available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Review – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

Comparison of Abiraterone Acetate and Docetaxel with Androgen Deprivation Therapy in High-risk and Metastatic Hormone-naïve Prostate Cancer: A Systematic Review and Network Meta-analysis

Christopher J.D. Wallis [a,†,*], *Zachary Klaassen* [a,b,†], *Bimal Bhindi* [c], *Hanan Goldberg* [a,b], *Thenappan Chandrasekar* [a,b], *Ann M. Farrell* [d], *Stephen A. Boorjian* [c], *Girish S. Kulkarni* [a,b], *Robert Jeffrey Karnes* [c], *Raj Satkunasivam* [a,e]

[a] *Division of Urology, Department of Surgery, University of Toronto, Toronto, ON, Canada;* [b] *Division of Urology, Department of Surgery, Princess Margaret Hospital, University Health Network, Toronto, ON, Canada;* [c] *Department of Urology, Mayo Clinic, Rochester, MN, USA;* [d] *Mayo Clinic Libraries, Mayo Clinic, Rochester, MN, USA;* [e] *Department of Urology and Center for Outcomes Research, Houston Methodist Hospital, Houston, TX, USA*

Article info

Article history:
Accepted October 2, 2017

Associate Editor:
Giacomo Novara

Statistical Editor:
Melissa Assel

Keywords:
Metastatic prostate cancer
Locally advanced prostate cancer
Hormone-naïve
Docetaxel
Abiraterone
Androgen deprivation therapy

Abstract

Context: Randomized clinical trials have recently examined the benefit of adding docetaxel or abiraterone to androgen deprivation therapy (ADT) in hormone-naïve advanced prostate cancer (PCa).
Objective: To perform a systematic review and network meta-analysis of randomized clinical trials, indirectly evaluating overall survival (OS) for men treated with abiraterone acetate plus prednisone/prednisolone with ADT (Abi-ADT) versus docetaxel with ADT (Doce-ADT) in hormone-naïve high-risk and metastatic PCa.
Evidence acquisition: Medline, Embase, Web of Science, Scopus, and Clinicaltrials.gov databases were searched in August 2017. We pooled results using the inverse variance technique and random-effects models. The Bucher technique for indirect treatment comparison was used to compare Abi-ADT with Doce-ADT. A priori subgroup and sensitivity analyses were performed.
Evidence synthesis: Overall, 6067 patients from five trials were included: 1181 (19.5%) patients who received Doce-ADT, 1557 (25.7%) patients who received Abi-ADT, and 3329 (54.9%) patients who received ADT-alone. There was a total of 1921 deaths: 391 in the Doce-ADT group, 353 in the Abi-ADT group, and 1177 in the ADT-only group. The pooled hazard ratio (HR) for OS was 0.75 (95% confidence interval [CI]: 0.63–0.91, $I^2 = 51\%$, 3 trials, 2951 patients) for Doce-ADT versus ADT-alone and 0.63 (95% CI: 0.55–0.72, $I^2 = 0\%$, 2 trials, 3116 patients) for Abi-ADT versus ADT-alone. The indirect comparison of Abi-ADT to Doce-ADT demonstrated no statistically significant difference in OS between these approaches (HR: 0.84, 95% CI: 0.67–1.06). Findings were similar in various a priori subset analyses, including patients with metastatic disease. Bayesian analyses demonstrated comparable results (HR: 0.83, 95% CI: 0.63–1.16). Despite the lack of statistical significance, Surface Under the Cumulative Ranking Analysis demonstrated an 89% probability that Abi-ADT was preferred.

† These authors are co-first authors.
* Corresponding author. Division of Urology, Department of Surgery, University of Toronto, 149 College Street, Room 503G, Toronto, ON M5T 1P5, Canada. Tel. +1 416 77 2960; Fax: +1 416 480 6934.
E-mail address: wallis.cjd@gmail.com (Christopher J.D. Wallis).

https://doi.org/10.1016/j.eururo.2017.10.002

Conclusions: We did not identify a significant difference in OS between Abi-ADT and Doce-ADT for men with hormone-naïve high-risk or metastatic PCa, although Bayesian analysis demonstrates a high likelihood that Abi-ADT was preferred.
Patient summary: We synthesized the evidence available from studies examining the administration of docetaxel or abiraterone in combination with hormonal therapy for patients with newly diagnosed, advanced prostate cancer. While these studies did not directly compare these agents, we used methodological techniques to indirectly compare them and found no significant difference in overall survival.

