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General Information

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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

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alibhai-signedcoijune2016.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

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

Research Proposal

Project Title

Predictors of radiographic progression in metastatic castration-resistant prostate cancer: Retrospective analysis of COU-AA-301

Narrative Summary:
Men with prostate cancer that has spread to other organs (metastatic) are monitored by bone scans and other imaging to see if the cancer continues to grow or spread (progression). If progression is seen, cancer treatment may be changed or stopped. The optimal frequency of imaging for monitoring these patients is not known.

Our objective is to use data from a large clinical trial of drug therapy in men with metastatic prostate cancer to identify characteristics of patients and/or their cancer that predict when cancer is progressing. This information may be used to tailor the frequency of imaging based on such characteristics and lead to better utilization of imaging.

Scientific Abstract:
Background: Imaging is used for ongoing surveillance of disease progression for mCRPC patients to make decisions about treatment (for example, stopping or changing drug treatments). However, imaging, particularly CT scans and MRIs, is costly and access is limited. The optimal frequency of imaging for mCRPC patients is not known.

Objective: The objective of the proposed work is to identify predictors of radiographic progression in men with mCRPC with the goal of modifying the frequency of imaging based on patient and/or disease characteristics. Ultimately, this work will lead to better utilization of imaging in these patients.

Study Design: Retrospective cohort study.

Participants: mCRPC patients from COU-AA-301 treated with abiraterone or placebo post chemotherapy.

Main Outcome Measures(s): Time to radiographic progression defined as the time from randomization to the disease progression in bone or soft tissue.

Statistical Analysis: We will use multivariable Cox proportional hazards modelling to assess the association of covariates with time to progression. We will first include all baseline covariates and use a manual backward selection of statistically significant variables. The number of variables in the model may be reduced based on lack of effect on the c-index. Time-dependent covariates including PSA response, patient-reported outcomes and adverse effects will then be added and their contribution assessed with partial log likelihood test and c-index. The analysis will be performed in all subjects and separately in the abiraterone and placebo group.

Brief Project Background and Statement of Project Significance:
About 90% of advanced prostate cancer patients develop bone metastases and serial bones scans are commonly used to identify progression to metastatic disease. In metastatic castrate-resistant prostate cancer (mCRPC), the goal of imaging is to monitor further progression of disease to make decisions about treatment options (for example, stopping or changing drug treatments). Changes in existing bone metastases are not easily or reliably measured; therefore, the appearance of new bone metastases (after ruling out bone flare) is used to assess progression in bone [1]. CT or MRI scans can be used to detect new metastases in soft tissue (nodes and visceral) and to measure changes in soft tissue metastases using modified Response Evaluation Criteria in Solid Tumors

(RECIST) criteria [2].

In a clinical trial of mCRPC patients being treated with abiraterone (or placebo) prior to chemotherapy, approximately 40% of men progressed in bone only, 40% progressed in soft tissue only, and 12% progressed in both bone and soft tissue [3, 4]. Only 6% of men died before evidence of progression. These results suggest that both bone scans and CT or MRI scans are needed to ensure that evidence of progression is detected. In this trial, radiographic progression of disease occurred on average around 14 to 16 months from treatment initiation, but the timing of progression was variable between men; with some men progressing by only 8 to 12 weeks [2]. The optimal schedule of imaging for mCRPC patients is not known and may differ depending on patient and disease characteristics.

Statement of Project Significance

Imaging, particularly CT and MRI, is costly and access is limited. Ongoing surveillance of disease progression is needed for mCRPC patients; however, the optimal frequency of imaging in terms of effectiveness and cost is not known. The goal of the proposed work is to identify predictors of radiographic progression of in men with mCRPC. These factors may be used to determine the appropriate/optimal monitoring schedule for subgroups of patients based on their characteristics and lead to better utilization of imaging. Based on studies of factors associated with overall survival in mCRPC patients [5-7], we hypothesize that several clinically available baseline patient and tumour characteristics will be associated with time to radiographic progression (see list of variables below). Changes in PSA levels and patient reported pain and/or the occurrence of adverse effects may also predict time to radiographic progression.

Data on time to disease progression is highly dependent on the schedule of assessments [4]. Therefore, data from clinical trials, where imaging is scheduled at standard intervals in all patients, are necessary for this type of analysis. Initially, we propose to use data from COU-AA-301. We plan to do similar analyses with data from COU-AA-302, which had a more frequent and standardized protocol of imaging, when they are available.

Specific Aims of the Project:
Overall Objective: To identify predictors of radiographic progression in men with mCRPC to facilitate better utilization of imaging in the follow-up of these patients.

Aim 1: To examine the association of clinically available baseline factors with radiographic progression (all subjects and stratified by treatment group).

Aim 2: To examine the association of clinically available baseline factors with radiographic progression in bone and soft tissue separately.

Aim 3: To examine whether changes in PSA, patient reported pain and/or the occurrence of adverse effects are associated with radiographic progression, independent of baseline variables.

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

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
The data source is COU-AA-301. All subjects included in the COU-AA-301 trial will be included in the proposed work. We propose to carry out similar analyses in patients from COU-AA-302 when the data become available.

Main Outcome Measure and how it will be categorized/defined for your study:
The main outcome measure is time to radiographic progression defined as time from baseline to occurrence of tumor progression in bone or soft tissue, or death.

The COU-AA-301 protocol included CT/MR/other imaging and bone scans at baseline and day 1 of cycle 4, 7 and 10 (every 12 weeks).

Radiographic progression was determined by at least one of the following (as described in Appendix 4 of the study

protocol):

Bone: Progression on bone scans with ? 2 new lesions not consistent with tumor flare, confirmed on a second bone scan ? 6 weeks later that shows ?1 additional new lesion.

