

# Medical Cannabis, Melatonin and Oxygen-Ozone as Integrative Therapies for the Treatment of Anaplastic Astrocytoma: A Case Report

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## Abstract

Astrocytoma is a brain tumor that is well known for its aggressiveness and limited survival rate. Standard medical treatments include chemotherapy, radiotherapy and surgery, but their use is associated with several long-term adverse effects. As a result, many patients are forced to interrupt their cure or to worsen their quality of life. Among the alternative therapies available to cancer patients, the combination of Melatonin (MLT), medical cannabis, and Oxygen-Ozone (O<sub>2</sub>O<sub>3</sub>) therapy has several advantages, both during and after the standard treatment course. In May 2017, after speech disorders and motor deficits in the right upper limb appeared in a 48-year-old Italian woman, Magnetic Resonance Imaging (MRI) was performed. An expansive lesion in the cortico-subcortical brain area was detected and an isocitrate dehydrogenase 1-wild-type- diffuse anaplastic astrocytoma was diagnosed. From September to November 2017, the patient underwent the first cycle of Radio Therapy (RT) and Chemo Therapy (CT). In January 2018, the patient started O<sub>2</sub>O<sub>3</sub> therapy. In July 2018, therapy was implemented with MLT and medical cannabis. In December 2018, the patient completed CT and RT but continued receiving this integrative therapy. In February 2019, a pet scan revealed no metabolically active disease in the brain and follow-up magnetic resonance imaging revealed that the lesion remained stable. After six years of integrative treatments, subsequent magnetic resonance imaging confirmed the stability of the tumor mass. This case report highlights the beneficial effects and long-term acceptability of an adjuvant therapy of medical cannabis, MLT and O<sub>2</sub>O<sub>3</sub> in a clinical context characterized by serious difficulties in approaching a standard protocol. Following several studies in which the anti-tumoral potentials of MLT, medical cannabis and O<sub>2</sub>O<sub>3</sub> therapy have been observed separately, the positive results observed in this case report may represent another step toward obtaining more innovative and less debilitating therapeutic options.

**Keywords:** Anaplastic astrocytoma; Medical cannabis; Melatonin; Oxygen-ozone therapy; Case report

## Abbreviations

ATRX: Telomere Binding Proteins Alpha Thalassemia/Mental Retardation Syndrome X-Linked; CBD: Cannabidiol; CT: Chemotherapy; HIF-1: Hypoxia-Inducible Factor1; IDH1: Isocitrate Dehydrogenase1; IDH2: Isocitrate Dehydrogenase (NADP(+)) 2; GBM: Glioblastoma Multiforme; GPCRs: G-Protein-Coupled Receptors; IGRT/IMRT: Intensity-Modulated and Image-Guided Radiation Technique; MLT: Melatonin; MMP2: Matrix Metalloproteinase; MRI: Magnetic Resonance Imaging; NADPH: Nicotinamide Adenine Dinucleotide Phosphate Hydrogen; NFkB/iNOS: Nuclear Factor-kB/Inducible Nitric Oxide Synthase; NHL: Large-Cell Non-Hodgkin Lymphoma; O<sub>2</sub>O<sub>3</sub>: Oxygen-Ozone; PET: Positron Emission Tomography; PI3K/AKT: Phosphatidylinositol 3-Kinase/Protein Kinase B; RCHOP: Rituximab, Cyclophosphamide, Doxorubicin Hydrochloride (Hydroxydaunorubicin), Vincristine Sulfate (Oncovin), Prednisone; ROS: Reactive Oxygen Species Relative Risk; RR: Relative Risk; RT: Radiation Therapy; TFEB: Transcription Factor EB; THC: Delta-9-Tetrahydrocannabinol; TMZ: Temozolomide; TP53: Suppressor Protein 53; WHO: World Health Organization

