Editorial

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Clinical implications and practical considerations for poly-ADP-ribose polymerase inhibitors as a new horizon for the management of urothelial carcinoma of the bladder

RATIONALE FOR USE OF POLY-ADP-RIBOSE POLYMERASE INHIBITORS IN UROTHELIAL CARCINOMA OF THE BLADDER

DNA damage repair (DDR) pathways recognize single- (SSBs) or double-strand breaks (DSBs) and meticulously restore them to ensure genomic stability; alternatively, pathways leading to apoptosis or senescence are activated when extensive or irreparable damage occurs [1-3]. The central DDR pathways include homologous recombination repair (HRR), non-homologous end joining (NHEJ), base excision repair (BER), direct repair, mismatch repair (MMR), nucleotide excision repair (NER), and translesion synthesis [1-3]. Notably, DSBs are the most toxic lesions in DNA and are sometimes repaired by NHEJ in human cells; however, this causes inevitable changes in the DNA sequence, as the broken ends are joined by DNA ligation, resulting in a loss of nucleotides at the joining site. On the other hand, HRR is a much more accurate way to repair DSBs than NHEJ because it leads to high-fidelity reparation and prevents information loss.

Genomic instability resulting from defective DDR is a hallmark of cancer. Many cancers display HRR deficiency (HRD) through functional disruption of HRR genes (e.g., *BRCA1/2*, *PALB2*, *RAD51*, *ATM*, *ATR*, *CHK1/2*, *BARD1*, *BRIP1*, and *FANC*) via inherited germline variants, acquired somatic mutations, epigenetic silencing, and somatic copy number variations, presenting the so-called 'BRCAness' phenotype [1-3]. Ironically, HRD provides therapeutic opportunities. Poly-ADP-ribose polymerase (PARP), a family of proteins involved in SSBs repair, bind tightly to DNA breaks, recruit effectors of the BER and NER systems through PARylation, and remodel the chromatin structure around the damaged DNA [2,3]. In patients with HRD, DSBs can be repaired only through NHEJ, an error-prone pathway that leads to genomic instability, mitotic damage, and cell death, consequently provoking "synthetic lethality". PARP inhibitors (PARPi) block the repair of DNA SSBs, and for tumors with HRD, they cause cell death due to inefficient cell repair mechanisms [2-4].

Activating mutations or fusions of fibroblast growth factor receptor (FGFR) 2 and FGFR3 have been validated as therapeutically actionable alterations, with erdafitinib currently approved for locally advanced or metastatic urothelial carcinoma of the bladder (a/m UCB) [5]. Several other potentially targetable genomic alterations have been implicated in a/m UCB, including alterations related to ErbB receptors, PI3K/Akt/mTOR pathway, Ras/MAPK pathway, chromatin remodeling, cell cycle regulation, and HRR [5]. Recently, a/m UCB was shown to have a high prevalence of pathogenic germline and somatic mutations in several HRR genes (23%–34%), such as *CHK1/2*, *RAD51*, *BRCA1/2*, *ATM*, *ATR*, *MDC1*, *RAD52*, and *FANCF* [1,6-9], suggesting the possibility of PARPi and synthetic lethality strategies exploiting HRD in a/m UCB.

CLINICAL TRIALS OF PARPi AS MONOTHERAPIES FOR UCB

Since 2014, four PARPi (olaparib, niraparib, rucaparib, and talazoparib) have been approved by the Food and Drug Administration and the European Medicines Agency for clinical use in several cancers with HRD, including breast, ovarian, prostate, and pancreatic cancers [2-4]. Based on pivotal phase II and III trials, olaparib and rucaparib have

recently received breakthrough approval for metastatic castration-resistant prostate cancer carrying germline or somatic aberrations in genes related to HRR that progressed following prior therapy that included a next-generation hormonal therapy.

