BANGLADESH JOURNAL OF
UROLOGY
Bangladesh J. Urol. 2023; 26(2): 58-63
www.banglajol.info/index.php/BJU
DOI: https://doi.org/10.3329/bju.v26i2.71179

Editorial

ISSN : 2304 - 8514 (Print)
ISSN : 2304 - 8522 (Online)

Genomic Testing and New molecular treatment of Prostate Cancer 2024

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Genetic testing for germline gene alterations in men with prostate cancer is now part of the standard of care and has been included in international guidelines. Different guidelines recommend testing non-metastatic patients with higher risk disease. Germline pathogenic variants in DNA repair genes have been reported in up to 12% of men with advanced or metastatic prostate cancer.[1] Men with *BRCA2* pathogenic variants have been reported to have more aggressive prostate cancer, with younger age of onset, lymph node involvement, and distant metastases at diagnosis.[2]

Genetic testing in prostate cancer (PCa) is becoming standard of care, as it can provide key information for clinical management, as well as offering crucial insights into familial cancer risk. Knowledge of genetic alterations present in prostate tumors offers prognostic insight and can aid with therapeutic decision-making.[3] In addition, PCa can be hereditary, and patients with PCa may carry germline (inherited) gene alterations that affect their risk of additional cancers.[4] Identification of germline gene alterations in PCa patients provides an opportunity for cascade testing in family members, opening up avenues for cancer prevention and early diagnosis in family members who may also carry the same germline gene alterations.[5]

Genes within the homologous recombination repair/DNA damage response (HRR/DDR) pathway are frequently altered in PCa, and these alterations are involved in disease development and progression. Deleterious alterations in HRR genes, such as *ATM*, *BRCA1*, and *BRCA2*, predict response to poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors.[6] These alterations may be somatic in origin, meaning that they are acquired by tumor cells during tumorigenesis and progression, or they may be germline. Germline or somatic alterations in mismatch repair (MMR) pathway genes, such as *MLH1, MSH2, MSH6*, and *PMS2*, also play roles in the development of PCa, and pathogenic alterations in these genes may predict response to immune checkpoint inhibitor therapy.[7] Both germline and somatic alterations are potentially actionable in terms of treatment with PARP inhibitors or immunotherapy.[8] Most prostate cancers are not associated with a hereditary predisposition, but prostate cancers that have spread or are more aggressive are more likely to be associated with a hereditary predisposition. The aggressiveness of prostate cancer is determined by what is called the Gleason score. Those with score of 7 or higher are considered more aggressive.

Mutations in the following genes can be passed down from a parent to a child and increase a man's chance of developing prostate cancer:BRCA 1 or BRCA 2, HOXB13 and ATM.The genomic landscapes for localized PCa and advanced PCa have recently been published. The Cancer Genome Atlas Research Network reported results for whole-exome sequencing of localized PCa (26% of the cohort had a Gleason's Score of 8) and noted that harmful germline or somatic mutations were relatively common in DNA damage repair genes (*BRCA1*, *BRCA2*, *CDK12*, *ATM*, *FANCD2*, and *RAD51C*).[9]

Genomic evaluations in PCa Screening

Recent studies have indicated that alterations in PCa susceptibility gene increase the risk of PCa [Table 1]. In particular, high-grade malignant PCa frequently occurs at an early age in patients with alterations in DNA repair genes, such as *BRCA1*, *BRCA2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, *CHEK2*, *HOXB13*, *PALB2*, and *RAD51D*. [10-12]

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Genomic evaluations for localized Prostate Cancer

Most men present with localized and potentially curable PCa. However, there is a broad spectrum of localized PCa cases, ranging from entirely indolent to cancer that requires aggressive treatment. Furthermore, approximately 30% of men will experience recurrence despite receiving radiotherapy or surgery for PCa.[16]

The patients with PCa that involves inherited mutations in *BRCA1* or *BRCA2* or *ATM* are more likely to die because of PCa at a young age.[14] The National Comprehensive Cancer Network guidelines have also addressed genetic testing for men with PCa (Gleason score of e"7) and specific family history features.[14] Therefore, better understanding of the genetic factors that drive aggressive PCa may help identify subtypes of localized PCa and guide effective treatment selection.

