Impacts of Temozolomide in Glioblastoma Patients

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Abstract

Glioblastoma presents significant challenges due to its rapid growth, invasiveness, and impact on critical brain functions. Despite advancements in treatment, including the standard procedures of surgery, radiation, and chemotherapy, the tumor is accompanied by a five-year mortality rate of 95%. Temozolomide, a type of chemotherapy, is a key form of glioblastoma treatment but is associated with severe side effects, including immunosuppression, fatigue, and nausea/vomiting. Temozolomide-induced immunosuppression weakens the immune system by reducing white blood cell counts, making patients more susceptible to symptoms such as infections, slower healing, and increased vulnerability to pathogens and cancer cells. Nausea and vomiting are also common side effects of temozolomide, triggered by the activation of the chemoreceptor trigger zone (CTZ) in the brain's medulla oblongata. The CTZ detects harmful substances in the blood and signals the vomiting center to induce vomiting, often accompanied by symptoms like severe pain, headaches, dizziness, and weight loss due to water depletion. Temozolomide can also cause fatigue, leading to low energy, irritability, and muscle weakness due to the body's increased energy output on the extra strain in restoring homeostasis. The paper discusses the balance between extending life and maintaining quality of life, highlighting the difficult choices faced by glioblastoma patients. Future research is needed to develop interventions that mitigate these side effects or alternative treatments that provide similar efficacy with fewer side effects, ultimately improving both survival and quality of life for glioblastoma patients.

Introduction

Introduction to Glioblastoma

Glioblastoma, or glioblastoma multiforme, is an extremely common malignant brain tumor that occurs mostly in adults. Glioblastoma is a grade IV tumor that mostly appears from glial cells within the brain. Glial cells are the supportive cells around the neurons that help them function. Grade IV tumors are the most aggressive and serious type of tumor, often growing quickly and spreading rapidly (Glioblastoma). Each year, about 15,000 adults are diagnosed with this brain tumor. Glioblastoma often arises in the cerebral hemisphere, which controls muscle functions, thoughts, speech, emotions, and reading (Glioblastoma Multiforme).

Glioblastoma can severely disrupt one’s normal brain function. This is due to its effect in critical areas of the brain that can negatively impact movement and speech, causing cognitive impairments (Glioblastoma Multiforme). Despite advancements in treatment, the fast growing and invasive tumor is accompanied by a 5 year mortality rate of 95% (Glioblastoma). Glioblastoma can often recur in patients, even after treatment. Additionally, the negative effect on day to day activities can decrease a patient's quality of life. Some activities that may be affected include ones that may require more energy and movement. With Glioblastoma, patients feel fatigued and may not have the energy to perform various activities.

The current standard of care and typical treatment plans for glioblastoma vary depending on age, severity, location, presence of mutations , and overall health (Current Standards of Care in Glioblastoma Therapy). Usually, treatment consists of 3 consecutive treatments involving surgery, radiation, and chemotherapy. Surgery consists of physically removing the tumor. Radiation is delivered from outside the body, usually daily over several weeks, after surgery

lasting an average of 6 to 7 weeks. Radiation therapy is used to target tumor cells to kill them. Finally, the last treatment is chemotherapy. Chemotherapy is often used to control the tumor and reduce the risk of recurrence through drug treatments that use powerful chemicals to kill fast-growing cells, including cancerous cells, in the body. This is often used after or concurrently with radiation therapy (Current Standards of Care in Glioblastoma Therapy). The most commonly used chemotherapy drug for glioblastoma is temozolomide.

Introduction to Temozolomide

Temozolomide is a lipophilic agent used for brain tumors. Lipophilic refers to a substance's ability to dissolve in fat. Lipophilic chemotherapy such as temozolomide is required to treat tumors in the brain because the brain has 60% fat (Temozolomide Description). Temozolomide alkalizes DNA, breaking hydrogen bonds and splitting the DNA, causing DNA to become single-stranded. This eventually leads to the death of tumor cells. Single-stranded DNA is more vulnerable to damage and mutations because it doesn't have the protective double-helix structure. The exposed bases are more prone to alterations, leading to mutations that can increase cancer progression (Kane et al. 133).

Temozolomide targets not only cancer cells, but all fast growing cells. This means that temozolomide may target both cancer cells and healthy cells, which can disrupt homeostasis. Since temozolomide can kill healthy cells, undesirable side effects may present with the treatment of temozolomide. Common side effects that can affect patients may include immunosuppression, fatigue, and nausea/vomiting (Temozolomide Side Effects). This research paper will discuss these three side effects of temozolomide and the molecular underpinnings to deeper understand where these side effects come from.

