Principal Investigator

First Name: Yao
Last Name: Zhu
Degree: m.d.
Primary Affiliation: fudan university
E-mail: changkungene@126.com
Phone number: 862164175590
Address: shanghai, no.270 dong'an road

City: shanghai
State or Province: shanghai
Zip or Postal Code: 200032
Country: china
SCOPUS ID: 22955119300

2017-1356

General Information

Key Personnel (in addition to PI): **First Name:** kun
Last name: chang
Degree: MD
Primary Affiliation: Fudan University, Shanghai, China
SCOPUS ID: 55816587400

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

yoda_project_coi_form_for_data_requestors_chang1.docx
yoda_project_coi_form_for_data_requestors_zhu_yao.docx

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

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

Research Proposal

Project Title

Does Body Mass Index predict efficacy of abiraterone acetate therapy in patients with metastatic castration-resistant prostate cancer?

Narrative Summary:
Recent studies have found that risk varies by stage of disease, tumor grade, and cause-specific mortality. Several meta-analyses have indicated that greater body mass index (BMI) is associated with increased risks of aggressive/advanced prostate cancer and prostate cancer– specific mortality, but the relationships for BMI and efficacy of abiraterone acetate therapy remain inconclusive. The aim of this study is to use data from a large clinical trial of drug therapy in men with metastatic prostate cancer to identify the relationship between BMI and efficacy of abiraterone acetate. The results may help establish an economical and accessible biomarker to predict the efficacy of abiraterone.

Scientific Abstract:
Background: The increase in prostate cancer incidence and mortality observed in immigrants from low-risk to high-risk countries suggests that lifestyle and dietary factors play an important role in the etiology of prostate cancer. Excess body weight comprehensively reflects lifestyle and dietary factors, which occurs when the expenditure (i.e., physical activity) is less than the intake (i.e., high-fat diets).[1-3] Excess body weight, as measured by BMI, has been considered a factor for decreased and increased risk of localized and advanced prostate cancer, respectively. However, the relationship between BMI and efficacy of abiraterone acetate therapy remains unclear.
Objective: The objective of this study is to use data from a large clinical trial of drug therapy in men with metastatic prostate cancer to identify whether BMI could provide some indication of efficacy of abiraterone acetate.
Study Design: Retrospective cohort study.
Participants: mCRPC patients from COU-AA-302 and COU-AA-301 treated with abiraterone or placebo.
Main Outcome Measures(s): Outcomes evaluated will include PSA progression-free survival, overall survival, progression free survival as well as response to subsequent therapies.
Statistical Analysis: Cox regression analysis will evaluate the role of BMI as a prognostic biomarker. Analyses will be stratified by treatment received, ECOG status, LDH, hemoglobin level, Gleason score, TNM stage and age, et al.

Brief Project Background and Statement of Project Significance:
Excess body weight, as measured by BMI, has been considered a factor for decreased and increased risk of advanced prostate cancer. There is a complex array of biological mechanisms through which obesity may influence prostate carcinogenesis and metastasis, including hyperinsulinemia, elevated insulin-like growth factor (IGF) hormone levels, dysregulation of sex steroid hormones, altered levels of adipokines, and chronic inflammation.[4-6] Obesity is also associated with chronic inflammation and biomarkers of inflammation in the body, such as higher levels of C-reactive protein, which have been associated with prostate cancer–specific mortality. [7,8] Obese men have been shown to exhibit reduced levels of androgens, and there is evidence that men with lower levels of testosterone have more aggressive tumors at clinical presentation.
Abiraterone functions by interference with steroid metabolism . Normally in the adrenal glands, adrenocorticotropic hormone (ACTH) stimulates metabolism of the steroid precursor pregnenolone. Pregnenolone can be further metabolized to aldosterone or to 17OH-pregnenolone, a common precursor for cortisol and testosterone. The action of 17[alpha]-hydroxylase converts pregnenolone to 17OH-pregnenolone, and 17,20-lyase further converts this product to dehydroepiandrostenedione (DHEA). DHEA is subsequently converted to an intermediary and finally testosterone. Abiraterone is a potent inhibitor of the 17[alpha]-hydroxylase and 17,20-lyase enzymatic functions of CYP17.[9] Recent preclinical work has also identified [DELTA]4-abiraterone, an active metabolite of abiraterone, that further inhibits 3[beta]-hydroxy steroid dehydrogenase, CYP17A1, and 5[alpha]-reductase. In the presence of ACTH stimulation and abiraterone, pregnenolone is shunted to mineralocorticoid synthesis. Abiraterone used without replacement corticosteroids to suppress ACTH results in a syndrome of mineralocorticoid excess.[10] Abiraterone thus was studied in conjunction with corticosteroids in its clinical development.
As a result, we supposed that excess body weight, as measured by BMI, may lead to the treatment resistance to the abiraterone of prostate cancer.

