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Editor's Choice

Characterising the castration-resistant prostate cancer population: a systematic review

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Disclosures
Professor Kirby has received funding for research, advice, lecturing and conference costs from the pharmaceutical industry. Dr Hirst is currently an employee of AstraZeneca R&D UK, and has previously worked as a consultant in epidemiology for several pharmaceutical companies. Professor Crawford has served as a consultant and speaker for GlaxoSmithKline, Sanofi-Aventis and AstraZeneca.

SUMMARY

Background: Castration-resistant prostate cancer (CRPC) is an advanced form of prostate cancer associated with poor survival rates. However, characterisation of the disease epidemiology is hampered by use of varying terminology, definition and disease management. The aim of this review was to conduct a systematic review to provide greater clarity on the sum of the available epidemiologic evidence and to guide future research into the disease prevalence, progression, characteristics and outcome. **Methods:** Systematic searches of PubMed and Embase were performed in March 2010 to identify relevant observational studies relating to the epidemiology, progression and outcomes of CRPC. Further studies were identified for inclusion in our review through manual searches of the authors' bibliographical databases and the reference lists of the included articles. **Results:** We identified 12 articles (10 full papers and 2 abstracts) reporting studies that included a total of 71,179 patients observed for up to 12 years for evaluation in our review. Five studies looked at the prevalence of CRPC in patients with prostate cancer. Together, the data indicate that 10–20% of prostate cancer patients develop CRPC within approximately 5 years of follow-up. Two studies reported the prevalence of bone metastases present at diagnosis of CRPC. Together, ≥ 84% were shown to have metastases at diagnosis. Of those patients with no metastases present at diagnosis of CRPC, 33% could expect to develop them within 2 years. The median survival of patients with CRPC was reported in five studies, with values varying from 9 to 30 months. A pooled, sample-weighted survival estimate calculated from the survival data included in this review is 14 months. Very few studies that met our inclusion criteria evaluated treatment patterns in CRPC. One study reported that only 37% of patients with CRPC received chemotherapy, with the remainder receiving only steroids and supportive care. The most common palliative therapies administered to patients with skeletal symptoms were radiotherapy, radionuclide therapy, bisphosphonates and opioids. **Conclusions:** This review highlights the poor prognosis of patients with CRPC, and demonstrates a survival of 9–13 months in those patients with metastatic CRPC. Furthermore, progression to CRPC is associated with deterioration in quality of life, and few therapeutic options are currently available to patients with CRPC. However, epidemiologic study of these patients is hampered by differing terminology, definitions and treatment paradigms. Our review highlights the need for further well-designed, epidemiological studies of CRPC, using standardised definitions and methods.

Review Criteria

Observational studies reporting epidemiological data on CRPC were identified through systematic searches of literature on PubMed, Embase and authors own databases. Articles were selected using predefined inclusion/exclusion criteria, and data were abstracted in a structured manner. Where possible and appropriate, meta-analysis of data was performed to provide pooled weighted means.

Message for the Clinic

This review of real-world evidence demonstrates that CRPC is a common and highly morbid progression of prostate cancer, with around 10–20% of prostate cancer patients progressing to this state within 5 years. Metastases are present in over 84% of CRPC patients, and the mean survival is around 14 months from CRPC diagnosis. Bone pain occurs in most patients, and fractures, spinal cord compression and vertebral collapse are common. Variability in definitions and clinical practice hinder the comparison of research, and efforts should be made to improve consistency in future research.

Introduction

Cancer of the prostate is the most common cancer occurring in the men of the USA and Europe (1,2). In the minority of patients whose cancers are aggressive or advanced, therapeutic options include prostatectomy, radiation therapy and, more commonly, androgen-deprivation therapy (3). Castration-resistant prostate cancer (CRPC) is an advanced form of prostate cancer characterised by disease progression following surgical or pharmaceutical (androgen deprivation) castration. The process by which prostate cancer cells become castrate resistant is unclear, but it has been proposed that androgen ablation pro-

vides a selective advantage to androgen-independent cells, which grow and eventually repopulate the tumour (4). Compared with castration-sensitive prostate cancer, the prognosis for patients with CRPC is poor and survival is reduced. Treatment options have, until very recently, been limited mainly to symptomatic relief of bone metastases, which are more common in CRPC than in castration-sensitive disease (5–8).

