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General Information

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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: Ride for Dad - Prostate Cancer Fight Foundation (Durham Chapter, ON, Canada)

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

Research Proposal

Project Title

Studying the Risk of Harmful Drug-Drug Interactions (DDI) in Patients with Castration-Resistant Prostate Cancer (CRPC) Treated with Abiraterone (ABI)

Narrative Summary:
ABI is inactivated via cytochrome P450 (CYP) 3A4, and inhibits various CYPs involved in the metabolism of other drugs commonly used in patients (pts) with CRPC. Thus, DDI may affect the activity or safety of both ABI and co-medications. A retrospective review of 84 CRPC pts treated with AA revealed potential DDI in 87% of pts, but small sample size and lack of systematic documentation of adverse events amongst others did not allow definite conclusions about the risk of harmful DDI-related adverse events. Hence, we plan to study baseline and on-treatment medication histories, and adverse events of CRPC pts undergoing ABI therapy within COU-AA-301 to identify the risk of harmful DDI.

Scientific Abstract:
BACKGROUND: ABI inhibits androgen synthesis by blocking CYP17, is inactivated by CYP3A4, and impairs numerous other CYPs involved in the metabolism of widely used medications. Hence, there is presumably a high potential for DDI either diminishing the efficacy of ABI or of concurrent medications, or increasing the risk of DDI-related adverse events. However, the frequency and nature of harmful DDI involving ABI are poorly known. OBJECTIVES: To study frequency, nature and severity of ABI-associated DDI in CRPC pts treated with ABI within COU-AA-301. STUDY DESIGN AND PARTICIPANTS: We will analyze baseline demographics, medication histories, on-treatment medication changes, and adverse events of pts undergoing ABI therapy within COU-AA-301 (n=797). To screen for and grade postulated DDI, we will use two commercial databases (Lexicomp, Micromedex). MAIN OUTCOME MEASURES: Rate of CRPC pts starting ABI considered at risk of significant DDI, most commonly used drugs/classes of drugs harboring potential risks for DDI with ABI, documented DDI-related adverse events. STATISTICAL ANALYSES: We will apply (1) descriptive analyses for continuous variables, and proportions for categorical variables, (2) a general linear mixed model for between- and within-subject variability of the percental change of medications from baseline to week 12, (3) univariate and multivariate general linear mixed model analyses to identify significant relationships between demographic and disease covariates, and (4) generalized estimating equations to search for significant predictive factors.

Brief Project Background and Statement of Project Significance:
ABI increases survival and delays symptomatic progression in pts with CRPC by impairing androgen biosynthesis through blocking CYP17 (1, 2). However, it also inhibits other CYPs involved in the metabolism of widely used medications (strong inhibition of CYP1A2, CYP2D6, and CYP2C8; moderate inhibition of CYP2C9, CYP2C19 and CYP3A4/5) (3). Hence, DDI may affect the activity or safety of both ABI and certain co-medications. Whereas the frequency and clinical relevance of ABI-related DDI is not well established, CRPC pts commonly use numerous medications for concurrent health conditions, including drugs with a narrow therapeutic range (4). The risk of clinically relevant DDI is further amplified in the often elderly and frail CRPC pts in which drug prescription is generally more challenging (5, 6).
We conducted a retrospective review of pharmacy records and medical charts of CRPC pts beginning ABI treatment between 01/2010 and 04/2014 at Sunnybrook Odette Cancer Centre (Toronto, ON, Canada), to retrieve demographic information, individual drug histories and adverse events during ABI therapy. Individual drug histories were analyzed for DDI using two commercial databases (Lexicomp, Micromedex). Amongst 84 informative pts, the most common drugs flagged by Lexicomp and/or Micromedex for potential DDI of high clinical significance with ABI (i.e., "avoid combination", or "consider therapy modification") were oxycodone (13% of pts), metoprolol (12%), morphine (11%), and clopidogrel (7%). Of note, we did not find any DDI at risk of affecting ABI levels. On the other hand, ABI is postulated to increase oxycodone, morphine and metoprolol drug levels, and to decrease the active metabolite of clopidogrel. At least 1 potentially significant DDI was found in 73 pts overall (87%; in 65 pts (77%) with Lexicomp, and in 44 pts (52%) with Micromedex). Most common adverse events were fluid retention seen in 16 pts (19%), fatigue in 14 (17%), liver-function test abnormalities in 11 (13%), hypertension in 13 (15%), all

corresponding to adverse events typically associated with the use of ABI.

We did not find unequivocal evidence for DDI-related adverse events, possibly due to widely applied DDI screening before initiation of ABI, followed by according medication modifications. However, our study had a number of limitations, including the relatively small sample size, the retrospective nature of data collection, a lack of systematic collection of adverse events, and incomplete information on modifications of baseline co-medications (before starting ABI, or during ABI therapy). Thus, although the use of commercial DDI databases reveals a substantial risk of potential DDI in CRPC pts undergoing ABI therapy, the clinical relevance of these interactions is difficult to determine to date.

