



Review

Diet as a Novel Treatment for Glioblastoma

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Abstract

Scientists are trying to develop combination therapies for the treatment of malignant diseases, such as glioblastoma, that will increase the survival rate and reduce the side effects. Studies have shown that the efficacy of the classic treatment for glioblastoma, surgical resection combined with chemotherapy and radiation, will be greater if the metabolism of cancer cells is modified by nutritional habits. A ketogenic diet with caloric restriction is a key strategy in killing tumor cells by decreasing the amount of glucose as a source of energy, suppressing oxidative stress in tumor cells, inhibiting the signaling pathways of tumor markers, and reducing tumor angiogenesis and growth factors. Moreover, the application of a ketogenic diet and caloric restriction reduces the side effects of the chemotherapy and radiation used in the treatment of cancer cells. Another advantage of a ketogenic diet in the treatment of glioblastoma is the accessibility and affordability of changing nutritional habits for all socioeconomic classes. In vitro and in vivo studies have shown the efficacy of a ketogenic diet, but more clinical studies are needed. Animal studies have demonstrated that a ketogenic diet increased the performance and survival of mouse models with malignant glioma. There are currently some pilot studies underway in the United States and Germany that will be completed by 2018.

Keywords: Brain tumor, caloric restriction, cancer, glioblastoma, ketogenic diet, metabolism, Warburg effect

There are three types of glial cells that can be developed to tumor cells. The most important cell is astrocyte which produces astrocytoma or glioblastoma. Glioblastoma is the most malignant primary brain tumor which has self-regenerating and tumorigenic cells. Therefore, it is a big challenge for oncologist surgeon to treat it appropriately. The survival rate of patients with aggressive therapy including surgery, chemotherapy, and radiotherapy is less than 10% in 5 years. Novel treatment methods such as antiangiogenic agents, mammalian target of rapamycin inhibitors, poly (ADP-ribose) polymerase-1 inhibitors and immunotherapies have increased survival from 12.1 to 14.6 months regarding Anton et al. 2012.^[1] As glioblastoma tumor cells are very infiltrative and malignant, they will not be removed by surgery completely. The rest of tumor cells will be killed by chemotherapy and radiotherapy however

a few cells left in the place will regrow and tumor mass recur after two years of primary event. Nowadays, biological markers targeted on individualized or personalized cancer therapy has gained significant attention in oncology. However, the major biomarkers used to allocate treatment in glioblastoma are age and Karnofsky Performance Scale score Weller et al. 2012.^[2] There are few therapeutic chemotherapy medications to suppress the tumor cells after treatment with temozolomide (TMZ); Therefore, molecular studies have created a specific genomic profiles for glioblastoma, Brennan et al. 2011.^[3] On the basis of genetic profile of GBM which is identified by genetic aberrations, gene expression, and protein expression, there are four molecular groups of GBMs. The ultimate goal of personalized medicine is to treat patients with GBM with identification of specific targets for the genetic profile. The barrier is that solid tumors

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are heterogeneous and primary GBM management and its recurrence is a big challenge.

Current cancer therapy for glioblastoma

Glioblastoma is currently treated by surgical removal followed by radiotherapy and chemotherapy using Temozolomide (TMZ).^[4] In addition to classic treatments, there are other adjuvant therapies such as glucocorticoids to reduce the peritumoral edema, antiangiogenic agents like bevacicumab (Avastin) which prolongs the progression-free survival;^[5] However, a randomized trial showed that patients who consumed bevacizumab suffered from hypertension, thromboembolic events, intestinal perforation, and neutropenia.^[6] Progressive brain volume loss have been observed with classic radio chemotherapy treatment resulting to neuropsychological changes in patients with glioblastoma.^[7] Although different types of cancer therapy have been applied for glioblastoma, the 5-year survival rate of patient is less than 10% because of heterogeneous complex tissue of glioblastoma, genetic mutations, and abnormal signal pathways.^[8, 9] Recently, novel therapeutic approaches evaluated the molecular characteristics of glioblastoma by setting of Glio-TEX project (GBM and Experimental Therapeutics) a GBM patient-derived cell line (GBM-PDCL) library.^[10] Nowadays, metabolic pathways have been on attention of scientists for treatment of glioblastoma tumor cells are depend on anaerobic glycolysis to get their energy sources and they are not able to uptake glucose to provide their energy needs; However, the Apolipoprotein Mortality Risk (AMORIS) data showed a paradoxical result which observed a reverse correlation between glucose consumption and glioma.^[11]