Defining epidemiological parameters of disease is an essential component of understanding how, when and where the disease develops; knowledge of the natural history of the disease and the likely outcomes of disease enable effective targeting and development of treatments. To give a clear picture of the burden of CRPC, one must take into account the prevalence of the disease, relative timing of onset in relation to prostate cancer diagnosis, characteristics of the patients including demographics and comorbidity, onset of metastatic disease, and likely survival. There is, however, a paucity of epidemiological evidence specifically characterising CRPC outside of controlled trial settings in which patients may not represent the general population and normal disease progression. This may result in suboptimal disease management; for example, identifying patients with CRPC who are at risk of developing metastases is currently hindered by poor understanding of the epidemiology of CRPC.

Identifying individuals with CRPC may seem straightforward to treating physicians, who are responsible for managing this progression of the disease after castration treatment. Characterising the disease in epidemiological terms, for example incidence, prevalence and survival, is, however, less clear. This may be attributed at least in part to the difficulty in defining, and hence studying, the patient population. The varying terminology – CRPC, HRPC (hormone refractory), AIPC (androgen independent), ERPC (endocrine resistant) – reflect subtle differences in definition which may hinder comparison of research. Physicians may also use different methods in diagnosis: PSA testing, development of metastases or other factors may determine whether a patient is defined as CRPC. The recently published European Association of Urology (EAU) guidelines aim to standardise CRPC diagnosis, and include a list of five defining factors of CRPC (3). These are:

- Serum castration levels of testosterone.
- Three consecutive rises of PSA 2 weeks apart resulting in two 50% increases over the nadir.
- Anti-androgen withdrawal for at least 4 weeks.
- PSA progression despite secondary hormonal manipulations.
- Progression of osseous or soft tissue lesions.

CRPC is a heterogeneous disease, and despite the availability of such practical guides to diagnose CRPC, in practice, this may vary. Furthermore, treatment pathways and clinical practice, in particular, the stage in the disease at which androgen-deprivation therapy is initiated, vary markedly between geographical locations and even individual clinics. Therefore, establishing common epidemiological estimates for the CRPC population becomes highly complex and risks becoming less relevant to individual scenarios.

The aim of this review was to improve the clarity of epidemiological evidence around CRPC, by systematically identifying, evaluating and describing the most relevant studies that characterise the CRPC patient population using observational data. From this, we aim to provide clearer guidance on measurement of epidemiological estimates of disease prevalence, progression and outcome, and to guide future research into CRPC.

Methods

PubMed and Embase searches were performed in March 2010 using the search terms detailed in Figure 1. Searches were limited to journal articles published in the previous 10 years reporting studies in men. Observational epidemiological studies were sought, as they were considered the best source of real-world non-interventional data on disease epidemiology, and randomised controlled trials, *in vitro studies*, editorials, letters, practice guidelines, reviews, case reports and comments, were excluded.

Relevant articles were screened, first, on the basis of the title and then on the abstract as outlined in Figure 1. Articles were then further screened based on the full text, and those that explored the epidemiology, time course and outcomes of CRPC were selected.

Further studies were identified for inclusion in our review through manual searches of the authors' bibliographical databases and the reference lists of the included articles.

The definition of CRPC, prevalence, metastatic status and survival of patients with CRPC were evaluated for each of the included studies, and symptoms, quality of life, and treatment patterns were also described if reported in the studies. Where possible, data were pooled to provide estimates for each of the epidemiological parameters.

Results

The PubMed and Embase searches identified 3329 unique articles. From these, six relevant articles were

