Review Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2014, Volume 2, Issue 7
ISSN:2321–3647(online)

A Review on Glioblastoma Multiforme (Brain Tumour) -Grade IV Glioma

Gaurav Kumar[1*], Ms Nonita Kawatra[2], Pragya Sharma[3], Raghvendra Sharma[3]
1. *RA Executive, B L Life Science Pvt. Ltd. Kasna, Greater Noida, (U.P.) India 201306.*
2. GM Operations, B L Life Science Pvt. Ltd. Kasna, Greater Noida, (U.P.) India 201306.
3. Asst. Professor, Department of Pharmaceutics, Aligarh College of Pharmacy, Aligarh (U.P.) India 202001.

ABSTRACT

Worldwide, there are an estimated 240,000 cases of brain and nervous system tumours per year – GBM is the most common, and the most lethal, of these tumours. The treatment a patient receives depends on the location of the tumour in the brain and their overall health and age, but the current standard of care for GBM is surgery followed by treatment with both chemotherapy and radiotherapy, after which patients continue with chemotherapy alone. Biological therapies (also called targeted therapies) are a relatively new approach to GBM treatment. Unfortunately, most patients ultimately lose their life to GBM; therefore, maintaining optimal quality of life is very important to patients and their caregivers and is a significant consideration when selecting potential treatment options. This review provides an overview of glioblastoma, including its incidence, risk factors, symptoms, diagnosis and treatment options.

Keywords: Gliomas, Glioblastoma multiforme, Common risk factors, Symptoms, diagnosis and treatment regarding GBM

*Corresponding Author Email pharmacy2014@rediffmail.com
Received 12 June 2014, Accepted 05 July 2014

Please cite this article in press as: Gauravkumar *et al.*, A Review on Glioblastoma Multiforme (Brain Tumour) -Grade IV Glioma. American Journal of Pharmacy & Health Research 2014.

INTRODUCTION

The brain has two main types of cells; neurons and glial cells. Neurons act as 'messenger' cells, they are highly specialized cells that process and transmit information throughout the nervous system by electrical and chemical sig naling. Glial cells provide support for the neurons and help to regulate the signal transmission (from the word glial meaning 'glue' in Greek). It is estimated that there are 10 times as many glial cells as neurons in the nervous system. Tumors can develop in both neuron and glial cells. Gliomas are the most common tumor of the brain. Gliomas start from glial cells that protect and nourish nerve cells in the central nervous system. Glioma is one of the most challenging types of brain tumors to be treated or controlled locally.[1]

Gliomas have a variety of grades and rates of aggressiveness. They are typically subdivided into low grade gliomas (i.e. grade I and II) or high-grade gliomas (i.e. grade III or IV). The most commonly used grading system proposed by World Health Organization (WHO) categorizes tumors into four groups according to the presence of certain criteria, such as growth rate and cell differentiation (how 'normal' a cell looks under a microscope).

1. Grade I: Slow proliferation, cells look like normal, long survival rate.
2. Grade II: Relatively slow proliferation, cells look like almost normal, may invade, may reoccur as higher grades.
3. Grade III: Rapidly producing, cells look like normal, vascular proliferation, invade surrounding tissue, and tends to reoccur.
4. Grade IV: Very rapid proliferation, very abnormal appearance of cells, invade to large areas, reoccurs, necrotic core, and forms new vascularisation to support growth.

High-grade astrocytic tumors most commonly include Grade III anaplastic astrocytomas (AA) and grade IV gliomas, glioblastoma multiforme (GBM) grow very fast and infilterates to the brain parenchyma. Both types are usually surrounded by edema and the gradeIV forms a network of blood vessels and a necrotic core. GBM is the most invasive and malignant type (grade IV) tumor.[2]

Glioblastomas (GBM) are tumors that arise from astrocytes—the star-shaped cells that make up the "glue-like," or supportive tissue of the brain. Glioblastomas are generally found in the cerebral hemispheres of the brain, but can be found anywhere in the brain or spinal cord. It is not unusual for these tumors to contain cystic mineral, calcium deposits, blood vessels, or a mixed grade of cells. Glioblastomas are usually highly malignant—a large number of tumor cells are reproducing at any given time, and they are nourished by an ample blood supply. Dead cells

may also be seen, especially toward the center of the tumor. Because these tumors come from normal brain cells, it is easy for them to invade and live within normal brain tissue.

