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2016-1103

General Information

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?: Data Holder (Company)
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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

The neutrophil to leukocyte ratio (NLR) in metastatic castrate resistant prostate cancer(mCRPC) patients treated with abiraterone acetate

Narrative Summary:

The identification of biomarkers which may be used to select optimal treatments in patients with metastatic castrate resistant prostate cancer (mCRPC) is needed. Derived from routine blood work, the neutrophil to leukocyte ratio (NLR) has been demonstrated to be a biomarker of prognosis in multiple cancers. It remains unknown how the NLR changes over time in mCRPC patients. This study aims to evaluate the evolution of the NLR as a biomarker for patients.. The results are anticipated to provide detailed information as to the utility of this biomarker in men with CRPC and may help establish it as an economical and accessible biomarker.

Scientific Abstract:
Background: The identification of biomarkers which may be used to select optimal treatments in patients with metastatic castrate resistant prostate cancer(mCRPC) is presently needed. In particular, there remain questions of optimal timing and sequencing of AR-targeted therapy such as abiraterone acetate(AA) and enzalutamide. The neutrophil to leukocyte ratio(NLR) ratio is a biomarker of prognosis in multiple cancers including prostate cancer, though how this biomarker changes over the course of treatment and disease progression is not understood.
Objective: To evaluation the NLR in men metastatic castrate resistant prostate cancerreceiving abiraterone
Study Design: This retrospective cohort study will evaluate longitudinal changes in the NLR in the COU301 study of AA + prednisone vs prednisone
Participants: All men enrolled in trial
Main Outcome Measure: NLR will be evaluated as a prognostic biomarker in men before, during and after treatment with AA and placebo. Outcomes evaluated will include overall, survival, progression free survival as well as response to subsequent therapies.
Statistical Analysis: Cox regression analysis will evaluate the role of NLR as a prognostic biomarker. Analyses will be stratified by treatment received, ECOG status, LDH, hemoglobin level and age.

Brief Project Background and Statement of Project Significance:
The neutrophil to leukocyte ratio(NLR) ratio is a biomarker of prognosis in multiple cancers including prostate cancer, though how this biomarker changes over the course of treatment and disease progression is not understood. Further, its relevance in patients who are receiving abiraterone plus prednisone is not well established. Different thresholds for a NLR indicating poorer risk vary in the literature, with values ranging from 1.5 to 5 commonly used in validation studies[2,4]. NLR is calculated as the absolute neutrophil count divided by the absolute lymphocyte count. The derived NLR is an approximation which evaluates the ratio of neutrophils to the difference of total white blood cells and neutrophils. Therefore, this value does not require absolute lymphocyte counts to be included in the differential analysis. What is most appealing about NLR as a biomarker is that it is easily accessible to all clinicians and does not occur any extra tests.
Several studies to date have evaluated the NLR in metastatic castrate resistant prostate cancer(mCRPC) patients. A post-hoc analysis of the TROPIC trial of cabazitaxel as second line taxane therapy demonstrated improved outcomes in men with lower NLR ratios, in particular those who experienced severe neutropenia[1]. These results suggest therapies which exert an impact on the tumoral immune milieu may result in more durable responses. In an evaluation of the TAX327 and VENICE randomized trials which studied respectively docetaxel + prednisone vs prednisone and docetaxel + prednisone vs aflibercept plus prednisone, the authors report that the NLR was prognostic for men with mCRPC receiving chemotherapy[2]. Interestingly, in this study NLR was a stronger prognostic factor than duration of response to ADT, which itself has been associated with response to abiraterone acetate. Similarly, a high NLR was prognostic in men with mCRPC post-docetaxel in the SUN-1120 trial of sunitinib[3]. In an analysis of patients at the Princess Margaret Cancer Centre and the Royal Marsden cancer center, a NLR ?5 and restricted metastatic spread were the only variables found to be predictive of a PSA response to AA[4].
Prior data suggest the NLR is not a predictive biomarker to taxane based therapy[2]. There remains a paucity of data on whether NLR can be used as a predictive marker of response to potent AR-directed therapies in CRPC. A small study of men receiving enzalutamide suggests that NLR may change over the course of progression of disease[5].

