Systematic Review

Economic evaluations of *Cabazitaxel* for treatment of post-docetaxel metastatic castration-resistant prostate cancer; evidence from a systematic review

Abstract

Background and Objectives: Prostate cancer is an ever-increasing global incidence and has become the fifth leading cause of cancer-related mortality in men. A significant number of patients with prostate cancer develop metastatic castration-resistant prostate cancer (mCRPC). There are a few second-line treatment options for patients with post-docetaxel mCRPC. This systematic review aimed to assess the cost-effectiveness of cabazitaxel for the treatment of mCRPC.

Material and Methods: Electronic bibliographic databases including: PubMed/Medline, NICE, CRD, and Scopus were searched in January 2018 for identifying full economic evaluations published in English and Persian. The risk of assessment bias and descriptive analyses of individual studies' findings were presented.

Results: Three articles that fulfilled the inclusion criteria were included in the current study. All the included records had a reasonable quality. Cabazitaxel was not recommended as the most cost-effective option for the treatment of docetaxel-refractory mCRPC. Abiraterone acetate and radium-223 were the recommended cost-effective treatments for mCRPC treatment.

Conclusion: we found that, in general, while cabazitaxel had equal or slightly higher improvement in Quality-adjusted Life Year (QALY) as compared to the alternatives, it incurred

a high cost. Despite the inclusion of a few studies in this review, cabazitaxel was not found to be a cost-effective option. Therefore, we recommend full economic evaluations to be conducted in this area.

Keywords: Cabazitaxel, cost-effectiveness, abiraterone acetate, radium-223, enzalutamide; mitoxantrone.

Introduction

Prostate cancer (PCa) is the second commonly diagnosed cancer in men [1]. The incidence of PCa increased by 3.7 folds globally from 1990 to 2015 and it is now the fifth leading cause of cancer-related mortality in men[2,3]. Localized prostate cancer management is done either by surgery or radical radiotherapy with or without androgen-deprivation therapy (ADT) [4]. However, roughly 10% to 20% of patients develop castration-resistant prostate cancer (CRPC) within 5 years of follow-up. Furthermore, more than 84% of CRPC at the diagnosis stage show metastasis and 33% of non-metastasis CRPCs are expected to metastasize within 2 years [5]. The metastasis to the bone leads to complications like pathologic fractures, anemia, fatigue, and pain that severely compromise the quality of life [6-9].

In 2004, Docetaxel became the first breakthrough in the management of metastasized castration-resistant prostate cancer (mCRPC) [10]. Cabazitaxel, a second-generation taxane, was approved as a second-line treatment for mCRPC after the TROPIC study in 2010 [11]. Cabazitaxel plus prednisone arm improved overall survival by a median of 2.4 months and reduced mortality to 30% over mitoxantrone plus prednisone arm[11]. Afterward, several studies have ascertained the clinical efficacy of cabazitaxel [12-14]. In recent years, hormonal therapies of abiraterone acetate (androgen biosynthesis inhibitor) and enzalutamide (androgen-receptor inhibitor) have been also

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approved [15,16]. Furthermore, sipuleucel T and alpha-emitter Radium-223 (Ra-223) have been also used for the treatment of CRPC [17].

The most common hematologic complication of cabazitaxel is neutropenia and both grade III and above neutropenia (58%) and febrile neutropenia (8%) were frequently seen during the treatment [11]. The neutropenia and its clinical complications are the causes of cabazitaxel treatment-related death. The other frequent adverse outcome of cabazitaxel is diarrhea [11]. However, studies showed that the safety profile of cabazitaxel is manageable and quality of life is maintained in the current clinical practice [18,19].

The second-line treatment options for patients with prior docetaxel treatment have shown varied efficacy and safety profiles [16]. This warrants the need for a cost-effectiveness evaluation in order to reasonably control the ever-increasing healthcare cost. However, there is no systematic review that tried to assess the cost-effectiveness of cabazitaxel. Therefore, the aim of this study is to evaluate the cost-effectiveness of cabazitaxel-based treatment in mCRPC with prior docetaxel treatment.

Material and Methods

Search strategy

The Electronic bibliographic databases (PubMed/Medline, NICE, CRD, and Scopus) were searched for full economic evaluations. The articles published only in English and Persian languages were included. The keywords used were “cabazitaxel”, “cabazitaxelum”, “Jetvana”, “economic evaluation”, “cost-effectiveness”, “cost-utility”, “pharmacoeconomic”, “cost-minimization”, “cost-benefit”, “Markov”, “decision tree", “model”, and "cost/QALY.” Different combination of keywords was used to increase the search outcome.

Study selection

Two independent reviewers screened the titles, abstracts, and full-texts of the records. As the inclusion criterion, the present study used full economic evaluations (cost-effectiveness and cost-utility analyses) of adults (aged ≥18) with CRPC and prior docetaxel therapy and compared cabazitaxel with alternative treatments or placebo. Partial economic evaluations and letter to editors or editorials were excluded from the review.

