OLAPARIB IN COMBINATION WITH ABIRATERONE IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER: A SYSTEMATIC REVIEW

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ABSTRACT

Metastatic castration-resistant prostate cancer (mCRPC) is characterized by high levels of prostate-specific antigen even in scenarios with serum testosterone levels lower than those of castration. Thus, it consists of a tumor progression resistant to androgen blockade therapy. In this context, the objective of this study is to evaluate the efficacy and tolerability of Olaparib in combination with Abiraterone compared to placebo plus Abiraterone in patients with mCRPC. This work is a systematic literature review, whose data were obtained from the search for primary studies in the Embase, Medline, Lilacs, Cochrane Central Register of Controlled Trials, and PubMed databases. The search was based on the use of the following health descriptors in English: "Castration-Resistant Prostatic Neoplasms"; "Drug Therapy"; "Abiraterone Acetate" and "Olaparib". The obtained results evidenced that the use of Olaparib in monotherapy or in association with Abiraterone demonstrated significant benefits in progression-free survival and overall survival in patients with mCRPC harboring BRCA1, BRCA2, and ATM mutations whose disease had progressed with a next-generation hormonal agent. This same benefit was also observed in the general trial population with alterations in homologous recombination repair genes. Therefore, it is concluded that this combination results in a combined antitumor effect, which implies a better quality of life for the patient under treatment, optimizing pain relief and any other complications inherent to a metastatic disease requiring palliative therapy.

Keywords: Metastatic Castration-Resistant Prostate Cancer; Antineoplastic Protocols; Olaparib; Abiraterone.

INTRODUCTION

Men with advanced prostate cancer who have evidence of disease progression (e.g., an increase in serum prostate-specific antigen [PSA], new metastases, or progression of existing metastases) and who have castration levels of serum testosterone (<50 ng/dL) are considered to have metastatic castration-resistant prostate cancer (mCRPC) (DAWSON et al., 2024).

mCRPC is also characterized as a heterogeneous disease with a reserved prognosis. The choice of initial systemic treatment for mCRPC depends on many factors, including previous systemic treatments, the location and extent of disease involvement, and the presence or absence of symptoms. Current treatment options in

the first-line mCRPC setting mainly comprise next-generation hormonal agents (e.g., abiraterone and enzalutamide) or chemotherapy with docetaxel. However, despite the reported activity of these agents, overall survival in clinical trial settings is approximately 3 years (CLARKE et al., 2022; DAWSON et al., 2024).

These tumors, in up to 30% of patients, harbor deleterious aberrations in genes involved in DNA damage repair (ABIDA *et al*., 2017). Among the most common alterations are BRCA1, BRCA2, and ATM. Loss-of-function alterations in these and other genes with a direct or indirect role in homologous recombination repair are associated with more aggressive prostate cancers and higher mortality than those with proficient homologous recombination repair (DE BONO et al., 2020).

Regarding therapeutic options, the use of abiraterone is currently considered for controlling tumor progression in castration-resistant prostate cancer. Studies have been conducted to ensure the efficacy of this medication. The main and most recent findings regarding the implications of abiraterone-based drug therapy involve trials comparing this medication with other therapeutic lines (KHALAF *et al.*, 2019).

Furthermore, recent evidence has shown that tumors with genetic alterations affecting homologous recombination repair are sensitive to poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors (HUSSAIN *et al*., 2020). PARP inhibitors block the repair of single-strand DNA breaks and, for tumors associated with homologous recombination repair deficiency (HRD), they result in cell death due to inefficiencies in cellular repair mechanisms. Several PARP inhibitors have been studied in men with metastatic CRPC and DNA repair mutations, and two (olaparib, rucaparib) are now approved for use in HRD-deficient CRPC. Of all HRD deficiencies involving DNA damage response pathways, men with BRCA2 mutations appear to benefit the most (DAWSON et al., 2024).

Therefore, it is noted that new evidence has been addressing the efficacy and tolerability of olaparib in combination with abiraterone compared to placebo plus abiraterone in patients with mCRPC (CLARKE *et al.*, 2018). Given this, the present study aims to evaluate whether this strategy is associated with a better response rate and increased overall disease-free survival in the treatment setting of metastatic castration-resistant prostate cancer.

METHODOLOGY

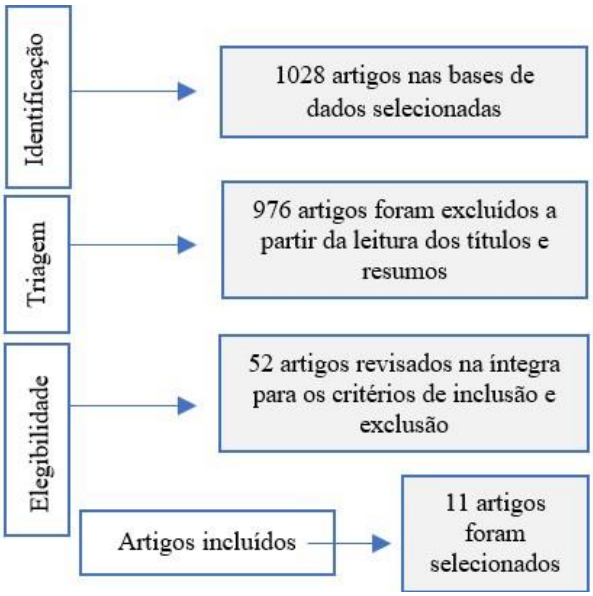
This work is a systematic literature review conducted in accordance with the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions and structured according to the steps suggested by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol.