GBM is often located in a region of the forebrain known as the cerebrum, which controls some of the most advanced processes such as speech and emotions. While GBM is highly locally invasive (invading normal brain tissue), it rarely spreads to other organs beyond the brain. GBM is a highly aggressive, fast-growing cancer and treatment is often limited by the tumour location and the ability of a patient to tolerate surgery. Consequently, it is a particularly difficult cancer to treat.[5] GBM is the most frequent primary malignant brain tumor, accounting for 12-15% of all brain tumors. GBM occurs most frequently in the frontal and temporal lobes of the brain but can often invade the basal ganglia and brain stem. GBM occurs in patients of all ages, races and genders but men have a higher GBM mortality rate than women by a ratio of 3:2.[3]

Causes And Risk Factors

GBM generally occurs spontaneously and without an identifiable cause, however, certain factors have been linked to an increased risk of developing the disease:

- Age: Although GBM can occur at anyage, including in infants and children, the risk increases with age – the average age at diagnosis is 64 years.
- Gender: GBM is more frequently diagnosed in men, though the reason for this is unknown.
- Genetics: There is an increased incidence of GBM in families with a very rare hereditary disorder called Li-Fraumeni syndrome (LFS), the incidence and prevalence of which is unknown.13 Patients with LFS are susceptible to a variety of different cancers, including brain cancer, breast cancer and leukemia. The syndrome is thought to arise from mutations in a gene which plays a role in tumour suppression.
- Radiation: Evidence suggests that exposure to ionizing radiation (for example, previous radiotherapy to the head or working in the nuclear industry) may increase the risk of developing GBM.[4]
- Other factors: There has been much speculation over a link between mobile phone use and brain tumours and many studies have found conflicting results. No definitive association between the two has yet been found. The long term risks of mobile phone use remain unknown.

Symptoms

As GBM is an aggressive disease that progresses rapidly, patients can deteriorate quickly. The symptoms of GBM can vary depending on the size and location of the tumour in the brain. The following are common symptoms:

- Increased intracranial pressure (pressure build-up in the head) manifesting as headaches, nausea and vomiting
- Cognitive impairment or slowing of cognitive function (e.g. losing the ability to speak or think clearly)
- Changes in personality, mood or concentration
- Visual impairment
- Seizures
- Motor dysfunction such as paralysis
- Sensory loss e.g. numbness, weakness

The symptoms of GBM are often distressing to patients and their caregivers as they significantly and negatively impact on quality of life as well as ability to carry out activities of daily living. Because of this, symptom management can be as important as treatment of the disease.

Diagnosis

Diagnosis often begins with a medical history. The doctor will ask the patient about his symptoms and past illnesses and treatments. The doctor will also do a neurological examination—Reflexes, Coordination, Feeling, Muscle strength. Doctor may check your eyes for signs of increased pressure or swelling.

The doctor may also order one of the following imaging tests:

- **Magnetic resonance imaging (MRI).** MRI uses a large magnet and radio waves to take detailed pictures of the brain and spinal cord.
- **Computed tomography (CT) scan.** A CT scan takes detailed pictures of the brain using an x-ray camera that rotates around the body.
- **Positron emission tomography (PET) scans.** PET scans use radioactive substances to see how organs and tissues are working.
- **Magnetic resonance spectroscopy (MRS).** MRS is a brain scan that looks at biochemical processes in the brain.

Doctor takes a sample of the tumor, which is then examined under the microscope. This the only way to be sure that a brain tumor is a glioblastoma.[5]

Treatment Options

The need for the novel treatment strategies for primary and recurrent GBM is crucial to the lives of the patients. These tumors are usually highly malignant (cancerous) because the cells reproduce quickly and they are supported by a large network of blood vessels. GBM diagnosis is associated with the worst prognosis of all brain tumors. Glioblastoma can be difficult to treat because the tumors contain so many different types of cells. Some cells may respond well to certain therapies, while others may not be affected at all. This is why the treatment plan for glioblastoma may combine several approaches.

Due to the high growth rate of glioblastoma, tumor cells compete for nutrition and oxygen. They get the necessary nutrition from the periphery. The cells in the center of the tumor get less amount of nutrition in the competition and start to die. The dead cells form a necrotic area in addition, to this the high demand for nutrition, tumor needs more blood flow. So it starts the process of forming new network of blood vessels which is called vascularization. High grade variations of these tumors grow very fast, often leading to a life-threatening condition.

