VALUE IN HEALTH 16 (2013) 872–890

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Efficacy, Patient-Reported Outcomes (PROs), and Tolerability of the Changing Therapeutic Landscape in Patients with Metastatic Prostate Cancer (MPC): A Systematic Literature Review

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ABSTRACT

Objective: New therapies have attempted to improve on efficacy outcomes observed with docetaxel in patients with metastatic prostate cancer (MPC) who are hormone-therapy refractory or castration-resistant. In addition to the efficacy, patient-reported outcomes (PROs) and tolerability need to be assessed to define treatment benefit, as PROs measure the patient's subjective experience and can be correlated with hard outcomes. The main objective of this study was to evaluate the survival benefit of new therapies and secondary efficacy-related outcomes. Assessment of the number of studies reporting PROs and tolerability was also conducted. **Methods:** A predefined search strategy was conducted on major academic/governmental databases and conference proceedings (2007–2011). Exclusion criteria were applied. **Results:** Of 77 studies identified, 26 (34%) evaluated survival as an end point; 14 (18%) assessed PROs/tolerability. In chemotherapy-naive patients (no/minimal symptoms), median overall survival (OS) was 26 months for sipuleucel-T. In relapsed patients, the survival benefit of cabazitaxel/abiraterone was 15 months and that of enzalutamide was 18 months. Denosumab prolonged time to first on-study skeletal-related event (20.7 months denosumab, 17.1 months zoledronic acid; $P = 0.0002$, noninferiority; $P = 0.008$, superiority). Similar benefit was documented with radium-223, a new bone-targeted α-particle–emitting radiopharmaceutical. Radium-223 also significantly improved the OS (two-sided $P = 0.00185$). Specific to PROs, they were incorporated primarily as secondary end points, and improvements in pain response (most commonly evaluated) were variable among the agents. Last, the therapies were associated with unique toxicities requiring careful consideration. **Conclusions:** The results of this review demonstrate that the therapeutic landscape of MPC has changed dramatically and many therapies in MPC now show OS improvements of about 4 months in the postdocetaxel setting.

Keywords: bone metastases, castration-resistant prostate cancer, chemotherapy, hormonal therapy, overall survival, patient-reported outcomes, prostate cancer, radiopharmaceuticals, skeletal-related events.

Introduction

Prostate cancer (PC) is the most common noncutaneous malignancy in men in the United States, and rates are second only to lung cancer as the cause of cancer-related mortality in men [1]. The American Cancer Society's statistics for 2013 estimate that about 238,590 new cases of PC will be diagnosed and 28,790 men will die from this cancer [1]. The majority of cases of PC are diagnosed in the early stages, with a 5-year survival rate of 100% [2]. Patients with early-stage PC are managed with curative intent by using definite primary treatment such as surgery and radiation [3].

Unfortunately, as many as 10% to 50% of men who are initially diagnosed with localized PC may experience disease progression, most commonly to lymph nodes and bone [4]. Furthermore, at initial diagnosis, 4% of the patients have metastatic PC (MPC), and the 5-year survival rate for this population is poor at only 28.7% [2]. Therefore, treatment of locally advanced PC and MPC is far more challenging, with androgen deprivation therapy (ADT) being commonly used as the upfront treatment option [3,5]. In clinical practice, patients with PC have two equally effective ADT options: medical castration using a luteinizing hormone–releasing hormone agonist or surgical castration using bilateral orchiectomy [5]. Treatment with ADT reduces prostate-specific antigen (PSA) and shrinks tumors because of initial dependence on circulating androgens; however, response rates are not durable [6].

Consequently, patients who relapsed after primary ADT have a progression-free survival (PFS) of only 18 to 24 months and develop castration-resistant PC (CRPC) [7,8]. CRPC (the preferred term because many men respond to additional androgen manipulations) is defined as sequential PSA rising and/or disease progression despite castrate blood levels of testosterone (formerly referred to as androgen-independent, or hormone-

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1098-3015/$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2013.03.1628

refractory PC) [9,10]. Although chemotherapy has long been used in CRPC, prolongation of survival has not been achieved historically in this patient population [11]. CRPC was considered nearly incurable, and no therapeutic approach had shown a survival advantage until 2004, when two large prospective trials concluded that a docetaxel-based treatment prolonged median overall survival (OS) by around 3 months and docetaxel became the standard first-line regimen in symptomatic patients with CRPC [12,13].

