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SNI: Neuro-Oncology

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Original Article

Adjuvant effect of low-carbohydrate diet on outcomes of patients with recurrent glioblastoma under intranasal perillyl alcohol therapy

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Received : 18 July 2020
Accepted : 16 October 2020
Published : 11 November 2020

DOI
10.25259/SNI_445_2020

Quick Response Code:

ABSTRACT

Background: Standard of care for glioblastoma (GB), consisting of cytotoxic chemotherapy, steroids, and high-dose radiation, induces changes in the tumor microenvironment through its effects on glucose availability, which is a determinant for tumor progression (TP). Low-carbohydrate diet (LCD) reduces the glucose levels needed to drive the Warburg effect.

Methods: To investigate LCD's effect on GB therapy, we have begun a clinical trial using LCD as an addition to intranasal perillyl alcohol (POH) for recurrent GB (rGB) patients. This study involved 29 individuals and evaluated, over a period of 1 year, the adjuvant effect of LCD associated with POH therapy in terms of toxicity, extent of peritumoral edema, reduced corticosteroid use, seizure frequency, and overall survival. POH group (n = 14) received solely intranasal POH without specific diet regimen, whereas POH/LCD group (n = 15) received intranasal POH in combination with nutritional intervention. Patients' assessment was based on clinical reviews and magnetic resonance data.

Results: In the 1-year follow-up, the POH/LCD group showed a 4.4-fold decrease in the proportion of patients who needed treatment with corticosteroids, as well as a reduction in tumor size and peritumoral edema, as compared to the POH group. While 75% of patients undergoing POH treatment experienced seizures, this fraction was reduced to 56% in the POH/LCD group. A 2.07-fold increase in the proportion of patients with stable disease, along with a 2.8-fold decrease in the proportion of patients with TP, was seen in the POH/LCD group.

Conclusion: The results presented in this study show that the LCD associated with intranasal POH therapy may represent a viable option as adjunctive therapy for rGB to improve survival without compromising patients' quality of life. Prospective cohort studies are needed to confirm these findings and validate the efficacy of this novel therapeutic strategy.

Keywords: Intranasal administration, Low carbohydrate diet, Perillyl alcohol, Recurrent glioblastoma

INTRODUCTION

Glioblastoma (GB) remains the most common and highly heterogeneous primary brain tumor in adults. Current treatment consists of maximal safe resection when possible, followed by

combination of radiotherapy and adjuvant temozolomide chemotherapy (TMZ).[18] Although standard therapy promotes survival benefits, GB often recurs after 6–9 months of initial treatment with a highly invasive and aggressive tumor phenotype.[1] Aiming to obtain favorable results in the management of recurrent GB (rGB), additional glioma resection, re-irradiation, and/or second-line chemotherapy are available options, although with generally disappointing results in terms of disease control.[23] Thus, for rGB there is no consensus on the therapeutic strategy with improved efficacy.

One of the impediments to the efficacy of conventional treatment for gliomas has been the degree of invasiveness of tumor cells into the surrounding tissue and peritumoral microenvironment.[34] The inflammatory tumor environment produces factors that activate mechanisms of tissue repair. The production of reactive oxygen and nitrogen species by leukocytes and stromal cells often creates a favorable microenvironment that contributes to the attraction of malignant cells into the adjacent tissue.[2] In this respect, it is possible to infer that those GB cells surviving multi-modality therapeutic strategy may shift the cell population profile through inflammatory mediators.[19] Thus, they interact with the host in a way that impacts tumor recurrence and affects the efficacy of subsequent therapies.

In the above context, reprogramming the energy metabolism of the tumor cells and the tumor inflammatory microenvironment[19,20] may provide novel targets to improve therapeutic intervention in the pathogenesis of GB. In view of this, our group has been exploring an innovative therapeutic strategy with intranasal perillyl alcohol (POH), a naturally occurring monoterpene. This compound has been shown to inhibit angiogenesis and to potently modulate reactive oxygen species activity with pleiotropic function[14] for patients with rGB, while showing promising therapeutic outcomes along with low toxicity.[10,11] Evaluation of the available preclinical and clinical data supports the idea that nasal delivery of POH may represent a breakthrough advancement in the fight against rGB.[9-11]

