ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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PARP Inhibitors

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H&O What are poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors, and what is their mechanism of action?

RP PARP inhibitors were first developed as radio- or chemo-potentiating agents that sought to overcome cancer cell resistance to a DNA-damaging agent by preventing repair of the potentially lethal damage to the cancer cell caused by the treatment. Most of the PARP inhibitors currently undergoing clinical investigation have been designed to compete with NAD+ for its substrate-binding site. It is likely that these drugs inhibit both PARP1 and PARP2. Inhibition of PARP1 compromises a cell's ability to overcome damage to the genome by repairing DNA single-strand breaks. The enzyme binds to damaged DNA and is then activated, and the PARP inhibitors competitively block binding of the substrate.

H&O Where has the most benefit been demonstrated regarding the use of PARP inhibitors?

RP Two preclinical papers published in *Nature* in 2005 demonstrated hypersensitivity of *BRCA*-deficient cancer cells to single-agent PARP inhibitors, which initiated clinical research of these agents as monotherapy. In their tumors, these patients have lost 1 DNA repair pathway (double strand break repair), and blocking the second pathway pharmacologically causes synthetic lethality in tumour cells. This single-agent activity is where the drugs have currently gone furthest in the clinic. However, it is not where they initially started. PARPs were originally identified in 1963; the potential for PARP inhibition to enhance DNA damage caused by cytotoxic chemotherapy was first considered in 1980, and these agents have done that in preclinical models. Some attempts have been made to replicate this effect in the clinic, but that has been much more challenging because if a PARP inhibitor is combined with a chemotherapy drug, increased side effects occur in normal tissues, as well as in the tumor. Achieving a proper balance has been more difficult in this setting. That is why the ability to use PARP inhibitors as a single agent, which minimizes toxicity in the normal tissues, is an exciting development.

H&O What toxicities have been observed with PARP inhibitors, and how has this challenged their development?

RP When discussing toxicities observed with PARP inhibitors, it is important to distinguish between single-agent PARP inhibition and PARP inhibition in combination with chemotherapy. The drug that has been used most in the clinic on its own is olaparib (AstraZeneca). It is being administered as a single agent twice daily at a high dose, and there have been some side effects reported, including anemia, decreases in blood count, nausea, vomiting, and fatigue. Two other drugs, veliparib (Abbott Laboratories) and rucaparib (Clovis Oncology/Pfizer/Cancer Research UK), have been used as single agents at slightly lower doses than olaparib, and there have not been the same problems with toxicity. These observations provide hope that there can be efficacy without higher doses, thereby alleviating toxicities of PARP inhibitors administered as single agents.

In some of the first studies of PARP inhibitors in combination with chemotherapy, a higher level of myelosuppression was observed than would have been expected with the chemotherapeutic agent alone. This finding presents a few challenges, such as determining whether clinical studies should be designed with the maximum dose of chemotherapy possible or with the maximum dose of

the PARP inhibitor and a reduction in the chemotherapy dose. There is also a need to investigate the mechanism by which PARP inhibitors enhance damage to normal tissue when used with other agents, such as taxanes, where repair of cytotoxic damage is not thought to be achieved via a PARP-dependent mechanism.

H&O Despite the general promise of benefit observed in phase I and II studies of PARP inhibitors, the phase III trial of iniparib in metastatic, triple-negative breast cancer failed to uphold such positive results. How has this affected the view of PARP inhibitors as a promising class of novel anticancer agents?

RP Iniparib (Sanofi-Aventis) does not appear to be a true PARP inhibitor. Although it does have properties that result in toxicity to tumor cells, its mechanism of action does not appear to be the same as the other agents in the class, which compete for NAD+ binding. Biologically, however, there were patient groups from the phase III trial of iniparib by O'Shaughnessy and associates that showed benefit. In the earlier phase II study of iniparib, some of the patients clearly benefited from iniparib. From our understanding of triple-negative breast cancer biology, there is a group of these patients who have a *BRCA*-like tumor phenotype and should benefit from a PARP inhibitor. It will be a shame if this "negative" trial diminishes enthusiasm to continue investigating the role of PARP inhibitors in this poor prognosis tumor type.

H&O What are the major areas of focus for the future clinical development of PARP inhibitors?

RP It would be nice to see a PARP inhibitor made widely available to patients with genetically-inherited breast or ovarian cancer, as it is very clear that these patients benefit from PARP inhibitors. However, the development of PARP inhibitors as chemo-potentiating agents has been limited by an increase in observed toxicities, mainly myelosuppression, necessitating dose reductions of the cytotoxic chemotherapeutic agent and the PARP inhibitor. This raises the question of whether administering the combination is more efficacious than administering full doses of the chemotherapeutic agent alone, as well as the need to design clinical trial strategies to improve the therapeutic index of these combinations. It seems likely that optimizing the use of PARP inhibitors in the future will require the development of predictive assays to determine the presence of unsuspected defects in DNA damage repair pathways in tumors. Overall, identification of that molecular signature or diagnostic biomarker in order to determine which patients will benefit is of utmost importance. Much of the work in PARP inhibitor development must be focused on this issue.

Suggested Readings

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