the standard care subgroup ($p<0.001$), and is shown in Figure 2. Univariate analysis of baseline variables, trial enrollment and treatment strategy were done: the variables were dichotomized and patients with missing values were separately analyzed (see supplementary Table S6). After multiple imputation of missing values, we performed multivariate analysis of the pooled imputed data. After correction for baseline differences, independent significant prognostic factors for survival were Gleason score, period on ADT, hemoglobin, alkaline phosphatase (ALP), PSA and ECOG performance status (see Table 3). Treatment with abiraterone, enzalutamide and radium-223 in chemotherapy-naïve patients, as well as treatment with cabazitaxel, abiraterone, enzalutamide and radium-223 post-docetaxel was associated with longer survival (Hazard ratio (HR) 0.53; $p<0.0001$ and HR 0.46; $p<0.0001$, respectively). However, trial enrollment was no longer significant for OS (HR 0.95, $p=0.658$).

Discussion

To our knowledge, this is the first registry of this size in which outcomes are registered independent of the treating doctors. The design of the registry allowed the inclusion of patients without histologic confirmation of prostate cancer or not meeting the CRPC definition by the EAU but regarded as CRPC by the treating doctor. Therefore, the outcomes in this study truly reflect daily practice.

The population includes 6% of patients without a histologic diagnosis of prostate cancer and 41% without measurement of testosterone during the course of disease. It is unlikely that patients are enrolled in trials without histological diagnosis or without an objective CRPC status, however the baseline period in our study (90 days before to 90 days after CRPC diagnosis) differs from the date of trial enrollment. This explains missing or unknown data on CRPC status in the trial subgroup.

We observed a median OS in the total population of 26 months, and a significant longer OS in the trial subgroup compared to standard care (35 vs 24 months, $p<0.001$). This difference may at least partly be explained by confounding factors, including baseline differences or differences in treatment. After correction for baseline prognostic factors and treatment effect, trial participation was not associated with a significantly lower risk of death (HR 0.95, $p=0.658$).

Trial patients differed mainly from standard care patients with regards to age (67 vs 76 years), comorbidity (no comorbidity 76% vs 54%) and treatment strategy (docetaxel treatment 85% vs 40%).

Baseline characteristics of recent clinical trials in docetaxel-naïve populations are relatively similar to this study, particularly to the trial subgroup [11-13]. The median OS in the trial subgroup of 35 months compares slightly favorably to the median OS of the trial comparator arms in chemotherapy-naïve CRPC trials of 21.7 to 30.2 months [11-13]. We observed subsequent docetaxel therapy in the trial subgroup in 85% of patients, whereas subsequent therapy with docetaxel in the comparator arms of the trials ranged from 50 to 57% [11-13]. In a single-center analysis of trial participants only, chemotherapy-naïve CRPC patients (median age 67 years) had a median OS of 30.6 months and subsequent docetaxel treatment was given in 64% [14]. In conclusion, the baseline characteristics, systemic treatment and outcomes of our trial subgroup are representative for known trial populations.

Missing values are a limitation of our study. This is inherent to the retrospective method of the study. For this analysis, we have analyzed baseline differences at the moment of CRPC diagnosis, not at the start of each subsequent treatment. In the baseline period, evaluation of disease stage (CT-scan and bone scintigraphy) and laboratory parameters (hemoglobin, ALP, LDH), as well as performance status registration, were frequently incomplete. LDH and visceral disease status were missing in >50% of cases, but were included because of known prognostic relevance. Missing values were less frequent at the start of subsequent treatment, especially in life-prolonging drugs (data not shown), reflecting daily practice and the absence of direct need of documentation of these parameters at progression on ADT. Gleason scores may be missing if no histologic biopsy was taken, or if the biopsy dates from the period prior to the introduction of the Gleason scoring system in 2004 [15]. However, we adapted tumor grades to Gleason scores if possible (see Appendix 1). When excluding all patients with missing values in prognostic factors, only 113 patients were available for multivariate

analysis, which consequently lacked statistical power. Imputation of missing data provides a valid and reproducible solution for this problem, allowing multivariate analysis on the complete study population [10].

Known predictors of survival in metastatic CRPC include disease site (visceral disease), Gleason score, performance status, ALP, hemoglobin, PSA and LDH [16]. After imputation of missing values, we confirmed these predictors of survival in our population (see supplementary Table S7). Moreover, after correction for baseline differences, independent significant prognostic factors for survival did also include period on ADT.

The treatment effect is difficult to assess in this analysis. Treatments were given sequentially with differential sequences in a non-protocolled manner. Therefore we analyzed the prescription of life-prolonging drugs (abiraterone, enzalutamide, radium-223, docetaxel and cabazitaxel) as a proxy for treatment effect. We observed that patients in the trial subgroup were treated with more treatment lines and more life-prolonging drugs. Treatment with life-prolonging drugs was associated with increased survival in multivariate analysis.

Trial patients were enrolled in more than 15 different trials. A total of 264 trial treatments were registered, with a substantial number of treatments in a trial with survival benefit but placebo-controlled (n=28), a trial with no difference in outcome between the study arms (n=96) or a trial that has no results yet (n=93). Although we did not aim to answer the question if trial participation is an independent prognostic factor for survival, we hypothesize that placebo treatment or treatment in trials without proven survival benefit over standard treatment may have diluted a positive effect of trial treatment on survival, if present.

Based on a systematic review in 2001, it was concluded that there is weak evidence to suggest that clinical trials have a positive effect on the outcome of participants, possibly through enhancing quality of care, stringent patient selection criteria, and adapting aggressive measures for treating patients in trials [17]. Two recent reports on patients treated with docetaxel for metastatic CRPC either in a trial or outside a trial resulted in improved OS for trial participants [18;19]. In our study participation in trials does not yield survival benefit after adjusting for baseline characteristics and treatments received. We hypothesize that this may reflect the high availability of novel treatment options and mandatory health care insurance in the Netherlands. A limitation may therefore be the lack of external validity to populations outside the Netherlands, especially those populations with different access to healthcare.

In conclusion, we have shown that baseline characteristics of patients enrolled in a trial differ from patients who are not, as well as the percentage of patients treated with docetaxel. The difference in OS between trial patients and standard care patients did not retain statistical significance after correction for baseline differences and treatment effect. These results may indicate that trial results cannot easily be translated to real world practice. Further studies are needed to assess clinical outcomes, patient reported outcomes and cost-effectiveness of treatment in real world populations.

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