Genomic evaluations for patient with Active Surveillance

Active surveillance (AS) is one option for patients with a favorable low risk PCa risk profile, but it can be difficult to select AS candidates who will proceed to stage and grade migration. The genomic information or may help more accurately identify indolent and lethal PCa. Wu et al.[17] Men undergoing Active surveillance (AS) with inherited mutations in *BRCA1*, *BRCA2*, and *ATM* were more likely to have aggressive PCa and that carriers of *BRCA2* mutations had a 5 times higher risk of reclassification from GG 1 to GG > 3 (vs. noncarriers). Therefore, when selecting patients for AS, urologists should consider the presence of germline alterations in *BRCA1*, *BRCA2*, and *ATM*, as these patients may be more likely to develop aggressive Pca.[18]

Role of Genomic in conventional treatments for localized PCa

A recent study of localized PCa revealed a difference in the survival rate after radical prostatectomy or external beam radiation therapy according to the presence or absence of *BRCA1* or *BRCA2* alterations.[19,20] For example, relative to noncarriers, carriers of germline *BRCA2* mutations had significantly lower metastasis-free survival rates at 5 years (94% vs. 72%) and at 10 years (84% vs. 50%, $p < 0.001$). Moreover, carriers had significantly lower cancer-specific survival (CSS) rates at 5 years (94% vs. 76%) and at 10 years (84% vs. 61%, $p < 0.001$). However, it is interesting that there was no significant difference in the CSS rates after radical prostatectomy between *BRCA2* mutation carriers and noncarriers, although a significant difference in CSS after radiotherapy was observed between *BRCA2* mutation carriers and noncarriers[20] Thus, the poorer survival outcomes for carriers of germline *BRCA2* mutations may be more relevant among patients who receive radiotherapy.[21] Nevertheless, that study only evaluated a small sample of patients and that their characteristics were not balanced.

Genomic evaluation for mCRPC

Approximately 90% of patients with mCRPC harbor clinically actionable molecular alterations, which frequently involve *AR* (62%), the *ETS* family (56.7%), *TP53* (53.3%), and *PTEN* (40.7%). Some experts have suggested routine genomic evaluations for all men with mCRPC. Finally, aberrations in *BRCA1*, *BRCA2*, and *ATM* have been observed in approximately 20% of patients with mCRPC.[22]

Poly ADP Ribose Polymerase Inhibitors (PARPi)

In 2005, a novel inhibitor of poly[adenosine diphosphate-ribose] polymerase was reported to specifically kill cell lines with silenced or lost *BRCA1/2* expression.[23,24] The introduction of PARP inhibitors (PARPi) in prostate cancer is a milestone and provides a pathway to hope in fighting this disease. It is the first time that drugs, based on the concept of synthetic lethality, have been approved for prostate cancer. In addition, it is also the first time that genetic mutation tests have been included in the therapeutic algorithm of this disease, representing a significant step forward for precision and personalized treatment of prostate cancer.

The US Food and Drug Administration subsequently approved the use of olaparib (a poly ADP ribose polymerase (PARP) inhibitor) for treating patients with mCRPC who harbored *BRCA1*, *BRCA2*, or *ATM* alterations and had previously received taxane-based chemotherapy or ARSI treatment.

Several landmark studies demonstrated that PARP inhibitors were associated with an increased response rate in men with mCRPC harboring *BRCA1/2* alterations.[25,26] The TOPARP-A trial also revealed that 88% of patients with *BRCA1/2* alterations responded to PARP inhibitors, although only 6% of patients without these alterations responded to PARP inhibitors.

Nevertheless, preliminary results from the TRITON2 study revealed that men with mCRPC harboring *ATM* mutations did not respond as well to rucaparib as men harboring *BRCA1/2* alterations.[27] Similarly, patients with mCRPC and *ATM* mutations had a lower rate of response to olaparib treatment than patients with *BRCA1/2* mutations.[28] Therefore, alternative treatments are needed for patients with *ATM* mutations.