Several clinical trials have recently been conducted to investigate PARPis monotherapy or combination therapy in UCB. However, data on PARPi in UCB are limited, and only interim results have been reported. Two ongoing phase II trials (NCT03375307 and NCT03448718) evaluated olaparib as monotherapy for a/m UCB. Another clinical trial, ATLAS (NCT03397394) was an open-label, phase II study that evaluated the efficacy and safety of rucaparib for patients with previously treated a/m urothelial carcinoma (UC), independent of tumor HRD status [10]. The primary endpoint was the overall response rate (ORR) in the intent-to-treat and HRD-positive populations. Of the 97 enrolled patients, 20 were HRD-positive, 30 were HRD-negative, and 47 were HRD-indeterminate. Unfortunately, there were no confirmed radiographic responses, suggesting that rucaparib monotherapy does not significantly benefit patients with previously treated a/m UCB. Furthermore, there was no difference in ORR among the HRD subgroups, indicating that additional methods may be required to define a predictive biomarker for response to PARPi. The effect of rucaparib on multiple tumor types, including UCB with selected HRR gene alterations, is being further evaluated in the LODESTAR trial (NCT04171700).

PARPi have also been evaluated as maintenance therapy for a/m UCB. In the phase II ATLANTIS trial, switch maintenance using rucaparib following platinum-based combination chemotherapy (PBCT) extended progression free survival (PFS) in biomarker-selected patients with mUCB (at least 10% genome-wide loss of heterozygosity, a somatic alteration in one of 15 HRR genes, or a germline *BRCA1* or *BRCA2* mutation) [11]. Notably, 74 of the 279 screened patients were biomarker-positive. Meet-URO12 (NCT03945084), another phase II trial, compared maintenance treatment with niraparib plus best supportive care (BSC) versus BSC alone in patients with a/m UCB that did not progress after first-line PBCT [12]. Of 47 patients with molecular information, 21 had HRR alterations; 6 had known pathogenic mutations, and 15 had variants of unknown significance. Although maintenance niraparib plus BSC did not prolong PFS in the 21 patients with HRR mutations, a larger sample size of patients with DDR genetic alterations might be necessary to observe a clinically meaningful efficacy.

RATIONALE TO COMBINE PARPis AND IMMUNE CHECKPOINT INHIBITORS IN UCB

Multiple lines of evidence have demonstrated that DDR and immune responses are interconnected [6,13]. The potential mechanistic rationale for PARPi and immune checkpoint inhibitors (ICIs) combinations includes the ability of cancer cells to accumulate DNA damage to activate the stimulator of interferon genes (STING) pathway. This innate immune cascade boosts type 1 interferon signaling and results in the activation of anti-tumor immunity. Additionally, it has been suggested that DSBs induced by PARPi upregulate programmed death-ligand 1 expression by activating the STING pathway, ATM-ATR-CHEK1, and inactivation of glycogen synthase kinase 3-beta. Interestingly, PARPi also amplifies DNA damage, especially in tumors that show the HDR phenotype, augmenting the mutational burden and promoting immune priming of the tumor by increasing neoantigen exposure.

Therefore, a synergistic combination of ICIs with PARPi has been introduced in recent clinical trials for UCB [14-16]. A phase II trial in the neoadjuvant setting before radical cystectomy in patients with cT2-T4a muscle-invasive UCB (NCT03534492, NEODURVARIB) demonstrated the tolerability and efficacy of the combination of durvalumab plus olaparib [14]. Olaparib plus durvalumab was also evaluated in another phase II trial (NCT03459846, BAYOU) as first-line treatment for platinum-ineligible patients with metastatic UC [15]. Among all randomized 154 patients at baseline, 20% had mutations in HRR genes. Median PFS was not significantly different for durvalumab and olaparib versus durvalumab and placebo; however, in a pre-specified subset of patients with HRR mutations, the PFS was significantly improved in the group receiving olaparib and durvalumab (5.6 months vs. 1.8 months).