The research was based on the delimitation of guidelines, provided by the PICOS strategy (Population, Intervention, Control, Outcome, Study Design). Thus, the following guiding question was formulated: "What is the efficacy and tolerability of using olaparib in combination with abiraterone compared to placebo plus abiraterone in patients with mCRPC?".

To answer this question, a broad search was executed, aiming to minimize publication biases. The search was performed in the following databases: Embase, Medline, Lilacs, Cochrane Central Register of Controlled Trials, and PubMed. The search was based on the recurrence of the following health descriptors in English: "Castration-Resistant Prostatic Neoplasms"; "Drug Therapy"; "Abiraterone Acetate" and "Olaparib".

As detailed in Figure 1, the initial search yielded 1028 results. After removing duplicate records and studies with an exclusion criterion based on title/abstract review, 52 remained and were fully reviewed for inclusion and exclusion criteria. Finally, a total of 11 studies were included in this systematic review.

Figura 1. Diagrama de fluxo PRISMA de triagem e seleção de estudos



Fonte: Autores, 2024

It was not necessary to review additional ethical issues, as all data used came from previously published and publicly available studies.

RESULTS

Recent studies have shown that a substantial number of men with prostate cancer, particularly those with intraductal histology, carry germline mutations that can affect therapeutic decisions. Furthermore, it is known that DNA repair gene alterations are present in about a quarter of patients with advanced prostate cancer (DE BONO et al., 2019; DAWSON et al., 2024).

Homologous recombination repair (HRR) is a DNA repair pathway of clinical interest due to the sensitivity of HRR-deficient cells to poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors and potentially to platinum-containing chemotherapy. The investigation of these modifications has been the focus of several clinical studies, as they are often associated with clinical benefits in the use of targeted therapies, especially with PARP inhibitors. In this context, olaparib was tested in the treatment of patients with metastatic castration-resistant prostate cancer harboring these alterations in the phase III PROfound study. This study compared olaparib with an androgen receptor pathway inhibitor (abiraterone or enzalutamide) in 387 men with mCRPC. The results showed clinically and statistically significant benefits, which led to

regulatory approval by ANVISA for the use of this treatment in patients with mutations in the BRCA1, BRCA2, and ATM genes, included in cohort A of the study (DE BONO et al., 2020; ABIDA & ANTONARAKIS et al., 2024).

The use of olaparib also delayed the deterioration in health-related quality of life (HRQoL) scores and was associated with a reduction in pain burden and better HRQoL over time compared to an androgen receptor pathway inhibitor (THIERY-VUILLEMIN et al., 2022; ROUBAUD et al., 2022; ABIDA & ANTONARAKIS et al., 2024).

Another study also analyzed the antitumor effect of this combination. The phase III PROpel study investigated the synergistic potential of combining a new antiandrogen agent with a PARP inhibitor, also exploring this approach in patients without alterations in DNA repair genes. The results showed that the combined treatment provided a benefit in terms of radiographic progression-free survival, with medians of 24.8 months compared to 16.6 months (CLARKE et al., 2022).

Regarding overall survival, although the data are still immature, the intention-to-treat analysis also indicated superiority of the combined treatment, with medians of 42.1 versus 34.7 months (CLARKE et al., 2023).

Based on these results, the American Society of Clinical Oncology (ASCO) issued a provisional clinical guidance supporting the performance of somatic and germline genomic testing in cases of metastatic or advanced cancer, including prostate cancer. That is, genomic testing is recommended for men with advanced prostate cancer who may be candidates for targeted molecular therapies, such as the use of PARP inhibitors (CHAKRAVARTY et al., 2022).

CONCLUSION

The overall results of this review demonstrate clinical benefits of olaparib in combination with abiraterone in the first-line treatment of patients with mCRPC. Periodic follow-up is mandatory, providing an opportunity for therapeutic and palliative alternations.

Thus, it is undeniable that new drug therapies have had a considerable impact on the progression-free survival and overall survival of patients with mCRPC. However, there is no "standard" treatment that fits all cases, making therapeutic individualization

essential. One must take into account the characteristics of the metastases, the clinical status and symptoms of the patient, the treatments already performed, as well as factors such as cost, availability of therapies, and, finally, the active participation of patients and their caregivers in decision-making.

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