## Introduction

Astrocytoma is an aggressive, hormone-sensitive brain tumor that originates from astrocytes [1]. It has an incidence rate of 0.48 per 100,000 people [2] and it is characterized by poor diagnosis and limited survival rates, with a significantly higher incidence in females than in males (ratio 4:1) [1,3]. Starting in 2021, the World Health Organization (WHO) identified four types of astrocytomas, ranging from Grade I to Grade IV, based on genetic, morphological and clinical aspects [4]. Among these, Grade III, or anaplastic astrocytoma, is characterized by invasiveness and fast growth. The specific causes of its occurrence have not yet been clarified, but exposure to chemical agents or ionizing radiation or Mendelian disorders, including neurofibromatosis, tuberous sclerosis and Li-Fraumeni syndrome, is thought to play a significant role in astrocytoma emergence and development [1,5]. From a genetic perspective, anaplastic astrocytoma is characterized by genetic mutations, including mutations in isocitrate De Hydrogenase 1 (IDH1) enzymes, the telomere-binding protein Alpha Thalassemia/Mental Retardation Syndrome X-Linked (ATRX) and the Tumor Suppressor Protein 53 (TP53) [6]. Interestingly, anaplastic astrocytoma with the IDH wild-type form is linked to a negative prognosis and TP53/ATRX mutations contribute to uncontrolled cellular proliferation and increased tumor aggressiveness [3,7].

Currently, the standard treatment protocol for patients with astrocytoma involves surgical resection when feasible, followed by Radiation Therapy (RT) and concurrent Chemotherapy (CT) using procarbazine, lomustine, vincristine, or Temozolomide (TMZ) [8]. Despite these established protocols, the treatment of anaplastic astrocytoma continues to pose significant clinical challenges, with a median survival time of 2-3 years [9]. Targeting approaches such as IDH1 or isocitrate De Hydrogenase 2 (IDH2) inhibitors (e.g., ipilimumab, nivolumab, and pembrolizumab) are being tested in clinical trials as new therapeutic options for treating astrocytoma [10]. Another important area of exploration involves the use of adjuvant therapies, including the protagonists described in this report. The Oxygen-Ozone ( $O_2O_3$ ) therapy as integrative therapies in reduction of pain, improvement of physical function, reduction of inflammation and infection was reported [11]. It has several mechanisms of action that may support its inclusion in cancer therapies. First,  $O_2O_3$  induces oxidative damage to cell membranes by targeting fatty acids and consequently, generating Reactive Oxygen Species (ROS), such as hydroperoxides and aldehydes. While antioxidant enzymes partially counteract this damage, insufficient Nicotinamide Adenine Dinucleotide Phosphate Hydrogen (NADPH), which is commonly observed in cancer, exacerbates oxidative stress, resulting in cellular damage and the activation of signaling pathways [12]. Second,  $O_2O_3$  therapy induces the activation of antitumor T lymphocytes and natural killer cells, enhancing the efficacy of RT and chemotherapeutic agents [13]. Last, studies have suggested that  $O_2O_3$  therapy can mitigate CT-induced side effects, such as nausea, hair loss and fatigue [14]. Melatonin (MLT), or N-acetyl-5-methoxytryptamine, is an endogenous hormone produced by the pineal gland in response to light [15]. As well

documented by several studies, its therapeutic role is supported by its anticancer, immunostimulant and antioxidant properties [16-18]. Phyto cannabinoids, particularly Cannabidiol (CBD), are employed to treat various conditions, including epilepsy, cachexia associated with diseases such as AIDS and multiple sclerosis, anxiety and cancer-related symptoms [19]. Their role in inhibiting tumor progression has been extensively studied at the preclinical level, both *in vitro* and *in vivo* [20,21]. Additionally, evidence from phase Ib and phase II clinical trials involving the use of delta-9-Tetra Hydro Cannabinol (THC) and CBD further supports their therapeutic potential in managing high-grade gliomas [22,23]. Herein, we report the case of a 48-year-old woman diagnosed with IDH wild-type diffuse anaplastic astrocytoma. She underwent therapy with  $O_2O_3$ , medical cannabis and MLT during and after conventional therapy, yielding noteworthy outcomes. These results prompted us to share our findings and to further investigate this adjuvant treatment as a potential future strategy against cancer.

