STRATAGEM

CA17104

New Diagnostic and Therapeutic Tools against Multidrug-Resistant Tumours

First Working-Group Meeting

WG 1 – WG 4

Abstract Book

Turin, Italy

30th – 31st January 2019

cost EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Funded by the Horizon 2020 Framework Programme of the European Union

DSTF DIPARTIMENTO DI SCIENZA E TECNOLOGIA DEL FARMACO UNIVERSITÀ DEGLI STUDI DI TORINO

UNIVERSITÀ DEGLI STUDI DI TORINO

The role of antioxidant, coenzyme Q10, in suppressing invasion of temozolomide resistant rat glioma

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Development of chemoresistance and the invasion of cancer cells into surrounding brain tissue are major obstacles to successful glioma treatment. New therapeutic approaches are warranted to improve the survival of glioma patients. The purpose of this study was to assess the potential of lipophilic antioxidant coenzyme Q10 (CoQ10) to increase sensitivity to temozolomide (TMZ) and suppress glioma cells invasion. Therefore, we have developed TMZ resistant RC6 rat glioma cell line with altered antioxidant capacity and high invasion potential. CoQ10 in combination with TMZ exerted a synergistic effect additionally confirmed in a 3D model of microfluidic devices. Co-treatment with TMZ increased expression of mitochondrial antioxidant enzymes in RC6 cells. The anti-invasive potential was studied by gelatin degradation and 3D spheroid invasion assays. Inhibition of MMP9 gene expression as well as decreased N-cadherin and vimentin protein expression implied that CoQ10 can suppress invasiveness and the epithelial to mesenchymal transition in RC6 cells. Therefore, CoQ10 supplementation could be used with standard glioma treatment due to its potential to inhibit cancer cells invasion through modulation of the antioxidant capacity.

Pt(IV) cisplatin carrying epigenetically active ligands shows enhanced anti-cancer activity in vitro and in vivo

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Platinum-based cytotoxic compounds represent a substantial part of anticancer therapies. However, therapy with these compounds is characterized by frequent occurrence of resistance and severe adverse effects thereby limiting efficient chemotherapy. To overcome these drawbacks, kinetically inert Pt(IV) prodrugs were developed that are activated by reduction in the hypoxic conditions of malignant tissue. The axial ligands of Pt(IV) prodrugs provide a broad range of possibilities to combine individual drugs in a single prodrug that targets cancer cells. [1]

The synergism of chemotherapy and epigenetically active anticancer compounds has been demonstrated in various studies. [2], [3] Here, we investigated the anti-cancer activity of two Pt(IV) compounds carrying the histone deacetylase (HDAC) inhibitor 4-phenylbutyrate (PhB) as the axial ligand. Preliminary in vitro data showed enhanced cytotoxicity of the cisplatin derivatives ctc-$[Pt(NH_3)_2(PhB)(OH)Cl_2]$ (1) and ctc-$[Pt(NH_3)_2(PhB)_2Cl_2]$ (2) compared to cisplatin. [4] Moreover, compound 2 showed significantly enhanced anti-proliferative activity in mice bearing melanoma or colon tumors. In addition, organ distribution of 2 was measured by ICP-MS 24 h after drug application. In conclusion, we provide evidence that conjugation of 4-phenylbutyrate to Pt(IV) cisplatin results in superior anti-cancer activity in vitro and in vivo. Further studies are planned to understand the mechanisms underlying this enhanced cytotoxic combinatory effect.

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