Enhancing Temozolomide Temodar Treatment
How Enhance the Effectiveness of Glioblastoma Temozolomide Treatment

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www.NaturalCancerReports.com
Introduction

I felt I shouldn’t wait until I’m finished writing to share this FREE Glioblastoma Brain Cancer Alternative Treatment Report. I’m in the process of writing the complete series of Glioblastoma Brain Cancer Reports.

You need this information now and can start implementing the supplements listed in a couple of days.

This is a work in progress and has not been proofed by my editor. Please excuse the grammar and spelling mistakes. I’m sure my Okie accent comes through at times!

Please check back every few days to see if I have uploaded a newer version. Take a note of the version (upload date) at the bottom of the pages. I’ll place the version on the web page next to the link.

Praying and wishing you the best,

Keith
How to Enhance Temozolomide Temodar Glioblastoma Treatment

Why I have Glioblastoma Brain Cancer Alternative Treatment Tips in each section.

1. I’ve been in health care since 1977, and a clinical nutritionist since 1998. In that time I’ve learned an enormous amount of information. When appropriate I want to share some of this knowledge for the general public. Since each person, cancer and medication is unique I can provide only general information rather than specific recommendations.

2. I also provide links to supplements I use in my practice. I’ve selected supplement companies that provide effective, outstanding quality, cGMP products. You may click on the link to go to an information page to learn more about the supplement.

3. I do make a commission on the supplements if you purchase them through my registration page. This allows me to concentrate on writing this lifesaving information rather than running a retail store.

We both win when you purchase a product!

I do appreciate your support!

you purchase an item you are supporting my effort in providing FREE information to you and others in desperate need of improved outcomes.

I’ve spent hundreds (yes hundreds) of hours researching and writing this “FREE” report. *(I didn’t work this hard when I was in pharmacy school!)* When
**FDA Disclaimer**

*These statements in the report and on www.NaturalCancerReports.com have not been evaluated by the Food and Drug Administration.*

Dietary supplements are not intended to diagnosis, treat, cure or prevent any disease.

**Use Disclaimer**

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You should consult with your doctor before making any changes in your cancer treatment program. It may be helpful to give this report to your doctors when requesting a change in your cancer treatment program.
COX-2 Inhibitors

Combined treatment of pioglitazone (Actos™) and rofecoxib (Vioxx™) were combined with capecitabine or temozolomide in patients with high-grade glioblastoma or anaplastic glioma. Disease stabilizations lasting longer than 3 months were noted in 4 of 14 patients (29%). Researchers state the study demonstrates that this novel regimen is moderately active and well tolerated in patients with high-grade gliomas. As a comparably small proportion of patients responded.

Researchers found the combination of Temozolomide and celecoxib was safe and potentially effective in the treatment of metastatic melanoma.

Restricting glucocorticoid (cortisone) use in the treatment of patients with a solid tumor may help improve outcome. This patient received celecoxib (Celebrex™) rather than dexamethasone to prevent brain edema in a patient with a cerebellar glioblastoma multiforme grade IV upon the patient's request. The cerebrospinal fluid level of celecoxib was 54 times below serum concentration levels known to inhibit COX-2.

This patient took Celebrex 400mg twice daily. The normal dose for Celebrex is 200mg twice daily. Even at recommended doses Celebrex may increase the risk of stomach and esophagus irritation and ulcers. Higher doses of Celebrex may have even higher risk of stomach and esophagus irritation and ulcers and should be done only under the supervision of a doctor.

A group of 22 children with relapsed tumors, who already have been extensively pretreated, were given a 4-drug protocol named COMBAT (Combined Oral Maintenance Biodifferentiating and Antiangiogenic Therapy). The children received celecoxib (COX-2 inhibitor), 13-cisretinoic acid (vitamin A), temozolomide (Temodar™) and etoposide (Eposin, Etopophos, Vepesid, VP-16), each in a specific cycle for a period of 1 year. 9 of the 14 patients demonstrated evidence of treatment benefit manifested as prolonged disease stabilization or response. The group of medications was well tolerated with minimal side effects. Researchers suggested further exploration of this and/or similar


In an animal study, a group of rats were injected with rat glioma cancer cells. One group of rats received celecoxib, one group was the control and did not receive medications, the second group received celecoxib, the third group received temozolomide, and the fourth group received a combination of celecoxib and temozolomide. The rats were sacrificed 18 days after treatment and tumor volume, tumor cell proliferation, microvessel densities and apoptosis were evaluated.

