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Valproic Acid and Celecoxib Enhance the Effect of Temozolomide on Glioblastoma Cells

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Abstract

Introduction: Glioblastoma (GB) is one of the deadliest human brain tumors. The prognosis is unfavorable, chemotherapy with temozolomide (TMZ) may extend the survival period for a patient. The paper aims to evaluate the survival rates among relapsing GB patients, who have been treated with valproic acid (VPA), and to study its effect on tumor cells when combined with TMZ and celecoxib (CXB).

Materials and methods: The research is based on retrospective analysis of the data from GB patients who had been treated with VPA as a part of a complex treatment protocol and reoperated due to a GB relapse. The experimental study involved cancer cells of C6, U87, and T98G lines. GB was modeled on Wistar rats. The research was approved by the ethics committee. Differences in groups were considered significant at $p < 0.05$ Results: The median of overall survival among GB patients who took VPA was 22 months, and for those who did not take VPA - 13 months. The in vitro experiment showed the half-maximal inhibitory concentration (IC50) of TMZ for various lines of cancer cells (CCs) varying from 435.3 to 844 μM. IC50 VPA for CCs of U87MG, T98G, and C6 lines was 1510, 3900, and 3600 μM: IC50 CXB for those lines of CCs was 30.1 μM, 41.07, and 48.4 μM respectively. VPA significantly enhanced the anti-glioma effect of TMZ on the U87 line of CCs, while CCs of C6 and T98G lines proved to be most susceptible to the combination of CXB and TMZ. The combination of VPA with CXB increased the anti-glioma effect of TMZ both in vitro and in vivo, also reducing the tumor size ($p < 0.05$) and prolonging the survival period among experimental animals.

Conclusion: VPA and CXB enhance the effect of TMZ on glioblastoma cells.

Keywords: Glioblastoma (GB); celecoxib (CXB); chemoradiation therapy (CRT); temozolomide (TMZ); valproic acid (VPA)..