Side Effects of Temozolomide

Immunosuppression

One side effect from temozolomide is immunosuppression. Immunosuppression occurs when our bodies' immune system is weakened and can no longer fight secondary infections/cancers such as Glioblastoma as well (Weakened Immune System). Some physical symptoms that are present with immunosuppression may include an increase in chances of sickness/disease, inflammation, and wounds may take a longer time to heal (Immunosuppression).

The immune system is the body's defense system against diseases and bacteria. The immune system is made up of mostly white blood cells, including lymphocytes, neutrophils, and monocytes/macrophages (Immune System and PI). These white blood cells fight different bacteria/diseases in the body, making up 1% of the blood in the body. However, when one has immunosuppression, the amount of white blood cells decreases, and therefore, the defense against these diseases also decreases. This may cause people with immunosuppression to get sick more frequently and heal slower (White Blood Cells). Immunosuppression can occur when immune cells are killed. When cells are killed through temozolomide, the balance of the immune system is disrupted and is not as able to fight off pathogens. Without the necessary immune cells, patients are more susceptible to bacteria, viruses, cancer cells, and parasites. When immune cells can't recognize bacteria, it can no longer kill the bacteria (Immunosuppression).

Nausea and Vomiting

Another side effect of temozolomide is nausea and vomiting. Some physical symptoms that may be present with nausea and vomiting include severe pain, headaches/migraines, urges to vomit, and lightheadedness/dizziness (Nausea and Vomiting).

This side effect may be caused by the chemoreceptor trigger zone, or the area postrema. It is located in the medulla oblongata of the brain, on the floor of the fourth ventricle. When the chemoreceptor trigger zone (CTZ) is stimulated, vomiting may occur (Vomiting Mechanisms). The CTZ contains receptors that detect substances that cause vomiting in the blood and transfers that information to the vomiting center, which is then responsible for inducing the vomiting reflex (Matsui et al.). The CTZ contains receptors for dopamine, serotonin, opioids, acetylcholine and other neurotransmitters. When stimulated, these receptors fire up pathways, leading to vomiting and nausea (Vomiting Mechanisms). Accompanying vomiting, another side effect that may be present is weight loss. This is because vomiting removes water weight from the body, rather than food calories, which can lower one's body weight (Nausea and Vomiting).

Fatigue

The final side effect of temozolomide is fatigue. Symptoms of this side effect are low energy, irritability, and muscle weakness (Fatigue).

This side effect is caused because temozolomide may cause an extra strain on the body that doesn't occur during homeostasis. When the human body is not in homeostasis, the body works with an extra strain to help the body fight and return back to homeostasis. This extra strain usually takes a lot of energy from the body, causing people experiencing it to feel fatigued, or irritable and low in energy (Hsu et al.).

Discussion and Conclusion

Balancing extending life with quality of life using temozolomide

Glioblastoma remains one of the most complex and aggressive forms of brain cancer, with severe side effects despite advancements in research and treatment strategies such as temozolomide. This paper has explored the multifaceted nature of glioblastoma and temozolomide, including its complex molecular biology, which contribute to its side effects. Temozolomide presents itself with a heavy debate towards quality of life vs. quantity of life.

While temozolomide may extend a glioblastoma patient's life by 6 months to a year, a patient's quality of life may decrease during this time. Some patients may prioritize quality of life over a short extension in survival, especially if the side effects of treatment significantly reduce their ability to enjoy their remaining time. For these patients, treatment in temozolomide would not be considered beneficial or worth it. However, for patients who prioritize spending more time with family/friends over their satisfaction towards life during these elongated months may find that temozolomide is a good form of treatment and is considered worth it. Whether temozolomide is "worth it" depends on individual preferences and circumstances. For some, the possibility of extending life by a few months or more may be highly valuable, despite the side effects. For others, the focus may be on maintaining the best possible quality of life without the burden of chemotherapy.

Future directions

In the future, however, additional medication can be created to use as an intervention for addressing the side effects of temozolomide in glioblastoma patients. This way, all patients are able to elongate their survival time while also maintaining a high quality of life. Another

alternative in the future could be to create new forms of treatment with the same efficacy but fewer side effects. Both of these future options can provide glioblastoma patients with extended lives accompanying a satisfying quality of life regardless of treatment option.

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