Perillyl alcohol inhalation concomitant with oral temozolomide halts progression of recurrent inoperable glioblastoma: a case report

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Abstract

Aim: Glioblastoma multiforme (GBM), the most common and lethal primary brain tumor in adults, inevitably recurs despite standard of care, consisting of surgical resection, radiotherapy (RT), and alkylating temozolomide (TMZ). High content of the repair enzyme MGMT (O\textsubscript{6}-methylguanine-DNA methyltransferase) contributes to drug resistance and tumor recurrence. The monoterpene perillyl alcohol (POH) induces apoptosis and cytotoxicity of TMZ-resistant and TMZ-sensitive glioma cells independently of MGMT expression.

Case presentation: We report the case of an adult patient with non-resected inoperable recurrent GBM that was successfully treated with POH inhalation in combination with oral TMZ, after failing to respond to standard treatment. A 51-year-old white woman with a sudden, intense and refractory headache with no underlying cause showed brain image (MRI) with diffusely infiltrating lesion, prominent edema, and marked mass effect with midline shift, consistent with inoperable high-grade malignant glioma in the right temporal lobe. A complex histological feature, characterized by ischemic necrosis and glomeruloid microvascular proliferation, confirmed the diagnosis of malignant glioma. Immunohistochemical evaluation showed marked EGFR (epidermal growth factor receptor) staining; active proliferative status was confirmed by high Ki67 and p21 expression; there was strong p53 tumor suppressor labeling but faint cytoplasmic PTEN staining; expression of MLH1 and MSH6, two proteins associated with mismatch DNA repair and resistance to TMZ, was elevated. Indeed, 6 months after onset and despite specific treatment (RT+TMZ), this patient had tumor recurrence at same site. She developed adverse reactions including thrombocytopenia and resistance to alkylating TMZ, and was indicated for palliative treatment. The patient was then enrolled (December 2012) in the clinical trial for treatment with POH inhalation concomitant with 300 mg TMZ oral schedule during 5 days. MRI scans performed 3, 7, 12 and 24 months later (December 2012 to December 2014) revealed marked reduction of enhancing lesion without further recurrences.

Conclusion: Despite increased expression of DNA repair proteins supporting drug resistance, combined POH+TMZ therapy reduced tumor mass, halted tumor recurrence, and increased patient’s survival. This case highlights the therapeutic efficacy of combined POH intranasal administration with systemic TMZ in a patient with non-resected inoperable GBM, who failed prior therapy and was under supportive treatment.

Keywords: Perillyl alcohol, intranasal administration, glioblastoma multiforme, combination therapy, temozolomide, drug resistance
therapy consisting of radiation therapy (RT) and chemotherapy, followed by combined radio-chemotherapy with alkylating drugs to destroy residual tumor cells [1-3]. The alkylating agent temozolomide (TMZ) is able to bypass the blood-brain barrier (BBB) and has become the gold standard chemotherapy for glioblastoma [4]. Failure to treatment is mainly related to indefinite borders of the lesion with unnoticed tumor cell infiltration and extensive neoangiogenesis into the surrounding tissue, preventing accurate complete surgical removal. A better prognosis is associated with younger age, extensive surgical resection, and efficient response to TMZ and RT. Yet, there is no ordinary treatment for tumor recurrence after patients’ failure to respond to combined radio-chemotherapy. Further progression to a poor outcome within a few months [1] could be partly related to the content of highly tumorigenic, radioresistant glioma stem cell that differs between tumors with the same histological type [5].

Particularly important in GBM is the methylation status of cellular DNA repair protein O6-methylguanine-DNA methyltransferase (MGMT) that removes mutagenic alkylating adducts from the O6-position of guanine, thereby causing resistance to alkylating drugs [6,7]. TMZ and other alkylating agents modify the O6-position in guanines, thus forming critical DNA cross-link lesions that arrest cell proliferation. Methylation of the promoter silences the MGMT gene, and this is a predictive factor for therapy response and survival of GBM patients treated with TMZ and RT [8]. Once GBM patients become resistant to TMZ, there are very limited treatment options available. Besides, glioma cells often present multiple gene mutations, oncogene activation, and/or loss of tumor suppressor genes required for encoding proteins critical in signal transduction pathways. Indeed, Ras-RAF-ERK hyperactivity due to increased activity of EGFR and PDGFR upstream regulators is essential for maintenance of glioma cells [9-11]. Moreover, amplification of the EGFR gene results in overexpression of the transmembrane tyrosine kinase EGFR and its EGFRvIII variant, which is characterized by a truncated extracellular domain with ligand-independent constitutive activity [12]. Therefore a pharmacological-based therapy with the monoterpene perillyl alcohol (POH), which inhibits FTase (farnesyl transferase) activity [10,13] and Ras/mTOR signaling pathways, but induces cytotoxicity in TMZ-resistant and TMZ-sensitive glioma cells independently of MGMT expression, may be a suitable approach limiting glioma cell proliferation [14-16]. POH is a naturally occurring monoterpene that exerts significant antitumor activity and has been used orally in several clinical trials [17-19]. However, when administered orally, POH therapy is associated with dose-limiting adverse effects. Standard chemotherapeutic protocols for brain tumors are frequently inefficient, mostly due to the inability of drugs to reach and maintain effective concentrations within the brain tissue for an appropriate length of time [20,21].

