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Germline DNA-repair Gene Mutations and Outcomes in Men with Metastatic Castration-resistant Prostate Cancer Receiving First-line Abiraterone and Enzalutamide

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Abstract

Background: Inherited DNA-repair gene mutations are more prevalent in men with advanced prostate cancer than previously thought, but their clinical implications are not fully understood.
Objective: To investigate the clinical significance of germline DNA-repair gene alterations in men with metastatic castration-resistant prostate cancer (mCRPC) receiving next-generation hormonal therapy (NHT), with a particular emphasis on *BRCA/ATM* mutations.
Design, setting, and participants: We interrogated 50 genes for pathogenic or likely pathogenic germline mutations using leukocyte DNA from 172 mCRPC patients beginning treatment with first-line NHT with abiraterone or enzalutamide.
Outcome measurements and statistical analysis: We assessed the impact of germline DNA-repair gene mutation status on ≥50% and ≥90% PSA responses, PSA progression-free survival (PSA-PFS), clinical/radiologic progression-free survival (PFS), and overall survival (OS). Survival outcomes were adjusted using propensity score-weighted multivariable Cox regression analyses.
Results and limitations: Among 172 mCRPC patients included, germline mutations (in any DNA-repair gene) were found in 12% (22/172) of men, and germline *BRCA/ATM* mutations specifically in 5% (9/172) of men. In unadjusted analyses, outcomes to first-line NHT were better in men with germline *BRCA/ATM* mutations (vs no mutations) with respect to PSA-PFS (hazard ratio [HR] 0.47; $p = 0.061$), PFS (HR 0.50; $p = 0.090$), and OS (HR 0.28; $p = 0.059$). In propensity score-weighted multivariable analyses, outcomes were superior in men with germline *BRCA/ATM* mutations with respect to PSA-PFS (HR 0.48, 95% confidence interval [CI] 0.25–0.92; $p = 0.027$), PFS (HR 0.52, 95% CI 0.28–0.98; $p = 0.044$), and OS (HR 0.34, 95% CI 0.12–0.99; $p = 0.048$), but not in men with non-*BRCA/ATM* germline mutations (all $p > 0.10$). These results require prospective validation, and our conclusions are limited by the small number of patients ($n = 9$) with *BRCA/ATM* mutations.
Conclusions: Outcomes to first-line NHT appear better in mCRPC patients harboring germline *BRCA/ATM* mutations (vs no mutations), but not for patients with other non-*BRCA/ATM* germline mutations.
Patient summary: Patients with metastatic castration-resistant prostate cancer and harboring germline mutations in *BRCA1/2* and *ATM* benefit from treatment with abiraterone and enzalutamide.

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1. Introduction

While prostate cancer is known to be one of the most heritable human malignancies [1], the prevalence of high-penetrance cancer-susceptibility alleles in prostate cancer patients has only recently begun to be elucidated. To this end, current estimates suggest that inherited germline mutations in DNA-repair genes may be found in 7–12% of men with metastatic prostate cancer; approximately 60–75% of these involve the *BRCA1*, *BRCA2*, and *ATM* genes (absolute prevalence in metastatic prostate cancer of 5–8%) [2,3]. It is now known that germline mutations in certain DNA-repair genes (particularly *BRCA2*) are associated with early-onset prostate cancers with higher Gleason grades and higher recurrence rates following definitive local therapy [4]. In addition, our group has recently shown that germline *BRCA2* and *ATM* mutations distinguish lethal from indolent prostate cancers, and are associated with shorter survival times and earlier age at death [5].

