COMMENTARY

Genetic perspectives on prostate cancer: unveiling the impact on targeted radionuclide therapies

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ABSTRACT

Prostate cancer (PCa) is the second most common malignancy in males and the leading cause of cancer-related deaths among men. In recent years, novel therapies have emerged for metastatic castration-resistant prostate cancer including immunotherapy, androgen-receptor signaling inhibitors, and radio-nuclide therapies. DNA Damage Repair (DDR) genes are frequently mutated in advance PCa and are useful biomarkers for targeted therapy such as poly ADP ribose polymerase inhibitors. DDR gene defects may affect tissue radio-sensitivity and could serve as biomarkers for therapy with alpha and beta-emitting radionuclides. Preliminary clinical reports suggest a potential trend toward longer survival in DDR+ subjects when treated with α-emitters, however, survival benefit was not significant in patients treated with β-emitting radionuclides. A comprehensive study regarding the impact of DDR genes in PCa patients treated with alpha emitters is vital.

Keywords: Prostate cancer, radionuclide, genomics, therapy, DDR.

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Introduction

Prostate cancer (PCa) is the second most common malignancy in males and the major cause of cancer-related deaths among men [1]. Primary treatment includes radical prostatectomy or radiation therapy for localized cases, while advanced-stage patients commonly receive androgen deprivation therapy [2]. However, many patients develop castration-resistant prostate cancer (CRPC), leading to limited treatment options and poor prognosis [3]. Novel therapies have been developed in the current decade for metastatic CRPC including immunotherapy, androgen-receptor signaling inhibitors, and radio-nuclide therapies. Notably, radionuclide-based therapies especially targeted alpha therapy (TAT) with ^{223}Ra-therapy gained Food and Drug Administration (FDA) approval for metastatic castration-resistant prostate cancer (mCRPC) followed by positive outcomes in the ALSYMPCA trial [4,5].

Despite the success of ^{223}Ra therapy for bone metastases, effective therapies for mCRPC with both skeletal and visceral localizations are required. Prostate-specific membrane antigen (PSMA) is overexpressed in PCa as compared to normal prostate tissue and could act as a surrogate marker of absorbed dose. Some small molecules bind to the PSMA-enzymatic domain and are tagged with radio-nuclides for imaging and treatment purposes in a theranostic approach [6,7]. The VISION trial demonstrated improved survival outcomes with β -emitters [^{177}Lu] Lu-PSMA-617 therapy, leading to FDA approval for radio-ligand therapy (RLT) of mCRPC [8].

DNA damage repair (DDR) genes play a vital role in maintaining genome integrity. DDR defects are frequent in advanced PCa and are useful biomarkers for selecting patients for poly ADP ribose polymerase (PARP) inhibitors. The synthetic lethality phenomenon, where combinations of independent nonlethal causes result in cell death, has been observed in PCa with DDR gene mutations when treated with PARP inhibitors [9,10]. Both ^{223}Ra-therapy and RLT target DNA for radiation-induced effects, and it is hypothesized that DDR gene mutations may influence PCa sensitivity to radio-nuclide-based therapy. However, scientific data on this topic is limited. In this article, we will examine the role of DDR gene mutations in patient selection for radio-nuclide therapy.

PSMA-Targeted RLT (α and β-Emitters)

Kratochwil et al. [11] carried out a mutational analysis of DDR genes retrospectively in mCRPC patients with visceral and skeletal metastases undergoing [^{225}Ac] Ac-PSMA-617 TAT. In 60 patients, 10 individuals showed

poor response to RLT despite uniform PSMA overexpression at tumor sites. Seven patients underwent biopsy to stratify for treatment with PARP inhibitors. The PARP inhibitors are normally administered in case of DDR defects. The study revealed that DDR abnormalities were common in mCRPC patients' refractory to [^{225}Ac] Ac-PSMA-617. Notably, all resistant patients had undergone extensive prior treatments, including four previously treated using beta-emitting radio-nuclide [^{177}Lu] Lu-PSMA-617 which might have influenced the response to treatment [11]. The poor response to alpha therapy despite the presence of DDR defects might be due to previous extensive treatment and treatment history could influence the response to radionuclide therapy.

In another study, 40 mCRPC patients with known DDR status were evaluated for response to PSMA-targeted RLT with β and α emitters ([^{177}Lu]/ [^{225}Ac] PSMA-617 or PSMA-I&T). PSMA expression was evaluated by Positron Emission Tomography/Computed Tomography (PET/CT) using [^{68}Ga] or [^{18}F]-PSMA. Seventeen of the 40 patients were DDR+, with BRCA1/2 being the most frequently mutated gene. No significant difference was observed in Prostate-Specific Antigen (PSA) response or progression-free survival (PFS) in DDR+ and DDR- groups [12].

Satapathy et al. [13] assessed the prevalence and clinical effects of DDR mutations in mCRPC patients undergoing RLT. DDR alterations were observed in 10 out of 15 patients, with BRCA2, TP53, and Ataxia Telangiectasia Mutated (ATM) being the most frequently mutated genes. However, DDR alteration did not appear an important marker of response to [^{177}Lu] Lu-PSMA-617 therapy [13].

Van der Doelen et al. [14] conducted an observational study involving 13 mCRPC patients subjected to [^{225}Ac] Ac-PSMA-617 RLT. Overall survival (OS) was taken as the primary endpoint. The PSMA expression was assessed by immunohistochemistry and PET/CT before therapy. The median OS was 8.5 months. The study suggested that longer survival is linked to prognostic factors such as the absence of previous treatment with [^{177}Lu] Lu-PSMA-617 therapy, PSMA expression, and the presence of DDR defects [14].