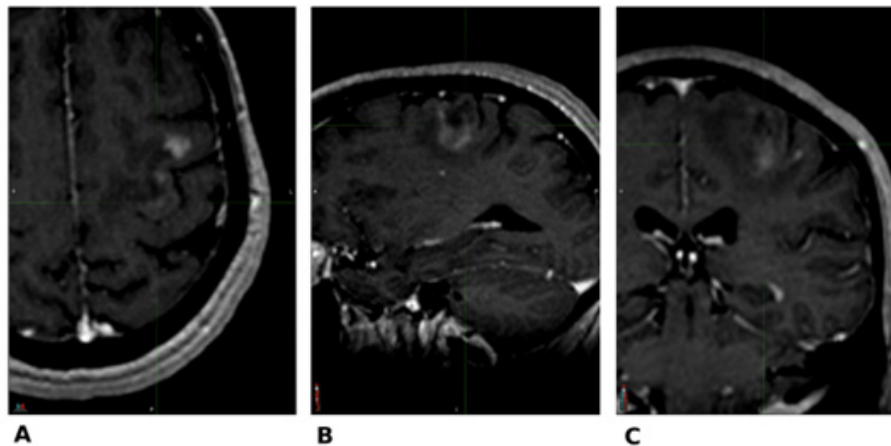
## Case Presentation

In July 2017, a 48-year-old Italian woman after the sudden appearance of speech disorders and motor deficits in the right upper limb, underwent Magnetic Resonance Imaging (MRI), and an expansive lesion was detected in the cortico-subcortical area (Figure 1). The patient was a former smoker, with a family history of glioblastoma and lung cancer. The lesion was visible on T2 and FLAIR as signal hyperintensity, which then took up contrast medium. A stereotactic biopsy was subsequently performed, revealing millimetric fragments of brain tissue with morphological and immunophenotypic characteristics consistent with a grade 3 astrocytoma IDH-wild type (immunophenotype: GFAP+, IDH1-, EGFR-, p53 12–13%, Ki67 <5%). From September to November 2017, the patient underwent brain RT via the intensity-modulated and Image-Guided Radiation Technique (IGRT/IMRT), and 54 Gy was delivered in 30 daily fractions of 1.8 Gy each. CT with TMZ was also performed at a dose of 120mg daily for 5 days each month over a period of 8 months. In January 2018, the patient initiated integrated  $O_2O_3$  therapy while receiving CT and RT. The treatment protocol included rectal administration of  $O_2O_3$  at a dose of 2.5mL/kg, consisting of 97% oxygen and 3% ozone, at a concentration of 80µg/mL. This regimen was administered daily for four consecutive days each week. After completing three months of  $O_2O_3$  therapy, the patient discontinued treatment for a period of five months.

