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General Information

Key Personnel (in addition to PI):

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)

Conflict of Interest

https://yoda.yale.edu/system/files/coi_disclosure_signed_15_mai_2020.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

The neutrophil to leukocyte ratio(NLR) as a biomarker in metastatic castrate sensitive prostate cancer(mCRPC) patients treated with abiraterone

Narrative Summary:

There is a need to personalize treatments for patients with metastatic castrate sensitive prostate cancer(mCSPC). The neutrophil to lymphocyte ratio(NLR) is an accessible and inexpensive biomarker which is widely used in different cancers to estimate prognosis. Following prior work suggesting NLR may also predict the response to the prostate cancer drug abiraterone in patients with resistant prostate cancer, we here perform a re-analysis of a pivotal abiraterone trial to assess whether the NLR may predict response to abiraterone among patients with mCSPC. These results may help further justify the use of NLR in clinical practice among patients where abiraterone is a treatment option.

Scientific Abstract:

Background: The identification of biomarkers to select optimal treatments in patients with metastatic castrate sensitive prostate cancer(mCSPC) is increasingly important as multiple treatment options become available for these patients. Most current biomarkers requiring genomic testing of patient tumor samples or blood samples, which may incur significant costs and result in treatment delays. The neutrophil to leukocyte ratio(NLR) ratio is a biomarker derived from routine blood tests and thus remains highly accessible, rapid and inexpensive.
Objective: To evaluation the utility of NLR as a predictive biomarker in mCSPC patients

Study Design: This retrospective cohort study will evaluate the NLR as a biomarker in the pivotal LATITUDE study of abiraterone acetate(AA) + prednisone + androgen deprivation (ADT) vs ADT alone in men with high-risk mCSPC

Participants: All men enrolled in the LATITUDE trial

Main Outcome Measure: NLR will be evaluated as a biomarker in participants before, during and after treatment with AA and placebo. Outcomes evaluated will include overall survival, progression-free survival and response to subsequent chemotherapy.

Statistical Analysis: Cox regression analysis will evaluate the role of NLR as an independent biomarker after adjusting for known prognostic factors. Adjustment variables will include ECOG status, lactate dehydrogenase(LDH), hemoglobin level and age.

Brief Project Background and Statement of Project Significance:

The neutrophil to leukocyte ratio (NLR) is a recognized biomarker for multiple cancers. It is a reflection of cancer-related and host inflammation which in recent years is recognized as one of the hallmarks of cancer progression(1). An elevated NLR may be associated with both an increased neutrophil-dependent systemic inflammatory response and a lower lymphocyte-mediated antitumor immune response, reflecting a supportive tumor microenvironment(2). Indeed, our prior study demonstrated NLR increased following progression of prostate cancer. NLR has known prognostic value in multiple studies among castrate resistant prostate cancer patients(2), with elevated values portending worse outcomes(3–6).
Prior studies of NLR have focused on patients with treatment-resistant disease. 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(7). In an evaluation of the TAX327 and VENICE randomized trials which studied respectively docetaxel + prednisone vs prednisone and docetaxel + prednisone vs aflibercept + prednisone, the authors report that the NLR was prognostic for men with metastatic castrate resistant prostate cancer (mCRPC) receiving chemotherapy(8).Interestingly, in this study NLR was a stronger prognostic factor than duration of response to ADT, which itself has been associated with response to AA. Similarly, a high NLR was prognostic in men with mCRPC post-docetaxel in the SUN-1120 trial of sunitinib(9). Finally, an analysis of patients with resistant prostate cancer 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 prostate specific antigen(PSA) response to AA(10).
Our previous study in in the COU-302 trial of AA plus prednisone among minimally or asymptomatic patients with castrate-sensitive indicated that baseline NLR may be used as a predictive biomarker of response to AA(11). This is an important finding but remains to be validated, as there remains limited other data to indicate whether NLR may be a predictive biomarker. Prior data suggest the NLR is not a predictive biomarker to taxane based therapy(8). A small study of men receiving enzalutamide suggests that NLR may change over the course of progression of disease(12). Therefore, further studies in patients receiving androgen receptor axis targeting therapy is warranted.

Specific Aims of the Project:

In this study, we aim to evaluate the role of neutrophil-to-lymphocyte ratio (NLR) as a biomarker in a population of prostate cancer patients with metastatic castrate sensitive disease who received androgen deprivation therapy(ADT) or abiraterone acetate(AA) plus prednisone plus ADT. As has been seen in more resistant populations of patients with advanced prostate cancer, we anticipate that NLR will also serve as a prognostic biomarker in previously untreated patients with metastatic prostate cancer. Further, we hypothesize that in this population of patients with no prior therapy, the NLR will serve as a predictive biomarker for AA therapy, with patients with an NLR <2.5 possessing better overall survival, radiographic progression-free survival and time to initiation of chemotherapy.

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:

We will include all patients in the LATITUDE trial, excluding only participants with incomplete data.

Main Outcome Measure and how it will be categorized/defined for your study:

Outcome measures will include overall survival, radiographic progression-free survival and time to initiation of chemotherapy as defined in the original publication(13).

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

NLR is defined as the ratio of neutrophils to lymphocytes in blood work collected as part of per protocol clinic visits. This will be assessed as pre-ADT or post-ADT on pre-randomization values using trial data; analyses will be stratified accordingly.

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

Laboratory values of lactate dehydrogenase(LDH), hemoglobin(Hgb) prior to randomization will be used as adjustment covariates. Additional variables of interest include ECOG status, presence of liver metastases, number of bone metastases and presence of Gleason pattern 5.

Statistical Analysis Plan:

Descriptive statistics will assess median NLR values +/- IQR at baseline, and at per-protocol blood work during subsequent follow up for ADT or abiraterone acetate(AA) + prednisone ADT arms of the study. Baseline NLR (< or > median) values will be compared for differences in for prognostic factors such as LDH, Hgb, ECOG status, presence of liver metastases and prostate specific antigen(PSA)(14–16).
Univariate and multivariate cox proportional regression analyses will evaluate the hazard ratio(HR) of baseline NLR values on outcomes of overall survival(OS), radiographic progression-free survival(PFS) and time to initiation of chemotherapy. This will be performed separately for both arms of the trial. Area-under-the curve analyses will compare the relative predictive ability of NLR to predict response to AA compared to known prognostic factors. Kaplan-Meier analysis will compare survival between baseline NLR < or > median. In separate analysis in each trial arm, we will also assess whether changes in NLR values over time are prognostic, as previously reported in the castrate resistant prostate cancer(CRPC) population(11).
Software Used:
STATA
Project Timeline:

Anticipate project start date: <1 month from access approval
Analysis completion date: by 9 months
Draft manuscript completed: by 11 months
Submission for publication : by 12 months

Dissemination Plan:

The results of this project are anticipated to result in the development of a manuscript suitable for publication in an oncology or urology journal. Results will be presented at oncology conferences such as the Genitourinary Cancers Symposium or European Society of Medical Oncology meeting.

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