Soft Tissue: Progression is defined as a 20% increase in sum of longest dimension of target lesions or the appearance of 2 or more new lesions as measured on CT, MRI or by chest x-ray if lesions are clearly defined.

Patients who did not show progression were alive at last follow-up will be will be censored at that time. Patients with no baseline assessment will be censored at randomization.

The following variables are needed to calculate time to progression:
Time from baseline to radiographic progression or last follow-up
Type of radiographic progression (bone or soft tissue or death)

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
There is not one main predictor variable for the proposed work. We will assess the association of various factors with time to radiographic progression (see list below). While we recognize that multiple testing may be an issue when examining several variables, we note that most of the variables in the table have been shown to be associated with OS for mCRPC [4-6] (including in COU-AA-301); therefore, we hypothesize a priori that they will be associated with time to radiographic progression. Progression measured in a similar manner in patients taking abiraterone prior to chemotherapy (COU-AA-302) was strongly positively associated with OS [2].

Baseline Variables:
1 Treatment Arm (Abiraterone or placebo)
2 Age at entry (continuous)
3 Body Mass Index (continuous)
4 ECOG Performance Status* (Categorical:0, 1, 2)
5 Type of disease progression at baseline (PSA only/radiographic/or both)
6 Presence of liver metastases* (Present/Absent)
7 Presence of bone metastases (Present/absent)
8 Presence of nodal metastases (Present/absent)
9 Presence of visceral metastases (Present/absent)
10 Time from start of initial LHRH to abiraterone treatment* (continuous)

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
Baseline (cont'd)
11 Albumin* (continuous)
12 Alkaline Phosphatase* (continuous)
13 Lactate Dehydrogenase* (continuous)
14 Gleason Score (Ordinal)
15 Hemoglobin (continuous)
16 Presence of Pain (BPI-SF item 3) (ordinal)
17 Baseline PSA (continuous)
18 Prior radiation therapy (Yes/No)
19 End of chemotherapy to start of abiraterone (months) (continuous)
20 Start of chemotherapy to start of abiraterone (months) (continuous)
21 Prior duration of docetaxel treatment (months) (continuous)
22 No. of prior chemotherapy regimens (1 or 2)
23 Prior prostatectomy (Yes/no)

* reported as prognostic for overall survival in COU-AA-301 in ref. 5 and 6
Note: Continuous variables may be categorized after data examination.

Post baseline variables:
PSA:
PSA progression (Yes/no)
Time to PSA progression (continuous)

PSA at each visit (continuous)
Pain:
Presence of Pain (BPI-SF item 3) at each visit (Ordinal)
Analgesic score at each visit (0 =none, 1 for non-opioid analgesics, 2 for opioids for moderate pain, and 3 for opioids for severe pain)

Adverse Effects: Presence of Grade 3 or 4 adverse effects at each visit (Yes/No)

Statistical Analysis Plan:
All analyses will be stratified by treatment group (abiraterone vs placebo) because predictors of progression may differ by treatment.

The distribution of baseline characteristics and outcome measures will be examined by descriptive statistics and graphically using histograms. Transformations will be applied as appropriate.

Univariate: We will plot Kaplan Meier curves of survivorship functions for all categorical variables and for categories of continuous variables. The hazard ratio (HR) and 95% confidence intervals (CI) will be estimated using the Cox proportional hazards (PH) model.

Multivariate: We will use multivariable Cox PH modeling to assess the independent association of covariates with time to progression. We will first include all baseline covariates (Table 1) and use a manual backward selection of statistically significant variables ($P < 0.05$). We may reduce the number of variables in the model based on their lack of effect on overall concordance (C-index) of the model, for reasons of parsimony. Time dependent variables for PSA, pain and adverse effects will be added to the baseline model and their contribution assessed tested with partial log likelihood test and change in the C-index.

The validity of the PH assumption will be checked by testing interactions between time and each variable in the models and by plotting ?ln{?ln(survival) vs ln(time)) to check for parallel lines. Continuous variables will be dichotomized to graphically assess the PH assumption. All statistical analyses will be performed using the Statistical Analysis System (version 9; SAS Institute, Cary, NC).

Sample Size/Power: The statistical power depends on the number of events of progression. The numbers of subjects with radiographic progression are not provided in the publication (7); therefore, we estimated the number of events from the Kaplan Meier curve at 12 months follow up (approximately the median time of follow for the cohort) from figure 3 in Ref. 7. We estimate a total of 996 events of progression (638 in abiraterone group and 358 in control). We plan to examine a maximum of about 30 variables (see list above) which gives us about 33 events per variable (higher than the guideline of 10 events per predictor variable in a model).
Chi (2016) developed a prognostic model for overall survival using the 301 data in each treatment group separately. They examined 15 baseline variables using about 330 events of death and ended up with a model containing 6 independent significant predictors. We would have about 2 times the number of events for radiographic progression.
We note that the endpoint of radiographic progression includes evidence of progression on scans OR death. If we model only evidence of progression on scans the number of events will be somewhat less. Conservatively, if we subtract the total number of deaths from the total number radiographic progression, we are left with 442 events which is still adequate for our modeling purposes.

Project Timeline:
1. Completion of Contract: July 2016
2. Obtain dataset: August 2016
3. Analysis: Sept-Nov 2016
4. Submit report to YODA: Dec 2016
5. Circulate Abstract for ASCO: Jan 2017
5. Circulate paper: Feb 2017

Dissemination Plan:
Abstract presentation for ASCO 2017
Paper – potential journals – Clinical Cancer Research, European Urology, Annals of Oncology

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