Research on risk factors of cancer has shown the impact of glucose metabolism in the development and growth of GB.[5,6] It is well established that malignant cells are highly dependent on glycolysis for ATP generation, known as the Warburg effect,[15,36] in which withdrawal of glucose results in apoptosis of GB cell lines but not normal human astrocytes.[17] Likewise, a study demonstrated that high glucose levels promoted the proliferation of a human GB cell line.[4]

Published studies have conceptualized that ketogenic metabolic therapy exerts simultaneous action on the energy metabolism of tumor cells, on neoangiogenesis, and on neuroinflammation, thus representing a promising strategy for the treatment of GB and other types of brain tumors.[3,21,22,24,26] Recently, our group suggested that ketogenic diet (KD) associated with intranasal POH may represent a viable option as an adjunct therapy for rGB.[25]

The rationale underlying our efforts to combine KD with POH treatment centers on specific features that are known to originate from cellular endoplasmic reticulum (ER) stress. ER stress represents a cellular mechanism that is based on antagonistic modules, where low stress levels trigger its protective module aimed at re-establishing homeostasis, but where excessive stress turns on its pro-apoptotic module, leading to cell death to protect the organism as a whole. Tumor cells generally are experiencing elevated basal levels of chronic ER stress (due to oxidative stress, acidification, hypoxia, hypoglycemia, etc.) and therefore are more susceptible to killing by treatment conditions that aggravate ER stress even further[19,30] Intriguingly, the ER stress response system has been recognized as a potential therapeutic target in GB[13,21]and related studies have established that POH is able to aggravate ER stress in GB cell lines *in vitro*[9] we, therefore, hypothesized that the combination of two ER stress-inducing treatments (KD: exacerbating tumor hypoglycemia, and POH: further aggravating ER stress) would result in potent tumor cell death. On the other hand, as normal cells ordinarily lack pre-existing chronic ER stress, normal tissue would be less susceptible to the toxic action of this treatment combination and therefore few, or no, major side effects would be expected.

The aim of the present study was to evaluate the adjuvant effect of the low-carbohydrate diet (LCD) on outcomes of patients with rGB under continuous therapy with intranasal POH. The assessment was based on the following parameters: toxicity, extent of peritumoral edema, reduced corticosteroid use, seizure frequency, and overall survival (OS).

MATERIALS AND METHODS

Patient selection and treatment

Prior study approval was provided by the Ethics Committee of the Medical School of the Fluminense Federal University (UFF-CAAE: 14613313.8.0000.5243), according to local legal requirements and with principles laid down in the Declaration of Helsinki. The prospective study was carried out at the Antonio Pedro University Hospital by convenience sampling.

Inclusion criteria at enrollment required adult subjects aged >18 years with rGB on palliative care and under symptomatic treatment after failing to respond to the previous standard treatments, including surgery, and/or radiation, and multimodal chemotherapy specific for GB. Patients had measurable contrast-enhancing tumor on magnetic resonance imaging (MRI) and Karnofsky performance scale of ≥70. Each patient and a next-of-kin signed a written informed consent before enrollment in the clinical trial of

intranasal POH delivery. Patients were followed up for 1 year. To form the two treatment groups, the patients were self-selected: those who wished to adhere to a LCD formed the LCD/POH group, and those who preferred not to adhere to a restricted carbohydrate diet formed the POH group.

Formulation of POH for nasal inhalation delivery was supplied by the Multidisciplinary Laboratory of Pharmaceutical Sciences at Rio de Janeiro Federal University (Rio de Janeiro, Brazil). POH was inhaled 4 times daily (55 mg, 0.3% v/v) totaling 220 mg/day.

Diet details

The anthropometric and biochemical status of each patient was assessed periodically during the study as part of the clinical laboratory routine assessment. Patients of the LCD/POH group received LCD for 1 year. LCD was prescribed according to the following distribution: energy (25–30 kcal/kg); protein 1.5 g/kg of body weight; and 30–35% of total calories from carbohydrate (up to 130 g/day),[13] approximately 55% from lipids; cholesterol ≤200 mg/day and fiber (20–30 g/day). All patients received B-complex vitamins and minerals to maintain nutrients and clinical laboratory values under normal parameters. This level of carbohydrate restriction did produce nutritional ketosis.

