Genetically-informed treatment for advanced and metastatic prostate cancer

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The landscape of genetic testing for prostate cancer is rapidly evolving. There is increasing evidence that individuals with germline mutations in DNA-repair genes are more responsive to targeted therapies. Due to potential implications for treatment, these genes should be taken into consideration when determining the scope of genetic testing.

Key Words: genetic testing, treatment decision making, prostate cancer

Introduction

Germline genetic testing is a critical aspect of care for men with metastatic prostate cancer. Consensus guidelines include recommendations for consideration of genetic counseling and testing for all men with metastatic prostate cancer, and men with high-risk localized prostate cancer with a family history.[1,2] Despite this guidance, there are multiples challenges in appropriately implementing these recommendations, especially given inconsistent insurance coverage for testing, limited number of genetic counselors, and busy clinical work-flows. We review an evolving list of genes that are highest priority for identification in treatment decisions for prostate cancer.

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Prioritizing genes of interest

There is increasing evidence that individuals with mutations in genes involved in homologous recombination (HR) or mismatch repair (MMR) pathways may drive cancers that are sensitive to treatments targeting these deficiencies. The rate of alterations exceeds 10% in men with metastatic prostate cancer.[3] *BRCA2* mutations account for the majority of hereditary prostate cancer cases, but other gene mutations also occur commonly.[4] These mutations may confer sensitivity to poly (ADP-ribose) polymerase (PARP) inhibitor or checkpoint (CP) inhibitor therapies, Table 1.

Homologous recombination

Mateo et al assessed the effectiveness of olaparib in metastatic castration-resistant prostate cancer (mCRPC) in the TOPARP-A trial, a phase 2 trial including 50 men who underwent biopsies and next generation sequencing to characterize germline and

TABLE 1. **Proposed prioritized list of genes to test to inform treatment of men with advanced or metastatic prostate cancer**

Gene	Protein function	Therapy
ATM	Ser/Thr protein kinase involved in repair of DNA double strand breaks (DSB)	PARP
ATR	Ser/Thr protein kinase that acts as a DNA damage sensor	PARP
BARD1	Heterodimerizes with *BRCA1* to mediate DNA damage response and repair	PARP
BRCA1	Phosphoprotein that assists in repairing DSBs	PARP
BRCA2	Phosphoprotein that promotes binding *RAD51* onto single-stranded DNA for repair	PARP
BRIP1	DNA-dependent ATPase and 5′ to 3′ DNA helicase required for the maintenance of chromosomal stability	PARP
CDK12	Cyclin-dependent kinase that regulates expression of genes involved in DNA repair	PARP
CHEK2	Ser/Thr protein kinase required for activation of repair in response to DSBs	PARP
EPCAM	Antigen that can upregulate c-myc, e-fabp, and cyclins A&E; mutations can disrupt *MSH2* expression	CP
ERCC3	ATP-dependent 3′-5′ DNA helicase involved in nucleotide excision repair of damaged DNA	PARP
FAM175A (ABRAXAS1)	Binds RAP80 and *BRCA1* to target sites of DNA damage	PARP
FANC family	Fanconi Anemia pathway proteins respond to interstrand cross-links	PARP
GEN1	Nuclease that resolves intermediate DNA structures that form during homologous recombination and DSB repair	PARP
HDAC2	Responsible for the deacetylation of lysine residues on the N-terminal part of the core histones	PARP
MLH1	Heterodimerizes with PMS2 to form MutL alpha, a component of the post-replicative DNA MMR system	CP
MLH3	Member of the MutL-homolog (MLH) family of DNA MMR genes	CP
MRE11	Component of the MRN complex that plays a central role in DSB repair	PARP
MSH2	Forms two different heterodimers (*MSH2-MSH6* and *MSH2-MSH3* heterodimers) that bind DNA mismatches	CP
MSH6	Heterodimerizes with *MSH2* to form MutS alpha, which binds to DNA mismatches	CP
NBN	Component of the MRN complex that plays a central role in DSB repair	PARP
PALB2	Recruits *BRCA2* and *RAD51* to DNA breaks	PARP
PPP2R2A	Ser/Thr phosphatases implicated in the negative control of cell growth and division	PARP
PMS2	Heterodimerizes with *PMS2* to form MutL alpha, a component of the post-replicative DNA MMR system	CP
RAD50	Component of the MRN complex that plays a central role in DSB repair	PARP
RAD51C	Involved in the homologous recombination repair pathway of DSB breaks	PARP
RAD51D	Involved in the homologous recombination repair pathway of DSB breaks	PARP
RAD54L	Functions in the recombinational DNA repair pathway	PARP