Risk of bias

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement-checklist [20] was used to assess the bias in the selected records. The overall quality of individual studies was reported based on the percentage of their completeness.

Study synthesis

The core characteristics of the selected records were described and the results of cost-effectiveness for individual studies were qualitatively reviewed. The incremental cost-effectiveness of cabazitaxel was calculated against all alternatives based on the data from the published articles whenever the calculation was not done. As qualitative pooled analysis is not recommended for the results section in economic evaluations [21], only a narrative review of the results was done.

Results

The database search revealed 176 records and three articles that fulfilled the inclusion criteria and were consequently included in the current review (Fig. 1). The summary of the characteristics of the reviewed studies is shown in Table 1.

The reviewed studies fulfilled 83.3%[22] and 87.5%[23,24] of CHEERS statement checklist. The studies generally represented a good quality. The quality assessment of the included studies is shown in the supplementary file 3.

Descriptive analysis

The follow-up period of the reviewed articles was 18 months [22,24] and 5 years [23]. All the three studies did not recommend cabazitaxel for the treatment of docetaxel-refractory mCRPC. Two of the studies [22,24] suggested abiraterone as a treatment, whereas a study by Peters ML.et al. [23] recommended radium-223 as a cost-effective option for docetaxel-refractory mCRPC patients.

Cabazitaxel versus placebo (prednisone only)

Compared to prednisone, cabazitaxel was costlier and more effective only for patients with mCRPC who were previously treated with docetaxel. The ICER values of $244,769.70/QALY and $163,787.88/QALY were far higher than the cost-effectiveness threshold of the US (100,000/QALY), where the studies were conducted.

Cabazitaxel versus mitoxantrone

Cabazitaxel was costlier and more effective than mitoxantrone; however, the ICER ($291,876.00/QALY) was unacceptably higher than the cost-effectiveness threshold of the US.

Cabazitaxel versus Abiraterone acetate

A study by Peters ML.et al.[23] showed that cabazitaxel dominated abiraterone acetate, whereas studies by Wilson L.et al. and Zhong L. et al revealed cabazitaxel as costlier and more effective than abiraterone acetate. Moreover, the ICER values of $337,983.33 /QALY and $918,166.67/QALY were far above the cost-effectiveness threshold of the US.

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Cabazitaxel versus Enzalutamide

The studies by Peters ML.et al.[23] and Wilson L.et al.[22] showed that cabazitaxel was costlier and more effective than enzalutamide. The ICER (€41785.71) was below the informal cost-effectiveness threshold of the Netherlands (€80,000). However, the ICER value of $240,333.33 was very higher than the cost-effectiveness threshold of the US.

Cabazitaxel versus Radium-223

A study by Peters ML.et al.[23] showed that radium-223 dominated cabazitaxel.

Discussion

This review revealed that, in general, cabazitaxel improved the QALY of docetaxel-refractory mCRPC patients; however, in terms of the current cost of care, it did not provide good value for money when compared to other alternatives. In particular, when compared with placebo, mitoxantrone, abiraterone acetate, and radium-223, it was either dominated by alternative treatments or its ICER was too high to recommend it as a second-line treatment. Moreover, the cost-effectiveness of cabazitaxel compared to enzalutamide was inconclusive as it was found to be below (above) the cost-effectiveness threshold in the Netherlands and the US. A recent guideline has also recommended cabazitaxel as the third-line agent for mCRPC [16].

Despite a slightly higher QALY than abiraterone acetate, cabazitaxel has an unaffordable cost per QALY as the result of associated neutropenia treatment. The study by Peters ML.et al. [23] has shown the dominance of cabazitaxel over abiraterone acetate; however, this study mainly aimed to reveal the cost-effectiveness of Ra-223 and considered the symptomatic skeletal-related events from cabazitaxel to be identical with Ra-223. Abiraterone acetate improves overall survival of patients with prior docetaxel exposure within 4.6 months over placebo [25]. A recent study also

showed no significant difference in overall survival and time of treatment failure among mCRPC patients treated by abiraterone and cabazitaxel [26]. Grade 3-4 adverse effects such as fatigue, anemia, and back and bone pain resulting from abiraterone were not significantly different from placebo [25]. Furthermore, current guidelines recommend cabazitaxel in the third-line setting following docetaxel, abiraterone, and enzalutamide [16,27].

Cabazitaxel showed a better effectiveness than enzalutamide and an acceptable value for money in the Netherlands. However, studies in the US did not come up with this finding and rather revealed how expensive it is based on the current cost-effectiveness threshold. Enzalutamide has a well-evidenced effectiveness in post-docetaxel mCRPC [28,29]. Although there are no head-to-head comparative studies, the most common grade $\geq$ 2 adverse effects of enzalutamide like fatigue, musculoskeletal pain, and seizure are relatively easier to manage than the life-threatening neutropenia and febrile neutropenia resulting from cabazitaxel [11,28,29].

