Resveratrol and Temozolomide have additive citotoxic effect, induce autophagy and cell cycle alterations in U87-MG cells

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Glioblastoma Multiform (GBM) are the most common and malignant tumors of the Central Nervous System, with a median survival of only 12-15 months after diagnosis. Thus, the development of new therapy strategies is urgently needed. Resveratrol (RSV) is a natural polyphenol which is, in one hand, neuroprotective on normal neural cells but, in other hand, cytotoxic on several types of tumor cells. We aimed to evaluate some biological aspects of the human GBM cell line U87-MG, emphasizing the effect of the combination of RSV (30uM, 100uM) with Temozolomide (TMZ – 100uM, 300uM, 1000uM), the major chemotherapeutic agent used for GBMs, on these parameters: cell proliferation and viability, cell cycle distribution and autophagy, in cells exposed to these compounds, isolated and in combination. Statistical analysis was conducted by ANOVA followed by SNK, with $p<0,05$ being considered significant. All treatments (RSV, TMZ and combinations) reduced the cell number and viability, being RSV more cytotoxic than TMZ and the combined treatment showing an important additive effect. RSV induced arrest in G2/M in 24h and increased sub-G1 (apoptotic) population in 48h. TMZ induced arrest in G2/M. This arrest was, however, reversed by RSV, in a dose-dependent manner. Finally, both compounds induced autophagy in U87-MG cells. RSV induced greater density of autophagosomes than TMZ and induced both autophagy and apoptosis in the same cell. Thus, RSV showed a high cytotoxic effect in U87-MG cells and induced changes that characterize it as a potential drug against MG, both for single as well as associated therapy.

Keywords: Glioblastoma Multiforme, resveratrol, temozolomide