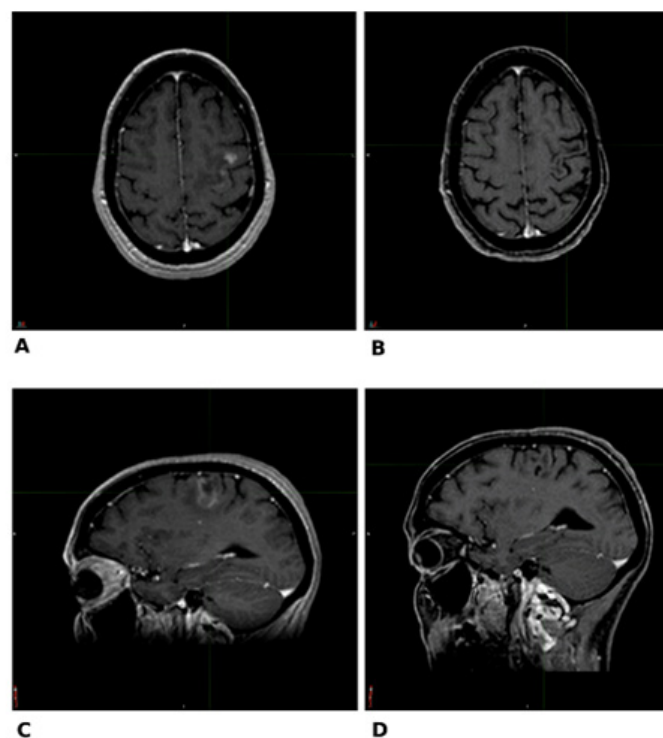
The therapy was subsequently resumed and maintained to the present, with a reduction in frequency from four sessions per week to two, alternating between three months of active treatment and three months without therapy. During the check-up visits, monthly blood and biochemistry tests were carried out. At the July 2018 follow-up, the patient reported an overall sense of well-being during the  $O_2O_3$  therapy cycles with a reduction in chemotherapy-related side effects. However, she experienced mild asthenia during breaks from  $O_2O_3$  therapy. Compared with the beginning of the integrated treatment, the patient reported improvements in her speech and a reduction in bloating. In July 2018, integrative therapy with  $O_2O_3$  was implemented with MLT and medical cannabis. MLT was initially

set at a dosage of 100mg daily and was administered orally, with a gradual increase of 100mg every 4 days, reaching a maximum dose of 2g. The dosage was then stabilized and maintained at 2g per day. For medical cannabis, the patient initially received a dose of 50mg of Bedrolite (CBD 9%,  $\Delta^9$ -THC 0.4%) four times daily and 100mg of Bedrocan ( $\Delta^9$ -THC 22%, CBD <1.0%) four times daily. In December 2018, the patient completed chemotherapy and radiotherapy but continued receiving integrative therapy. Starting in 2019, the Bedrolite regimen was modified to 50mg twice daily

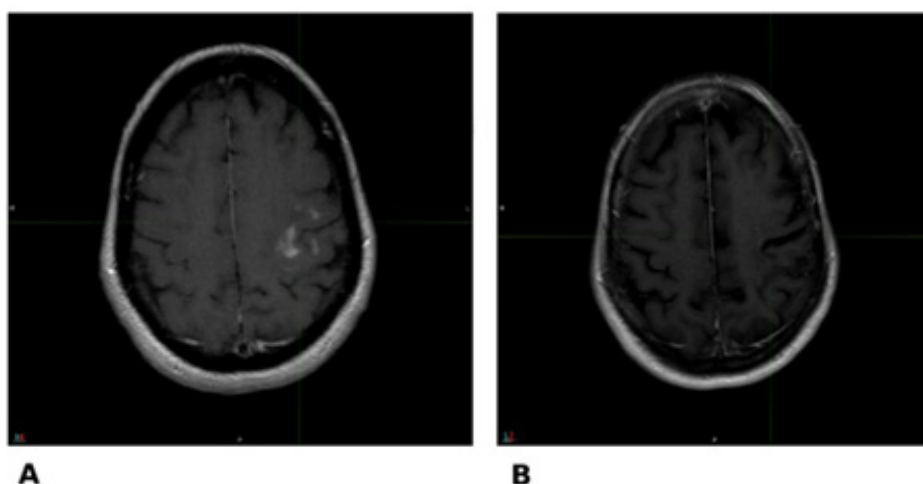
during the O<sub>2</sub>O<sub>3</sub> therapy pause phase and 30mg once daily during the O<sub>2</sub>O<sub>3</sub> therapy period. On February 2019, a pet scan revealed no metabolically active disease in the brain and a follow-up MRI on May 2019 revealed no changes, with the lesion remaining stable, no enhancing and unchanged (Figure 2). Over five years of integrative treatments, subsequent MRI confirmed the stability of the tumor mass, including the most recent imaging on October 2024 and allowed the patient to be considered cured and able to lead a normal life (Figure 3).



