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Systematic Review and Network Meta-Analysis of Treatments for Chemotherapy-Naive Patients with Asymptomatic/Mildly Symptomatic Metastatic Castration-Resistant Prostate Cancer

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ABSTRACT

Objectives: To estimate the relative effectiveness of enzalutamide in chemotherapy-naive metastatic castration-resistant prostate cancer by conducting a systematic literature review and a network meta-analysis (NMA). **Methods:** A systematic literature review identified randomized controlled trials comparing enzalutamide, abiraterone/prednisone, radium-223, sipuleucel-T, or docetaxel with each other or placebo in chemotherapy-naive or mixed populations (with and without prior chemotherapy) with asymptomatic/mildly symptomatic metastatic castration-resistant prostate cancer. Feasibility assessment evaluated the trials' suitability for NMA inclusion. The main outcomes were hazard ratios (HRs) for overall survival (OS) and radiographic progression-free survival (rPFS). **Results:** Searches of relevant bibliographic databases, trial registers, Web sites, and conference abstracts conducted in October 2014 identified 25,712 records. Ten randomized controlled trials were eligible for the NMA. Enzalutamide was superior to placebo for OS and rPFS (fixed-effects model). NMA results (fixed-effects model) showed no evidence of a difference between enzalutamide and abiraterone/prednisone (HR 0.95 [95% CrI 0.77–1.16]), sipuleucel-T (HR 1.07 [95% CrI 0.84–1.37]), or radium-223 (HR 1.10 [95% CrI 0.87–1.37]) for OS. HRs were similar for the random-effects model. Nevertheless, results (fixed-effects model) suggested that enzalutamide was superior to abiraterone/prednisone (HR 0.59 [95% CrI 0.48–0.72]) and sipuleucel-T (HR 0.32 [95% CrI 0.25–0.42]) for rPFS. Results also suggested superiority of enzalutamide versus placebo, abiraterone/prednisone, or sipuleucel-T for time to chemotherapy. **Conclusions:** For rPFS, the NMA suggests that enzalutamide is superior to abiraterone/prednisone and sipuleucel-T. There is no evidence of a statistically significant difference in OS between enzalutamide and abiraterone/prednisone, sipuleucel-T, or radium-223. Given the limitations in network construction and underlying assumptions made to complete these analyses, results should be interpreted with caution.

Keywords: enzalutamide, metastatic castration-resistant prostate cancer, network meta-analysis, systematic literature review.

Introduction

Prostate cancer (PCa) is one of the most prevalent cancers in men, both in Europe [1] and globally [2], with substantial mortality. A 2012 study demonstrated PCa to be the third and fifth most frequent cause of male death from cancer in Europe (9.5% [n = 92,000] of total) [1] and worldwide (6.6% [n = 307,000] of total) [2], respectively. Androgen-deprivation therapy (ADT) is the principal treatment for metastatic disease; although patients initially respond, resistance to castration develops and the cancer eventually progresses to castration-resistant PCa (CRPC) [3]. Patients with metastatic CRPC (mCRPC) have poor prognosis and, until recently, had few treatment options [4]. Second-line ADT with estrogen, anti-androgens, or corticosteroids (CSs) has been widely used, but with limited response rates and no improvement in survival [5]. Mitoxantrone has shown improved palliation but no survival benefit [6,7].

Although traditional hormonal therapy for mCRPC does not confer survival benefit [8], docetaxel has shown evidence that it can extend life [9]. Nevertheless, it is associated with potentially debilitating or life-threatening toxicities [10]. Therefore, many patients may prefer to delay chemotherapy for as long as possible [11], whereas others may not be considered for such additional treatment [12].

In recent years, new treatments for mCRPC have emerged with various therapeutic mechanisms of action [13]. In addition, many novel agents are indicated in the prechemotherapy setting, including enzalutamide (androgen receptor signaling inhibitor) [14], abiraterone (androgen synthesis inhibitor) [8], sipuleucel-T (an immunotherapy) [15], and radium-223 (radiopharmaceutical

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and calcium mimetic) [16], although in 2015, marketing authorization for sipuleucel-T in the European Union was withdrawn at the request of the marketing authorization holder [17].

In clinical studies, enzalutamide improved overall survival (OS), progression-free survival (PFS), and health-related quality of life (HRQOL) in mCRPC in both pre- and postchemotherapy settings [18–21]. Nevertheless, at the time of phase III studies, new comparators had yet to be licensed in the prechemotherapy indication and so no head-to-head trials have been performed. Comparative efficacy data are, however, needed for economic modeling and so an alternative approach is necessary to evaluate and compare the available clinical data for these treatments.

We performed a systematic literature review (SLR) and a network meta-analysis (NMA) to estimate the relative efficacy of enzalutamide versus relevant comparators for the treatment of chemotherapy-naive patients with asymptomatic/mildly symptomatic mCRPC.