To verify nutritional ketosis, participants received urinalysis strips with instructions for use, and they performed measurements 3 times a week with results being reported weekly to researchers. The level of ketone bodies (5–15 mg/dL) in the urine confirmed patients' adherence to LCD and a slight increase of urinary ketone bodies. Although the hallmark of nutritional ketosis is the level of ketosis in the blood, a non-invasive method (urinary ketone test strips) was chosen. This was out of necessity because measuring urinary ketones at home was the only possible way for most patients to participate in this part of the study.

Assessment of outcome: tumor size, peritumoral edema, and OS

MR images and updated clinical records were reviewed for all patients. Image examinations were performed at a range of institutions using a 1.5 Tesla MR scanner with a brain coil device. All examinations were included in the complete routine for MR evaluation with multiplane T1W acquisitions prior and subsequent to the venous administration of paramagnetic contrast with volumetric series in 3D, T2, T2/fluid-attenuated inversion recovery (FLAIR), diffusion, and susceptibility-weighted imaging. MR proton spectroscopy and MR perfusion were also performed, and MR images were analyzed by two radiologists with expertise in neuroradiology. A consensus diagnosis was established using a workstation with a picture archiving and communication system at the time of diagnosis and for follow-up data. The image analysis focused on the following characteristics: lesion distribution and volume, signal intensity and T2/FLAIR image characteristics, peritumoral edema, diffusion restriction patterns, and contrast enhancement. Evaluation of tumor response was based on RANO (Response Assessment in Neuro-Oncology) criteria for high-grade gliomas.

Statistical analysis

Kaplan-Meier and log-rank test were selected to evaluate patients' evolution, where events for consideration included disease progression and death. SPSS 20.0 software was employed for this analysis.

RESULTS

Demographic data

The cohort included 29 patients with rGB and the following distribution: 17 (58.6%) male with a median 50 years of age (range: 28–65 years); and 12 (41.4%) female with a median 50.5 years of age (range: 27–61 years). Fifteen patients formed the LCD/POH group (8 males; 58.3%). The POH group included 14 patients (9 males; 64.3%).

Survival profile

Kaplan–Meier survival plot during the 1-year follow-up period showed that near the 3rd month rGB subjects in the LCD/POH group had a better evolution in comparison to the POH group, although the log rank statistical test did not provide statistical significance between the two groups ($P = 0.232$; Graph 1).

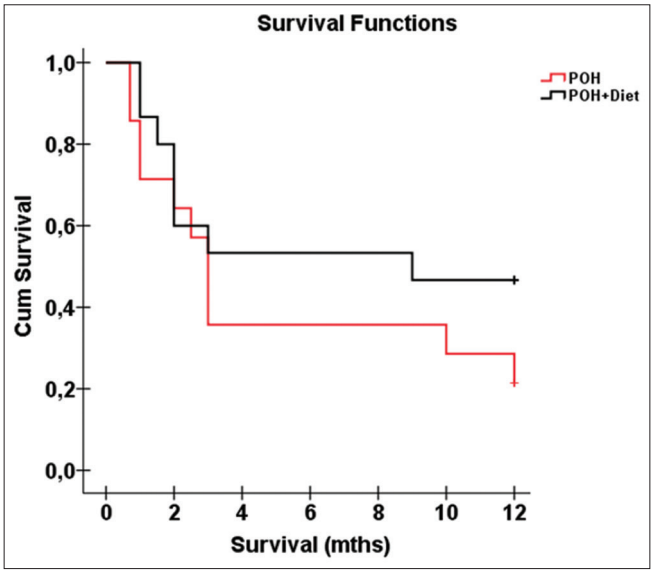
Disease course according to interventional strategies

After 1 year of follow-up, the disease course was documented. Among the 15 patients in the LCD/POH group, seven (46.6%) showed stable disease (SD), two (13.3%) showed tumor progression (TP), and six (40%) deceased. Among the 14 patients in the POH group, SD was observed in three (21.4%), TP was verified in five (35.7%), and six (42.9%) succumbed to disease. It was also noticed that 46.6% ($n = 7$) of patients in the LCD/POH group showed a 2.17-fold increase in the proportion of SD, compared to 21.4% ($n = 3$) of the POH group. Conversely, the proportion of patients with TP ($n = 2$) in the LCD/POH group was 2.81-fold decreased when compared to the POH group ($n = 5$) [Graph 2]