In COU-AA-301, drug histories (including treatment modifications) and adverse events were collected prospectively in 797 CRPC pts undergoing ABI therapy. Using this dataset will enable us to study the frequency and relevance of potential interactions flagged by DDI database screen, and to formulate lists of drug combinations that should be avoided, or may be considered safe.

Specific Aims of the Project:

Hypothesis: When applying commercial DDI databases, many CRPC pts undergoing ABI therapy are expected to use co-medications associated with the risk of potentially relevant DDI.

Primary endpoints: (1) to describe the rate of CRPC pts starting ABI treatment considered at risk of significant DDI; (2) to identify the most commonly used drugs/classes of drugs harboring potential risks for DDI with ABI.

Secondary endpoints: (3) to analyze medication changes between baseline, week 4 and week 12; (4) to identify the number of pts that suffered adverse events possibly related to DDI; (5) to identify drugs/classes of drugs involved in relevant DDI; (6) to determine if there are demographic covariates or disease characteristics that predict relevant DDI.

What is the purpose of the analysis being proposed? Please select all that apply. New research question to examine treatment safety
Research that confirms or validates previously conducted research on treatment safety
Preliminary research to be used as part of a grant proposal

Research Methods

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

We will include all patients randomized to the ABI plus prednisone arm of COU-AA-301 (n=797) for which there are complete medications histories available at baseline and throughout the first 12 weeks of ABI treatment.

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

Primary endpoints:

Patients at risk of significant DDI according to DDI database screening will be defined as follows: (1) Lexicomp database: DDI flagged as "avoid combination", or "consider therapy modification"; (2) Micromedex database: DDI flagged as "contraindicated", or "major risk". Because the identification of DDI differs between Lexicomp and Micromedex (based on our previous experience), we will calculate separate percentages of patients at risk for DDI according to Lexicomp and Micromedex, and separate percentages of patients using specific therapeutic classes of drugs at risk of DDI.

Secondary endpoints:

We plan to analyze medication changes using the following categories: (1) cessation of medications at risk for DDI with ABI; (2) introduction of safer drug alternatives to prevent predicted DDI; (3) other changes. Postulated DDI are called if the patient experiences an adverse event grade ?2 (CTCAEv3.0) that was predicted by the type of DDI (e.g., hypotension/bradycardia due to ABI-mediated inhibition of metoprolol metabolism), and the causality of which is "probable", or "definite" (see Table 1 in 'Supplementary Material' for definitions).

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

To determine if there are demographic covariates or disease characteristics that predict relevant DDI, we will study the impact of the following variables on the aforementioned outcome measures: geographical origin of the patient (North America vs Europe vs Australia), age (<70, >70-80, >80), performance status (0-1 vs 2), number of co-medications at baseline (0 vs 1-5 vs >5), PSA as a marker of disease burden (below vs above the median PSA of 128.8 in the ABI arm of COU-AA-301), and liver metastases (absent vs present; given the importance of hepatic drug metabolism).

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

Statistical Analysis Plan:
Descriptive analyses will be conducted using mean, standard deviation, median and ranges for continuous variables, and proportions for categorical variables. For all pts and for subgroup of pts according to covariates of interest, we plan (i) to calculate the rate of CRPC individuals who are identified at risk of significant DDI, (ii) to estimate the proportions of drugs used harboring potential risks for DDI, and (iii) to calculate the proportions of pts that suffered adverse events possibly related to DDI. To investigate the percental change of medications from baseline to week 12, a general linear mixed model will be applied to account for between- and within-subject variability. Univariate and multivariate general linear mixed model analyses will be performed to search for significant relationship between medication changes and covariates of interest. For the endpoint of "any" risk of significant DDI during the study (yes vs no), univariate and multivariate logistic regression analyses will be conducted to see if there is significant association. To investigate the "proportion change" of pts with risk of significant DDI at baseline, at week 4, or at week 12, generalized estimating equations will be used to search for significant predictive factors. All analyses will be performed using Statistical Analysis Software (SAS), p-values < 0.05 will be considered as statistically significant.

Project Timeline:
Data collection/extraction: months 1-4.
Data analyses: months 5-8.
Manuscript preparation and submission: months 9-12.

Dissemination Plan:
We plan to present the data at 1-2 international meetings (eg ASCO GU, ASCO), and to submit an according manuscript to a urological oncology journal such as European Urology (Impact Factor 12.48). Based on our previous work there is also a keen interest for educational materials that facilitate the safe use of AA.

Bibliography:
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Supplementary Material: table_1_causality_assessment.docx