^{223}Ra-Therapy for PCa (α-Emitter)

A study was conducted recently regarding mutations in DDR genes involved in the homologous recombination (HR) pathway. In this study, 28 patients with bone metastases from mCRPC were tested for HR mutations using next-generation sequencing (NGS) followed by ^{223}Ra-therapy. Ten cases were identified with mutations (HR+), while 18 patients showed no abnormality in the HR pathway. The purpose of the study was to compare the clinical benefits of ^{223}Ra-therapy in participants with and without mutations in the HR pathway. Among all subjects, 64% exhibited a significant decrease in alkaline phosphatase (ALP) levels within 12 weeks. Furthermore, the HR+ group responded more favorably than the HR wild-type group (80% *vs.* 39%, respectively). In addition, the HR+ positive group had a considerably longer interval of ALP progression and an extended duration before the start of the next systemic treatment. Remarkably, HR-deficient individuals showed a better outcome with an OS of 36.9 months compared to 19.0 months for the HR-proficient group [15].

In another retrospective study by van der Doelen et al. [16], 93 mCRPC patients without soft tissue metastases underwent screening for mutations in DDR genes using NGS before ^{223}Ra-therapy. There were 28 patients (30.1%) with DDR mutations, while the rest were categorized as DDR wild type. Among DDR mutated cases, ATM (8.6%), BRCA2 (7.5%), and CDK-12 (4.3%) were the most frequently mutated genes. OS was taken as the primary endpoint and it was significantly longer in the DDR mutant group compared to the DDR-wild type (36.3 *vs.* 17.0 months). In the DDR mutant group, secondary endpoints such as time to ALP progression and time to next therapy were also extended [16].

In another investigation, the impact of ^{223}Ra therapy was assessed in 127 cases of mCRPC patients having various alterations in DDR genes. The frequently mutated genes were TP53 (51.7%), BRCA1/2 (15%), and PTEN (13.4%). Within the whole cohort, 22.6% showed PSA response, whereas 69.8% exhibited ALP response. Nevertheless, none of the DDR alterations emerged as a significant indicator of PSA or ALP response. No appreciable difference was observed in OS and PFS of patients with and without DDR abnormalities. However, the presence of TMPRRSS2-ERG gene fusion was associated with a lower OS of 15.4 months and Retinoblastoma (RB) deletion was linked to short PFS of 6 months [17].

Discussion

In recent years, notable progress has been achieved in targeted radio-nuclide therapies through the application of Radium-223 therapy for PCa, subsequent employment of [177Lu] Lu-oxodotreotide for neuroendocrine tumors, and the recent introduction of [177Lu] Lu PSMA-617 for mCRPC [8,18]. This renewed interest in radionuclide-based treatments has reshaped the therapeutic landscape in oncology. However, it has also created a pressing need for patient stratification to identify individuals more likely to respond to specific therapeutic regimens. A hypothesis has been posited that defects in DDR genes could act as biomarkers for patient selection before administering radio-nuclide therapies. This hypothesis is primarily based on observations that PCa tumors with DDR mutations exhibit high Gleason scores and PSMA expression. In addition, the link between DDR genes and radiation-induced DNA damage raises the possibility that they play a part in the "synthetic lethality" mechanism [19,20].

The prevalence of DDR defects is remarkably high in advanced PCa patients (30%-42%) undergoing systemic

therapies. However, there is a substantial divergence in the possible influence of DDR alterations on patient outcomes after targeted radionuclide therapy. Markedly, three papers reported an encouraging impact of DDR defects on patient results, while the other three investigators found no significant influence of DDR alteration on the end results. Remarkably, the three studies showing a survival benefit in mCRPC subjects with DDR mutations exclusively used alpha emitters (^{223}Ra-therapy, n = 2; [^{225}Ac] Ac-PSMA-617, n = 1). Whereas studies showing no therapeutic advantage in the DDR+ group include patients treated predominately with beta emitters such as [^{177}Lu] Lu-PSMA. This choice of radio-pharmaceuticals might introduce bias, given the distinct mechanisms of action of alpha and β-emitters in inducing DNA damage [11-13, 15-17, 14].

It is noteworthy that damage caused by radiation is highly dependent on the energy and kind of particles involved. In clinical practice, β-emitters such as ^{177}Lu or ^{90}Y are commonly employed radionuclides. Despite having a low linear energy transfer (LET), their anti-tumor effects are dependent on a longer range in tissue (approximately 11 mm), resulting in a cross-fire effect and indirect harm through reactive oxygen species. In contrast, α-emitters, which have a shorter range and higher LET than β-emitters, must be internalized and localized to the cell nucleus. They induce double-strand (ds) DNA breaks, which are challenging to repair, resulting in complex chromosomal rearrangements and DNA cross-linking. Furthermore, cells adopt distinct DNA damage response mechanisms for single or double-strand break repairs [21]. Considering these factors, three research studies used only α-emitters and consistently observed a survival benefit. Therefore, it may be acceptable to hypothesize that DDR mutations might have a contributory role in the setting of α-emitting radionuclides.

Conclusion

In summary, DDR gene mutations are commonly detected in advanced PCa patients. Preliminary clinical reports suggest a potential trend toward longer survival in subjects harboring DDR mutations when treated with alpha emitters. No impact of DDR mutations was observed in subjects treated with beta-emitting radionuclides. Further prospective studies with larger sample sizes are imperative to enhance our understanding regarding the role of DDR genes in PCa patients undergoing treatment with α-emitters.

List of Abbreviations

Ac	Actinium
ALP	Alkaline phosphatase
DDR	DNA damage repair
HR	Homologous recombination
LET	Linear energy transfer
Lu	Lutetium
mCRPC	Metastatic castration-resistant prostate cancer
OS	Overall survival
PFS	Progression-free survival
PSMA	Prostate surface membrane antigen
Ra	Radium

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this article.

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