ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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PARP Inhibitors in Ovarian and Other Cancers

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H&O What is the mechanism of action for poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors?

RP PARP is an enzyme involved in the cell's response to DNA damage, and it is activated by both single- and double-strand breaks. PARP uses nicotinamide adenine dinucleotide (NAD) to make polymers of poly ADP-ribose, which signals recruitment of other complexes to repair the DNA. All the PARP inhibitors currently in clinical development have been designed to bind competitively in that highly conserved NAD binding site and thereby block the action of the PARP enzyme. Additionally, there may be more than straightforward enzyme inhibition at work. If the inhibitor binds very tightly while PARP is attached to the DNA, then the inhibitor can effectively "trap" PARP on the damaged DNA.

H&O Which PARP inhibitors are currently US Food and Drug Administration (FDA) approved?

RP Olaparib (Lynparza, AstraZeneca) is the only FDA-approved PARP inhibitor. It was the second PARP inhibitor to go into the clinic, and was tested as a single agent for patients with advanced ovarian cancer who had a germline mutation in the *BRCA* gene. A pivotal trial by Kaufman and colleagues included 193 patients who had previously received platinum-based therapy. They found a 31% response rate and a 1-year overall survival of 64%. Additionally, Ledermann and colleagues showed that maintenance treatment with olaparib following a response to platinum-based therapy improved survival in patients with *BRCA*-related ovarian cancer, and this is the indication for which olaparib is licensed.

H&O Are there any other PARP inhibitors currently in clinical trials for ovarian cancer?

RP Yes, there are a number of other PARP inhibitors. For example, talazoparib is in a phase 2 clinical trial for patients with ovarian cancer and a *BRCA* mutation who have progressed after a prior PARP inhibitor treatment (NCT02326844).

Rucaparib is in a phase 3 study for patients with high-grade serous ovarian cancer; it is being given as single-agent maintenance therapy after a positive outcome from platinum-based chemotherapy (NCT01968213). This study is interesting because it is recruiting patients who do not have germline *BRCA* mutations. Some studies—including a study by Mukhopadhyay and colleagues—have suggested that high-grade serous ovarian tumors behave in the same way as tumors with *BRCA* mutations. This hypothesis appears to be confirmed in the clinic with the emerging data from a trial that is investigating whether genomic loss of heterozygosity predicts sensitivity to rucaparib (NCT01891344). This hypothesis is exciting because, if correct, it will expand the proportion of patients who may benefit from this therapy.

Niraparib is in a phase 3 clinical trial as maintenance therapy for patients with ovarian cancer who responded well to platinum-based therapy (NCT01847274). This study includes not only patients with *BRCA* mutations, but also patients with high-grade serous ovarian cancer.

H&O Are there other cancers for which PARP inhibitors are being tested?

RP Yes, these inhibitors are being tested in a range of cancers, many of which also are associated with *BRCA* mutations. Because breast cancer is common in patients with *BRCA* mutations, PARP inhibitors are frequently being tested in this setting as well, although so far there appears to be less clinical activity in this setting with lower reported response rates.

Olaparib is being investigated for multiple different cancers. In breast cancer, the drug is being used as an adjuvant treatment in patients with *BRCA* mutations who are human epidermal growth factor receptor 2 (HER2)–negative (NCT02032823). This could provide a new treatment option for this group of patients with poor prognosis. It has also been tested in previously treated patients with *BRCA* mutations in breast, pancreatic, and prostate cancer. In a phase 2 study, Kaufman and colleagues found a 12.9%, 21.7%, and 50.0% response rate in patients with breast, pancreatic, and prostate cancer, respectively.

Niraparib is also in a phase 3 clinical trial for patients with breast cancer with *BRCA* mutations (NCT01905592). Similar to olaparib, it is being tested in patients who are HER2-negative.

Rucaparib is also being tested in other cancers, including in a phase 2 study as monotherapy. This study is recruiting patients with locally advanced or metastatic pancreatic cancer with germline or tissue *BRCA* mutations who have progressed after 1 or 2 prior therapies (NCT02042378). The drug is also in a phase 1 trial for patients with advanced solid tumors (NCT01482715).

Talazoparib is currently in a randomized phase 3 clinical trial for patients with advanced or metastatic breast cancer with germline *BRCA* mutations (NCT01945775). This drug is also in a phase 2 study for patients with multiple types of advanced or metastatic cancer (NCT02286687). Importantly, this study is comparing the response to therapy for patients with different genetic alterations, including *PTEN* mutations and genomic loss of heterozygosity.

Veliparib is currently being used in multiple trials, mainly in combination with other therapies. A randomized phase 3 trial for patients with metastatic or advanced HER2-negative *BRCA*-mutated breast cancer is examining veliparib in combination with chemotherapy (NCT02163694). In a phase 2 trial, the drug is being investigated with chemotherapy in patients with advanced or metastatic pancreatic cancer (NCT01585805). The drug is also being investigated in phase 1 and 2 trials for non–small cell lung cancer in combination with chemotherapy and radiotherapy (NCT01642251 and NCT01386385).

H&O What are the potential biomarkers for patients who may respond especially well to PARP inhibitors?