Metabolism of tumor cells

In 1927, Warburg et al. showed that the survival of cancer cells depended on aerobic glycolysis called "Warburg effect".^[12] In fact, it is necessary for cancer cells to provide the demands of their rapid proliferation by cellular energy metabolism for the transition from normal to cancer cells. Tumor cells should have their energy by fast and accessible method regardless of oxygen availability. We know that normal cells rely of oxygenation for generating ATP and their energy however malignant cells regenerate and proliferate producing ATP by glycolysis rather than oxygenation phosphorylation even in the presence of oxygenation. Glycolysis happens before oxygenation in the process of tumorigenesis. As more research have been done to understand the tumor metabolism, scientist have discovered more molecular pathways in pathogenesis of GBM un-dependable on higher rate of glycolysis. It has been found

that there is a balance in cancer cell's growth between the availability of energy, sufficient macromolecular synthesis for increased growth, modulation of reactive oxygen species (ROS), nutritional needs of cancer cells, metabolomics, and proteomics of tumors.^[13]

A lot of studies have been done to fight with cancer cells on the basis of Warburg effect. Reducing the amount of glucose and providing lactate have been tried to challenge the cancer metabolism however new techniques such as the discoveries of oncogenes, tumor suppressor genes, growth factor pathways, molecular subtypes of cancers have overshadowed the Warburg effect recently. Many pathways of cancer tumorigenesis, angiogenesis, tumor cell growth, apoptosis, and therapy resistance have been recognized in combination with cellular metabolism.^[14] For instance, Puzio-Kuter mentioned that p53 tumor suppressor has an important role in cancer pathways as it can influence several aspects of metabolism through different mechanisms. The p53 promotes a variety of cellular responses to hypoxia, DNA damage, and oncogene activation; however, recently it has been found to regulate glycolysis and assist in maintaining mitochondrial integrity.^[15] The p53 protein decreases intracellular concentrations of fructose-2,6-bisphosphate by inducing the transcription of the TIGAR gene, and overall levels of intracellular reactive oxygen species (ROS).^[16] One of the most active signaling pathway in many cancers is stress-responsive PI3K/AKT mechanism which is linked to cancer metabolism and under low glucose conditions results in rapid tumor cell death.^[14] A novel method of cancer therapy is inhibiting the activity of hypoxia-inducible factor 1 (HIF-1) by blocking the transport of glucose into cells, decreasing the conversion of glucose to pyruvate and a concomitant decrease of mitochondrial mass and mitochondrial metabolism.^[17] Another oncogene, Myc, in combination with p53 and HIF-1 have a pivotal role in upregulation of proteins in glycolysis and intracellular pH regulation. These studies indicate to consider metabolic changes in cancer pathways for more classic therapeutic targets.^[18]

Methods

To study the nutritional treatment of glioblastoma, we analyzed and screened all clinical literature and ongoing clinical trials investigating the role of ketogenic diet as an adjuvant therapy for malignant glioblastoma. We searched databases PubMed/MEDLINE, EMBASE, Cochrane CENTRAL and Google Scholar for published clinical reports, as well as the WHO ICTRP and ClinicalTrials.gov (NIH) registries for ongoing clinical trials on ketogenic diet for use in glioma patients.

