Curcumin Potentiates Antitumor Activity of Paclitaxel in Rat Glioma C6 Cells

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Despite the low percentage of cases, cerebral glioma possesses high mortality and morbidity rate. Especially, glioblastoma is the most aggressive and malignant brain cancer with rapid development. Furthermore, glioma cells possess enhanced resistance to radiotherapy- and chemotherapy-induced death. Paclitaxel (PTX), a microtubule stabilizing agent with highly potent anticancer potential, is recommended as a first-line strategy chemotherapeutic agent against many kinds of cancers. However, the clinical efficacy of PTX in brain tumor is limited by drug resistance, besides serious several side effects, and limited bioavailability and cancer penetration. Current clinical practice for treating cancer includes the co-administration (usually sequentially) of more drugs acting with different mechanisms of action or on different molecular targets, to overcome cell resistance to chemotherapy. In this scenario, curcumin (Cur), a yellow pigment from the spice turmeric (Curcuma longa), has been reported for its potential chemopreventive and chemotherapeutic activity through influence on cell cycle arrest, differentiation, and apoptosis in different kinds of cancer, and there has been considerable interest in its ability to inhibit NF-κB pathway activity, playing a main role in the control of oncogenesis, tumor progression, and chemotherapy resistance of diverse types of malignances. Taken into account this background, in view of a possible employment of the two drugs, Cur and PTX, combined together to overcome PTX limitations, the present study was undertaken to investigate, through in vitro experiments on human glioma C6 cells, the capability of Cur to ameliorate the cytotoxicity of PTX by modulating the activity of specific cell signalling pathways.

Our data confirmed the strong inhibition rate of PTX on glioma C6 cells (LC50 68 nM). Interestingly, combination with Cur increased cytotoxic effects of PTX in a dose-dependent way, so that a significant decrease of LC50 values was observed. PTX and Cur effects were also confirmed with the clonogenic assay. Furthermore, combination therapy most impressively activated caspase-3, the effector of extrinsic and intrinsic apoptosis pathway, and reduced the expression of the anti-apoptotic protein Bcl-2 more than single drug treatment. Our data demonstrated also the involvement of p53-dependent p21 activation mechanism in cell growth arrest. Drugs combination significantly induced p53 and p21 when compared to single drug treatment. Since aberrant activation of NF-kB has been reported in glioblastoma biopsies, the effects of two drugs on this transcription factor were evaluated. PTX and Cur showed inhibitory activity on NF-kB (p65) nuclear translocation and reduced cytoplasmic p-IkB, while their combination totally inhibited NF-kB pathway as observed by the lack of p65 nuclear levels.

In conclusion, the data of our research indicated that the combinational strategy exerted much higher efficacy in glioma growth delay than single administration of Cur or PTX, thus it may help in reducing dosage and in minimizing side effects of cytotoxic therapy.