Extended Abstract International Research Journal of Pharmacy and Pharmacology 2021
Vol.9 No.3

Evaluation of temozolomide and flubendazole effects on glioblastoma cells in vitro - Barbora Vítovcová - Charles University

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Abstract

Glioblastoma multiforme (GBM) is the most invasive and aggressive form of gliomas. Its current therapy consisting of surgical resection, radiotherapy, and chemotherapy with orally administrated temozolomide (TMZ) is often unsuccessful. The aim of this study was to compare the effect of TMZ and repurposed drug flubendazole (FLU) on GBM stabilized cell line (A-172) and primary culture obtained from a patient´s biological sample.

The effects of TMZ and FLU on GBM cells was evaluated via measurement of cell proliferation rate (WST-1), changes in cellular morphology (phase contrast) and appearance and subcellular localization of microtubular cytoskeleton (fluorescent microscopy). Expression of select chemoresistance markers was determined by western blotting while intracellular accumulation of tested drugs and their metabolites was measured by LC-MS analysis.

Our results show that both cellular models differed in their sensitivities to the respective drugs; in both tested cell lines FLU was generally more effective. FLU inhibited proliferation of tested cell, induced formation of multinucleated cells, caused significant changes in microtubules and stimulated cell death. Conversely, TMZ had comparatively lowed antiproliferative effect and did not induce observable cell death. Moreover, its efficiency seemingly corresponded with the expression levels of MRP1 resistance marker (in particular GBM primary cells) and TMZ intracellular accumulation and metabolism.

Despite different techniques like medical procedure, radiotherapy, chemotherapy and in any event, utilizing a mix of various modalities, it is yet a deadly infection with poor visualization which does not offer totally compelling and valuable strategy for the treatment of glioma. Therefore, creating present day systems for treatment is basic for such patients. Temozolomide (TMZ) is as of now the standard chemotherapeutic medication and radio sensitizing agent that is utilized for the treatment of glioblastoma. The advancement of TMZ tranquilize goes back to mid-1980s when the medication was first blended by researchers at Aston University. TMZ is orally accessible, imidazotetrazine-based, and DNA alkylating agent. TMZ is steady in acidic conditions, yet the pace of debasement increments at high pH. The strength of TMZ in acidic condition permits it to be regulated orally. TMZ can endure the high causticity state of the stomach before entering the foundational dissemination and passing blood-mind obstruction (BBB). Spontaneous hydrolysis of TMZ and change of pH convert its particles into dynamic metabolite structure and thus does not require hepatic digestion for its activity. The capacity of TMZ in postponing the development of tumor cells and its simple remedy has transformed it into a famous alternative for the treatment of glioblastoma. The counter tumor impact of TMZ is methylation of tumor cell DNAs. Its cytotoxicity impact is obviously practiced by adding methyl gathering to N7 and O6 position of guanine in DNA. This medication instigates O6-MeG injury lastly causes apoptosis death. The point of the current examination was to explore cytotoxic and radio sensitizing impacts of TMZ on U87MG cell line in vitro. We endeavored to assess the degree of cell harm by TMZ in mix with gamma-beams of CO-60 in monolayer cells culture of glioma and essential fibroblast cells by MTT examine. The 3-(4,5-dimethylthiazolyl-2)- 2, 5-diphenyltetrazolium bromide (MTT) assay is a quantitative colorimetric technique to quantify and look at the metabolic suitability of the cells in vitro under various treatment protocols. The aftereffects of this investigation could be considered as a powerful advance to decide the remedial system of applying radio sensitizing specialists for the treatment of harmful tumors, for example, glioma Foundation: Glioma is the most widely recognized essential cerebrum tumor with poor visualization. Temozolomide (TMZ) has been utilized with light (IR) to treat gliomas. The point of the current examination was to assess the cytotoxic and radio sensitizing impact of TMZ when joined with high-portion and high-portion pace of gamma light in vitro. Strategies: Two 'U87MG' cell lines and skin fibroblast were refined and allotted to five gatherings for 24, 48,

and 72 hours. The gatherings were to be specific, TMZ gathering (2000 µM/L), IR gathering (5 Gy), TMZ in addition to IR gathering, control gathering, and control dissolvable gathering. MTT measure was applied to assess cell practicality. Information was broke down with SPSS 21.0 programming utilizing single direction ANOVA and Kruskal-Wallis test. P<0.05 were considered factually critical. Results: The slant of development bend U87MG cells in semi-logarithmic scale was equivalent to 27.36±0.89 hours. The reasonability of cells was resolved for various TMZ and IR treatment gatherings. As far as cell suitability, there were no critical contrasts between the control and control dissolvable gatherings (P=0.35) and between rewarded bunch by IR (5 Gy) alone and TMZ (2000 µM/ml) alone (P=0.15). Information got for the cell reasonability of consolidated TMZ in addition to IR in both cell lines contrasted with TMZ or IR rewarded bunch alone demonstrated a critical distinction (P=0.002). End: The assessment of cells reasonability indicated that TMZ in blend with IR on glioma cells prompted a noteworthy radio sensitivity contrasted with IR alone.