Control Group tumor volume: 111.5 mm$^3$
Celecoxib tumor volume: 65 mm$^3$
Temozolomide tumor volume: 71.8 mm$^3$
Celecoxib and temozolomide tumor volume: 18.7 mm$^3$. Smallest tumor size.

Researchers stated, “In the combination group, there was increased tumor cell apoptosis as well as decreased microvessel density and tumor cell proliferation relative to the control and single-agent therapy ($P<0.05$). Collectively, the data suggest that the combination celecoxib and temozolomide may provide a novel and effective approach to the treatment of glioblastoma.”

Non-prescription dietary supplements that have COX-2 inhibition action include:

- Curcumin
- Salicin
- Quercetin
- Resveratrol

Glioblastoma Brain Cancer Alternative Treatment Tips


9 Bonaterra GA, Kelber O, Weiser D, Metz J, Kinscherf R. Source Centre for Biomedicine and Biomedical Technology Mannheim, University of Heidelberg, Mannheim, Germany. Gabriel.Bonaterra@medma.uni-heidelberg.de

10 Cancer Detect Prev. 2007;31(2):129-39. Epub 2007 Apr 6. Willow bark extract (BNO1455) and its fractions suppress growth and induce apoptosis in human colon and lung cancer cells. Hostanska K, Jürgenliemk G, Abel G, Nahrstedt A, Saler R. Source University Hospital Zürich, Department of Internal Medicine, Institute for Complementary Medicine, FGen 102, Ramistrasse 100, CH-8091 Zürich, Switzerland. katarina.hostanska@access.unizh.ch


How to Enhance Temozolomide Temodar Glioblastoma Treatment

- Pterostilbene
- EPA & DHA

Foods that have COX-2 inhibition include:
- Olive oil and red wine

Products used in my practice:
- CurcuPlex CR
- Saloxicin
- OmegaPure – CodPure Plus

Pterostilbene inhibits colorectal aberrant crypt foci (ACF) and colon carcinogenesis via suppression of multiple signal transduction pathways in azoxymethane-treated mice. Chiou YS, Tsai ML, Wang YJ, et.al.
Pterostilbene is more potent than resveratrol in preventing azoxymethane (AOM)-induced colon tumorigenesis via activation of the NF-E2-related factor 2 (Nrf2)-mediated antioxidant signaling pathway. Chiou YS, Tsai ML, Nagabhushanam K, et. al.
Curcumin/turmeric

Glioblastoma cancer cells have a tendency to become resistant to temozolomide and all other chemotherapy drugs. Researchers added curcumin to U87 glioblastoma cells in a laboratory study. Curcumin inhibited the Fanconi anemia pathway activation and caused increased sensitivity to temozolomide. Curcumin appeared to decrease temozolomide chemotherapy resistance.\(^\text{19}\)

Surprisingly the combination of curcumin and temozolomide has not been studied. This does not mean the combination does not work. Please not the previous section about COX-2. Curcumin enhances most other chemotherapy programs via the COX-2 pathway and had dramatic effect on glioblastoma cancer.\(^\text{20-22}\)

Drug companies are currently creating semi-synthetic versions of curcumin for glioblastoma treatment.\(^\text{23-24}\)

In my practice:

CurcuPlex is a cornerstone in my Glioblastoma Program.


\(^{22}\) BMC Cancer. 2010 Sep 14;10:491. The nontoxic natural compound Curcumin exerts anti-proliferative, anti-migratory, and anti-invasive properties against malignant gliomas. Senft C, Polacin M, Priester M, Seifert V, Kögel D, Weissenberger J. Source Department of Neurosurgery, Goethe-University, Schleusenweg 2-16, 60528 Frankfurt, Germany. c.senft@med.uni-frankfurt.de Abstract


Dexamethasone

Dexamethasone causes hyperglycemia (high blood glucose (sugar) levels) and may decrease survival rates in many cancers.25 26

In patients newly diagnosed with Glioblastoma and good baseline Karnofsky score, hyperglycemia (high blood glucose) was associated with shorter survival. The patients with the highest blood glucose levels had a 57% higher risk of dying compared to those with normal glucose levels. Researches state: “The effect of intensive management of glucocorticoid-related hyperglycemia on survival deserves additional study in patients with Glioblastoma multiforme.”28

In patients newly diagnosed with Glioblastoma, and good baseline Karnofsky performance score, The association between higher mean glucose and shorter survival persisted after adjustment for mean daily glucocorticoid dose, age, and baseline Karnofsky performance score (KPS). Compared with patients in the lowest mean glucose quartile, those in quartile two (adjusted hazard ratio [HR], 1.29; 95% CI, 0.85 to 1.96), quartile three (adjusted HR, 1.35; 95% CI, 0.89 to 2.06), and quartile four (adjusted HR, 1.57; 95% CI, 1.02 to 2.40) were at progressively higher risk of dying (P = .041 for trend).