The intranasal route provides a practical, noninvasive method for transportation of lipophilic and apolar drugs straight to the central nervous system (CNS), thus bypassing the BBB, minimizing systemic exposure, and dramatically reducing adverse side effects [20-23]. The role of the olfactory epithelium as a gateway for substances entering the CNS lead us to develop a novel and ground-breaking methodology for POH delivery to treat patients with malignant brain tumors [22,23]. Long-term administration of POH as a single agent by inhalation treatment of patients with recurrent malignant glioma substantially increased survival rate with virtually no adverse side effects. Inasmuch radiation-induced injury creates a favorable niche for proliferation of highly tumorigenic radioresistant glioma stem cell clusters associated with perivascular and/or necrotic regions, independently of the patient’s MGMT and p53 status [24], it was important to assess the therapeutic efficacy of combined POH intranasal administration with systemic TMZ in a patient with inoperable GBM, who had failed prior standard of care therapy and was under supportive treatment.

Case presentation

The present study was approved by the University Hospital Ethics Committee and the Brazilian Ministry of Health (CONEP 9681 no. 124 25000.009267/2004-25), and was carried out in the Hospital Medical School of the Fluminense Federal University. Before inclusion in the protocol, the patient signed a written informed consent to enroll in the Phase I/II clinical trial. POH was formulated for inhalation delivery and the preparation supplied by the Multidisciplinary Laboratory of Pharmaceutical Sciences at Rio de Janeiro Federal University, according to US Patent Application 20040087651 May 6, 2004, and BR Patent Number PI0107262-5. POH (55 mg; 0.3% v/v) was administered by inhalation 4 times daily, totaling 266.8 mg/daily.

A 51-year-old white woman, with no significant past medical record and without family history of brain tumor or neurological disease, complained of sudden and intense headache that did not improve with analgesics. The patient was then referred to the neurological emergency outpatient unit (April 2012), where magnetic resonance imaging (MRI) of the brain with and without contrast (Figure 1) revealed a highly infiltrating lesion in the right temporal lobe that enhanced with gadolinium. The large irregular space-occupying lesion with prominent edema and marked mass effect with midline shift was consistent with a diffuse high-grade malignant tumor in the right temporal lobe. The tumor was considered as non-resected GBM meaning that could not be surgically removed without risking extensive neurological damage. Therefore patient underwent a stereotactic needle biopsy and histological analysis carried out by three different pathologists, further confirming the diagnostic of malignant glioma (GBM). The tumor lesion presented hy-percellularity with marked nuclear atypia/pleomorphism, hypercromatic nuclei (Figure 2A), hemorrhage, ischemic necrosis and microvascular proliferation (Figure 2B), with tumor cells showing intense EGFR (epidermal growth factor receptor)
staining (Figure 2C). Further immunohistochemical analysis showed features (Figure 3) indicating that glioma cells had active proliferative status, characterized by high Ki67 (Figure 3A) and p21 (Figure 3B) expression; furthermore, there was high tumor suppressor p53 (Figure 3C) but faint cytoplasmic PTEN (Figure 3D) staining. In addition, glioma cells also showed strong staining for MLH1 (Figure 3E) and MSH6 (Figure 3F) mismatch DNA repair proteins. Such pattern was characteristic of hypoxic conditions (e.g., ischemic necrosis), where PTEN and p53 work in tandem to induce maspin, a tumor suppressor protein involved in sensitizing cells to chemotherapy [25].

