The Combination of Cannabidiol and Δ^9-Tetrahydrocannabinol Enhances the Anticancer Effects of Radiation in an Orthotopic Murine Glioma Model

Katherine A. Scott, Angus G. Dalgleish, and Wai M. Liu*

Author Affiliations

***Corresponding Author:**
Wai Liu, Department of Oncology, Division of Clinical Sciences, St George's, University of London, Second Floor, Jenner Wing, London, SW17 0RE, United Kingdom. Phone: 44-20-8725-5037; Fax: 44-20-8725-0158; E-mail: w.liu@sgul.ac.uk

Abstract

High-grade glioma is one of the most aggressive cancers in adult humans and long-term survival rates are very low as standard treatments for glioma remain largely unsuccessful. Cannabinoids have been shown to specifically inhibit glioma growth as well as neutralize oncogenic processes such as angiogenesis. In an attempt to improve treatment outcome, we have investigated the effect of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) both alone and in combination with radiotherapy in a number of glioma cell lines (T98G, U87MG, and GL261). Cannabinoids were used in two forms, pure (P) and as a botanical drug substance (BDS). Results demonstrated a duration- and dose-dependent reduction in cell viability with each cannabinoid and suggested that THC-BDS was more efficacious than THC-P, whereas, conversely, CBD-P was more efficacious than CBD-BDS. Median effect analysis revealed all combinations to be hyperadditive [T98G 48-hour combination index (CI) at FU_{50}, 0.77–1.09]. Similarly, pretreating cells with THC-P and CBD-P together for 4 hours before irradiation increased their radiosensitivity when compared with pretreating with either of the cannabinoids individually. The increase in radiosensitivity was associated with an increase in markers of autophagy and apoptosis. These *in vitro* results were recapitulated in an orthotopic murine model for glioma, which showed dramatic reductions in tumor volumes when both cannabinoids were used with irradiation (day 21: 5.5 ± 2.2 mm^3 vs. 48.7 ± 24.9 mm^3 in the control group; $P < 0.01$). Taken together, our data highlight the possibility that these cannabinoids can prime glioma cells to respond better to ionizing radiation, and suggest a potential clinical benefit for glioma patients by using these two treatment modalities. *Mol Cancer Ther; 1–13. ©2014 AACR*.

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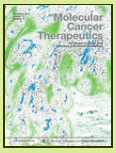

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