Hyperbaric oxygen therapy for Glioblastoma

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- Clinical research framework proposal for ketogenic metabolic therapy in glioblastoma
- Key Genes Involved in the Beneficial Mechanism of Hyperbaric Oxygen for Glioblastoma and Predictive Indicators of Hyperbaric Oxygen Prolonging Survival in Glioblastoma Patients
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Hyperbaric oxygen therapy (HBOT) has been explored as a potential adjunctive treatment for glioblastoma, one of the most aggressive and lethal forms of brain cancer. Glioblastoma treatment typically includes surgery, radiation therapy, and chemotherapy (commonly with temozolomide). Despite these interventions, the glioblastoma prognosis remains poor, prompting investigations into new therapeutic strategies, including HBOT.

Mechanism of HBOT in Cancer Therapy

HBOT involves breathing pure oxygen in a pressurized environment, which increases the oxygen concentration in the blood and tissues. This has several proposed benefits in cancer therapy:

1. **Increased Oxygenation of Tumor Cells**: Glioblastomas are often hypoxic (low in oxygen), which can make them more resistant to standard treatments like radiation therapy and chemotherapy. By increasing oxygen levels in the tumor, HBOT may enhance the effectiveness of radiation therapy, which relies on oxygen to generate free radicals that damage cancer cells.
2. **Enhancement of Chemotherapy**: HBOT may also improve the delivery of chemotherapeutic agents to the tumor by increasing oxygen levels and improving blood flow in hypoxic regions, which are otherwise difficult for drugs to reach.
3. **Reduction of Hypoxia-Induced Resistance**: Hypoxia in tumors promotes a more aggressive, therapy-resistant phenotype by activating pathways like HIF-1α (hypoxia-inducible factor 1-alpha). By alleviating hypoxia, HBOT could reduce this resistance and potentially improve treatment outcomes.

Clinical Evidence

Several preclinical studies and early-phase clinical trials have evaluated the role of HBOT in glioblastoma treatment. Some key findings include:

1. **Preclinical Studies**: Animal models have shown that HBOT, in combination with radiation or

chemotherapy, can reduce tumor growth and improve survival. These studies suggest that the increase in oxygen tension may enhance the sensitivity of tumor cells to treatment.
2. **Clinical Trials**: Limited early-phase clinical trials have been conducted, with mixed results. Some studies suggest that HBOT in combination with radiation and chemotherapy can improve local control of the tumor and potentially extend survival, while others show minimal benefit. For example, a small phase II trial explored HBOT with radiation and temozolomide, showing some promise but not enough to conclusively change clinical practice.

Current Limitations and Future Directions

1. **Lack of Large-Scale Evidence**: Although preclinical data are encouraging, large-scale randomized clinical trials are needed to definitively determine the benefits of HBOT for glioblastoma patients.
2. **Logistical and Practical Challenges**: HBOT requires specialized equipment and facilities, making it less accessible to many patients. Moreover, the optimal timing, duration, and pressure for HBOT in the context of glioblastoma therapy remain unclear.
3. **Potential Risks**: While generally safe, HBOT can have side effects, such as barotrauma (damage to the lungs or ears), oxygen toxicity, or seizures, particularly in patients with brain tumors.

Conclusion

HBOT is an intriguing area of research in glioblastoma treatment, especially for its potential to improve the efficacy of standard therapies by reversing hypoxia in tumor cells. However, more robust clinical evidence is needed before it can be integrated into standard glioblastoma care. Researchers continue to investigate its use, often in combination with other treatments like radiation and chemotherapy.

Preclinical in vitro experimental studies

In a Preclinical in vitro experimental study, Ren et al. aimed to test candidate genes in HBO-exposed glioblastoma cells and to analyze their correlation with the survival of glioblastoma patients.

Methods: Glioblastoma cell lines exposed to repetitive HBO or normobaric air (NBA) were collected for RNA isolation and microarray data analysis. GO analysis, KEGG pathway analysis, and survival analysis of the differentially expressed genes (DEGs) were performed.

Results: HBO not only inhibited hypoxia-inducing genes including CA9, FGF11, PPFIA4, TCAF2, and SLC2A12 but also regulated vascularization by downregulating the expression of COL1A1, COL8A1, COL12A1, RHOJ, and FILIP1L, ultimately attenuated hypoxic microenvironment of glioblastoma. HBO attenuated the inflammatory microenvironment by reducing the expression of NLRP2, CARD8, MYD88, and CD180. HBO prevented metastasis by downregulating the expression of NTM, CXCL12, CXCL13, CXCR4, CXCR5, CDC42, IGFBP3, IGFBP5, GPC6, MMP19, ADAMTS1, EFEMP1, PTBP3, NF1 and PDCD1. HBO upregulated the expression of BAK1, PPIF, DDIT3, TP53I11, and FAS, whereas it downregulated

the expression of MDM4 and SIVA1, thus promoting apoptosis. HBO upregulated the expression of CDC25A, MCM2, PCNA, RFC33, DSCC1, and CDC14A, whereas it downregulated the expression of ASNS, CDK6, CDKN1B, PTBP3, and MAD2L1, thus inhibiting cell cycle progression. Among these DEGs, 17 indicator genes of HBO prolonging survival were detected.

Conclusions: HBO is beneficial for glioblastoma. Glioblastoma patients with these predictive indicators may prolong survival with HBO therapy. These potential therapeutic targets especially COL1A1, ADAMTS1 and PTBP3 deserve further validation.

Keywords: differentially expressed gene; gene enrichment analysis; glioblastoma; hyperbaric oxygen; survival analysis. [1].

There exists a consensus that combining hyperbaric oxygen (HBO) and chemotherapy promotes chemotherapy sensitivity in Glioblastoma cells. However, few studies have explored the mechanism involved. HIF1A and HIF2A are the two main molecules that contribute to Glioblastoma malignant progression by inhibiting apoptosis or maintaining stemness under hypoxic conditions. Moreover, Sox2, a marker of stemness, also contribute to Glioblastoma malignant progression through stemness maintenance of cell cycle arrest. Briefly, HIF1α, HIF2α, and Sox2 are highly expressed under hypoxia and contribute to Glioblastoma growth and chemoresistance. However, after exposure to HBO for Glioblastoma, whether the expression of the above factors is decreased, resulting in chemosensitization, remains unknown. Therefore, Wang et al. performed a series of studies and determined that the expression of HIF1α, HIF2α, and Sox2 was decreased after HBO and that HBO promoted Glioblastoma cell proliferation through cell cycle progression, albeit with a decrease in stemness, thus contributing to chemosensitization via the inhibition of HIF1α/HIF2α-Sox2 [2].

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