



Ursolic acid nanocrystals as a MGMT inhibitor in the treatment of glioblastoma.

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Glioblastoma is treated via the Stupp protocol which consists of tumor resection followed by radiotherapy and chemotherapy using temozolomide (TMZ). One of the causes of resistance to treatment is the expression of the O6-methylguanine-DNA-methyltransferase (MGMT). MGMT naturally removes methyl groups from DNA to protect it [1], however it is exactly the mechanism used by TMZ to kill tumor cells. Since the action of TMZ is impaired by the expression of MGMT and since the proportion of patient expressing the protein was of about 45% [2], our goal in this study is to inhibit the expression of MGMT to restore the efficacy of TMZ in the treatment of glioblastoma. One inhibitor of MGMT that could be used is ursolic acid (UA) [3]. UA is a pentacyclic triterpene that has been studied on two human glioblastoma cell lines, one expressing MGMT (T98G) and the other not (U-87 MG). UA decreases the expression of both the protein and the transcript in the MGMT-expressing cell line. UA has also been formulated in about 200nm nanocrystals using an antisolvent precipitation method. FRET inducing dyes were used in the formulation of UA nanocrystals which allowed the study of their destabilization. The nanocrystals were able to be internalized in MGMT-positive cells after 6 hours of contact. These results are promising for the treatment of TMZ-resistant glioblastoma but should be further studied in a cotreatment with TMZ.

References

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