The ketogenic diet

A growing number of studies showing that ketogenic diet including high fat, low carbohydrate and protein, caloric restriction, and fasting resulting a metabolic change, specifically, a reduction in blood glucose and an increase in blood ketones in brain tumor cells.^[19] In addition, other neurological disturbances such as epilepsy in children can be managed by ketogenic diet.^[20] Ketogenic diet mimics the fasting process by increasing ketone bodies, oxidation of fatty acids and producing Acetyl-CoA. The extra amount of Acetyl-CoA is being consumed by brain cells. Learning disorders have been improved by dietary restriction.^[21] The neuroprotective effects of ketogenic diet have been shown in many neurological diseases such as Alzheimer,^[22] learning disabilities, traumatic brain injury, and amyotrophic lateral sclerosis.^[23] According to Warburg effect, brain tumor cells cannot metabolize ketone bodies because of their disrupted genetic map and mitochondrial defects; therefore, they are dependent on glucose as their primary source of energy. Moreover, ketone bodies can destroy tumor cells because ketogenic diet can reduce the amount of reactive oxygen species (ROS).^[24] On the other hand, ketogenic diet may change the gene expression profile of tumor cells and inhibit the signal pathways of many growth factors. Therefore, by offering the ketogenic diet to patients with glioblastoma, we are restricting the accessibility of tumor cells to glucose and increasing the amount of ketone bodies to tumor cells. It is unlikely that the only mechanism of action is Warburg effect because there is a complexity of mechanisms on how ketogenic diet can inhibit tumor cells growth. For instance, the reduction of ROS by ketogenic diet have a great effect on tumor cells inhibition because ROS are involved in many signaling pathways including apoptotic responses, genotoxic stress, inflammation, hypoxia.^[25, 26] Role of oxidative stress has been demonstrated in tumor initiation and progression by inducing genomic instability. Reactive oxygen species (ROS) have affected many signaling pathways in tumorigenesis and metastasis by regulating vascular endothelial growth factor (VEGF) and HIF-1.^[25] Studies have shown that caloric restriction with ketogenic diet had anti-angiogenic and anti-proliferative effects on glioblastoma in experimental mouse and human brain models.^[27, 28] The only anti-angiogenic agent approved by FDA is bevacizumab, a monoclonal antibody, which is inhibiting VEGF using for GBM patients, especially in those with recurrent glioblastoma.^[29] A challenge for the treatment of glioblastoma is peritumoral edema which is caused by leaking of fluid around tumor from vascular network around the tumor mass. Currently Dexamethasone is given to reduce the peritumoral edema in GBM patients,

however, the side effects of glucocorticoids including hyperglycemia, osteoporosis, cardiovascular, weight gain, infection affect the patient survival and quality of life.^[30] There are some studies that have described the efficacy of caloric restriction and ketogenic diet in reduction of peritumoral edema and suppression of abnormal vascular network around tumor. Energy-restricted ketogenic diet (ERKD) protocol was used in a pilot clinical study and two cases had long remissions without any major side effects due to KD.^[31]

Ketogenic diet as an adjuvant therapy

Although studies show that KD has great anti-cancer effects by its own, combination therapy with radiation and chemotherapy will increase the efficacy of KD compared with KD therapy alone. A study demonstrated that a mouse model of malignant glioma had greater survival when treated with KD and radiation in combination with temozolomide (TMZ).^[32] It clearly indicated that KD significantly increased the efficacy of anti-tumor activity when combined with radiation. Interestingly, the animals had complete remission of tumor with KD combined with radiation even after they fed back with normal diet. Combination therapy of KD, radiation and chemotherapy has had the same result in mouse model with lung cancer which decreased tumor cell growth and increased survival. The other preclinical and clinical studies also described the anti-cancer effects of combination therapy including caloric reduction diet with radiation and chemotherapy.^[33–36]

