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EGFR inhibition sensitizes human brain tumor cells to TMZ treatment

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The combination of procarbazine, lomustine and vincristine (PCV) is the most commonly used chemotherapy in brain cancer. The alkylating agent TMZ is another therapeutic approach used for the treatment of both low and high grade astrocytic tumors, largely replacing the PCV treatment, as a result of its oral administration and minor side effects. However, the enthusiasm for TMZ treatment decreased successively since it became clearly that the TMZ treatment provides survival benefits only for a subgroup of patients that have an altered O6-methylguanine-DNA methyltransferase (MGMT). In addition to MGMT, many other molecules that regulate tumor growth and survival have been suggested to interfere with brain tumor cells response to TMZ. Several growth factor receptor family members are overexpressed or over activated in glioma, playing an important role in treatment resistance. EGFR dysfunction is considered as one of the most common causes of TMZ therapy failure in glioma patients. In this paper, we aim to determine the effect of EGFR inactivation on glioma cells response to TMZ treatment. GB1B and AC1B glioma cell lines used in this study were low passage cultures established from fresh tissues obtained from consented glioma patients undergoing surgery at the "Bagdasar–Arseni" Hospital, Bucharest. Cell viability was quantified by hemocytometer cell counting, using trypan blue. Interactions between TMZ and EGFR inhibitor were classified by the multiplicative model. We found that TMZ inhibits cell viability in human glioma cells in vitro. TMZ, administered alone as a single-dose treatment, induced a persistent cell death in grade II astrocytoma (AC1B cell line) and in glioblastoma (GB1B cell line), 15 days after the treatment. We also found out that TMZ effect was more preeminent in glioblastoma than in low grade astrocytoma. AG556, an EGFR substrate-site competitor that belongs to the class of low molecular weight compounds, induced cell growth inhibition in GB1B and AC1B cells, but glioblastoma GB1B cells were significantly more sensitive to EGFR inhibition than low grade astrocytoma AC1B cells. Unexpected, in AC1B cells that were minor sensitive to TMZ or AG556 single treatment, the action of the two drugs together generated synergistic or additive response in the most of the treatment combinations. In summary, we found that both TMZ and AG556 treatment decreased GB1B and AC1B cells viability. Our results also indicated that TMZ or AG556 treatment alone was more efficient in inducing cytotoxicity in GB1B cells while the drugs concomitant administration was more potent in AC1B cell line. These findings may help to improve the design of coming clinical trials for evaluating the effect of EGFR inactivation on TMZ sensitization in glioma patients.

Biography

Oana Stefana Purcaru received her license in Physical Chemistry in the year 1998 and the License in Pharmacy in the year 2003.She completed her PhD Degree in 2011. She is working as a Lecturer since 2012, teaching and doing research activity at Biochemistry Department, University of Medicine and Pharmacy of Craiova, Romania. She has published more than 10 published papers in ISI journals, 5 books in national publishing and 3 chapters in international publishing. She has also served as a Research Team Member in many Projects and also been a member of numerous National and International Scientific Societies.

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