Cancer Research

Experimental and Molecular Therapeutics

Abstract 3082: Targeting hypoxic pancreatic cancer cells with glucose conjugated lactate dehydrogenase inhibitor NHI-Glc-2

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DOI: 10.1158/1538-7445.AM2019-3082 Published July 2019

Proceedings: AACR Annual Meeting 2019; March 29-April 3, 2019; Atlanta, GA

Abstract

Pancreatic ductal adenocarcinoma (PDAC) is an abysmal disease with a 5-year survival rate of merely 8%. The tumor microenvironment of PDAC is one of the factors contributing to drug resistance. More specifically, the hypoxic tumor core and the metabolic switch to aerobic glycolysis (the Warburg effect), contribute to the lack of drug response. Therefore, we investigated the effect of several novel lactate dehydrogenase (LDH-A) inhibitors (N-Hydroxyindole-based LDH-A inhibitors, NHI-1 and NHI-2, and the glucose conjugate NHI-Glc-2) in PDAC cells *in vitro* and *in vivo*, in combination with the standard drug gemcitabine. For this purpose we used our primary PDAC cancer cell cultures, tested growth inhibition with the SRB chemosensitivity assay, used 3D cultures and established an *in vivo* orthotopic bioluminescent model. Additionally, LDH-A enzyme activity inhibition by NHI-Glc-2 was assessed by spectrophotometry. LDH-A is overexpressed in PDAC and its expression is correlated with the prognosis of metastatic PDAC. The glucose transporter 1 (GLUT-1) is also overexpressed in PDAC, which would enable an increased uptake of NHI-Glc-2 by the tumor cells. LDH-A mRNA expression and enzyme activity were about 2-fold higher under hypoxic conditions. NHI-1, NHI-2 and NHI-Glc-2 were 4-15-fold more effective under hypoxic conditions compared to normoxia, but gemcitabine was 10-20-fold less active under hypoxia. NHI-1 showed a

synergistic effect with gemcitabine in hypoxic PANC-1 and LPC006 cells (combination index 0.14 ± 0.06 and 0.29 ± 0.53, respectively). NHI-Glc-2 inhibited PDAC cell growth in micromolar range under hypoxic conditions and also showed a synergistic effect with gemcitabine. In a 3D spheroid culture (with a hypoxic core), NHI-Glc-2 disrupted the spheroid integrity. Moreover, in an orthotopic PDAC model NHI-Glc-2 showed a more pronounced inhibition (almost complete) of tumor growth compared to gemcitabine. NHI-Glc-2 also showed a favorable pharmacokinetics with a peak plasma concentration of 26 μM at 4 hr, which is higher than the IC_{50}. In conclusion, LDH-A is a viable target in PDAC, and novel LDH-A inhibitors offer an innovative therapeutic tool. Remarkably, the LDH-A inhibitors NHI-1 and NHI-2 increased the effect of gemcitabine under hypoxic conditions, while the glucose conjugated NHI-Glc-2 showed an improved uptake possibly because of the increased GLUT-1 expression, leading to a pronounced *in vivo* effect.

Citation Format: Btissame El Hassouni, Rocco Sciarrillo, Valentina Edith Gómez, Mina Maftouh, Giulia Mantini, Christian M. Vonk, Carlotta Granchi, Niccola Funel, Filippo Minutolo, Godefridus J. Peters, Elisa Giovannetti. Targeting hypoxic pancreatic cancer cells with glucose conjugated lactate dehydrogenase inhibitor NHI-Glc-2 [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2019; 2019 Mar 29-Apr 3; Atlanta, GA. Philadelphia (PA): AACR; Cancer Res 2019;79(13 Suppl):Abstract nr 3082.

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July 2019
Volume 79, Issue 13 Supplement
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