INPLASY PROTOCOL

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None declared.

Comparative efficacy of second-generation androgen receptor inhibitors for treating prostate cancer: A systematic review and network meta-analysis

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Review question / Objective: **Second-generation androgen receptor inhibitors (SGARIs), namely enzalutamide, apalutamide, and darolutamide, are good for improving survival outcomes in prostate cancer patients, but some researchers have shown that using SGARIs increases side effects, which complicates clinicians' choice of. Therefore, we performed this network meta-analysis to assess the efficacy and toxicity of several SGARIs in the treatment of patients with metastatic hormone-sensitive prostate cancer (mHSPC), non-metastatic castration-resistant prostate cancer (nmCRPC), and metastatic castration-resistant prostate cancer (mCRPC).**
Information sources: **We will search articles in three electronic database including PubMed, EMBASE and Cochrane Library. All the English publications until December 2022 will be searched without any restriction of countries or article type. Reference list of all selected articles will independently screened to identify additional studies left out in the initial search.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 January 2023 and was last updated on 29 January 2023 (registration number INPLASY202310084).

INTRODUCTION

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hormone-sensitive prostate cancer (mHSPC), non-metastatic castration-resistant prostate cancer (nmCRPC), and metastatic castration-resistant prostate cancer (mCRPC).

Condition being studied: Prostate cancer is the second most common cancer worldwide and the sixth leading cause of cancer death in men. Age, African ancestry, and family history are the only established risk factors of prostate cancer. Approximately 80-90% of prostate cancers are androgen-dependent at initial diagnosis, and 27-53% of early-stage prostate cancers progress with biochemical recurrence. Although ADT and/or the use of first-generation competitive androgen receptor inhibitors can temporarily arrest tumor growth, most men develop castration-resistant prostate cancer (CRPC) after 14-20 months on ADT therapy. Additionally, 3–5% of patients present with metastatic disease either before or after a cure attempt, which is known as metastatic hormone-sensitive prostate cancer (mHSPC). In the past few years, the US Food and Drug Administration has approved three second-generation androgen receptor inhibitors (SGARIs), namely enzalutamide, apalutamide, and darolutamide, to treat prostate cancer. Compared to first-generation ARIs, SGARIs possess a higher affinity for AR and improve survival outcomes. However, the potential side effects of SGARIs and patient resistance cannot be ignored. A meta-analysis has indicated that the administration of SGARIs is associated with a significantly increased risk of cardiovascular events including stroke, heart failure, and peripheral vascular disease. The overall benefits of different types of SGARIs are difficult to assess given the need to weigh the risk of side effects against the efficacy of SGARIs for treating prostate cancer.

METHODS

Participant or population: Eligible patients were adult (defined according to local regulation) males with pathologically confirmed prostate adenocarcinoma, without neuroendocrine differentiation, signet-cell, or small-cell features, and an Eastern Co operative Oncology Group performance status score of 0 or 1. Eligible patients had hormone-sensitive metastatic dis ease, either de novo or after recurrence after prior local therapy, documented by a positive bone scan, or metastatic lesions on computed tomography or magnetic resonance imaging. Enrollment was based on investigator-assessed metastases; after study entry, metastasis was evaluated by independent central review. Prior ADT and up to six cycles of prior docetaxel chemotherapy were permitted. Patients who experienced disease progression prior to randomiza tion while receiving ADT and/or docetaxel were excluded.

Intervention: Patients took enzalutamide, apalutamide and darolutamide plus androgen deprivation therapy.

Comparator: Patients took placebo plus androgen deprivation therapy.

Study designs to be included: Randomized controlled trials (RCTs) will be included.

Eligibility criteria: The inclusion criteria for eligible studies were as follows: (a) the study employed a randomized controlled design; (b) only one SGARI was tested in each trial intervention; (c) mHSPC, mCRPC, and nmCRPC had all progressed during the study; (d) primary and secondary endpoints were included; and (e) either the hazard ratio (HR) or the number of events could be extracted from the text. The exclusion criteria were as follows: (a) publications were duplicated or contained poor-quality information; (b) the study contained insufficient primary data or incomplete study data; and (c) the publications were reviews, abstracts, commentaries, letters, or case reports.

Information sources: We will search articles in three electronic database including PubMed, EMBASE and Cochrane Library. All the English publications until December 2022 will be searched without any restriction of countries or article type. Reference list of all selected articles will

independently screened to identify additional studies left out in the initial search.

Main outcome(s): Overall survival (OS), metastasis-free survival (MFS), radiographic. progression-free survival (rPFS).

Additional outcome(s): Time to CRPC occurrence, time to pain progression, time to initiation of new antineoplastic therapy, time to PSA progression as defined by PCWG2, and time to first skeletal-related event.

Quality assessment / Risk of bias analysis: The quality of the included trials was assessed using the Cochrane Collaboration tool to assess the risk of bias in the randomized controlled trials.

Strategy of data synthesis: Data were processed using Stata 16.0 and R 4.4.2. To investigate the effect of SGARI on selected primary and secondary endpoints, we first performed a direct meta-analysis. During model selection, a random effects model was chosen when I2 > 50%, and a fixed effects model was chosen when I2 < 50%. Next, a Bayesian network meta-analysis was performed using the GeMTC package to make indirect comparisons between different drugs. Rankograms were constructed to assess the ranking probability of each drug.

Subgroup analysis: We used age, race, region, receiving previous hormonal therapy, baseline PSA, and PSA doubling time in the subgroup analysis.

Sensitivity analysis: We excluded one article in turn, and the remaining articles were combined for meta-analysis, and we assessed whether the original meta-analysis results were significantly changed by observing the changes in the combined results by certain studies.

Country(ies) involved: China.

Keywords: Second-generation androgen receptor inhibitors; Metastatic hormone-sensitive prostate cancer; Non-metastatic castration-resistant prostate cancer; Metastatic castration-resistant prostate cancer; Enzalutamide; Apalutamide; Darolutamide.

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