The future perspective of PARP inhibitors

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The protein poly (ADP-ribose) polymerase (PARP) plays an important role in DNA base excision repair and repair of DNA single-strand breaks and might also be involved in DNA double-strand break repair. For tumor cells with homologous recombination deficiency (HRD), such as ovarian cancer cells with BRCA1/2 mutations, interfering with PARP activity leads to unrepaired single-strand DNA breaks and subsequent formation of double-strand breaks. This results in synthetic lethality of cancer cells with HRD. In 2005, the antitumor effect of inhibiting the PARP enzyme in BRCA1/2-mutated cancer cells was first demonstrated in preclinical tumor xenografts. After a decade of developing drugs targeting PARP for clinical use in patients with BRCA-mutated cancer, in recent years several PARP inhibitors have finally been approved by the U.S. Food and Drug Administration for the treatment of ovarian cancer.

Lynparza (olaparib) was the first PARP inhibitor approved by the FDA to treat ovarian cancer with germline BRCA mutations, in December 2014. Since then, another PARP inhibitor, Rubraca (rucaparib), was approved for ovarian cancer patients with both germline and somatic BRCA mutations, in December 2016. In March 2017, an additional PARP inhibitor, Zejula (niraparib), was approved as a maintenance treatment for women with recurrent ovarian, fallopian tube, or primary peritoneal cancer. Unlike the previous two approved PARP inhibitors, with niraparib the presence of BRCA mutations or other biomarker status is not a prerequisite for treatment. Unfortunately, PARP inhibitors do not work for all patients with ovarian cancer, and approaches to manage PARP inhibitor-resistant disease are urgently needed. Researchers are now exploring whether combining PARP inhibitors with other targeted therapeutics might increase response rate and lead to broader efficacy.

The quest for combination treatments to enhance the antitumor effects of PARP inhibitors is being pursued in many preclinical settings. Through screening of drugs that acted synergistically with olaparib in homologous recombination (HR)-proficient breast, ovarian, and prostate cancer cells, bromodomain and extraterminal domain inhibitors (BETis; JQ1, I-BET762, and OTX015) were identified. Another combination treatment with c-Met inhibitor and PARP inhibitor has also been shown to synergistically suppress the growth of breast cancer and lung cancer using tumor xenograft models. The combined c-Met and PARP1 inhibitors also synergistically inhibited tumor growth using mouse mammary tumor cells (A1034) in a syngeneic FVB mouse model, but efficacy did not appear as robust as in the xenograft nude mouse model.

In another study, transient treatment with PARP inhibitor has been shown to upregulate the activity of the RAS/MAPK pathway. Thus, combining MEK inhibitor with PARP inhibitor was tested. The synergistic activity of this combination was demonstrated in multiple types of cancer cells with KRAS mutations, including PARP inhibitor-resistant cancer cells, in both in vitro and in vivo xenograft models and in a syngeneic breast cancer model. Other combinations with PARP inhibitor include the combination of rucaparib with MDM2 inhibitor and the combination of olaparib with PI3K inhibitor (BKM120). However, these combinations have been tested in cell culture models only.

Recent studies have shown that most small molecules
targeting PI3K, mTOR, MAPK, and CDK signaling and transcriptional regulators such as histone deacetylase and survival molecules (e.g., Bcl-2) restricted the proliferation of T-cells at the doses that are active on cancer cells[13,14]. Thus, combining PARP inhibitors with targeted therapeutics will need to consider the effect of the chosen drugs on immune cells in additional to tumor cells. A recent validation study confirmed that the number of cytotoxic CD8+ tumor-infiltrating lymphocytes in high-grade serous ovarian carcinoma is significantly associated with longer overall survival[15]. Thus, there is an intrinsic protective antitumor immunity in ovarian cancer patients, although it may not be active enough to eradicate the tumor. Given the recent success of immunotherapies, showing that enhancing pre-existing T-cell activation and proliferation can result in tumor shrinkage, understanding how different immune cells are affected by small molecule inhibitors to be used with PARP inhibitors could lead to a more effective intervention. The combination of PARP inhibitors with immunotherapy could be the future for ovarian cancer treatment, as demonstrated in a BRCA1-deficient murine ovarian cancer model[16], and several phase I/II clinical trials combining PARP and checkpoint inhibitors are ongoing (NCT02849496, NCT02484404, NCT03308942, and NCT03330405).

The use of xenograft tumors in immunocompromised athymic nude mice with deficient T-cell function is important, but this preclinical method cannot interrogate the effect of combination therapies on the pre-existing T-cell responses. There is a need to conduct future mechanistic research to identify drugs that will perform well not only in immunocompromised mice but also in immunocompetent mice using genetic mouse models.

In summary, other than for ovarian cancer, PARP inhibitors have not been approved for other cancers. However, it is anticipated that the clinical use of PARP inhibitors will be extended beyond ovarian cancer. Recent preclinical data suggest that PARP inhibitors also have activity in the treatment of breast cancer[17] and prostate cancer[18]. Combining PARP inhibitors with other types of therapies will likely be the focus of treatment in the decade to come. However, the immunosuppressive effects of such combinations should be considered in both preclinical and clinical studies.

References
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