Olaparib Nanoformulation in H-Ferritin for the Triple Negative Breast Cancer Treatment

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Extended Abstract

Poly(ADP-ribose) polymerase (PARP) inhibitors are a novel promising strategy toward triple-negative breast cancer (TNBC). TNBC is a breast cancer subtype that represents one of the main clinical challenges in cancer treatment due to its heterogeneity, biological behavior, invasiveness and poor prognosis. Moreover, it often shows genomic instability and/or BRCA mutations. However, clinical results obtained with PARP inhibitors are controversial, and no benefits were demonstrated in case of wild type BRCA, possibly due to poor bioavailability and inadequate nuclear delivery [1-4]. Nanotechnology could overcome these major limitations with the development of nanocaged-drugs. Among these, the most promising is represented by H-ferritin (HFn): natural protein-based nanoparticles with native capability of targeting tumor cells thanks to its specific interaction with the TfR1, which is overexpressed in tumor cells. HFn are constituted of self-assembling human H-ferritin monomers arranged in a hollow structure. HFn also possess some other unique features very appealing from the clinical point of view: i) uniform cage architecture, which allows the precise control of the amount of encapsulated drugs; ii) negligible toxicity and immunogenicity; iii) stability in physiological environment as a result of their protein nature, which increases circulation time, protects the cargo molecule from degradation and improves bioavailability[5-7].

The aim of this study was to assess the anticancer efficacy of H-Ferritin nanoformulated Olaparib (HOla) vs. free Olaparib (Ola) on BRCA-mutated and non mutated TNBC cells exploiting both the natural targeting of H-ferritin toward the transferrin receptor-1 and also its physiological tropism toward the nuclear compartment.

BRCA-mutated HCC1937 cells and BRCA-wild type MDA MB-231 and MDA MB-468 cells were treated with HOla or Ola in vitro. All TNBC cell lines over-expressed TfR-1 and were successfuliy recognized by H-Ferritin, displaying a fast internalization of nanocages into the cells, with intracellular persistence detected up to 48 h by confocal microscopy. H-Ferritin nanoformulation results in a marked increase in nuclear concentration of drug as it was observed with HOla compared to Ola, due to a strongly improved nuclear delivery promoted by HOla mediated self-triggered mechanism. HOla induced remarkable cytotoxic effect, exhibiting 1000-fold higher anticancer activity in all TNBC cell lines at 50 nM and 100 nM, while no significant antiproliferative effect was observed after treatment with free Ola at 10 nM, 50 nM or 100 nM. A possible toxic contribution from H-Ferritin was excluded by treating cells with void nanoparticles and evidences of the strongly improved HOla cytotoxic efficacy at a molecular level compared to Ola was provided by an increased proportion of cleaved PARP-1 and DNA double strand breaks evaluated using phosphorylated histone H2A.X as biomarker.
Our findings suggest that the H-Ferritin nanoformulation strongly enhances cytotoxic efficacy of Ola as a PARP inhibitor in stand-alone therapy on both BRCA-mutated and wild type TNBCs, allowing for targeted delivery into TNBC cells and prompt drug homing into their nuclear compartment.

References