PRELIMINARY STUDIES OF PERILLYL ALCOHOL INTRANASAL ADMINISTRATION IN ADULTS WITH RECURRENT MALIGNANT GLIOMAS. (ABSTRACT)*. THESIS. RIO DE JANEIRO, 2007

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This work discusses intranasal delivery of perillyl alcohol (POH) as a potential adjuvant therapeutic strategy for patients with relapsing malignant gliomas. POH is a monoterpene with preclinical antitumor activity in several types of tumor in rodent models and is currently under phase I and phase II clinical trials. The proposed mechanism of action involves inhibition of post-translational isoprenylation of small G proteins, including p21-Ras, thereby blocking signal transduction. Deregulated p21-Ras function, as a result of mutation, overexpression or growth factor-induced overactivation, contributes to growth of malignant gliomas. Intranasal delivery is a practical and non-invasive approach that allows therapeutic agents which do not cross the blood-brain barrier (BBB) to enter the Central Nervous System (CNS), reducing unwanted systemic side effects. Applying this method we performed a phase I / II study of POH in patients with relapsed malignant gliomas after standard treatment: surgery, radiotherapy and chemotherapy. POH was administrated in concentration 0.3% volume/volume (55 mg) 4 times daily.

The objective of this study was to evaluate the toxicity and progression-free survival after 6 months of treatment. The cohort consisted of thirty-seven patients including 29 with glioblastoma multiform (GBM), 5 with grade III astrocytoma (AA) and 3 with anaplastic oligodendroglioma (AO). Neurological examination and suitable image analysis (tomography - CT, magnetic resonance – MRI) established disease progression. *Complete Response* was defined as neurological stability or improvement conditions, disappearance of CT/MRI tumor image and corticosteroid withdraw; *Partial Response* defined as ≥50% reduction of CT/MRI tumor image, neurological stability or improvement conditions and corticosteroid requirement; *Progressive Course* was defined as ≥25% increase CT/MRI tumor image or appearance of a new lesion; *Stable Disease* was defined as lack of any changes in the CT/MRI tumor image or neurological status.

After 6 months of treatment it was observed the following: *Partial Response:* 3.4% (n=1) with GBM and 33,3% (n=1) with AO; *Stable Disease:* 44.8% (n=13) with GBM, 60% (n=3) with AA and 33.3% (n=1) with AO; *Progressive Course:* 51.7% (n=15) with GBM, 40% (n=2) with AA and 33.3% (n=1) AO. The progression free survival (sum of partial responses and stable disease) was 48.2% for patients with GBM, 60%, 66.6% for AA patients and 66.6% for AO patients.

The present work indicate for the first time, that intranasal administration of the signal transduction inhibitor, perillyl alcohol, is a safe, non invasive, low cost and regression of tumor size in some patients is suggestive of antitumor activity.

KEY WORDS: perillyl alcohol, gliomas, intranasal administration.

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