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Evaluation of the role of oxidative stress in the anticancer effects of CHK1 and PARP-1 inhibitors in HepG2 cells

POST-CONFERENCE REPORT

WIKTORIA BĘBENEK, AGNIESZKA MARCZAK, ANETA ROGALSKA

University of Lodz, Faculty of Biology and Environmental Protection, Pomorska 141/143, 90–236 Lodz, Poland
E-mail: wiktoria.bebenek@edu.uni.lodz.pl

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Olaparib (PARP-1i) is a poly(ADP-ribose) polymerase inhibitor used in the treatment of advanced ovarian cancer, particularly in patients with mutations in the *BRCA1* and *BRCA2* genes, which acts by blocking the repair of single-stranded DNA breaks. CHK1, on the other hand, is a kinase that controls cell cycle and DNA repair. The effect of olaparib in combination with CHK1i on liver cancer cells is unknown. The combined effect of the drugs may prevent metastasis of ovarian cancer to the liver, but also to the bones, lungs, and brain. Indeed, the liver is crucial for detoxification and is therefore more susceptible to damage caused by replication stress, especially because of suppression of intracellular antioxidant defence systems.

The aim of this study was therefore to assess the potential role of oxidative stress in the cytotoxic effects of CHK1 and PARP-1 inhibitors in monotherapy as well as in combination therapy against HepG2 liver cancer cells.

The MTT metabolic activity assay was used to estimate cytotoxicity in the HepG2 line, and the concentrations of the compounds tested (CHK1i and PARPi) used in combinations were determined. Oxidative stress levels in liver cancer cells were also determined using MitoSox Red and H2DCF-DA fluorescent probes. Experiments were performed in variants of pre-incubation with an antioxidant, N-acetylcysteine.

Concomitant application of olaparib with CHK1i induced a cytotoxic effect in liver cancer cells. The greatest synergistic effect was observed with the combination of olaparib 2.5 μM and CHK1i 5 μM, which, after five days of incubation, resulted in a decrease in survival of the HepG2 line to approximately 30% compared with the respective mono-therapies (PARPi approximately 90%; CHK1i approximately 40%). These results clearly indicate a significant increase in the antitumor activity of olaparib in the presence of a CHK1 inhibitor. The experiments performed showed no significant changes in the levels of reactive oxygen species up to 48 hours of incubation with the tested inhibitors.

The combination of olaparib with a CHK1 inhibitor appears to be a promising strategy for the treatment of liver cancer, which, if introduced into clinical practice, would represent a potential benefit for a

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broad group of ovarian cancer patients previously treated with olaparib, where resistance to olaparib resulted in liver metastasis.