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COX-2 Inhibitor NS398 Counteracts Chemoresistance to Temozolomide in T98G Glioblastoma Cell Line

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Abstract : Glioblastoma multiforme (GBM) is a high-grade primary brain tumor refractory to current forms of treatment. The survival benefits of patients with GBM remain unsatisfactory due to the intrinsic or acquired resistance to temozolomide (TMZ), an alkylating agent, used as the first-line chemotherapeutic drug to treat GBM patients. Its cytotoxic effect is visualized by the induction of O6-methylguanine (O6MeG) within DNA. Cyclooxygenase-2 (COX-2), an inflammation-associated enzyme, has been implicated in tumorigenesis and progression of GBM, its inhibition shows anticancer activities. In the present study, it was verified if the combination of a COX-2 selective inhibitor, NS398, with TMZ could counteract the TMZ resistance. In particular, the effect of NS398 mixed with TMZ was investigated in the GBM TMZ-resistant cell line, T98G. Cells were pretreated with NS398 (100μM, 24 hours) and then exposed to TMZ alone (200μM), NS398 alone, or both for 72 hours, after which cell growth rate and cycle phases, as well as apoptosis level, were evaluated. Coadministration of NS398 and TMZ caused a significant decrease in cell growth and a progressive increase of dead cells detected by trypan blue staining. Moreover, a significant level of apoptotic cell percentage and alteration of cell cycle phases were observed in T98G treated with TMZ-NS398 combination when compared to untreated cells or TMZ-treated cells. TMZ-resistant tumors, as GBM, express elevated levels of DNA repair enzyme O6-methylguanine-DNA methyltransferase (MGMT). The mixture drastically reduced MGMT expression in the TMZ-resistant cell line T98G, known to express high levels of MGMT basically. Moreover, while TMZ alone did not influence the COX-2 protein expression, the combination successfully reduced it. In conclusion, these results demonstrated that NS398 enhanced the efficacy of TMZ through cell number reduction, apoptosis induction, and decreased MGMT levels, suggesting the ability of drug combination to reduce the chemoresistance. This drug combination deserves attention and could be considered as a promising therapeutic strategy for GBM patients.

Keywords : COX-2, COX-2 inhibitor, glioblastoma, NS398, T98G, temozolomide
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