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General Information

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Requires Data Access? Yes

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Requires Data Access? Yes

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/03/Jun-Wang.pdf
https://yoda.yale.edu/wp-content/uploads/2024/03/Junliang-Zhao.pdf
https://yoda.yale.edu/wp-content/uploads/2024/03/Xinyang-Cai.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT01715285 - A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naive Prostate Cancer (mHNPC)
2. NCT00887198 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer

3. NCT00638690 - A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

The effect of ACEi/ARB on survival outcome of metastatic prostate cancer patients treated with Abiraterone acetate (AA)

Narrative Summary:

Abiraterone acetate (AA) was proved to improve prognosis of metastatic prostate cancer (mPCa) by blocking androgen biosynthesis through selectively inhibiting CYP17. However, AA could lead to increased mineralocorticoid levels causing hypertension[1], which need to be controlled by antihypertensive drugs including angiotensin converting enzyme inhibitors (AECis), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), or diuretic drugs[2]. ACEis and ARBs could decrease mineralocorticoid levels through inhibiting Ang II generating or combining with angiotensin II type 1 receptor (AT1R), while CCBs and diuretic drugs could not[2, 3]. The mechanism of ACEis and ARBs might result in better outcomes in mCRPC patients treated with AA. However, the effect of different types of antihypertensive drugs on prognosis of mPCa remain unclear. Thus, We aim to explore whether concomitant AECis or ARBs use in patients with mPCa treated with AA in the COU-AA-301, COU-AA-302 and LATITUDE trials improve overall survival (OS) and progression-free survival (PFS).

Scientific Abstract:

Background: Androgen deprivation therapy (ADT), such as abiraterone acetate (AA), has emerged as a standard treatment for metastatic prostate cancer (mPCa). However, long-term ADT treatment may increase the incidence of cardiovascular adverse events, such as hypertension, which are a common cause of death in patients receiving ADT. Therefore, it is crucial to select appropriate antihypertensive drugs that effectively control blood pressure and improve prognosis of these patients.
Objective: To explore whether concomitant ACEis or ARBs use in patients with mPCa treated with abiraterone acetate (AA) improve overall survival (OS) and progression-free survival (PFS).
Study design: Post-hoc analysis of patients participating in randomized controlled trials.
Participants: Patients with advanced prostate cancer who were enrolled in COU-AA-301, COU-AA-302, and LATITUDE.
Main Outcome Measure: Progression-free survival (PFS) and overall survival (OS) will be determined.
Statistical Analysis: Baseline data will be described by descriptive statistics (median ±SD), and comparison between groups will be performed by student t test or chi-square test. PFS and OS will be estimated by Kaplan-Meier analysis, with hazard ratios calculated using a multivariate Cox proportional-hazard model.

Brief Project Background and Statement of Project Significance:

Palliative treatment based on androgen deprivation therapy (ADT) is the standard treatment for metastatic prostate cancer (mPCa)[4, 5]. After receiving ADT alone for about 1-2 years, mPCa will progress to metastatic castration-resistant prostate cancer (mCRPC). Drug resistance will eventually occur in the novel hormone therapy (NHT) and the prognosis is poor.

Abiraterone acetate (AA) has been proved to improve prognosis of mPCa (both hormone-sensitive and castration-resistant). However, by inhibiting CYP17, AA may lead to increased mineralocorticoid levels causing hypertension[1]. Cardiovascular adverse events are common causes of death in patients treated with ADT, thus, selecting appropriate drugs to manage cardiovascular adverse events is crucial.
ACEis and ARBs could decrease mineralocorticoid levels through inhibiting Ang II generating or combining with angiotensin II type 1 receptor (AT1R), while CCBs and diuretic drugs could not[2, 3]. This mechanism of ACEis and ARBs might result in better outcomes in mCRPC patients treated with abiraterone. However, the effect of different types of antihypertensive drugs on prognosis of mCRPC patients is unclear. The purpose of this study is to retrospectively compare the progression-free survival (PFS) and overall survival (OS) of mPCa patients treated with abiraterone acetate (AA) concomitant using ACEi/ARBs or not to explore the effect of ACEi/ARBs on prognosis of mPCa. The results are expected to provide guidance for management of mPCa and benefit more patients with advanced prostate cancer.