Methods

SLR

An SLR identified all studies of enzalutamide and relevant comparators that could contribute to an NMA. The review was based on a protocol agreed a priori (specifying review inclusion criteria and methods) and was informed by guidance from the University of York Centre for Reviews and Dissemination [22] and UK National Institute for Health and Care Excellence (NICE) [23]. Searches were conducted in October 2014 to inform a NICE single technology appraisal (STA) for enzalutamide for treating mCRPC before chemotherapy is indicated.

Patient and trial eligibility

Studies of adult patients (≥18 years) with asymptomatic/mildly symptomatic mCRPC (i.e., disease progression despite castrate testosterone [≤50 ng/dl]) who had not received prior chemotherapy (chemotherapy-naive) were eligible. Studies including patients described as "hormone-sensitive" or "castration-sensitive" were not eligible.

Initial screening indicated that, for some comparators, studies did not exist when all patients were specified as chemotherapy-naive. To facilitate a connected network for NMA, studies of mixed populations (with and without prior chemotherapy) were included for comparators with no studies of chemotherapy-naive populations. Thus, all patients had asymptomatic/mildly symptomatic mCRPC, even though in some studies previous treatment was mixed.

Eligible studies were randomized controlled trials (RCTs) published in English that compared enzalutamide, abiraterone + prednisone (abiraterone/prednisone), radium-223, sipuleucel-T, or docetaxel with one another, with placebo, or with any of the following: best supportive care (BSC), prednisone, bicalutamide, flutamide, nilutamide, cyproterone acetate, megestrol acetate for the treatment of asymptomatic/mildly symptomatic patients with mCRPC who were chemotherapy-naive or part of a mixed population.

Studies reporting data on one or more of the following outcomes were eligible for inclusion:

- OS;
- PFS;
- radiographic PFS (rPFS);
- response rate: prostate-specific antigen (PSA) response;
- time to (cytotoxic) chemotherapy initiation;
- time to antineoplastic therapy (cytotoxic or hormonal);
- time to skeletal-related event (SRE);
- HRQOL, including
  - o time to pain progression;
  - o time to increase in analgesia;
  - o time to decline in performance status.
- time to PSA progression;
- time to HRQOL deterioration (≥10-point decline in Functional Assessment of Cancer Therapy – Prostate).

A literature search strategy was developed for MEDLINE (Ovid interface) to identify relevant studies on enzalutamide, abiraterone/prednisone, radium-223, sipuleucel-T, or docetaxel. The strategy was devised using a combination of subject indexing terms and free text search terms in the title, abstract, keyword heading word, and registry number/name of substance fields. Initial searches were not limited by date range/language. The MEDLINE strategy was translated appropriately for other databases and information sources searched (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.03.012). Full search strategies for all databases are described in Appendix Figure 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.03.012. In addition to specified interventions, strategies for the core bibliographic databases included terms for comparator drugs of interest: bicalutamide, flutamide, nilutamide, cyproterone acetate, megestrol acetate, mitoxantrone, and prednisone. These were included in case comparator-versus-comparator trials were needed to complete linkages in the NMA. Methods to identify ongoing and recently completed research included searching Web sites of key conferences to identify abstracts from the last 3 years.

Records were downloaded from the databases and loaded into bibliographic software. After de-duplication, an information specialist selected records for further assessment on the basis of information provided in the title and abstract (first pass). Obvious false-positive records were removed. The remaining records were assessed by one reviewer for relevance to the review and NMA on the basis of the title and abstract; quality checking was undertaken on 30% of records by a second reviewer, with a third reviewer arbitrating disagreements. After initial screening, full-text copies of all potentially relevant records were obtained and evaluated by a single reviewer in more detail against the predefined eligibility criteria. Again, quality checking was undertaken on a sample by a second reviewer, and the third reviewer resolved inconsistencies.

NMA

Data extraction and feasibility assessment

To ensure sensible and robust comparisons in the NMA, the similarity of included studies was assessed. In the absence of internationally agreed guidelines on how to assess homogeneity in this context, guidance on best practice, for the conduct of indirect and mixed treatment comparisons, produced by the Australian Pharmaceutical Benefits Advisory Committee [24] was adapted. Key study characteristics relating to methods, populations, trial settings, treatments, and outcomes were extracted to inform the similarity assessment. For each included study, one reviewer extracted similarity elements from the full article, capturing the information on a standardized data extraction form. These data were validated by a second reviewer, and a third reviewer arbitrated disagreements.

Studies were assessed to determine whether they were sufficiently similar to be included in an NMA and whether they contributed to a connected network. Networks were then developed, taking into account the available data, similarity of trials and outcome measures, and potential value of including off-label dosing. Final networks were presented as diagrams that depict treatments as nodes and individual studies as links (see