Specific Aims of the Project:
NLR has been studied as a biomarker associated with multiple cancers because of its link to inflammation caused by tumors. This study specifically aims to uncover the role of NLR as a biomarker in mCRPC patients treated with Abiraterone Acetate(AA) in combination with prednisone. It has as an objective to test its value as a biomarker in men with CRPC.
Our first hypotheses is that a low NLR?3 in mCRPC patients treated with Abiraterone Acetate along with Prednisone have a better prognosis measureed by overall survival or progression-free survival.
Our second hypotheses is that treatment with abiraterone plus prednisone will induce a change in the NLRfrom ?3 to >3 in some patients and that this increase will signal a poor response to subsequent therapies, defined by overall

survival.

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: 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.
Inclusion criteria: all patients in the trial
Exclusion criteria: missing data

Main Outcome Measure and how it will be categorized/defined for your study:
Outcome measures will be defined as follows: Overall survival, progression-free survival as indicated in the original publication[6]
Response to subsequent therapies will be defined as: Overall survival from progression on placebo or AA until death

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
NLR will be defined as the ratio of neutrophils to lymphocytes in complete blood counts performed as part of per protocol clinic visits. Pending confirmation of the distribution in the dataset, we anticipate using a cutoff NLR value of 3.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
Other variables to be included in this analysis will include ECOG status, treatment received, reported pain scale, presence and number of metastases, time to PSA or radiographic progression, overall survival, best PSA response, baseline LDH and LDH at protocol follow up bloodwork. These will appropriately be used as categorical and continuous variables. Time will be measured from randomization, but analyses for AA will be based on treatment received.

Statistical Analysis Plan:
Descriptive statistics will assess median NLR values +/- IQR at baseline, and at per-protocol blood work during subsequent follow up for placebo or AA treatments. Baseline NLR (< or > 3 or alternate cut-off) values will be compared for differences in known baseline prognostic factors such as LDH, Hgb, ECOG, pain status, number of metastases and PSA.
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 NLR 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 NLR to predict response to AA as measured by best PSA response.
Kaplan-Meier analysis will compare survival between baseline NLR < or >3, as well as categories of NLR values over time: stable, decreasing or increasing.

Project Timeline:
Day 0: Approval of the project
Day 30: Data transfer
Day 60: Data processing
Day 90: Data analysis
Day 120: Manuscript writing
Day 180: 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:

1. Meisel, A. et al. Severe neutropenia during cabazitaxel treatment is associated with survival benefit in men with metastatic castration-resistant prostate cancer (mCRPC): A post-hoc analysis of the TROPIC phase III trial. Eur J Cancer 56, 93-100, doi:10.1016/j.ejca.2015.12.009 (2016).
2 van Soest, R. J. et al. Neutrophil-to-lymphocyte ratio as a prognostic biomarker for men with metastatic castration-resistant prostate cancer receiving first-line chemotherapy: data from two randomized phase III trials. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 26, 743-749, doi:10.1093/annonc/mdu569 (2015).
3 Sonpavde, G. et al. Prognostic impact of the neutrophil-to-lymphocyte ratio in men with metastatic castration-resistant prostate cancer. Clinical genitourinary cancer 12, 317-324, doi:10.1016/j.clgc.2014.03.005 (2014).
4 Leibowitz-Amit, R. et al. Clinical variables associated with PSA response to abiraterone acetate in patients with metastatic castration-resistant prostate cancer. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 25, 657-662, doi:10.1093/annonc/mdt581 (2014).
5 Conteduca, V. et al. Persistent Neutrophil to Lymphocyte Ratio >3 during Treatment with Enzalutamide and Clinical Outcome in Patients with Castration-Resistant Prostate Cancer. PLoS One 11, e0158952, doi:10.1371/journal.pone.0158952 (2016).
6 Ryan, C. J. et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 368, 138-148, doi:10.1056/NEJMoa1209096 (2013).