From May to July 2012, the patient received radiation therapy (59.4 Gy total) concomitant with TMZ (150-200 mg/m²/day) chemotherapy on a 28-day cycle schedule. This combined therapy (RT+TMZ) reduced tumor mass (Figure 4A), but did not cause any further changes on brain MRI taken few months later (Figure 4B). Indeed, 6 months later (October 2012), a new brain MRI revealed tumor recurrence, showing a large and infiltrative lesion in the right temporal lobe (Figure 5A). Patient then started additional TMZ (150-200 mg/m²/day) cycle, but treatment had to be discontinued (November 2012)
Figure 3. Pattern of immunohistochemical staining for (A) Ki67, (B) p21, (C) wild-type p53, (D) PTEN, (E) proteins associated with mismatch DNA repair genes MLH1, (F) MSH6 in formalin-fixed paraffin embedded biopsy tumor lesion. Arrows show positive staining. x400; Scale bar 100 µm.

Figure 4. (A). Combined therapy (RT-TMZ) reduced tumor mass. (B). Did not cause any further changes on brain MRI taken few months later.

Figure 5. MRI shows tumor recurrence 6 months (December/2012) after RT-TMZ (A) with large and infiltrative lesion in the right temporal lobe, and reduction of tumor lesion (B) in July/2013 after combined POH-TMZ treatment.

due to side effects with adverse reactions (nausea, vomiting, headache), thrombocytopenia (43,000/mm³) but not neutropenia or altered hepatic function. At that time, patient was considered out of therapeutic possibilities and indicated for supportive (palliative) treatment. Subsequently (December 2012), the patient was enrolled in the Phase I/II clinical trial for treatment with POH inhalation concomitant with 300 mg TMZ oral schedule during 5 days, because she had normalized platelets count (350,000/mm³) without evidence of myelosuppression (red blood cells 4.7 million/mm³; leukocyte count 7,980/mm³). Since then, combined POH+TMZ treatment has efficiently reduced tumor size (Figure 5B) and improved clinical condition without any neurological symptoms related to tumor recurrence or clinical adverse effects to treatment. From December 2012 up to now (December 2014), the patient has remained in good health under exclusive POH inhalation therapy combined with TMZ schedule, without any evidence of tumor recurrence, and only taking anti-seizure medication but no stertoidal drugs. Recent clinical laboratory analysis showed hematologic and biochemical parameters within normal range values, without any signs of neurologic, hepatic and renal toxicity or clinical adverse effects.

Discussion

GBM is an aggressive heterogeneous brain tumor in adults with distinct histologic and molecularly features accordingly to their presumed cell of origin and extent of brain infiltration [26,27]. Its dismal prognosis is partly due to increased angiogenesis and altered brain microvascular permeability leading to extensive vasogenic peritumoral edema. The novelty in this report relates to the efficacy of combined POH+TMZ treatment in a patient with recurrent inoperable malignant glioma. At the onset, histological analysis of the tumor lesion showed pleomorphism with increased mitotic activity, pseudopalisading necrosis and microvascular proliferation. Marked EGFR expression confirmed the characteristic of highly malignant glioma. Additionally, EGFR amplification, high p53 but weak PTEN cytoplasmic staining, was a pattern characteristic of hypoxic conditions associated with ischemic necrosis [25]. Moreover, high MLH1 and MSH6 staining of proteins associated with
Mismatch DNA repair processes, which was present at the onset of disease, was a predictive factor partly responsible for resistance to TMZ alkylating chemotherapy and this patient's successive recurrence [6,7,14].

Standard treatment of malignant glioma with maximal surgical resection, followed by RT and concomitant adjuvant cytotoxic DNA alkylating drugs, is limited due to adverse side effects, and to date lacks curative potential. Moreover, combined RT and TMZ treatment may select a relatively quiescent subset of glioma stem cells responsible for sustaining the production of highly proliferative tumor cells [28] ensuing relapse or progression, and resulting in 3 to 9 months overall survival range [2]. GBM recurrence and drug resistance is associated with modification of enzymes, non-coding RNAs and cell mutations in different cell types from the original glioma cell [27,29]. The occurrence of treatment resistance for GBM patients is frequently associated to the overexpression of MGMT (O6-methylguanine DNA methyltransferase), a DNA repair protein that removes alkyl groups located at the O6-position of guanine [30-32], but loss of the transcription factor GATA4, a negative regulator of normal astrocyte proliferation, may also trigger glioma formation due to promoter hypermethylation and/or induction of novel somatic mutations [33]. Indeed, elevated levels of alkyl purine DNA glycosylase (APNG) other DNA base excision repair enzyme that directly repairs alkylated bases at N7 guanine and N3 adenine is associated with poor overall survival [33].