What is less clear is the prognostic significance of germline DNA-repair gene alterations in the context of systemic therapies for metastatic castration-resistant prostate cancer (mCRPC) [6]. Early reports suggest that mCRPC patients with germline *BRCA2* mutations may respond more favorably to poly ADP-ribose polymerase (PARP) inhibitors as well as platinum-based chemotherapies [7,8], although these observations require confirmation. In addition, a recent publication suggested that patients with germline DNA-repair defects demonstrate poorer responses to first-line androgen deprivation therapy as well as next-generation hormonal therapies (abiraterone, enzalutamide) compared to those without germline mutations [3]. By contrast, a separate study evaluating germline and/or somatic DNA-repair mutations found that patients carrying mutations had superior responses to first-line abiraterone treatment than patients with the wild-type counterparts [9]. Therefore, the clinical impact of germline DNA-repair alterations in mCRPC patients receiving next-generation hormonal therapy remains uncertain [10].

To shed additional light on this issue, we conducted an analysis investigating the clinical significance of germline DNA-repair gene mutations on the efficacy of next-generation hormonal therapy (NHT) among 172 mCRPC patients beginning treatment with first-line abiraterone or enzalutamide. Given the role of the androgen receptor (AR) in mediating and promoting DNA repair functions [11,12], we hypothesized that AR-targeted therapies would induce a "synthetic lethality" in patients with an inherited DNA repair–deficient state, resulting in superior responses to abiraterone and enzalutamide in men harboring germline DNA-repair gene mutations compared to those without germline mutations. We further hypothesized that this difference in outcomes would be driven primarily by mutations in *BRCA1/BRCA2/ATM* rather than other DNA-repair gene alterations, given the predominant role played by these genes in terms of both disease susceptibility and prognosis.

2. Patients and methods

2.1. Patients

This study included 172 consecutive men with mCRPC who were beginning NHT using enzalutamide or abiraterone: 115 men were prospectively enrolled at the time of first-line NHT, and 57 men were prospectively enrolled at the time of second-line NHT (requiring retrospective first-line NHT data). Patients were not selected based on prior knowledge of germline/somatic mutations, and thus this sample was not artificially enriched for DNA-repair alterations. Patients had to have histologically confirmed prostate adenocarcinoma, progressive disease despite "castration levels" of serum testosterone ($<$50 ng/dl), and radiographic metastases on computed tomography (CT) or technetium-99 bone scans. Patients had to have three or more rising serum prostate-specific antigen (PSA) values measured $\geq$2 wk apart, consistent with Prostate Cancer Working Group (PCWG2) guidelines [13]. Patients were excluded if they received additional concurrent anticancer therapies. Prior taxane chemotherapy was permitted, as was previous treatment with first-generation hormonal agents (eg, flutamide, bicalutamide, ketoconazole). This study was approved by the Johns Hopkins University institutional review board, and all patients provided written informed consent before providing blood samples.

2.2. Study design

This was an observational study involving 172 men with mCRPC prospectively enrolled at the time of starting abiraterone or enzalutamide treatment as first-line (n = 115) or second-line (n = 57) NHT (for the latter, clinical outcomes data were collected retrospectively). We evaluated the presence or absence of germline DNA-repair gene mutations in general, as well as *BRCA1/BRCA2/ATM* mutations specifically, to predict the clinical benefit from first-line NHT (abiraterone or enzalutamide). Patients were asked to provide peripheral blood samples for germline DNA analysis. Enzalutamide was given at 160 mg daily, and abiraterone was given at 1000 mg daily (with prednisone 5 mg twice daily). Clinical outcomes to first-line NHT were collected prospectively for those starting first-line NHT (n = 115) and retrospectively for those starting second-line NHT (n = 57). In both groups, patients generally had PSA measurements every 1–2 mo, as well as CT (chest/abdomen/pelvis) and technetium-99 bone scans every 2–4 mo. Therapy with enzalutamide or abiraterone was generally continued until PSA progression or clinical/radiographic progression, or unmanageable drug-related toxicity.

2.3. Detection of germline DNA-repair gene mutations

Inherited gene mutations were examined using whole-exome sequencing (WES) of germline DNA extracted from leukocytes (Supplementary material). For the purposes of this study, we focused on the exonic regions of 50 genes, most of which are established DNA-repair genes (except for

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