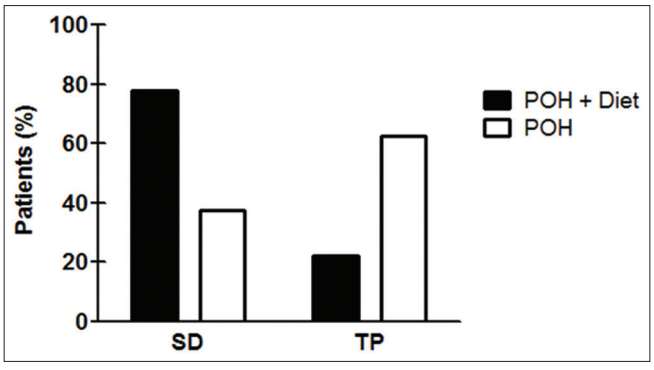
Corticosteroid requirement and seizure frequency in treatment groups

Treatment with high-dose corticosteroids is often required to minimize development of cerebral edema as the main

life-threatening complication for rGB patients. In our study, combined POH and LCD decreased the necessity for high-dose steroid treatment, and as a result rGB patients received just maintenance doses. At the time of initial recurrence, that is, at the onset of our study, therapy with high-dose dexamethasone (16 mg/day) was not significantly different between the two groups. However, 3 months after the initiation of our study, the requirement for dexamethasone sharply decreased (to 8 mg/day) in 33.3% (n = 5) patients in the LCD/POH group, as compared to 7.14% (n = 1) patients in the POH group. Thus, there was a 4.66 times greater dose-reduction benefit in the group of patients undergoing LCD/POH combination treatment. Such patients further showed improvement of clinical status and a reduction of tumor size and peritumoral edema based on MRI, although not all patients responded favorably [Figure 1; Tables 1 and 2].



Graph 1: Kaplan–Meier graphical plots of perillyl alcohol (POH)+Diet group (black line) show a tendency (P = 0.232) for higher survival probability of recurrent glioblastoma patients compared to POH control groups (red line) especially after the 3rd month of intervention onward.



Graph 2: Effect of the diet in recurrent glioblastoma (rGB) patients under perillyl alcohol (POH) therapy. Compared to POH group with only intranasal POH therapy, LCD/POH group caused a 2.07-fold increase in the proportion of patients with stable disease and 2.81-fold reduction in the proportion of rGB patients with tumor progression.

In our previous clinical studies, we observed that neurological deficits (51%) were the main complaint of rGB patients, including headache (43%) and seizures (24%).[24] Regarding reduction in seizure frequency, by the end of this study at 1 year, we observed that 44.4% (n = 4) rGB patients of the LCD/POH group did not present any clinical evidence of seizures, as compared to 25% (n = 2) of rGB patients in the POH group. Such findings reveal a 1.8-fold decrease in the frequency of seizures in the LCD/POH group compared to the POH group [Tables 1 and 2].

DISCUSSION

The present study was conducted to assess during a 1-year follow-up the effect of a low carbohydrate diet concomitant with intranasal POH for rGB patients. It showed that this strategy: (a) Reduced seizure frequency; (b) decreased the proportion of patients who required corticosteroid treatment; (c) reduced tumor size and peritumoral edema;

Table 1: Characteristics of patients with stable disease in the LCD/POH group.

Patient	Gender/ age	Seizure as initial symptom	Reduction in seizure frequency	Reduction in corticosteroid requirement
1	M/54	Yes	Yes	Yes
2	F/55	Yes	Yes	Yes
3	F/36	No	-	Yes
4	M/53	No	-	No
5	F/51	Yes	Yes	Yes
6	M/31	Yes	Yes	Yes
7	M/53	No	-	No
8	F/47	No	-	No
9	F/61	No	-	No

Table 2: Characteristics of patients with stable disease in the POH group.

