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177 - NOVEL PLATINUM-BASED CHEMOTHERAPEUTIC AGENTS HALT CHOLANGIOCARCINOMA PROGRESSION THROUGH THE INDUCTION OF INTER-STRAND DNA BREAKS, PREVENTING DNA REPAIR MECHANISMS

Irene Olaizola[1], Mikel Odriozola[2], Maitane Asensio[3,4], Paula Olaizola[1,4], Iván Rivilla[2,5], Amanda Guimaraes[2], Francisco J. Caballero-Camino[1], Elisa Herráez[3,4], Óscar Briz[3,4], Pedro M. Rodrigues[1,4,5], Maria J. Perugorria[1,4,6], Luis Bujanda[1,4], Jose J. Garcia-Marin[3,4], Fernando Cossio[2] and Jesus M. Banales[1,4,5,7]

[1]Department of Liver and Gastrointestinal Diseases, Biodonostia Health Research Institute-Donostia University Hospital, University of the Basque Country (UPV/EHU), San Sebastian. [2]Department of Organic Chemistry I, Center of Innovation in Advanced Chemistry (ORFEO-CINQA), Faculty of Chemistry, University of the Basque Country (UPV/EHU) and Donostia International Physics Center (DIPC), San Sebastian. [3]Experimental Hepatology and Drug Targeting (HEVEPHARM) Group, Institute of Biomedical Research of Salamanca (IBSAL), University of Salamanca. [4]National Institute for the Study of Liver and Gastrointestinal Diseases (CIBERehd, "Instituto de Salud Carlos III"). [5]IKERBASQUE, Basque Foundation for Science, Bilbao. [6]Department of Medicine, Faculty of Medicine and Nursing, University of the Basque Country (UPV/EHU), Leioa. [7]Department of Biochemistry and Genetics, School of Sciences, University of Navarra, Pamplona.

Resumen

Introduction and objectives: Cholangiocarcinoma (CCA) comprises a heterogeneous group of biliary malignant tumors characterized by dismal prognosis. The first-line treatment for advanced CCA [cisplatin (CisPt) and gemcitabine] is considered palliative due to the high chemoresistance of this cancer, barely impacting on patients' overall survival. Here, we aimed to design, synthesize and study a new generation of platinum (Pt)-derived chemotherapeutic drugs that produce inter-strand DNA breaks (vs classical single-strand breaks induced by CisPt and related compounds) and thus prevent the development of DNA repair mechanisms in cancer cells.

Methods: Ten Pt-derivatives (Aurki-Ptσ) were designed and synthesized. Atomic Force Microscopy (AFM) and Transmission Electron Microscopy (TEM) were used to characterize the binding of Aurki-Ptσ to DNA. The antitumoral effect of these Aurki-Ptσ was evaluated by measuring the viability of human CCA cells (EGI-1 and HUCCT1), newly generated CisPt-resistant EGI-1 CCA cells and normal human cholangiocytes (NHC). The DNA damage induced by the two best candidates (Aurki-Pt#1 and #2) was assessed using the comet assay. To ascertain the internalization mechanism of Aurki-Pt#1 and #2, substrate competition studies through flow cytometry and accumulation studies using HPLC-MS/MS were carried out. Finally, the effect of Aurki-Pt#1 and #2 was also tested in vivo on a subcutaneous xenograft model of CCA.

Results: Aurki-Ptσ induced inter-strand DNA breaks, and the subsequent DNA fragmentation, contrary to CisPt. Aurki-Pt#1 and #2 significantly reduced CCA cell viability. Both compounds triggered increased DNA damage in CCA cells when compared to CisPt, thus being more effective when inducing apoptosis *in vitro*. Importantly, Aurki-Pt#1 and #2 also promoted cell death in CisPt-resistant CCA cells, while this lethal effect was absent in NHC in culture. On the other hand, Aurki-Pt#1 and #2 decreased the proliferation of those CCA cells that survived but did not have any effect on NHC. Aurki-Pt#1 and #2 were

transported into cells through OCT1, OCT3, CTR1 and OATP1A2, which did not transport CisPt. Finally, Aurki-Pt markedly hampered tumor growth on a subcutaneous xenograft model of CCA in comparison with CisPt or vehicle control.

Conclusions: This new generation of Pt-derived chemotherapeutic drugs selectively diminishes CCA cell viability through the induction of inter-strand DNA breaks, representing a promising therapeutic tool for *naïve* or CisPt-resistant CCA tumors.