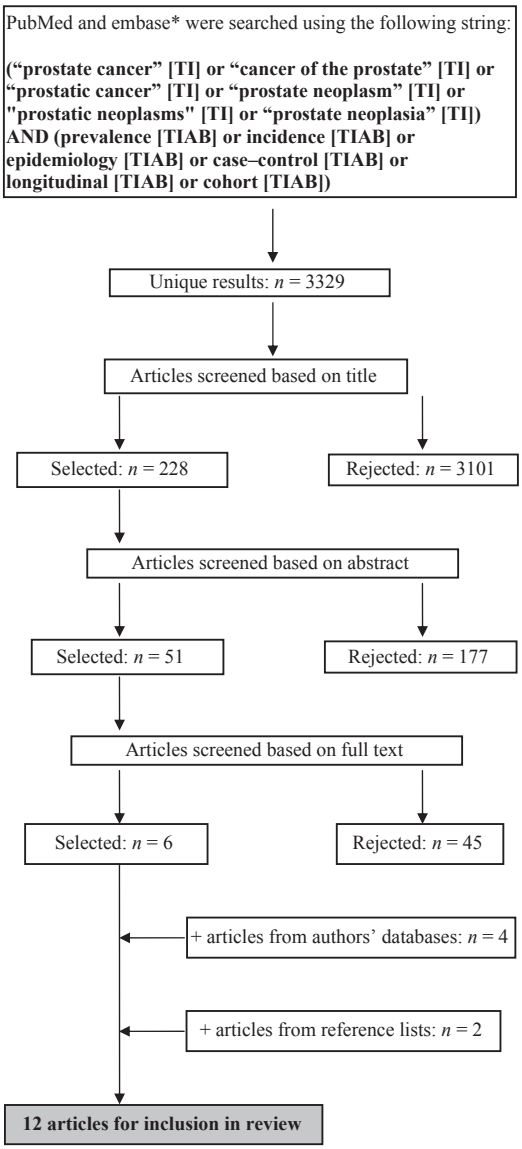

Figure 1 Search strategy. *The search string syntax was adapted for use in Embase

selected. The main reasons for excluding articles were a main focus on drug trial data (interventional study), the role of gene polymorphisms, the epidemiology of prostate cancer, in general (not CRPC) or that the prevalence/survival/progression of CRPC was not reported. Four further articles were selected from the authors' databases, and two were identified through searching of reference lists. This resulted in 12 articles (10 full papers and 2 abstracts) suitable for evaluation in our review.

Definition of CRPC used

Various diagnostic criteria were used by the 12 studies included in our review; none exactly matched with the EAU guidelines outlined above (3). Rising PSA levels were used to diagnose CRPC in nine (75%) of the studies (9–17). However, two of these also categorised patients who had a new lesion on a bone scan or growth of a lesion on a computed tomography (CT) scan as having CRPC (10,14). Another study relied upon observing worsening metastatic lesions by bone or CT scan in patients receiving hormone therapy (18). One study selected patients who had a diagnosis of symptomatic M1 metastatic CRPC using the Tumour Node Metastasis (TNM) staging criteria (19), and the final study assigned CRPC status to patients who failed to respond to postcastration hormone therapy and were switched to a third-line therapy (20).

The prevalence of CRPC in patients with prostate cancer

Five studies estimated the prevalence of CRPC in patients with prostate cancer (Table 1). Four of these evaluated patients were those who had been recently diagnosed with prostate cancer (9–11,20); the fifth study investigated patients with prostate cancer, who had undergone radical prostatectomy (12).

A statistical, propensity score algorithm was used by Alemayehu et al. to identify patients with CRPC from a pool of prostate cancer patients identified from a large US medical claims database (10). During a 6-year period, 15,361 hormone-treated patients (aged 40 years or over) were diagnosed with prostate cancer. In the same period, 2740 developed CRPC, which suggests a prevalence of 17.8%. The largest study of CRPC conducted to date used another US claims database, MarketScan (20). In total, 44,791 medically or surgically castrated adult prostate cancer patients were followed up until their exit from the database. Of these, 4266 (9.5%) developed CRPC (mean follow-up of approximately 2.1 years per patient). A similar study was conducted using data from UK primary care patients recorded in The Health Improvement Network (THIN) database (11). The data reveal that, in a 5-year period, 8678 patients aged 40 years or over were diagnosed with prostate cancer. Of these, 969 developed CRPC, a prevalence of 11.2%.

An Italian study of 211 secondary care patients with prostate cancer demonstrated that, within the 55 months following diagnosis, 53% of patients (median age 70 years) were considered to have CRPC (10). A further study investigated patients with prostate cancer who had undergone radical prostatectomy (12). The authors reported that 19% of patients developed CRPC within a median 55-month follow-up period.

As discussed above, the available CRPC definition guidelines (3) were not routinely used by the studies included in this review. Despite the heterogeneity between studies, the results of four of these five different studies suggest that 10–20% of prostate cancer patients develop CRPC in approximately 5 years of follow-up. It is likely that if similar study populations and disease definitions were used, this estimated range would be even tighter. The greatest outlier in these data came from the study that categorised patients who had a new lesion or growth of a lesion on a CT scan as having CRPC (10), which probably explains why this study estimated a higher prevalence (53%) than the studies that characterised CRPC on the basis of increasing PSA levels or treatment patterns.

