PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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PARP Inhibition in HRR Gene–Mutated Metastatic Castration-Resistant Prostate Cancer

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H&O What role do mutations in homologous recombination repair (HRR) genes play in metastatic castration-resistant prostate cancer (mCRPC)?

TD We have recently come to realize that as many as 20% of patients with advanced prostate cancer may have mutations in HRR genes, which is a higher percentage than we used to think. Cancer cells with HRR gene mutations are less proficient at repairing DNA breaks, meaning that these cells are more likely to die when they replicate and divide. DNA breaks are much more of an issue for cancer cells than for normal cells because cancer cells divide rapidly, so that they have less time to repair DNA damage, and cells with HRR gene alterations are already struggling with that process. The use of a poly(ADP-ribose) polymerase (PARP) inhibitor provides a second hit to that DNA repair system, creating a lethal state for some cancer cells. Normal cells, which divide more slowly, are less affected by PARP inhibitors and will not even have that first hit if the HRR gene mutation is somatic and present only in cancer cells.

H&O Which HRR genes are most often mutated in the setting of mCRPC?

TD The HRR gene most frequently mutated in mCRPC is *BRCA2*; this gene is mutated in approximately 10% of patients, followed by *ATM,* which is mutated in approximately 5% of patients. Other HRR genes that less frequently harbor mutations are *CDK12*, *CHEK2*, and *PALB2*.

H&O How do you test for these genetic alterations in your patients?

TD National Comprehensive Cancer Network guidelines recommend germline testing for all men with high-risk localized or metastatic prostate cancer, as well as men with unfavorable intermediate-risk localized disease and anyone with a significant family history. This approach detects inherited mutations. Testing for somatic alterations is typically conducted later, often at the mCRPC stage because this is the stage at which currently relevant approved therapeutics can be used. Somatic testing can involve DNA sequencing of a tumor specimen or liquid biopsy. If circulating tumor DNA (ctDNA) testing is done early, the result may be a false negative because of insufficient tumor DNA, so it becomes necessary to repeat testing later. It also should be noted that cancer cells can acquire mutations as they evolve through treatment.

H&O What is the mechanism of action of PARP inhibitors?

TD PARP is an enzyme that helps repair DNA breaks before cell division. PARP inhibitors interfere with this function, so that replication is stalled owing to excess DNA damage.

H&O What is the rationale behind combining androgen receptor (AR) inhibitors with PARP inhibitors?

TD Suppressing AR signaling with AR pathway inhibitors creates genomic instability and mildly impairs DNA

repair. PARP inhibitors can decrease the transcription of AR-regulated genes. These synergistic effects led to the hypothesis that the combination of AR pathway inhibition plus PARP inhibition could be broadly applied, with effectiveness even in patients without pre-existing DNA repair deficiencies.

H&O Which patients with HRR gene mutations benefit the most from PARP inhibition or combination therapy?

TD Patients with *BRCA2* mutations derive the most benefit from PARP inhibitors, both as monotherapy and in combination with AR inhibitors, followed by those with *BRCA1* mutations. Although an *ATM* mutation was initially considered predictive, recent findings suggest it is less predictive than we had hoped. As more patients with the less common mutations have received treatment, the US Food and Drug Administration (FDA) has been able to analyze pooled studies to give us a better sense of how patients with these mutations do. The analysis suggests that patients with *CDK12* mutations can benefit from combination therapy, whereas mutations in *ATM* and *CHEK2* were associated with lack of a response to combination therapy.[1]

H&O Could you discuss the studies that were the basis for the recent approvals of combination treatment?

TD The phase 3 PROpel study looked at the combination of abiraterone and olaparib (Lynparza, AstraZeneca) vs abiraterone alone as first-line therapy in an all-comer population of patients with first-line mCRPC. All patients underwent DNA sequencing, and a prespecified analysis was done to look at those who had HRR gene alterations. Participants were required to be taxane-naive. The patients also were largely naive to AR pathway inhibitors, so that the applicability of these results is limited because most patients in the current era receive an AR pathway inhibitor at the time metastatic disease is diagnosed; patients whose disease has already progressed during AR pathway inhibitor treatment are different from those who have never been exposed to an AR pathway inhibitor or whose exposure has been limited.

The study found a significant benefit in radiographic progression-free survival (rPFS) when the combination of abiraterone and olaparib was compared with abiraterone alone.[2] A subset analysis revealed that most of the benefit occurred in patients who had a *BRCA* mutation. Patients who had a *BRCA* mutation also had improved overall survival.[2] As a result of these findings, the FDA approved the combination of abiraterone and olaparib specifically for patients with *BRCA* alterations.

The phase 3 TALAPRO-2 study looked at talazoparib (Talzenna, Pfizer) plus enzalutamide (Xtandi, Astellas) vs enzalutamide alone as first-line therapy in patients who had taxane-naive mCRPC that had not previously progressed on an AR pathway inhibitor.[3] Although patients were permitted to have prior exposure to an AR pathway inhibitor, most did not. This population was very similar to that in PROpel; all enrolled patients were randomized and then later included in a subset analysis based on genomic alterations.