PARP = poly ADP ribose polymerase inhibitor; CP = checkpoint inhibitor

somatic mutations related to DNA damage repair and potential sensitivity to PARP inhibition.[5] Out of the 49 patients evaluated for response, 16 had tumor aberrations in DNA-repair genes; mutations were identified in *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *FANCA*, *HDAC2*, *MLH3*, *MRE11*, *NBN*, and *PALB2*. Participants

with DNA-repair mutations were more responsive to olaparib, with 14/16 (88%) meeting criteria for a response (reduction in tumor size by standard RECIST criteria, a decline in PSA, and a reduction in circulating tumor cell count), versus 2/33 (6%) without mutations.

The recently presented TOPARP-B trial included patients with mCRPC after progression on at least one line of taxane therapy, who were pre-selected for germline or somatic HRD mutations.[6] They were treated with olaparib in two formulations to assess response to therapy, robustness of the response based on dose, and the toxicity profile. The response rate among patients with HRD mutations varied by gene, with *BRCA2* carriers having an 80% response rate, and a median radiographic PFS of 8 months. Patients with *PALB2* mutations had a 57% response rate, while patients with *ATM* mutations had relatively mild responses (37%), but the durations were prolonged.

TRITON 2 (NCT02952534), is an open label phase 2 study evaluating rucaparib in patients with mCRPC and a germline or somatic mutation in an HRR gene, including *BRCA1*, *BRCA2*, *CDK12*, or *ATM* mutation. An interim report suggests that individuals with *ATM* mutations did not experience measurable response, suggesting that different PARP inhibitors may have differential effects by mutation.[7] PROfound (NCT02987543), a phase 3 trial evaluating olaparib versus abiraterone or enzalutamide in mCRPC patients with HRD mutations, has reportedly met its primary endpoint of prolonging radiographic free survival, though specifics have not yet been reported.

Mismatch repair (MMR)

The role of immunotherapy in prostate cancer treatment is still being defined. The use of checkpoint inhibitors, such as pembrolizumab, is predominantly driven by identifying MMR alterations and microsatellite instability (MSI), as pembrolizumab is approved for any patient with MSI. The inclusion of prostate cancer on the spectrum of Lynch syndrome cancers has been controversial. However, due to the possible response from checkpoint inhibitors, germline testing for these MMR genes is often included as part of the germline testing, especially if there is a suggestive family history.

A recent single institution retrospective review by Tucker et al reported on the effectiveness of pembrolizumab in 48 men with heavily pretreated mCRPC.[8] In this non-randomized study, 17% had a ≥ 50% PSA decline, and 8% had a PSA decline of ≥ 90% decline. Graff and colleagues reported a similar response rate in a study of 28 men with mCRPC progressing on enzalutamide; 18% experienced a ≥ 50% PSA decline when pembrolizumab was added to enzalutamide.[9]

Conclusions

There will be increasing demand for genetic testing and counseling for men with prostate cancer as treatment options are expected to be approved in the near future. Part of rationally integrating testing into practice is ensuring that clinicians prioritize those genes most likely to affect treatment decisions and cascade testing for familial cancer syndromes. The genes identified in this review are an evolving list that should be considered when integrating germline and somatic mutation testing into clinical practice for men with prostate cancer.

Disclosures

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