Metastatic CRPC

Bone scans were used to investigate the prevalence of metastases at the time of CRPC diagnosis in two small studies (13,14) (Table 2). A Japanese study reported that in a population of 151 patients with CRPC (defined as three consecutive increases in PSA after castration), 84% had bone metastases at diagnosis (13). A separate study conducted in Italy reported that, of 200 patients with CRPC, 95% had bone lesions at diagnosis; however, as bone lesions were a qualifying criterion for CRPC status in the study, this may be an overestimate.

The progression to development of metastases was shown in a further paper that evaluated patients with CRPC (mean age 73 years) who had no metastases present at CRPC diagnosis (defined as rising PSA levels despite androgen-deprivation therapy) (17) (Table 2). Between 1999 and 2002, 201 chemotherapy-naïve CRPC patients, were followed up for 24 months from CRPC diagnosis. Of those patients who had no metastases at CRPC diagnosis, 33% had developed one or more (identified by bone scanning and radiography) within 2 years of CRPC diagnosis.

Survival for patients with CRPC

The median survival of patients with CRPC was reported in five studies (13–16,18). Reported values varied from 9 to 30 months (Table 3). Again, there was heterogeneity between studies. The individual studies did not consistently report the mean patient age, and so evaluating the effect of age on survival is not possible from these data. The study populations also varied in terms of the proportion of patients with metastases and bone pain. Another factor affecting survival that was not comparable between studies was the use of chemotherapy. One study did not report the percentage of patients who received chemotherapy and the values reported by the other four studies ranged from 14% to 100%. Radiotherapy use was not consistently reported.

Two studies included the presence of metastatic lesions as one of their criteria for defining CRPC (15,18), and these studies reported the shortest survival estimates. In the first study, in which CRPC was defined as rising serum PSA concentrations and serum alkaline phosphatase activity, progressively worsening bone pain or the appearance or re-appearance of skeletal metastases on bone scintigraphy despite being androgen deprived, the mean survival after the development of CRPC in 84 patients was 8.6 months (15). The second study of 89 US patients with CRPC (mean age 73 years) reported the mean survival after the diagnosis of CRPC (defined as

Table 1 The prevalence of CRPC in patients prostate cancer

	Reference	Study sample	Country (years study conducted)	Patient age	Definition of CRPC	Follow-up period	Prevalence of CRPC
Patients with PC	Alemayehu (9)	Retrospective study of data from 15,361 patients with PC from a US medical care claims database	USA (records from 2001 to 2007 were analysed)	40 years or more at index date	At least two increases in PSA following surgical/medical castration. Furthermore, patients with CRPC were identified using a propensity score of multiple factors	Up to 6 years	17.8% of castrate patients with PC
	Cabrera (20)	Retrospective study of 44,791 patients with PC who had undergone castration, identified from a US medical care claims database	USA (records from 2000 to 2008 were analysed)	18–97 years	CRPC status was assigned to patients who failed to respond to postcastration hormone therapy, defined as a switch from their second-line hormone treatment to a third hormonal therapy or chemotherapy	Followed until exit from database, mean ~25 months	9.5% of castrate patients with PC
	Morgan (11)	Retrospective study of 8678 patients with PC using data from a UK primary care database	UK (records from 1998 to 2008 were analysed)	40 years or more at index date	A record of medical or surgical castration and temporal evidence of increasing levels of PSA	Up to 10 years	11.2% of patients with PC
	Berruti (10)	211 patients newly diagnosed with PC in secondary care	Italy (1996–2003)	Median: 70 (range: 47–87) years	Despite castrate levels of testosterone, two consecutive increases in PSA during androgen deprivation, a new lesion on a bone scan or growth of a lesion on a CT scan	Median: 55 months	53% of patients with PC in secondary care
Patients with PC who had RP	Bianco (12)	1045 patients with PC who had undergone RP	USA (1990–1999)	NR	Serum PSA > 0.4 ng/ml with an increasing trend	Median: 55 (range: 1–145) months	19% of patients with PC who have undergone RP

CRPC, castration-resistant prostate cancer; CT, computed tomography; NR, not reported; PC, prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy.

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