Inherited Variants in SULT1E1 and Response to Abiraterone Acetate by Men with Metastatic Castration Refractory Prostate Cancer

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Abbreviations and Acronyms

AA = abiraterone acetate
AR = androgen receptor
FDR = false discovery rate
HSD = 17β-hydroxysteroid dehydrogenase
IGF = insulin-like growth factor
LN = lymph node
mCRPC = metastatic castration refractory prostate cancer
PSA = prostate specific antigen
SNP = single nucleotide polymorphism
STS = steroid sulfatase
TTF = time to treatment failure

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Purpose: Germline variations in genes involved in androgen biosynthesis and metabolic pathways may predict the response to abiraterone acetate in men with metastatic, castration refractory prostate cancer. The variations may serve as prognostic and predictive biomarkers to allow for more individualized therapy.

Materials and Methods: We evaluated 832 single nucleotide polymorphisms from the OmniExpress genotyping platform (Illumina®) in the boundaries of 61 candidate genes reported to be involved in the androgen metabolic pathway. The purpose was to investigate them for an association with time to treatment failure in 68 white men with metastatic, castration refractory prostate cancer undergoing treatment with abiraterone acetate. Cox proportional hazard analysis was used with Gleason score, age, level of alkaline phosphatase and prostate specific antigen at treatment initiation as covariates. Each single nucleotide polymorphism was assessed using an allele carriage genetic model in which carriage of 1 or more minor alleles contributes to increased risk. Subset analyses were done to determine whether metastasis site, or prior treatment with ketoconazole or docetaxel would interact with the single nucleotide polymorphisms investigated.

Results: Six single nucleotide polymorphisms in the estrogen sulfotransferase gene *SULT1E1* were associated with time to treatment failure on abiraterone acetate therapy after false discovery rate (q value) correction for multiple testing while controlling for Gleason score, age, level of alkaline phosphatase and prostate specific antigen at treatment initiation ($q < 0.05$).

Conclusions: Single nucleotide polymorphisms in *SULT1E1* were significantly associated with time to treatment failure in men on abiraterone acetate therapy. The single nucleotide polymorphisms may serve as predictive markers for treatment with abiraterone acetate.

Key Words: prostatic neoplasms; polymorphism, single nucleotide; abiraterone; treatment failure; biomarkers

Given the hereditary component of prostate cancer, genome-wide association studies have gained considerable momentum in recent years and have identified approximately 100 SNPs associated with the overall risk of prostate cancer diagnosis.[1,2] Gene-phenotype correlates have evolved as attractive biomarkers for various stages of the disease from risk

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identification to disease detection, prognostication and risk prediction for response to therapy.[3]

The heterogeneity of prostate cancer implies the possibility of many somatic and germline genetic variations in the origin and progression of disease. Multiple gene mutations have been linked to pathological variations and individual response to therapy. Changes in ERG, PTEN and AR expression as well as TP53 mutations are widely associated with metastatic prostate cancer.[4] A recent multi-institutional study identified many somatic genomic alterations in mCRPC, including PI3K, Wnt and AR signaling, cell cycle and DNA repair pathways.[5]

Cytochrome P450 17α-hydroxylase/17,20-lyase (CYP17) is a key enzyme in the androgen synthesis pathway that has been implicated in the pathogenesis of prostate cancer.[6] AA is a CYP17 inhibitor that is widely used to treat mCRPC.[7] However, resistance to AA universally develops after varying periods of use and the androgen receptor splice variant AR-V7 has been implicated in therapy resistance to AA.[8] The high 71.3% frequency of AR pathway alterations noted by Robinson et al[5] indicates differential responses to second generation androgen deprivation therapy such as AA in patients harboring these mutations. In addition, the investigators found pathogenic germline variants in 8% of men with mCRPC, suggesting the possibility of an association of germline mutations with the response to systemic therapy.

Germline variations in genes involved in androgen biosynthesis and metabolic pathways have been suggested as predictive markers of the response to androgen deprivation therapy in men with advanced prostate cancer.[9–11] However, to our knowledge genetic correlates in the response to second line therapeutic agents such as AA in patients with mCRPC have not yet been reported. Therefore, the current study was performed to evaluate whether any association exists between germline SNPs and the therapy response to AA, and whether such association may predict treatment failure in patients with mCRPC undergoing AA therapy.

PATIENTS AND METHODS

Patient Selection

Patients with mCRPC treated with AA at the University of Utah Huntsman Cancer Institute from June 2011 to December 2014 were included in analysis. All patients provided informed consent for blood collection and genotypic analysis. The study was performed according to the guidelines of the University of Utah institutional review board.

Clinical Data and Primary Outcome Collection

The collected clinical variables included demographics, disease characteristics, including Gleason score and location of distant metastasis (visceral vs no visceral metastasis), prior systemic therapies, baseline PSA and alkaline phosphatase levels, and TTF when on AA. TTF was based on PSA progression as defined by PCWG2 (Prostate Cancer Working Group) criteria. Most patients were treated in the real world setting and did not undergo scans every 3 months if PSA was responding. Table 1 lists clinical variables used in the analysis of the therapy response to abiraterone.

DNA Isolation and Genetic Analysis

DNA was extracted from whole blood using standard techniques. Whole genome SNP genotyping was done using the OmniExpress genotyping platform. All SNPs in the gene boundaries of 61 candidate genes known to be involved in androgen pathways[9,12] were selected (supplementary table, http://jurology.com/). A total of 1,078 SNPs was included. All individuals exceeded 98% genotyping success on the OmniExpress array and any SNPs with any genotyping failure in this data set were removed. All remaining SNPs were in Hardy-Weinberg equilibrium in the larger data set from which these individuals were drawn. However, only the 832 SNPs that were polymorphic in this data set and without missing data were used for analysis.

Statistical Analysis

R (https://www.r-project.org/) was used for all analyses. Cox proportional hazards analysis was used to analyze TTF for all informative markers individually, controlling for Gleason score, level of alkaline phosphatase and PSA at treatment initiation. An allele carriage model (individuals carrying at least 1 rare allele vs no rare alleles) was used. Although it would eventually be of interest to investigate an additive or recessive mode of inheritance, this was not feasible in the current series due to the small sample size. A FDR (q value) method to adjust for multiple testing was used to determine significance.

RESULTS

A total of 68 patients with mCRPC were included in analysis. Prior therapies were permitted, including docetaxel. Median patient age at the initiation of AA therapy was 70.5 years (table 1). Eight patients had visceral metastasis while 53 had prostate cancer metastasized to bones or bones and LNs, and 7 had

Table 1. *Clinical variables at AA treatment*

Median age (range)	70.5	(53–95)
No. metastasis (%):		
Bone with/without LNs	53	(77.94)
LN alone	7	(10.29)
Viscera	8	(11.76)
No. Gleason score (%):		
2–4	4	(5.88)
5–7	24	(35.29)
8–10	40	(58.82)
Median μl alkaline phosphatase	107	(30–600)
Median ng/ml PSA (range)	62.25	(0.1–819.5)
No. prior therapy (%):		
Ketoconazole	14	(20.59)
Docetaxel	18	(26.47)

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