1. Introduction

In the USA and Europe, prostate cancer (PCa) is the second most common malignancy and second leading cause of cancer mortality among male patients [1]. The proportion of patients with metastatic disease in the US is approximately 3% [2], with higher rates globally [3]. For the past 70 yr, androgen deprivation therapy (ADT) has been the mainstay of therapy for locally advanced or metastatic disease, considering that the androgen receptor (AR) pathway is critical for PCa progression [4]. While the majority of patients will benefit from a biochemical and clinical response to ADT, most eventually develop castration-resistant prostate cancer (CRPC) despite castrate levels of testosterone [5].

Docetaxel chemotherapy has historically been utilized in the CRPC setting following two randomized clinical trials (RCTs) demonstrating improved overall survival (OS) when compared with mitoxantrone plus prednisone [6,7]. Similarly, abiraterone acetate, an inhibitor of cytochrome P-450c17, which is critical for androgen biosynthesis [8,9], demonstrated improved OS in the CRPC setting, both predocetaxel [10,11] and postdocetaxel treatment [12,13]. Recently, a number of RCTs have demonstrated that the addition of either docetaxel [14–16] or abiraterone [17,18] to ADT improves OS in men with hormone-naïve metastatic PCa, compared with ADT alone. However, the comparative efficacy of abiraterone with ADT (Abi-ADT) and docetaxel with ADT (Doce-ADT) remains to be assessed. As there are no published studies which directly examine this question, we employed a network meta-analysis to perform an indirect comparison of OS for men treated with Doce-ADT to Abi-ADT. Our secondary objective was to identify potential subsets of patients wherein one initial treatment approach may be superior to the other.

2. Evidence acquisition

2.1. Identification of eligible trials

We included only phase 3 RCTs. Observational studies, editorials, commentaries, review articles, and those not subject to peer review (ie, reports of data from Vital Statistics and dissertations or theses) were excluded. In instances where there was more than one publication resulting from the same patient cohort, we utilized the most recent publication for analysis. To facilitate indirect treatment comparisons, all studies had to include a control arm comprising treatment with ADT alone. In addition, they had to include an experimental arm which comprised either Abi-ADT or Doce-ADT.

The primary outcome was OS. While data on secondary outcomes including radiographic progression-free survival, biochemical progression-free survival, clinical progression-free survival, castrate-resistant PCa-free survival, failure-free survival, and skeletal-related event-free survival were abstracted, these were not reported consistently enough between trials to allow for pooling of data.

2.2. Data collection and study quality

We used Preferred Reporting Items for Systematic Reviews and Meta-analyses for reporting of this systematic review and meta-analysis. Medline and Embase (using the OvidSP platform), Web of Science, Scopus, and Clinicaltrials.gov databases were searched using the OvidSP platform for studies indexed from database inception to August 4, 2017 by a professional librarian (A.M.L). We used both subject headings and text-word terms for "hormone-naïve," "hormone sensitive," "castrate-naïve," "castrate sensitive," "prostatic neoplasms," "docetaxel," "abiraterone," and related and exploded terms including MeSH terms in combination with keyword searching. A full search strategy is presented in Supplementary data. Only English language publications were considered. No limitations were placed with respect to publication year. Following the literature search, all duplicates were excluded. References from review articles, commentaries, editorials, included studies, and conference publications of relevant medical societies were hand searched and cross-referenced to ensure completeness. Conference abstracts were excluded.

Two authors performed study selection independently (C.J.D.W. and Z.K.). Disagreements were resolved by consensus. Titles and abstracts were used to screen for initial study inclusion. Full-text review was used where abstracts were insufficient to determine if the study met inclusion criteria. One author (C.J.D.W.) performed all data abstraction with independent verification performed by another author (Z.K.).

A risk of bias assessment was conducted using The Cochrane Collaboration's tool for assessing risk of bias.

2.3. Statistical methods

Meta-analysis of the effect of combination therapy compared with ADT alone was performed independently for the Abi-ADT and Doce-ADT comparisons using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane

Please cite this article in press as: Wallis CJD, et al. Comparison of Abiraterone Acetate and Docetaxel with Androgen Deprivation Therapy in High-risk and Metastatic Hormone-naïve Prostate Cancer: A Systematic Review and Network Meta-analysis. Eur Urol (2017), https://doi.org/10.1016/j.eururo.2017.10.002