Patient	Gender/ age	Seizure as initial symptom	Reduction in seizure frequency	Reduction in corticosteroid requirement
1	M/47	Yes	Yes	Yes
2	M/51	No	No	No
3	M/55	No	No	No
4	M/49	Yes	No	No
5	F/50	No	No	No
6	M/28	Yes	Yes	No
7	F/27	No	No	No
8	M/28	No	No	No

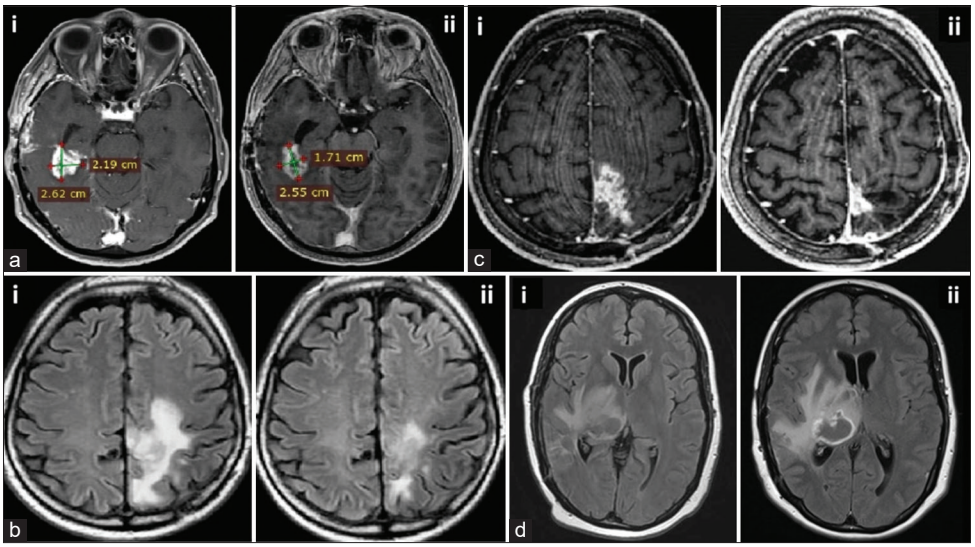


Figure 1: Magnetic resonance imaging (MRIs) of representative patients before and after treatment. (a-d) shows MRIs from four different patients (all treated with intranasal perillyl alcohol concomitant with low-carbohydrate diet) that were taken before (left image labeled "i") and after (right image labeled "ii") treatment. (a) MRI scan after 12 months of treatment (ii) shows 24% reduction of tumor size (4.36 cm^2 total area) as compared to the image obtained before the treatment (5.74 cm^2, i). (b and c) Additional examples of patients responding favorably to treatment, with reduction in tumor size after treatment (ii) as compared to the MRIs before treatment (i). (d) Example of patient not responding to treatment. First image (i; axial FLAIR) shows an expansive oval, isointense lesion in the right thalamus, with perilesional edema, causing a mass effect with distortion of the posterior horn of the right lateral ventricle, and slight compression of the third ventricle. Four months later, axial FLAIR (ii) shows irregular enhancement, indicating lack of response to treatment.

and (d) improved clinical condition with further beneficial outcomes for rGB patients. These promising results are encouraging because currently available protocols for rGB are associated with reduced OS and worsened quality of life, failing to achieve meaningful results in clinical trials.[27]

rGB represents the greatest challenge for neuro-oncological practice. Current treatments lack effective protocols for therapeutic conduct and have a propensity for high rate of complications. Indeed, several agents used for the treatment of rGB alone or in combination, failed to achieve meaningful results in clinical trials.[12] Trials that have used external beam radiotherapy for re-irradiation with concurrent chemotherapeutic drugs, such as temozolomide, resulted in overall median survival ofrGB patients of about 8 months.[29] Moreover, randomized controlled trials with bevacizumab combined with chemotherapy and single-agent therapy as treatment for rGB showed significantly improved progression-free survival compared to single-agent therapy. A recent meta-analysis of clinical trials with bevacizumab, either alone or in combination with other agents, showed median OS of 7.7-12.6 months for bevacizumab alone, and 6.9–12 months for bevacizumab in combination with chemotherapy. It concluded that bevacizumab did not prolong OS, but could lead to higher odds of adverse events.[8]

The present study was conducted to assess toxicity, as well as aspects of quality of life, in rGB patients under continuous intranasal POH therapy with concomitant tumor metabolism-targeted diet over a 1-year period. We observed an early two-fold increment in the proportion of rGB patients with SD, and nearly three-fold decrease in the proportion of TP among patients with POH+LCD, when compared to POH inhalation therapy alone. Such findings suggest an adjuvant effect of LCD combined with inhaled POH on halting TP.

