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PARP inhibitors are not all equal

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Too many investigators PARP1 is simply a substrate for caspase 3, and whose cleavage is thought indicative of apoptosis. However, in reality PARP1 plays a major role in the biology of the cell cycle and DNA repair.[1,2] PARP1 binds to damaged DNA where it becomes enzymatically activated and ADP ribosylates itself and other proteins. PARP facilitates DNA repair complex formation, e.g., with BRCA1/2, and the activation of the cell cycle regulatory enzymes ATM and ATR.[2] PARP inhibitors as a single agent have only shown any degree of efficacy in breast and ovarian cancer patients who lack BRCA1/2 function.[3,4] The present studies examined PARP1 inhibitor biology in a range of triple negative and non-triple negative breast cancer cell lines.

Using MTT assays and a growth assay of single cells/colonies, the PARP1 inhibitor olaparib was shown to be a more potent inhibitor of breast cancer growth than the PARP1 inhibitor iniparib.[5] No assays using siRNA knock down of PARP1 or other PARP isoforms were included to compare on- and off-target effects of the drugs with respect to their growth potential. The majority of the cell lines had IC_{50} growth values by MTT assay that were significantly above the C max values seen in patients for the PARP1 inhibitors, arguing that the best scenario for the use of PARP1 inhibitors will be in combination with other agents.[1] It was also of note that the IC_{50} value for MTT growth of cells with continuous exposure to drug was significantly higher than the IC_{50} value for the colony growth of cells with continuous exposure to drug, arguing that cell density plays an important role in the response of tumor cells to PARP1 inhibitors. The authors then performed drug combination assays in multiple breast cancer lines using olaparib combined with a CDK inhibitor or with suicide pan-ERBB1/2 inhibitors. In some cell lines an additive effect at suppressing colony growth was observed combining olaparib with the CDK inhibitor whereas in other lines the effect was less than additive. In the majority of cell lines an additive effect at suppressing colony growth was observed combining olaparib with the ERBB1/2 inhibitors (neratinib; afatinib). No short-term killing assays, e.g., Annexin-PI or molecular approaches were included to further define mechanism(s) of interaction, however it was of note that a simple correlation between the PARP inhibitor-induced reduction in PAR levels and drug effects did not simplistically correlate. Thus further studies will be required, presumably using molecular tools to selectively knock down each of the PARP inhibitor targets, to define which members of the PARP super-family are required for the actions of drugs such as olaparib.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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