CONCLUSION: In these patients with newly diagnosed GBM and good baseline KPS, hyperglycemia was associated with shorter survival, after controlling for glucocorticoid dose and other confounders.

Acetazolomide (ACZ) and dexamethasone (DXM) alleviate vasogenic edema and inflammation in glioblastoma patients. Temozolomide (TMZ) is used for treating glioblastoma. We compared modulatory effects of ACZ and DXM on TMZ mediated apoptosis in human glioblastoma T98G and U87MG cells. Cells were treated with drug(s) for 6 h and then left in drug-free medium for 48 h. Although ACZ or DXM alone did not induce apoptosis, TMZ alone induced significant amount of apoptosis. Interestingly, ACZ pretreatment enhanced apoptosis while DXM pretreatment decreased apoptosis. These results suggest that combination chemotherapy with ACZ and TMZ may control inflammation and enhance apoptosis in glioblastoma.29


Adjuvant TMZ was used in 44% of patients (n = 18). The MS of the total group was 13.6 months, with a 24% 2-year overall survival. The use of TMZ was associated with improved MS (19.6 versus 12.8 months; P = 0.035) and improved 2-year survival (43% versus 0%). A requirement of dexamethasone dose greater than 4 mg at the end of RT (P = 0.012) was associated with worse survival, but there was no association of MS with age, ECOG, tumour size or extent of surgery.

Restricting glucocorticoid (GC) use in the treatment of patients with a solid tumor may help improving outcome. Here, we report administration of celecoxib rather than dexamethasone to prevent brain edema in a patient with a cerebellar glioblastoma multiforme WHO grade IV (GBM) upon the patient's request, as well as determining cerebrospinal fluid (CSF) and serum concentrations. CSF concentration (0.04 microM) was 54 times below serum concentration (2.18 microM), or 2500 times below levels inhibiting GBM cells in vitro (100 microM), revealing a blood CSF barrier for celecoxib. The patient did not require dexamethasone for the entire treatment. GC administration hence was avoided successfully in this case. The role of COX-2 inhibitors in treatment of GBM is detailed, leading to the conclusion of a pressing need for a clinical evaluation of non-steroidal COX-2 inhibitors with the ability to penetrate into brain tumors.

Postoperative radiochemotherapy with 30-33 daily doses of temozolomide (75 mg/m(2)) is safe in patients with malignant glioma. The combined schedule is effective in oligodendroglioma patients and may prolong survival in glioblastoma. Effort should be taken to minimize corticosteroid doses, since both steroids and temozolomide lead to immunosuppression.

A new alkylating agent, temozolomide (TMZ), has recently been found efficacious in the clinical trials for glioblastoma. Steroids, such as dexamethasone (DXM), are often used concomitantly as a supportive therapy to treat cerebral edema. However, any possible modulatory effect of the steroids on the efficacy of TMZ has not yet been evaluated experimentally. In this study, we have examined whether DXM provides synergistic or antagonistic effect on TMZ-induced apoptosis in human glioblastoma T98G cells. T98G cells were pretreated with various doses of DXM followed by TMZ. The cell viability was assessed by the trypan blue dye exclusion test. Wright staining and the TdT-mediated dUTP nick-end labeling (TUNEL) assay were used to evaluate apoptotic cell death based on the morphological and biochemical (DNA fragmentation) features, respectively. More biochemical features of apoptotic death, such as upregulation of Bax:Bcl-2 ratio, calpain activity, and caspase-3 activity, were assessed by Western blot analysis. A significant number of T98G cells committed apoptosis after treatment with 200 microM TMZ. However, a pretreatment with 100

30 Improved median survival for glioblastoma multiforme following introduction of adjuvant temozolomide chemotherapy. Back MF, Ang EL, Ng WH, See SJ, Lim CC, Chan SP, Yeo TT. Ann Acad Med Singapore. 2007 May;36(5):338-42.
microM or 200 microM DXM protected T98G cells against TMZ-induced apoptosis, concomitantly decreasing Bax:Bcl-2 ratio, calpain activity, and caspase-3 activity. These experimental results indicate that DXM works as an antagonistic agent in combination with TMZ. Therefore, our investigation strongly implies that the combination of DXM and TMZ may be counteractive in treating human glioblastoma.

