ABSTRACT

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Title of diploma thesis: Repeated low-dose flubendazole treatment and its effect on glioblastoma cells

Glioblastoma (GBM) is one of the most aggressive and common primary brain tumours in the adults. GBM is resistant to current treatment and the median survival of treated patients with this disease is around 15 months. The very poor prognosis of this disease has prompted the research of new therapeutic strategies. A promising direction is represented by drugs already registered for other indications, such as the anthelmintic flubendazole (FLU) with potential antitumour activity. The aim of this work was to study the effect of FLU after repeated low-dose treatment of GBM cells.

Two cell lines, U87MG and U87MG-IDH1mut, were used for this work and the effect of repeated doses of FLU on cell viability (using the WST-1) and on cell morphology (via phase contrast microscopy) was investigated. Furthermore, changes in the expression of cell cycle markers, proliferation, growth, and resistance markers after FLU treatment were evaluated at the mRNA level (RT-PCR) and protein level (Western blotting). Subsequently, the activity of initiator and effector caspases was determined (by luminescence assay) and finally, the content of FLU and its metabolite in cells affected by repeated FLU administration was determined (LC/MS analysis).

Both tested cell lines showed high sensitivity to FLU treatment, FLU effectively inhibited cell viability and proliferation depending on the number of repetitions of FLU treatment and on the length of the treatment as well. FLU also induced changes in the morphology of both cell lines. In the cells treated with FLU, the decrease in the expression of proliferation and cell cycle markers at the mRNA level could be observed, but these trends were not confirmed at the protein level. FLU treatment increased the activity of initiator caspases 8 and 9 as well as effector caspases 3/7 and increased the content of FLU and its metabolite in cells after repeated treatment.