**Figure 1:** MRI performed for diagnosis (07/28/2017): (A) Axial; (B) Sagittal; (C) Coronal.



**Figure 2:** Comparative image between MRI dated 07/28/2017 (A axial and C sagittal) and follow-up MRI dated 05/22/2019 (B, axial e D, sagittal).



**Figure 3:** Comparative imaging between MRI dated 07/28/2017 (A) and last follow-up MRI dated 10/24/2024 (B).

## Discussion

In this case report, a 48-year-old woman diagnosed with an anaplastic astrocytoma underwent adjuvant therapy consisting of MLT, medical cannabis and  $O_2O_3$  therapy associated with standard RT and CT. Phyto cannabinoids, which are contained in medical cannabis, are derived from *Cannabis sativa* plants and  $\Delta^9$ -THC and CBD are the most prominent compounds. Several mechanisms are involved in the activity of these molecules, including acting as agonists or inverse agonists of cannabinoid receptors CB1 and CB2. Furthermore, cannabinoids target G protein-coupled receptors (GPCRs), including GPR12, GPR18, GPR35, GPR55, and GPR119, as well as opioid receptors, serotonin receptors, transient receptor potential vanilloid channels such as TRPV1 and TRPV2 [19]. Since 1975, Phyto cannabinoids have been widely investigated in different medical fields, obtaining interesting results in oncology. At first used to reduce CT side effects, including nausea, vomiting and cachexia [24], Phyto cannabinoids are also characterized by direct action on cancer cells [25].

With respect to brain tumors, particularly glioma cells, CBD reduces the expression and activity of Vascular Growth Factor Endothelial Receptor 2 (VEGFR-2), an important regulator of neovascularization in tumor [26]. A second mechanism for reducing the invasiveness of gliomas is the downregulation of Matrix Metalloproteinase-2 (MMP-2). [27,28] Last, Nabissi et al. [29]. suggested that CBD, through the activation of TRPV2, sensitizes Glioblastoma (GBM) cells to TMZ and BCNU increasing drug uptake and synergizing with these cytotoxic agents to induce apoptosis of glioma cells. Moreover, CBD is able to act on the tumor stem cell compartment promoting their differentiation both *in vitro* and *in vivo* mouse model [29]. The positive effects of cannabinoids observed in preclinical models have led to a placebo-controlled phase I clinical trial evaluating a cannabinoids combination alongside dose-intensive TMZ in GBM patients (clinical trial NCT01812603). A total of 21 adult patients with GBM and a

Karnofsky performance score of 60% or higher were randomized to take TMZ with placebo or nabiximols (a solution containing 27mg/ml THC and 25mg/ml CBD). The results revealed that while the control group demonstrated a 44% one-year survival rate, the TMZ plus nabiximols group achieved an 83% one-year survival rate and a median survival of over 662 days [22]. Further advancement was achieved with the ARISTOCRAT: A phase II, multicenter, double-blind, placebo-controlled, randomized trial [23].