Several trials are looking to integrate PARPi in combined therapies. There remains ongoing controversy on the need for genetic screening prior to treatment initiation as well as the optimal patient population, which would benefit most from PARPi. PARPi is an important asset in the oncological arsenal for mCRPC. New combinations with PARPi may improve outcomes in earlier phases of prostate cancer.[29]

DNA damage and repair mechanisms

Damage to cellular DNA is involved in mutagenesis and the development of cancer. The DNA in a human cell undergoes several thousand to a million damaging events per day, generated by both external (exogenous) and internal metabolic (endogenous) processes. Changes to the cellular genome can generate errors in the transcription of DNA and ensuing translation into proteins necessary for signaling and cellular function. Genomic mutations can also be carried over into daughter generations of cells if the mutation is not repaired prior to mitosis. Once cells lose their ability to effectively repair damaged DNA, there are three possible responses.

The cell may become senescent, i.e., irreversibly dormant. In 2005, multiple authorities reported that senescence could occur in cancer cells in vivo as well as in vitro, stopping mitosis and preventing the cell from evolving further.[30-34] The outcome of the DNA Damage may trigger an apoptotic signaling cascade, forcing the cell into programmed cell death or the the cell may become malignant, i.e., develop immortal characteristics and begin uncontrolled division.[34]

Role of PARPi in the treatment of Prostate cancer

DNA Damage appears to be a fundamental problem for life. There are evidences that the DNA Damages are a major cause of Cancer. DNA Damage mutation and can progress to cancer formation. Prostate Cancer is a heterogenous disease often driven by specific genetic mutation. Defect in DNA damage response or repair path way appear to be critical for increasing the risk of malignant transformation of the prostate. The enzyme Poly (adenosine diphosphatase Ribose Polymerase ADP-ribose Polymerase (PARP), BACA1, BRCA2and ATM (Ataxia Talengiesctasia Mutated) all play important role in the malignant transformation of Prostate cells. The unpaired single strand breakage (SSB) can be converted to Double strand Breakage (DSB).

The Poly (ADP-ribose) polymerase (PARP) family regulate many essential functions in cellular processes, including the regulation of transcription, apoptosis and the DNA damage response. PARP1 possesses Poly (ADP-ribose) activity and when activated by DNA damage, adds branched PAR chains to facilitate the recruitment of other repair proteins to promote the repair of DNA single-strand breaks. PARP inhibitors (PARPi) were the first approved cancer drugs that specifically targeted the DNA damage response in BRCA1/2 mutated Prostate, breast, ovarian and cancers.[35]

In December 2014, the FDA approved olaparib, a poly(ADP-ribose) polymerase inhibitor (PARPi) for ovarian cancer patients who have failed three or more lines of chemotherapy and have a germline BRCA1/2 mutation identified. The PARPi s are a novel class of anti-cancer therapies which compete with NAD^+ for the catalytically active site of PARP molecules. PARPi have shown to be effective in the treatment of homologous recombination repair (HR) deficient tumors. Specifically, PARP inhibitors have been used to target tumors with mutations in the essential HR genes, Breast Cancer Associated 1 and 2 (BRCA1 and BRCA2). Several PARP inhibitors have been approved for the treatment of BRCA-mutated ovarian, breast and pancreatic cancer and Prostate cancer. In addition, there are currently 269 clinical trials registered on Clinical trial examining the use of PARP inhibitors as an anti-cancer therapy in chemo-resistant germline or somatic BRCA1/2 mutated Prostate, breast, ovarian, lung, and pancreatic cancers.

Future of PARPi in the Treatment of Prostate Cancer

The introduction of PARP inhibitors (PARPi) in prostate cancer is a milestone and provides a pathway to hope in fighting this disease. It is the first time that drugs, based on the concept of synthetic lethality, have been approved for prostate cancer. In addition, it is also the first time that genetic mutation tests have been included in the therapeutic algorithm of this disease,

representing a significant step forward for precision and personalized treatment of prostate cancer.

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