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Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.

Project Funding Source: JSPS KAKENHI

How did you learn about the YODA Project?: Scientific Publication

Conflict of Interest

https://yoda.yale.edu/system/files/coi_fukuokay.pdf
https://yoda.yale.edu/system/files/coi_yanagisawa.pdf
https://yoda.yale.edu/system/files/coi_urabe.pdf
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https://yoda.yale.edu/system/files/coi_mori.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 - 212082PCR3011 - 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)

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

Research Proposal

Project Title
Bone modifying agent in treatment of patients with metastatic castration-sensitive prostate cancer

Narrative Summary:

Previous randomized controlled trials have demonstrated that bone modifying agents (BMAs) improved outcomes of patients with metastatic, castration-resistant prostate cancer. However, it remains uncertain whether these benefits extend to patients with metastatic, castration-sensitive prostate cancer (mCSPC) in the current era of treatment intensification. Consequently, the objective of this study is to investigate the effect of BMA use on the outcomes of patients with mCSPC receiving androgen deprivation therapy either alone or in combination with abiraterone acetate, using the data from the LATITUDE trial.

Scientific Abstract:

Background

Previous randomized controlled trials did not show the benefit of bone modifying agents (BMAs) in metastatic, castration-sensitive prostate cancer (mCSPC) who were treated with androgen deprivation therapy (ADT). Evidence regarding the effect of BMAs in patients with high-risk mCSPC receiving intensified treatment using ADT plus abiraterone acetate (AA) is scarce.

Objective

To examine the effect of baseline BMA use on the outcomes of patients with mCSPC treated with ADT alone or with AA.

Study Design

A post-hoc study, using the data on patients who participated in the LATITUDE trial.

Participants

Patients with high-risk mCSPC who enrolled in the LATITUDE trial. The LATITUDE trial is a double-blind, placebo-controlled, phase III RCT investigating the potential benefits of the addition of AA and prednisone on ADT in patients with newly diagnosed mCSPC.[5]

Main Outcome Measures

Main outcome measures will include overall survival and time to skeletal-related events (SREs) as per the trial protocol.[5]

Statistical Analysis

Baseline demographics will be adjusted using inverse probability of treatment weighting (IPTW) to account for the differences between BMA users and non-users. Time-to-event outcomes will be assessed through IPTW-adjusted Kaplan-Meier curves and compared using restricted mean survival times (RMSTs) and IPTW-adjusted Cox regression models. Additionally, interaction analysis will be conducted using interaction terms within the IPTW-adjusted Cox regression models.

Brief Project Background and Statement of Project Significance:

More than 80% of patients diagnosed with prostate cancer eventually develop bone metastasis.[6] These metastases have an impact on the quality of life, often leading to painful symptoms and potential skeletal complications, such as pathologic fractures, spinal cord compression, or the need for surgery or radiotherapy to the bone. Consequently, the prevention of these events, collectively referred to as skeletal-related events (SREs), has emerged as an important topic in the treatment of advanced or metastatic prostate cancer. Despite the majority of lesions manifesting as osteoblastic, evidence suggests increased osteolytic activity within the bone microenvironments of prostate cancer tumors.[7–9] This suggests that the administration of drugs capable of preventing osteolytic activity could potentially contribute to a reduction in SREs and an improvement of survival of patients with prostate cancer. Bone modifying agents (BMAs), such as zoledronic acid, pamidronate, and denosumab (an antibody targeting the receptor activator of nuclear factor ?B ligand), have been shown to prevent osteolytic activity within bone metastasis and play crucial roles in the treatment of bone metastasis.[10] Previous randomized controlled trials (RCTs) have demonstrated that the addition of zoledronic acid or denosumab, to the standard of care reduced SREs and improved survival in patients with metastatic, castration-
resistant prostate cancer (mCRPC).[1,2,11] However, the effectiveness of this approach in metastatic castration-sensitive prostate cancer (mCSPC) remains controversial. Two previous RCTs showed that zoledronic acid did not improve outcomes of patients with mCSPC.[3,4] In contrast, one RCT demonstrated that clodronate, a first-generation bisphosphonate, improved outcomes in mCSPC.[11] Currently, doublet/triplet treatment intensification, using a combination of androgen deprivation therapy with docetaxel and/or androgen receptor axis-targeted agents, is the standard of care for patients with mCSPC. An observational study demonstrated that the use of BMAs was associated with improved survival in patients with mCRPC receiving abiraterone acetate.[12] However, evidence regarding the effect of BMAs in mCSPC in this era of treatment intensification remains inconclusive.