RP Generally, investigators are examining mutations that affect the DNA damage response pathway, because the PARP enzyme is also involved in this process. The hypothesis is that the inhibitors will be more effective if the DNA repair pathways are already compromised. These studies are important because they potentially can expand the population for whom PARP inhibitors are effective.

Olaparib is approved for patients with germline *BRCA* mutations, which increase the inherited tendency to develop both breast and ovarian cancer. *BRCA*-mutated tumors have lost the DNA double-strand break repair pathway and are prone to DNA damage, making them a good target for PARP inhibitors.

Other studies have found that serous ovarian cancer and triple-negative breast cancer seem to biologically behave like the *BRCA*-mutated cancers, and there are a few studies investigating the action of PARP inhibitors in these patients. A review on these sporadic cancers that exhibit characteristics similar to *BRCA*-mutated cancers was published by Turner and colleagues.

Another clinical trial is investigating the PARP inhibitor rucaparib in patients with other genomic alterations, specifically homologous recombination DNA repair deficiency (HRD) (NCT01891344). This trial is attempting to define the molecular signature of HRD that correlates to rucaparib response by assessing loss of heterozygosity across the tumor genome. Instability in the genome indicates a DNA repair defect, meaning the tumor is likely susceptible to PARP inhibitors.

Similarly, another trial is investigating the effectiveness of talazoparib for a large number of different genomic alterations, including *PTEN,* and homologous recombination defects (NCT02286687).

Investigators have also been developing biomarkers that test circulating tumor cells or primary cell cultures for the ability to repair DNA damage. However, testing circulating tumor cells or primary cell cultures are difficult to do in the general clinic, so my feeling is that the biomarkers for a genetic signature that can be identified on paraffin-embedded tissue will be easier moving forward.

H&O What are the side effects or toxicities of PARP inhibitors?

RP The side effects are different depending on whether the PARP inhibitors are used as a single agent or in combination with other therapies. If a PARP inhibitor is used as a single agent, larger doses are safe, and the side effects are nausea, fatigue, and gastrointestinal upset, because these are oral agents. At higher doses there is also

myelosuppression, anemia, and neutropenia, but overall they are generally well tolerated.

When PARP inhibitors are given in combination with chemotherapy, smaller doses are used. This is because PARP inhibitors block DNA damage repair and chemotherapeutic agents cause such damage as their cytotoxic mechanism of action, so the normal toxicity we expect with chemotherapy is enhanced, especially myelosuppression.

H&O Are most of these PARP inhibitors being studied as single agents or in combination?

RP The majority of PARP inhibitors going through clinical trials at the moment are looking at the single-agent indication, with a few exceptions.

Niraparib is in a phase 1 and 2 clinical trial in combination with bevacizumab (Avastin, Genentech) in patients with platinum-sensitive ovarian cancer (NCT02354131).

Veliparib is undergoing multiple clinical trials with different combinations. In a randomized phase 3 trial, the drug is being used in combination with carboplatin and paclitaxel in patients with breast cancer (NCT02163694). In a phase 2 trial, veliparib is being combined with gemcitabine and cisplatin for patients with advanced or metastatic pancreatic cancer (NCT01585805). The drug is also being investigated in 2 different trials for non–small cell lung cancer in combination with cisplatin and etoposide (NCT01642251) or radiotherapy, carboplatin, and paclitaxel (NCT01386385).

However, these trials are in very early stages, so there are no clinical data of benefit yet. Therefore, I expect the next set of approved PARP inhibitors to be given as single agents.

H&O Are there any studies using PARP inhibitors as frontline therapy?

RP Most of the studies are investigating the inhibitors as maintenance or retreatment. At the moment, no one is very actively chasing first-line therapy.

H&O What are some of the challenges with using PARP inhibitors?

RP One challenge is minimizing toxicity. The single-agent data we have so far are from trials that used continual dosing to progression. Therefore, we do not know whether a lower dose might reduce some of the side effects while still maintaining efficacy. Minimizing toxicity when using drugs in combination is also challenging, because the normal target toxicity is enhanced.

Another difficulty is that we do not know the consequences of long-term use. This is especially important now that PARP inhibitors are being investigated earlier in the patients' disease. For example, some studies have started testing PARP inhibitors as adjuvant treatment. These patients might be cured of their cancer, but it is possible that blocking DNA repair may also increase the risk of a second malignancy later in life. It will take some time for us to fully understand these potential long-term consequences.

H&O What is your opinion on the future of PARP inhibitors?

RP I am quite an enthusiast for this class of agents and their potential. I think these drugs will eventually be used in a wide range of cancers, not just ovarian cancer with germline *BRCA* mutations. I am a bit wary about the adjuvant treatment, but if it is safe, this could be a way to avoid surgery for patients with germline mutations. I think this therapy is leading the field for other drugs that modulate DNA repair response pathways and is helping us understand how to develop better cancer treatments. I think PARP inhibitors have a bright future, even though it has been a varied path of clinical development over the last decade.

Suggested Readings

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Mukhopadhyay A, Elattar A, Cerbinskaite A, et al. Development of a functional assay for homologous recombination status in primary cultures of epithelial ovarian tumor and correlation with sensitivity to poly(ADP-ribose) polymerase inhibitors. *Clin Cancer Res.* 2010;16(8):2344-2351.

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