In the phase I/II clinical trials conducted by our group in adult glioma patients, the 6.3 mg/kg POH dosage administered by intranasal route on a long-term basis was safe, reduced tumor growth, and caused significant increase in overall survival of patients with recurrent malignant glioma [23]. Herein we report the efficacy of combined and prolonged POH+TMZ treatment for non-resected recurrent, inoperable GBM that had failed previous standard therapy. POH is an effective radio- and chemosensitizer [34] that arrests glioma cells in G2/M phase of the cell cycle, up-regulates the pro-apoptotic Bax protein, presents anti-angiogenic properties [35], and also exerts cytotoxicity to TMZ-resistant and TMZ-sensitive glioma cells independently of O6-methylguanine-DNA methyltransferase (MGMT) expression [14,36]. In addition to anti-angiogenic and antioxidant activities, POH markedly suppress proinflammatory cytokine production and NFK-B activation that strongly intensify neuroinflammation and cell damage [37], and further mediates neuroprotection in the experimental model of ischemia-reperfusion [36]. The mechanisms of radiation-induced injury are not yet understood, although radionecrosis is a continuous process associated with endothelial cell dysfunction due to tissue hypoxia and necrosis, with concomitant release of proangiogenic factors inducing vasogenic edema and progressive BBB dysfunction [2]. Besides, hypoxic conditions induced by radiation most likely enhanced cellular features rendering glioma stem cells resistant to treatment [24]. Moreover, increased proliferative state and extensive necrosis activated an angiogenic switch characterized by marked EGFR wild-type expression and signaling, and production of proangiogenic factors by both glial tumor and stromal cells. Regardless of increased expression of DNA repair proteins that are known to contribute to TMZ resistance, combined POH+TMZ was capable of reducing tumor mass, halting tumor recurrence, and increasing patient's survival. Such strategy may be a suitable therapeutic approach for the treatment of MGMT-positive glioma patients.

Conclusion
The main obstacle in effective treatment of malignant gliomas is the restricted drug access to the intracranial tumor site partly related to the drugs' molecular weight and presence of polar functional groups. Herein we demonstrate the efficacy of combined POH+TMZ treatment in a patient with recurrent non-resected inoperable malignant glioma. Regardless of existing resistance to TMZ alkylating drug, this novel therapeutic strategy reduced tumor invasion and discontinued further tumor recurrences for more than 24 months without obvious toxic side effects. Development of hybrid molecules containing the monoterpene POH as a carrier conjugated to conventional drugs may be a promising new therapy to treat brain tumors, and preliminary preclinical studies with POH covalently conjugated to TMZ have revealed promising outcomes [30].

List of abbreviations
GBM: Glioblastoma multiforme
POH: Perillyl alcohol
TMZ: Temozolomide
RT: Radiotherapy
MGMT: O6-methylguanine-DNA methyltransferase

Competing interests
The authors declare that they have no competing interests.

Authors' contributions

| Authors' contributions | COD | IPS | DSC | SR | LC | TQ |
|------------------------|-----|-----|-----|----|----|----|
| Research concept and design | ✓   | --  | --  | -- | -- | ✓  |
| Collection and/or assembly of data | ✓   | ✓   | ✓   | ✓  | ✓  | ✓  |
| Data analysis and interpretation | ✓   | ✓   | --  | ✓  | ✓  | ✓  |
| Writing the article | ✓   | --  | --  | -- | -- | ✓  |
| Critical revision of the article | ✓   | --  | --  | -- | -- | ✓  |
| Final approval of article | ✓   | ✓   | ✓   | ✓  | ✓  | ✓  |
| Statistical analysis | --  | --  | --  | -- | -- | -- |

Acknowledgement and funding
The authors thank Dr Roberto Toledo for helpful discussion and Dr Axel H. Schönthal from University of Southern California, USA for critical reading and linguistic improvement of the manuscript. This study was supported in part by grants from National Council Research (MCT/CNPq/CT-Saude 401943/2010-0; CNPq/Universal 481059/2011-3), Rio de Janeiro Research Foundation (FAPERJ: E-26/110.329/2011; E-26/110.948/2013), FOPESQ-UFF, and Euclides da Cunha Foundation-UFF.
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Citation:
Da Fonseca CO, Soares IP, Clemençon DS, Rochlin S, Cardeman I and Quirico-Santos T. Perillyl alcohol inhalation concomitant with oral temozolomide halts progression of recurrent inoperable glioblastoma: a case report. J Histol Histopathol. 2015; 2:12. http://dx.doi.org/10.7243/2055-091X-2-12