In the present study, using the data on the LATITUDE trial, we investigated the effect of BMAs on outcomes of patients with high-risk mCSPC treated with androgen deprivation therapy alone or with abiraterone acetate. The results of the present study may underscore the importance of the early BMA use in this population.

Specific Aims of the Project:

Evidence regarding the effect of bone modifying agents (BMAs) on outcomes for patients with metastatic, castration-sensitive prostate cancer (mCSPC) who are treated with androgen deprivation therapy (ADT), either alone or in combination with androgen receptor axis-targeted agents, remains limited. The present study aims to investigate the potential association between BMA use and outcomes of patients with mCSPC treated with ADT, either alone or in combination with abiraterone acetate.

The study hypotheses are as follows: 1) BMA use is associated with improved outcomes, as measured by time to skeletal-related events and overall survival, in patients with mCSPC. 2) This association between BMA use and improved outcomes is not specific to a particular treatment approach and is applicable across both ADT alone and ADT combined with abiraterone acetate.

What is your Study Design?:

Individual trial analysis

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

Research Methods

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

Inclusion criteria: all patients in this trial
Exclusion criteria: missing outcome data

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

Outcome measures will be defined as overall survival and time to skeletal-related event as indicated in the original publication.[5]

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

The primary assessed variable was any bone modifying agent use, categorized as a dichotomous, within a period of 90 days prior and 90 days after randomization.

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

The following variables will be included as covariates: age (categorical), race (categorical), Eastern Cooperative
Oncology Group performance status (categorical), baseline prostate-specific antigen (continuous), baseline body mass index (continuous), Gleason score at diagnosis (categorical), reported pain scale (categorical), prior local therapy (categorical), extent of disease (categorical), number of bone metastasis (categorical), presence of liver metastasis (categorical), presence of visceral metastasis (categorical), baseline hemoglobin (continuous), baseline albumin (continuous), baseline alkaline phosphatase (continuous), and baseline lactate dehydrogenase (continuous).

**Statistical Analysis Plan:**

Descriptive statistics will be used for the description of baseline characteristics. Unweighted and weighted patient characteristics will be stratified based on bone modifying agent (BMA) use. The association between BMA use and patient characteristics will be assessed using an unweighted multivariable logistic regression model. IPTW-adjusted Kaplan-Meier curves will be calculated to compare survival between BMA users and non-users. An IPTW-adjusted Cox regression model will evaluate the hazard ratio for BMA use on outcomes. Furthermore, the heterogeneity of treatment effect based on patient characteristics and treatment (androgen deprivation therapy alone or with abiraterone acetate) will be examined by testing interaction terms within the IPTW-adjusted Cox regression models. The study will also investigate the association between BMA use and adverse events of special interest, such as hypocalcemia or osteonecrosis of the jaw, occurring during the treatment.

Software Used:

RStudio

**Project Timeline:**

Day 0: Approval of the project
Day 60: Data transfer
Day 120: Data processing
Day 150: Data analysis
Day 180: Manuscript writing
Day 210: Manuscript submission

**Dissemination Plan:**

The results of this project are expected to result in the development of a manuscript suitable for publication in a uro-oncology journal. Results will be presented at appropriate uro-oncology conferences.

**Bibliography:**