While consistent adherence to the LCD can become a limiting factor over an extended period of time, the reduction in steroid dose and lower frequency of seizures generally contributes to the improvement of quality of life.[24,26] Kaplan–Meier plot of LCD/POH group showed an increased probability of survival when compared to POH group with single inhaled therapy [Graph 1], especially from around the 3rd month of intervention onward. However, this difference was not statistically significant by log-rank statistical analysis ($P = 0.232$), perhaps due to small sample size. It emphasizes a notable limitation of this present report, namely, its small sample size. Clearly, a greater number of patients will need to be recruited into follow-up studies, to validate these preliminary results. At this point, conclusions about any effects of this combination therapy on survival need to be viewed cautiously, although so far the observed trend appears encouraging.

Of note, we observed that rGB patients with reduced requirements for high corticosteroid therapy and anticonvulsant drugs had SD and low morbidity with improved clinical condition, mainly due to the absence of

treatment-related toxicities. In fact, intranasal POH+LCD halted TP, with almost 24% of tumor area reduction during 1-year of therapy adherence [Figure 1], without evidence of seizures. This is of interest, because seizures as the presenting symptom of GB are known to influence OS in adults younger than 60 years.[28]

Frequently, rGB patients present with deficits in brain areas controlling executive functioning and coordination, which impacts quality of life and requires costly integral home assistance. There is limited information on the humanistic burden among rGB patients; we, therefore, established parameters related to general improvement of conditions associated with reduced corticosteroid requirement and frequency of seizures as a reflection of overall quality of life.[9] In addition, we further observed less reports of anxiety among rGB patients under the effect of dietary intervention. Interestingly, rGB patients that adhered to POH+LCD maintained a strict dietary regimen, suggesting that this therapeutic strategy not only increased the survival but also extended the length of patients' independence. Clinical studies have reported that seizure prophylaxis prolonged survival of GB patients treated with anti-epileptic drugs.[35,37] We previously observed that such therapeutic strategies reduced peritumoral edema and the frequency of seizures, and concomitantly improved patients' quality of life.[9] The presence of peritumoral edema contributes to rGB symptoms and possibly plays a role in the morbidity and invasive potential of malignant gliomas.[9,30] Hence, the interaction between glioma cells and the cerebral microenvironment influences the malignant behavior and ultimately the prognosis. In our study, reduction of peritumoral edema in MR images was also a parameter for reduction of corticosteroid administration among rGB patients with SD after 1 year. The results obtained from tumor metabolism-targeted diet concomitant with POH inhalation (POH+LCD) reduced cerebral edema and seizures, which may be a criterion of quality of life measurement among rGB patients.[33]

In consonance with our results, preclinical models have shown glioma growth inhibition with low carbohydrate diet.[7] Overall, the results of the present study are encouraging. They showed that the LCD associated with intranasal POH therapy may represent a viable option as adjunctive therapy for rGB to improve survival without compromising patients' quality of life. We suggest the initiation of prospective cohort studies to validate the efficacy of this novel therapeutic strategy.

Acknowledgments

We thank the support given by the Clinical Research Unit (UPC/HUAP) providing the appropriate structure for patient care. JSG and GMF were affiliated with PhD postgraduate programs Ciencias Medicas (JSG), and Neurologia (GMF) of the Faculty of Medicine at the Universidade Federal Fluminense.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

This work was supported by Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro under Grant (E-26/110.329/2011; E-26/110.948/2013); FundaçãoEuclides da Cunha (FEC 3662 – Contract UFF 055/2015), and Coordenação de Aperfeiçoamento de Pessoal do Ensino Superior (CAPES) providing scholarship.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: da Fonseca C, Santos JG, Faria G, Da Cruz Souza Da Cruz W, Fontes CA, Schonthal AH, *et al*. Adjuvant effect of low-carbohydrate diet on outcomes of patients with recurrent glioblastoma under intranasal perillyl alcohol therapy. Surg Neurol Int 2020;11:389.