Radium-223's dominance over cabazitaxel can be due to the lower cost of drug, administration, and adverse drug effects [23]. In ALSYMPCA trial, Radium-223, an alpha-emitting radioisotope, improved the median of overall survival within 3.1 and 4.6 years in patients with/without prior docetaxel use [30,31]. Radium-223 has low grade 3-4 adverse effects associated with myelosuppression and less than 1% of patients developed febrile neutropenia [30-32]. Though there is no head-to-head comparison with cabazitaxel, the incidence of febrile neutropenia along with cabazitaxel (8%) is suggested to be too high[11].

This study has several limitations. A few studies done in the US and the Netherlands are included in the current review that severely constrains the generalizability of the results. In addition, the range of costs and the time horizon were different in the reviewed articles. Another

limitation was related to the costs of the reviewed articles which were unstandardized for a common base year.

Conclusion

The current review does not provide conclusive evidence on the cost-effectiveness of cabazitaxel. However, based on the findings, we cautiously recommend reducing the national cost of cabazitaxel or if it is not feasible, the use of abiraterone, enzalutamide, and radium-223 rather than cabazitaxel for the treatment of post-docetaxel mCRPC. The results of the present study are expected to offer an instrumental input for policymakers, health insurance companies, and prescribers in making recommendations for the management of mCRPC. Finally, we strongly recommend further economic evaluations to be done in this area.

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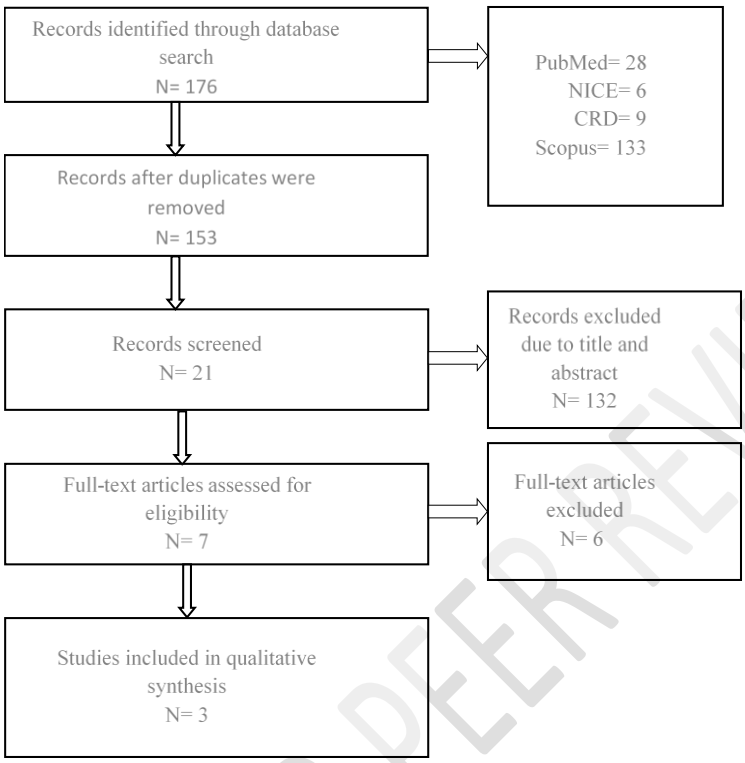

Fig.1. Bibliographical searches and inclusion processes

265 Table 1. Characteristics of the included studies

Authors	Population	Country	Perspective	Type of model	Time horizon	Treatment options compared	Cost	Effectiveness
Zhong L. et al., 2013[24]	mCRPC previously treated with docetaxel	US	Societal	Decision tree	18 months	Cabazitaxel	$156,140	0.76 QALYs
						Abiraterone acetate	$101,050	0.70 QALYs
						Prednisone	$75,366	0.43 QALYs
						Mitoxantrone	$83,171	0.51 QALYs
Wilson L. et al., 2014[22]	mCRPC previously treated with docetaxel	US	Societal	Decision tree	18 months	Cabazitaxel	$136,979	0.76 QALYs
						Abiraterone acetate	$116,700	0.70 QALYs
						Enzalutamide	$129,769	0.73 QALYs
						Placebo	$82,929	0.43 QALYs
Peters ML. et al., 2018[23]	mCRPC previously treated with docetaxel	Netherlands	Societal	Markov's model	5 years	Cabazitaxel	€ 82,783	0.79 QALYs/ 1.38 LY
						Radium-223	€ 78,318	0.8 QALYs/ 1.39LY
						Abiraterone acetate	€ 84,410	0.78 QALYs/ 1.36 LY
						Enzalutamide	€ 85,708	0.86 QALYs/ 1.50 LYs

266 mCRPC-metastasic castration-resistant prostate cancer, LYs- life years, QALYs-quality adjusted
267 life years

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