Freshly grown cells were treated with different doses of DXM or TMZ for 6 h followed by incubation in a drug-free medium for 48 h. Wright staining and ApopTag assay showed no apoptosis in cells treated with 40 microM DXM but considerable amounts of apoptosis in cells treated with 100 microM TMZ. Apoptosis in TMZ treated cells was associated with an increase in intracellular free [Ca^{2+}], as determined by fura-2 assay. Western blot analyses showed alternations in the levels of Bax (pro-apoptotic) and Bcl-2 (anti-apoptotic) proteins resulting in increased Bax:Bcl-2 ratio in TMZ treated cells. Western blot analyses also detected overexpression of calpain and caspase-3, which cleaved 270 kD alpha-spectrin at specific sites for generation of 145 and 120 kD spectrin break down products (SBDPs), respectively. However, 1-h pretreatment of cells with 40 microM DXM dramatically decreased TMZ induced apoptosis, decreasing Bax:Bcl-2 ratio and SBDPs.

CONCLUSION: Our results revealed an antagonistic effect of DXM on TMZ induced apoptosis in human glioblastoma U87MG cells, implying that treatment of glioblastoma patients with DXM prior to chemotherapy with TMZ might result in an undesirable clinical outcome.

Dexamethasone (used for the shortest time in the lowest effective doses) can provide symptomatic benefits. Osmotic diuretics such as mannitol reduce cytotoxic edema more rapidly.

Salicin and curcumin may be strong enough anti-inflammatories to allow decreased dose or elimination of dexamethasone during radiation. Ask your doctor to prescribe the lowest dose possible or to adjust the dose based on the amount of pain, edema, and swelling or paralysis symptoms.

Most important: limit the consumption of sugar, sweets, breads and other high glycemic index foods! Limit foods over glycemic index 41 and avoid foods over glycemic index 70.


Folate donates methyl groups to DNA and limits proliferation and increases the sensitivity to temozolomide-induced apoptosis in glioma cells.\textsuperscript{36}

\textbf{5-MTHF} is an example of an active safe form of folate that I use in my practice.

Do not use folic acid supplements! Folic acid is too strong genetically for some people and may increase their risk of breast cancer and colon cancer. Genetically 25-60\% of people cannot convert Folic Acid into the active forms. 5-methyltetrahydrofolate.

Green tea extract/EGCG

Human glioblastoma cells were implanted into mice. Researchers found EGCG enhanced the therapeutic efficacy of temozolomide. The mice treated with EGCG and temozolomide lived longer than the groups of mice that received only EGCG or temozolomide.³⁷

I use Green Tea 600 in my practice.

Green tea epigallocatechin gallate enhances therapeutic efficacy of temozolomide in orthotopic mouse glioblastoma models.
Source
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Hyperthermia

Localized Electro-hyperthermia to the brain tumor was performed on 12 patients with malignant glioma brain cancers. All of the patients were being treated with temozolomide and radiotherapy. The researchers exposed the tumors to 40 degrees C (104 degrees F). There was one complete remission, 2 partial remissions with a response rate of 25%. Researchers stated, "Electrotherapy appears to have some effectiveness in adults with relapsed malignant glioma."38

Several other studies show potential benefit with temozolomide and other types of cancers.39

Hyperthermia treatment is commonly used by alternative cancer treatment doctors in Germany and Mexico.

Researchers evaluated the effect temozolomide and quercetin had on glioma cancer cells in their laboratory. They found the combination of both drugs were much more effective in programmed cell death induction compared to single drug treatment. Temozolomide administered with quercetin seems to be a potent and promising combination which might be useful in glioma therapy.\(^\text{40}\)

I use Resveratin Plus for my Resveratrol and Quercetin source.

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\(^{40}\) Chem Biol Interact. 2010 Oct 6;188(1):190-203. Epub 2010 Jul 21. Temozolomide, quercetin and cell death in the MOGGCCM astrocytoma cell line. Jakubowicz-Gil J, Langner E, Wertel I, Piersiak T, Rzeski W. Source Department of Comparative Anatomy and Anthropology, Maria Curie-Sklodowska University, Akademicka 19, 20-033 Lublin, Poland. jjgil@poczta.umcs.lublin.pl
Resveratrol and temozolomide treatment of Glioblastoma has not been researched.

Resveratrol with temozolomide treatment of Melanoma skin cancer does show encouraging results in two laboratory cell studies.\textsuperscript{41,42}

I use Resveratin Plus for my Resveratrol and Quercetin source.