Tamoxifen in combination with temozolomide induce a synergistic inhibition of PKC-pan in GBM cell lines.


Abstract

BACKGROUND: Glioblastoma (GBM) is a highly proliferative, angiogenic grade IV astrocytoma that develops resistance to the alkylating agents used in chemotherapy, such as temozolomide (TMZ), which is considered the gold standard. The mean survival time for GBM patients is approximately 12 months, increasing to 14.6 months after TMZ treatment. The resistance of GBM to chemotherapy seems to be associated to genetic alterations and to the constitutive activation of several signaling pathways. Therefore, the combination of different drugs with different mechanisms of action may contribute to circumvent the chemoresistance of glioma cells. Here we describe the potential synergistic behavior of the therapeutic combination of tamoxifen (TMX), a known inhibitor of PKC, and TMZ in GBM.

METHODS: We used two GBM cell lines incubated in absence and presence of TMX and/or TMZ and measured cell viability, proliferation, apoptosis, cell cycle, migration ability, cytoskeletal organization and the phosphorylated amount of the p-PKC-pan.

RESULTS: The combination of low doses of TMX with increasing doses of TMZ shows an increased antiproliferative and apoptotic effect compared to the effect with TMX alone.

CONCLUSIONS: The combination of TMZ and TMX seems to potentiate the effect of each other. These alterations seem to be associated to a decrease in the phosphorylation status of PKC.

GENERAL SIGNIFICANCE: We emphasize that TMX is an inhibitor of the p-PKC-pan and that these combination is more effective in the reduction of proliferation and in the increase of apoptosis than each drug alone, which presents a new therapeutic strategy in GBM treatment.

Copyright © 2014 Elsevier B.V. All rights reserved.

KEYWORDS: Chemotherapy; Glioblastoma; Synergism; Tamoxifen; Temozolomide; p-PKC

PMID: 25554223 [PubMed - in process]