Furthermore, NCT02546661 (BISCAY), a multi-arm, multi-agent phase Ib trial, combined durvalumab with relevant, targeted therapies in biomarker-selected chemotherapy-refractory a/m UC populations, including (1) FGFR inhibitors in tumors with FGFR mutations; (2) PARPis in tumors with and without HRD; and (3) TORC1/2 inhibitors in tumors with DNA alteration to the mTOR/PI3K pathway. Mutations in HRR genes from archived tumors were identified in 15% of screened 391 patients [16]. Unfortunately, specific HRR alterations were not consistently associated with outcomes for olaparib and durvalumab, although a 36% response rate was observed among patients with HRR alterations.

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THE NEED TO INDENTIFY PREDICTIVE BIOMARKERS FOR OPTIMAL USE OF PARPi IN a/m UCB

To evaluate the benefits of PARPi in a/m UCB, it is urgent to identify novel and reliable biomarkers that can detect HRD in tumor specimens or the germlines. Deleterious mutations in *BRCA1* or *BRCA2* gene are a canonical example of HRD [1-4,17]. However, HRD can also occur through methylation changes in other HRR genes that decrease gene expression or epigenetic silencing without canonical HRR gene mutations. It is challenging to identify a standardized test to detect tumors with HRD, regardless of the mechanisms involved. Together with the commercialization of next-generation sequencing (NGS) testing, validation a novel predictive biomarker for HRD has become the focus of patient selection strategies for PARPi therapy and numerous companion diagnostic assays defining the HRD phenotype have been created.

At present, three types of HRD testing methods including HRR gene-level tests, identification of genomic scars or mutational signatures and functional assays that can indicate HRD have been suggested [1-4,6,7,18]. The myChoice® CDx HRD assay (Myriad Genetics, Salt Lake City, UT, USA) and FoundationOne CDx (Foundation Medicine, Cambridge, MA, USA) assays are the only NGS-based, prospectively validated, and commercially available tests for HRD status assessment. For example, myChoice® CDx combines BRCA gene mutation analysis and genomic instability score. Meanwhile, the instability score is derived from the genomic signature assessment and tumor mutational burden in the FoundationOne CDx kit. Mutational-signature-based approaches have recently been applied to improve the prediction of HRD because they detect the consequences of HRD rather than the underlying cause. For example, in a recent study, a significant number of UCB patients with wild-type BRCA1/2 showed HRD-associated mutational signatures as high as those observed in BRCA1/2 deficient cases, suggesting that mutational analysis of known HRR genes could be combined with mutational signature approaches to identify candidates for PARPi in UCB [7]. Moreover, there have been efforts to develop functional dynamic biomarkers for HRD. A histopathology-based detection of RAD51 nuclear foci in tumor cells could reflect the dynamic HRR status of the tumor and haver higher accuracy than HRR gene mutations and genomic HRD analysis for predicting the PARPi response [18].

CONCLUSION AND FUTURE PERSPECTIVES

PARPi may have the potential for use in a/m UCB patients with the HRD phenotype, both as a single agent and in combination with ICIs. Interestingly, optimal combination strategies involving cytotoxic chemotherapy, radiation therapy, and targeted agents are expected to broaden the range of indications for PARPi. However, the short durability of the response and the challenging toxicity profiles of the combined treatments are relevant clinical issues. Future translational research focusing on toxicity-predisposing factors, inherent and/or acquired resistance mechanisms, and meaningful molecular markers of response is needed to delineate which patients will benefit from PARPi.

CONFLICTS OF INTEREST

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Hye Won Lee[1], Ho Kyung Seo[1,2,3]
Corresponding Author: Ho Kyung Seo
ORCID: https://orcid.org/0000-0003-2601-1093
[1]Department of Urology, Center for Urologic Cancer, National Cancer Center, Goyang, [2]Division of Tumor Immunology, Research Institute, National Cancer Center, Goyang, [3]Department of Cancer Biomedical Science, Graduate School of Cancer Science and Policy, National Cancer Center, Goyang, Korea
E-mail: seohk@ncc.re.kr

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