In the past few years, various chemotherapies, targeted therapies, and immunotherapies have attempted to improve on the efficacy outcomes achieved with docetaxel in patients with CRPC. Therapeutic research has expanded options in CRPC for asymptomatic/minimally symptomatic and symptomatic populations and in patients failing docetaxel [5]. Over the last 2 years, three systemic agents (sipuleucel-T, cabazitaxel, and abiraterone) have been approved by the Food and Drug Administration (FDA) after demonstrating OS improvements in patients with CRPC [5]. The latest investigational agents, including radium-223, an alpha (α)-emitting radiopharmaceutical, and the recently FDA-approved enzalutamide (MDV3100), an androgen receptor signaling inhibitor, have also reported survival advantage in patients with CRPC [14,15]. Advances have also been made in the prevention and treatment of bone metastases. This is of high importance because the bone is the metastatic site in more than 80% of the patients with CRPC [16,17]. In addition to zoledronic acid, denosumab can be considered for the prevention of skeletal-related events (SREs), and radium-223 and enzalutamide may become valuable therapeutic options based on their positive SRE outcomes [14,15].

Even though traditional efficacy end points such as survival remain the most reliable and preferred end points in cancer decision making, patient-reported outcomes (PROs) have been increasingly recognized as providing evidence of clinical benefit of oncology therapies [18]. PROs, including a patient's quality of life (QOL), physical functioning, or tumor-related symptoms, can provide essential information on the overall burden of cancer and the effectiveness of therapies [18]. PROs assess the patient's subjective experience and can be correlated with hard outcomes (e.g., pain intensity and survival) [18]. The assessment of PROs is particularly important in patients with metastases who experience various skeletal-related complications [19]. In addition to PROs, tolerability of these agents needs to be assessed to fully define treatment benefit and make individualized treatment decisions in the CRPC population.

The growing number of therapeutic options highlights a need to systematically evaluate the role of new systemic therapies in patients with MPC. The present investigation will assess in a systematic manner the published evidence on efficacy, PROs, and tolerability of the emerging therapies in CRPC. The primary objective of this systematic review was to evaluate the survival benefit of new systemic therapies. Secondary efficacy outcomes (time to progression [TTP], PSA response rate, time to PSA progression, and time to first on-study SRE) were also assessed. In addition, the present investigation evaluated the number of studies reporting PROs and tolerability of new systemic therapies in CRPC.

Methods

Literature Search

Initially, we conducted a systematic literature search on documents and articles published in the English language between January 1, 2004, and April 30, 2011. The starting date for this systematic review was selected to evaluate both off-label and on-label evidence for docetaxel (FDA approval of May 19, 2004). Next, we performed a supplementary systematic literature search from May 1, 2011, until June 30, 2012, focusing on comparative studies for abiraterone, enzalutamide, and radium-223 to account for an emergence of new data. We used the following databases to identify relevant studies: MEDLINE (via PubMed), EMBASE, the Cochrane Library, Agency for Healthcare Research and Quality (AHRQ), Community of Science, research registries of ClinicalTrials.gov and National Research Register, and citation lists of published systematic reviews and health technology assessments. We also searched abstracts presented from 2007 to 2012 at major oncology conferences, including the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO). Detailed information on our search strategy is outlined in Table 1. Controlled clinical trials, retrospective cohort studies, and literature reviews were included to ensure that this systematic review was comprehensive in scope and reflective of a dynamic PC space, especially as it relates to a changing treatment paradigm. Studies in children, non-English language studies, case reports/series, and studies with preliminary/incomplete results were excluded.

Data Extraction and Evidence Rating

One reviewer used the titles and abstracts identified in the initial literature search to identify potentially relevant publications, the full-text versions of which were retrieved and evaluated by two reviewers. Study characteristics, including design/sample size/treatments, inclusion/exclusion criteria, and end points/results, were extracted and summarized on a standardized form for the included publications. Because the objective of the review was qualitative in nature, retrieved publications were not scored on the basis of predefined quality criteria.

The eligible articles (single-agent and comparative studies) were assigned a level of evidence as described by the AHRQ of the US Department of Health and Human Services: *level 1*, evidence from well-designed randomized, controlled trials; *level 2*, evidence from well-designed, nonrandomized controlled trials; *level 3*, evidence from well-designed observational studies with controls, including retrospective and case-control studies; and *level 4*, observational studies without controls, including cohort studies without controls and case series. In addition, a strength of evidence (SOE) was determined, as described by a modified version of the AHRQ, which includes the domains of bias, consistency, and directness (the domain of precision was not included in the rating): *high*, high confidence that the evidence reflects the true effect; *moderate*, moderate confidence that the evidence reflects the true effect; and *low*, low confidence that the evidence reflects the true effect. The SOE was assigned on the basis of a point value for the three domains ranging from 1 to 3, with more points given to studies with lowest bias, definite consistency, and directness: high, 2 to 3 points; moderate, 1 to less than 2 points; and low, 0 to less than 1 point. Literature reviews have been excluded from this evidence assessment because it was anticipated that their numbers would be small and not allow conclusive ratings.

Results

Study Disposition and Characteristics

Overall, 782 publications were identified through the database search and the ASCO/ESMO abstracts in the primary literature search. After removal of 282 duplicates, 500 publications remained. Subsequently, only 93 publications were included in this systematic literature review following evaluation by the