Synergistic Induction of Homologous Recombination Deficiency by Dual PARP and ATM Inhibitions: Precision Treatment for Cholangiocarcinoma

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Background and objectives: Mutations in homologous recombination repair (HRR) genes drive genomic instability and tumorigenesis but also create a therapeutic vulnerability to poly(ADP-ribose) polymerase (PARP) inhibition. PARP inhibitors (PARPi) induce DNA damage that is selectively cytotoxic to homologous recombination–deficient (HRD) cells, including those with BRCA1/2 mutations, and are approved for BRCA-mutated cancers. Ataxia telangiectasia mutated (ATM), a key regulator of HRR and the DNA damage response, can promote repair and attenuate PARPi efficacy in BRCA-proficient settings. We hypothesized that dual inhibition of PARP and ATM would induce a synthetic lethal response and enhance therapeutic responses in gemcitabine/cisplatin (Gem/Cis)-resistant cholangiocarcinoma (CCA) cells.

Methods: Genomic alterations in DNA damage repair (DDR) genes were explored using cBioPortal, and mutations in HRR and epigenetic modifier genes in CCA cell lines were characterized by whole- exome sequencing. Cytotoxicity was assessed in eight CCA cell lines. Cell-cycle distribution and apoptosis were evaluated by flow cytometry. DNA damage was quantified by γH2AX immunofluorescence, and expression of cell cycle– and DDR-associated proteins was analyzed by western blotting.

Results: Most established CCA cell lines were refractory to Gem/Cis chemotherapy, whereas the BRCA-mutant KKU-023 cell line was highly sensitive to PARPi. In BRCA-proficient KKU-100 cells, co-treatment with ATM inhibitors induced a synthetic HRD phenotype and sensitized cells to PARPi. The combination suppressed proliferation via G2/M arrest, downregulated cyclins A and B1, increased apoptosis, and elevated DNA double-strand breaks (γH2AX), while reducing RAD51, consistent with impaired HRR.

Conclusions: These findings support DDR-targeted strategies in CCA. PARPi monotherapy is effective in BRCA-mutant CCA, whereas combined PARP and ATM inhibition induces synthetic lethality in BRCA-proficient models.

Keyword: olaparib, niraparib, ATM inhibitor, synthetic lethality, DNA damage repair, cholangiocarcinoma

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