A planned primary analysis found that median rPFS was significantly longer in the talazoparib-plus-enzalutamide group than in the enzalutamide-alone group in both all comers and the patients with HRR mutations.[4] An exploratory analysis of the patients with *BRCA* mutations found that most of the improvement in rPFS with talazoparib among the patients with HRR mutations was in those with *BRCA* mutations. In addition, talazoparib was found to benefit patients whose HRR gene mutation status was negative or unknown. As a result, the FDA approved the combination of talazoparib plus enzalutamide in patients who had mCRPC with alteration in an HRR gene. This is a broader indication than for the olaparib-plus-abiraterone combination, but PARP combinations do not extend to genomically unselected patients with mCRPC at this time.

The MAGNITUDE trial compared the combination of abiraterone plus niraparib (Akeega, Janssen Biotech) vs abiraterone alone in mCRPC.[5] This study was different from PROpel and TALAPRO-2 in that the patients were divided into groups with and without HRR gene alterations for separate randomization at the outset of the study. Median rPFS was significantly longer with abiraterone plus niraparib than with abiraterone alone in both the entire HRR gene–altered group and the *BRCA*-altered subgroup. The cohort without HRR gene alterations was ended early because of futility. The FDA approved the combination of abiraterone and niraparib for use in patients with mCRPC that harbors a *BRCA* alteration.

H&O What are the risks seen with these combinations?

TD The most common toxicity with PARP inhibitors is anemia, so we need to be prepared for this when we add these agents to AR pathway inhibitors. Approximately one-quarter to one-third of patients on PARP inhibitor therapy may eventually require a blood transfusion. Although we are doing better at managing anemia and avoiding blood transfusions, this is a risk we need to address with patients as we prescribe these agents. We also need to use caution when giving PARP inhibitors to patients with pre-existing cytopenias. In addition, we see nausea and loss of appetite with PARP inhibitors. The

side effect profile of the combination of PARP inhibitors and AR pathway inhibitors did not include any new side effects, but some notable side effects, such as venous thromboembolism (VTE), may be more likely to occur when the 2 drug types are used together. We do not need to use VTE prophylaxis because the rates are very low, but clinicians should maintain a higher index of suspicion for VTE events when using an AR pathway inhibitor together with a PARP inhibitor.

H&O Can patients without biomarker-proven mutations in HRR genes benefit from PARP inhibition?

TD On the basis of the results of a study like TALAPRO-2, patients who have mCRPC without an HRR gene alteration can benefit from first-line combination treatment. This would be an off-label use, however. Right now, the use of these drugs is restricted to molecularly selected patient populations.

H&O Can you discuss any ongoing trials or emerging research that might expand the use of PARP inhibitors in prostate cancer?

TD It is very exciting to see trials of combination therapy move from mCRPC to metastatic hormone-sensitive prostate cancer (mHSPC). These trials are being conducted largely in *BRCA*-altered or other HRR gene–altered populations, although the EVoPAR-Prostate01 trial is testing saruparib in populations of patients with both HRR-altered and non–HRR-altered mHSPC (NCT06120491). It will be worthwhile to study combination therapy in all comers as well, given that the TALAPRO-2 study suggested that a unique synergy between the agents may exist that could be effective in patients without HRR gene alterations.

Interest is also being shown in studying combination therapy plus radiation. It is unclear how successful that strategy might be, but the phase 1/2 NRG-GU007 trial from NRG Oncology is looking at the use of niraparib (Zejula, GSK) and androgen deprivation therapy in combination with radiation in patients with high-risk prostate cancer (NCT04037254).

The phase 3 TALAPRO-3 study is looking at talazoparib plus enzalutamide vs androgen deprivation therapy plus enzalutamide in participants with HRR gene–altered mHSPC (NCT04821622). The phase 3 AMPLITUDE study is looking at niraparib plus abiraterone vs abiraterone alone in participants with HRR gene–altered mHSPC (NCT04497844). The single-arm phase 2 PROACT trial is looking at the use of olaparib plus abiraterone in HRR gene–altered mHSPC (NCT05167175). Finally, the phase 1/2 COMRADE study is looking at a combination of olaparib and the radioligand radium Ra 223 dichloride (Xofigo, Bayer) in men who have mCRPC with bone metastases, regardless of HRR deficiency status (NCT03317392). In addition, we will see the testing of new drugs to target the PARP pathway and other, similar pathways. We hope to see agents with less toxicity and broader applicability.

H&O What is the future of PARP inhibition in prostate cancer?

TD Assuming that DNA sequencing will be performed in increasing numbers of patients with prostate cancer, we can expect to see more patients who have an HRR gene alteration and can benefit from these agents. Sequencing remains a bit of a question, however. We learned from the phase 2 TRITON3 trial that in patients who had mCRPC with a *BRCA* alteration, rucaparib (Rubraca, Clovis Oncology) monotherapy was even more effective than control treatment with docetaxel, abiraterone, or enzalutamide.[6] This finding suggests that it may be valuable to sequence PARP inhibitors before chemotherapy in patients with mCRPC, at least in those with *BRCA* alterations. We do not know whether that sequence would hold for a different population, such as those with a *CHEK2* or *CDK12* mutation, in whom response rates are lower.

Also, now that we have the ability to use lutetium 177 (^{177}Lu)-PSMA-617 radioligand therapy before chemotherapy, we need to determine whether a patient who has an HRR gene alteration should receive a PARP inhibitor or the radioligand first. These are some of the questions we would like to have answered as we move forward.

Disclosures

Dr Dorff has done consulting for Astellas, AstraZeneca, Bayer, Janssen, and Novartis and has received institutional research funding from AbbVie, Amgen, and AstraZeneca.

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