Specific Aims of the Project:

Aims:
Using individual patient data from COU-AA-301, COU-AA-302, and LATITUDE trials which including advanced prostate cancer patients treated with abiraterone acetate (AA) to perform concomitant medication (ACEi/ARBs vs. no ACEi/ARBs) analysis for PFS and OS.

Hypothesis:
Our hypothesis is that concomitant using ACEi/ARBs could improve PFS and OS of mPCa patients treated with abiraterone acetate (AA).

Study Design:

Meta-analysis (analysis of multiple trials together)

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Confirm or validate previously conducted research on treatment effectiveness

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

1. A Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Participants With High-Risk, Metastatic Hormone-Naive Prostate Cancer (mHNPC) (NCT01715285)
2. Abiraterone Acetate in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer (NCT00887198)
3. Abiraterone Acetate in Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Chemotherapy (NCT00638690)

Inclusion criteria: all patients in the trials.
Exclusion criteria: missing data of dosing times.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary end points:

- Overall survival, defined as the time (months) from registered to death.
- Radiographic progression-free survival (rPFS), which will be defined as the time from registered to radiographic progression or death.
- Clinical progression-free survival (cPFS) or death, which will be defined as the time from registered to clinical progression, in months.

Secondary end points:
- PSA response rate (PSA30, PSA50, and PSA90), safety.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The ACEi and ARB medicine medication records, patients were divided into ACEI, ARB, non-ACEI or ARB groups according to whether they had taken such drugs. As long as any dose of the above drugs was taken, they were classified into the ACEI or ARB group.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Age (categorized), race, Eastern Cooperative Oncology Group (ECOG) performance status (0 or ?1), baseline prostate-specific antigen (PSA) (categorized), Gleason score at diagnosis (categorized), prior taxane (no or yes), Tumor Stage, Nodal Stage, Metastases Stage, time from diagnosis to randomization. Baseline laboratory test results (PSA, Hb, LDH, ALP, and ALB). Survival data (PSAprog-PFS, PFS and OS). PSA response rate (PSA30, PSA50, and PSA90), AEs.

Statistical Analysis Plan:

Participants who had the same treatment will be divided by ACEi or ARB medicine medication records. Baseline data will be described by descriptive statistics (median ±SD), and comparison between groups will be performed by student t test or chi-square test. Kaplan-Meier analysis and established multivariate Cox proportional-hazard model will be performed by survival and survminer package. AEs will be described by descriptive statistics (incidence rate).

Software Used:

RStudio

Project Timeline:

We anticipated start the project In June this year, finish the analysis before 1st Oct. 2024, and draft the manuscript for submission before 1st Mar. 2025.

Dissemination Plan:

The findings of this project are expected to result in the development of a manuscript suitable for publication in a urologic (European Urology, Journal of Urology) or oncology (Annals of Oncology, JAMA oncology) journal. In addition, the results will be presented at appropriate urologic (AUA, EAU) or oncology conferences (ASCO, ESMO).

Bibliography:

[1] Attard G, Reid A H, Yap T A, et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven [J]. J Clin Oncol, 2008, 26(28): 4563-4571.

[2] Laurent S. Antihypertensive drugs [J]. Pharmacol Res, 2017, 124: 116-125.

[3] Ahmad H, Khan H, Haque S, et al. Angiotensin-Converting Enzyme and Hypertension: A Systemic Analysis of Various ACE Inhibitors, Their Side Effects, and Bioactive Peptides as a Putative Therapy for Hypertension [J]. J Renin Angiotensin Aldosterone Syst, 2023, 2023: 7890188.

[4] Mottet N, Cornford P, Vanden Bergh R, et al. EAU-EANM-ESTRO-ESUR-ISUP_SIOG guidelines on prostate cancer [EB/OL].[2023-7-17]: https://uroweb.org/guidelines/prostate-cancer.

[5] Schaeffer EM, Srinivas S, An Y, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)Prostate Cancer. Version 1. 2023 [EB/OL].[2023-7-17] https://www.nccn.org/guidelines/guidelinesdetail?category=1&id=1459.