

In vitro cell growth inhibitory effects of HYDAMTIQ, a novel PARP inhibitor, on human tumor cell lines with defective DNA damage response pathways

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Introduction: The poly(ADP-ribose) polymerase (PARP) enzymes play key roles in the regulation of cellular processes (e.g. DNA damage repair, genomic stability). It has been shown that PARP inhibitors (PARPIs) are selectively cytotoxic against cells with dysfunctions in genes involved in DNA repair mechanisms (synthetic lethality).

Preclinical and clinical studies have shown activity of PARPIs as single agents or in combination with anticancer drugs in *BRCA1/2* mutated cancers that are unable to repair DNA by 'homologous recombination' (HR) and in colorectal cancer with microsatellite instability associated with *MRE11* mutations. Drug induced PARP inhibition may also potentiate the activity of anticancer drugs such as 5-fluorouracil by enhancing DNA damage, whose repair involves PARP1 activity.

Aims: To evaluate the effect of a novel PARPI, HYDAMTIQ, on human tumor cell lines, characterized by a different *BRCA1/2* gene mutation or microsatellite stability status, or expression of the ataxia telangiectasia-mutated (ATM) protein which mediates DNA damage responses.

Methods: A *BRCA2*-mutated pancreatic cancer cell line (CAPAN-1), its *BRCA2* wild-type clones (C2-6, C2-12, C2-14), a *BRCA1/2* wild-type breast cancer cell line (MCF-7), a *BRCA2* mutated colorectal cancer cell line (HCT-116), colorectal cancer cells with (HCT-8) or without (HT29) microsatellite instability, colorectal cancer cells with low (SW620) or high (H630) ATM protein expression levels were used. Cell viability was assessed by the sulforhodamine B (SRB) assay after drug exposures of 72-240 hrs; the analysis of ATM protein levels was assessed by immunofluorescence.

Results: HYDAMTIQ showed more potent cell growth inhibitory activity in *BRCA2* mutant cell lines (CAPAN-1, HCT-116) compared with wild-type cells (C2-6, C2-12, C2-14 clones and MCF-7). The cytotoxic effects of HYDAMTIQ were greater (after 240 hrs of exposure) in MS unstable HCT-8 cells than in MS stable HT29 cells. HYDAMTIQ induced higher antiproliferative effects in the ATM low expression SW620 cell line than in the ATM high expression H630 cell line. Also, the combination of HYDAMTIQ and 5-fluorouracil exerted a synergistic effect on inhibition of proliferation of SW620 cells and an antagonistic effect on that of H630 cells.

Conclusions: Our results confirm that the novel PARP inhibitor HYDAMTIQ inhibits the growth of human tumor cells with defective DNA damage response pathways and exerts synergistic cytotoxicity with 5-fluorouracil. These data provide relevant examples of synthetic lethality and evidence for further development of a novel PARPI.