This study involved a sample size of 234 patients randomized at a 2:1 ratio to receive either nabiximols or placebo in combination with standard TMZ treatment. Although data are still not available and the preliminary clinical findings cannot be deemed statistically significant owing to the small sample size, they further underline the importance of translational research on cannabinoids in the development of clinically effective therapies. In addition to CBD, the patient was supplemented with MLT during and after chemotherapy. MLT exhibits a range of antitumor effects, including antioxidant, cytostatic, antiproliferative, and proapoptotic activities, in addition to its ability to regulate epigenetic responses [30]. These properties have been investigated and documented in several studies on different cancer cells. Notably, Sung et al. [31]. demonstrated that MLT, with vorinostat (a histone deacetylase inhibitor), downregulates Transcription Factor EB (TFEB) and its oligomerization in GBM cells and glioma cancer stem cells. This suppression leads to increased apoptosis-related gene expression and promotes cell death. Another study by Fernandez-Gil et al. [32]. on GBM cells revealed the antiproliferative action of MLT, by increasing the metabolic switch from anaerobic glycolysis to an oxidative phosphorylation state in cancer cells. In colon cancer cells, MLT downregulates the Phosphatidylinositol 3-Kinase/Protein Kinase B (PI3K/AKT) and Nuclear Factor- $\kappa$ B/Inducible Nitric Oxide Synthase (NF $\kappa$ B/iNOS) signaling pathways, which are important regulators of differentiation, proliferation and cell survival [33]. Moreover, MLT synergistically affects the ability of 5-fluorouracil to inhibit Hypoxia-Inducible Factor 1 (HIF-1), a critical factor



employed by cancer cells to survive under low-oxygen conditions [34].

In the clinical field, the association of MLT with standard chemotherapy has resulted in an increase in its efficacy, the mitigation of its side effects and an improvement in patient quality of life [35,36]. A meta-analysis by Seely et al. [37]. reported the beneficial use of oral MLT, alone and in combination with chemotherapy, in a substantial number of patients [37]. A total of 3697 patients from 21 clinical studies with different types of cancer revealed a pooled Relative Risk (RR) of 0.63 for one-year mortality (95% CI=0.53-0.74;  $p<0.001$ ). Significant improvements were noted with MLT administration for complete response, partial response and stable disease, with RRs of 2.33, 1.90, and 1.51, respectively [37]. Moreover, a decrease in the incidence of alopecia, anemia, asthenia and thrombocytopenia associated with MLT administration was observed [37]. These findings strongly encourage the application of MLT in chemotherapy, even if further research is essential to elucidate its therapeutic potential. With respect to  $O_2O_3$  therapy in cancer, only a limited number of clinical trials have investigated its use as an antitumor or palliative treatment. *In vitro*, with its several mechanisms of action,  $O_2O_3$  notably reduces the growth of different types of cancer cell lines, including breast, lung, uterus and neuroblastoma cells [38,39]. A pivotal advancement in the investigation of this adjuvant therapy has emerged from studies by Luongo et al. [40]. on pancreatic ductal adenocarcinoma cell lines, which demonstrated the synergistic interaction between CBD and  $O_2O_3$  therapy, both as a standalone treatment and in combination with antineoplastic agents (gemcitabine and paclitaxel). The combined use of MLT, CBD and  $O_2O_3$  therapy has also been evaluated for the treatment of pancreatic ductal adenocarcinoma [41]. Both *in vitro* and *in vivo* experiments highlighted the anticancer effects of this combination. An increased response to standard chemotherapeutic agents commonly prescribed for the treatment of pancreatic ductal adenocarcinoma has also been reported, encouraging their use as an adjuvant therapy [41]. These findings underscore the therapeutic potential of this approach. It is also noted that expanded clinical data is required to validate these observations, as only one other case has reported the use of MLT, CBD and  $O_2O_3$  therapy in the context of cancer therapy [42].

## Conclusion

The data reported above and this patient experience support the rationale for using adjuvant therapy combining MLT, medical cannabis and  $O_2O_3$ . Significant benefits were observed both during conventional TMZ therapy and during the post treatment period. Notably, the patient demonstrated high compliance and a positive, proactive attitude toward the integrated treatment and no adverse effects or negative interactions with the ongoing oncological therapy were reported. Additionally, she opted to continue with MLT, medical cannabis and  $O_2O_3$  therapy for several years, highlighting its potential long-term acceptability. Nevertheless, only one other case report has described the synergistic effects of this combination therapy, limiting our ability to confirm these findings conclusively. However, this case report contributes to the

ongoing effort to fight against cancer and underscores the need for further investigation into innovative, less debilitating therapeutic options in oncology.

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