Mechanism of ketogenic diet

DNA damage might be the reason of tumor cell death by radiation while the normal cells can repair themselves and tumor cell cannot.^[37] In addition, Insulin-like Growth Factor-1 (IGF-1) and glucose have been reduced in tumor cells in response to genotoxic stress.^[38] The other studies described that KD and CR can boost the immune system. Moreover, the suppressed immune system in mouse models of malignant glioma could be reversed by KD and CR.^[39] Tumor cells destruction by radiation increases tumor antigens in the body which exposes immune system to them. This process could be potentiated by KD and boost the immune system more in combination with cancer radiotherapy. There are always some concerns among scientists that anti-cancer treatments might affect the normal cells as well but studies have shown that gene expression in tumor cells is different with normal cells.^[40] The ketone body Beta-hydroxybutyrate (bHB) works as an anti-cancer agent by substitution of glucose in KD and caloric reduction states such as fasting and exercises. In fact, ketone bodies like

bHB in combination with radiation has an increased efficacy in killing tumor cells.^[25] The other studies described that ketone bodies supplements, ketone monoester (KME), have protective effects in the brain by potentiating the KD and prevention of glucose consumption in brain cells.^[41, 42] The mechanism of bHB inhibiting oxidative stress has mentioned in some studies. The ketone body bHB increased the global histone acetylation in mouse model caused changes in transcription genes encoding oxidative stress resistance factors FOXO3A and MT2.^[45] Interesting data uncovered the role of bHB in reducing the growth of glioblastoma cells in the presence of glucose in some cancer cell lines and increasing the radio-sensitivity in vitro studies.^[41] Moreover, the efficacy of chemotherapy drugs has been increased by ketone bodies in vitro.

Human studies

The first study to discover the role of KD on human was two case reports of children in 1995. They were two pediatric patients who suffered from advanced glioblastoma (anaplastic astrocytoma and cerebellar astrocytoma) and responded well to KD in decreasing of glucose consumption and prolongation of the management period. An interesting report from Italy in 2010 explained that restricted ketogenic diet with 600 kcal/day disappeared tumor tissues in PET scan. She was a 65-year-old female with multiple lesions in her brain who became lesion free evaluated by fluorodeoxyglucose positron emission tomography (FDG-PET) or MRI, however, ten weeks after discontinuing the diet tumor cells appeared and treated with chemotherapy and survived for two years.^[44] There was a similar research in Germany where 16 patients were fed up with ketogenic diet and tolerated very well until they were on KD diet.^[45] A clinical trial in St. Joseph's Hospital and Medical Center, Phoenix, from 2013 to 2017, evaluated the role of KD 4/1 (fat/carbohydrate) in patients with GBM who had partial or complete surgical resection of tumor and used chemotherapy (Temozolomide) with external beam radiation (60 Gy/30 fractions), however, no data have been released from this study so far (ClinicalTrials.gov NCT02046187). There are some other pilot studies currently admitting patients to evaluate KD in patients with GBM in both Germany and United States (NCT01754350, NCT01865162).

Conclusion

Glioblastoma treatment is a very challenging and exhausting process with surgical resection of tumor followed by radiotherapy and chemotherapy which has a very low survival rate. Other adjuvant therapies have been used such as immunotherapy, anti-angiogenic agents (bevacizumab), glucocorticoids, and tumor suppressors but

patients suffered of side effects of these recent methods. Evaluating the metabolism of glioblastoma might shed light on complexity of its treatment and increase the efficacy of nutritional behavior of patients focusing on KD/CR. Scientists have found that KD/CR has potentiated the efficacy of current chemotherapy and radiotherapy which were confirmed with animal studies. It looks like that KD/CR works through suppression of inflammation, oxidative stress (ROS), and modifying growth factors (VEGF). There are not enough clinical trials to prove the efficacy of KD/CR on humans; however, there are some clinical studies are currently investigating which will be completed until 2018. Generally, KD/CR has great efficacy in increasing the survival rate and life quality of patients with glioblastoma but more clinical studies needed to be done in the future. In addition, we should consider the side effects of adding caloric restriction diet, less than 600 kcal/day, to patients who are under radiation and chemotherapy. This might be a great issue for the patients and their families because there is a risk of interacting with their immune system. In summary, metabolism of cancer therapy is a key strategy to cure malignant glioma and we have to wait until future clinical studies prove the KD/CR as an adjuvant therapy.

Disclosures

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