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Abstract

Differences in Durability of PARP Inhibition by PARP Inhibitors in Ovarian Cancer Cells †

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Abstract: Background: PARP inhibitors (PARPi) exploit defects in homologous recombination repair (HRR) to selectively kill tumour cells. Continuous PARP inhibition is required for cytotoxicity. PARPis rucaparib, olaparib, and niraparib have been approved for use in ovarian cancer on continuous schedules. Previous studies demonstrate prolonged PARP inhibition by rucaparib [1]. Aim: To determine if persistent PARP inhibition is a class effect. Methods: IGROV-1 (human ovarian cancer) cells were treated with 1 μM of rucaparib, olaparib, niraparib, talazoparib, or pamiparib for 1 h before drug was washed off and replaced with fresh media for 0, 1, 24, 48, or 72 h prior to harvesting. Cellular PARP activity was measured using a GCLP-validated assay [2] in comparison with untreated controls and where 1 μM inhibitor was added to the reaction. Results: rucaparib, olaparib, niraparib, talazoparib, and pamiparib each inhibited PARP activity in permeabilized cells > 99% when 1 μM was present during the reaction. After 2 h in drug-free medium, rucaparib-induced PARP inhibition was maintained at 92.3 ± 4.3%, but was much less with talazoparib (58.6 ± 5.0%), pamiparib (56.0 ± 4.5%) olaparib (48.3 ± 19.8%), and niraparib (37.3 ± 11.6%). PARP inhibition in rucaparib-treated cells was maintained for 72 h in drug-free medium (77.7 ± 12.3%). This sustained PARP inhibition was not observed with the other PARPis. PARP inhibition was only 12.3 ± 5.2% and 12.5 ± 4.9% 72 h after talazoparib and pamiparib, respectively, and undetectable with olaparib and niraparib. Conclusion: Rucaparib is unique in its ability to cause persistent PARP inhibition and it is not a class effect. These data have clinical implications for the different uses of PARPi, as a single agent use to exploit HRR defects vs. chemo and radiosensitization.

Keywords: PARP-1

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