Specific Aims of the Project:

The objective of this study is to use data from a large clinical trial of drug therapy in men with metastatic prostate cancer to identify whether BMI could act as a predictor of the efficacy of abiraterone acetate reffering to progression-free survival and overall survival.
Hypothesis: We supposed that excess body weight, as measured by BMI, may lead to the treatment resistance to the abiraterone of prostate cancer.

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:
Data source: COU-AA-302 and COU-AA-301
Inclusion criteria: all patients in the trial
Exclusion criteria: missing data

Main Outcome Measure and how it will be categorized/defined for your study:
Date of death (overall survival)
Date of PSA progression (PSA progression-free survival)
Date of Radiographic PFS (Radiographic progression-free survival)

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
Body Mass Index (continuous)

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
In this study, we will not only focus on one predictor. We seek to investigate the variables associated with all cause mortality and disease progression. The variables of interest include:
Age at study entry (continuous)
Race
Height (continuous)
Treatment Arm (Abiraterone or placebo)
Gleason Score (Categorized)
Date of Diagnosis
Presence of liver metastases (Present/Absent)
Presence of bone metastases (Present/absent)
Presence of nodal metastases (Present/absent)
Presence of visceral metastases (Present/absent)
Time from start of initial LHRH to abiraterone treatment (continuous)
Weight (kg, each visit record from inclusion to the end of follow-up)
Prior anti-cancer therapies (number of prior hormonal therapies, prior ketoconazole, prior chemotherapies(COU-AA-302))
Prior prostatectomy and/or radiation therapy (Y/N for each)
Investigations (PSA, Hgb, Cr, AlkPhos, LDH)
Pain score / presence of pain (binary Y/N)
Performance Status (ECOG)
Mode of progression (clinical, radiographic, toxicity)
Best PSA response (% reduction)
Date of Abiraterone or Prednisone initiation
Adverse events or complications occurred during the treatment

Statistical Analysis Plan:
Descriptive statistics will assess median BMI values at baseline, and at each time of visit during subsequent follow up for placebo or AA treatments. Baseline BMI (< or > 25 or alternate cut-off) values will be compared for differences in known baseline prognostic factors such as LDH, Hgb, AlkPhos, ECOG, pain status, presence of metastases and PSA, et al. Univariate and multivariate cox regression analyses will evaluate the HR of baseline and increases or decreases (based on linear regression of changes over time) in BMI values on outcomes of OS,

PFS and response to subsequent therapies. This will be performed separately for both arms of the trial based on treatment received. Area-under-the curve analyses will compare the relative predictive ability of BMI to predict response to AA as measured by best PSA response. All statistical tests will be done using R statistics package, version 2.8.1(http://www.r-project.org/).

Project Timeline:
Project start date: 3/2017
Analysis completion date: 4/2017
Date manuscript drafted/submitted: 5/2017
Results reported 8/2017

Dissemination Plan:
We plan to publish the results of this project in the form of a manuscript in oncology and urology medical journals.

Bibliography:
1. Cao Y, Ma J. Body Mass Index, Prostate cancer–specific mortality, and biochemical recurrence: A systematic review and meta-analysis. Cancer Prev Res.
2011;4(4):486–501.
2. Zhong S, Yan X, Wu Y, et al. Body mass index and mortality in prostate cancer patients: A dose-response meta-analysis. Prostate Cancer Prostatic Dis.
2016;19(2):122–31.
3. Chen Q, Chen T, Shi W, et al. Adult weight gain and risk of prostate cancer: A dose-response meta-analysis of observational studies. Int J Cancer. 2016;
138(4):866–874.
4. Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: New mechanistic insights from epidemiology. Nature Reviews Cancer. 2015;15(8):484–498.
5. Hsing AW, Gao YT, Chua S, et al. Insulin resistance and prostate cancer risk.
J Natl Cancer Inst. 2003;95(1):67–71.
6. Albanes D, Weinstein SJ, Wright ME, et al. Serum insulin, glucose, indices of
insulin resistance, and risk of prostate cancer. J Natl Cancer Inst. 2009;101(18):
1272–1279
7. De Marzo AM, Platz EA, Sutcliffe S, et al. Inflammation in prostate carcinogenesis. Nat Rev Cancer.
2007;7(4):256–269.
8. Platz EA, De Marzo AM. Epidemiology of inflammation and prostate cancer.
J Urol. 2004;171(2 Pt 2):S36–S40
9. Sternberg CN, Petrylak DP, Madan RA, et al. Progress in the treatment of advanced prostate cancer. Am Soc Clin Oncol Educ Book 2014:117-31.
10. Attard G, Reid AH, A'Hern R, et al. Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. J Clin Oncol 2009;27:3742-8.