Unfortunately, right now, no cure for glioblastoma. Treatment aims to:

- Relieve pain and symptoms
- Improve quality of life
- Prolong survival

Treatment depends on the patient's medical and personal situations. It generally includes surgery, radiation, and chemotherapy.

Surgery

The first step of treatment is to apply maximally safe surgical extraction. The primary objective of surgery is to remove as much of the tumor as possible without injuring brain tissue needed for neurological function (such as motor skills, the ability to speak and walk, etc.).The goal is to remove as much of the tumor as possible this helps to relieve symptoms. Surgical intervention is crucial because it provide clinicians with tissue samples that are used to confirm the histological status and malignancy of the tumor. But, the total resection of the tumor is not possible due to the infiltrative behaviour of gliomas. If these infiltrated cells are not destroyed timely, they will divide into new cells and diffuse to other tissues which will result in tumor recurrence and growth. Therefore, the process is followed by high dose radiotherapy and supplementary chemotherapy. Sometimes a biopsy is done instead of surgery to confirm the diagnosis. This might be done if a patient is not healthy enough to withstand surgery.[6]

Radiation Therapy

Patients usually get radiation treatment following biopsy or surgery. Radiation therapy is an effective non-invasive method to attack the infiltrated cells by some techniques such as intensity modulated radiation therapy (IMRT) or proton therapy. Despite this aggressive approach, the reported median survival is only 14.6 months, although a percentage of patients may survive more than 5 years. Those patients who choose only supportive therapy usually survive for only a few weeks to months.

Radiation therapy uses high-energy x-ray beams to stop or slow tumor growth. External beam radiation therapy aims high-powered x-rays at the tumor and surrounding tissues from outside the body. Another approach is called interstitial radiation or brachytherapy. In this case, radioactive substances are implanted directly into a tumor.

Proton therapy is a type of radiation often used for patients with glioblastoma. Proton therapy provides pinpoint focusing of the radiation beam to the tumor. This reduces the chance of damage to surrounding normal brain tissue. For very young children, radiation may be postponed until after age 3.

Chemotherapy

Chemotherapy is a versatile treatment strategy that allows for the development of the novel therapies against malignant gliomas. Chemotherapy uses drugs to stop the growth of cancer cells. Drug therapy may be used alone or in combination with other treatments such as surgery or radiation therapy. Some chemotherapeutics act as a “radiosensitizer” that enhance the effect of radiation therapy and are given concomitantly with radiation therapy. Chemotherapy is the initial treatment of choice. Most anti-cancer drugs act by inhibiting DNA synthesis or some other process in the cell growth cycle. Anticancer drugs are used to treat malignancies, or cancerous growth. It can be taken by mouth, injected into a vein or muscle, or placed directly into a body part. Oral dosage form is the most popular route for drug therapy. Some chemotherapy drugs destroy cancerous cells or prevent them from reproducing. Others alter a tumor's behavior by changing the environment around it. Several medicines are available to help manage the symptoms of glioblastoma. These drugs can reduce swelling around the tumor, control seizures, and lessen nausea and vomiting. The drug is administered every day during radiation therapy and then in six to eight cycles for five days at higher doses once radiation is completed. While the aim of chemotherapy is long-term tumor control, it does so in only about 20 percent of patients. The decision to prescribe other forms of chemotherapy for tumor recurrence is based on a patient's overall health, type of tumor and extent of the cancer.[7]

Agents used in GBM

The use of only those drugs which crosses blood-brain barrier has shown modest prolongation in patient survival Alkylating agents are the chemical agents that utilize the cellular property of electro negativity to add alkyl groups to cells. Electro negativity is a cell's ability to attract electrons. When a cell inadvertently attracts alkyl groups, the alkyl alters the cell's DNA, resulting in cell death or impaired mitosis. Alkylating agent is known to be effective to treat such type of brain tumors. This class of drug acts by inhibiting or altering DNA synthesis or some other process in the cell growth cycle. Mainly the alkylating agents are given in the solid oral dosage form which is the most acceptable form of delivering the medications. Delivery of the potent chemotherapeutics aims to lower the systemic toxicity while increasing the drug concentration directly to the tumor site. An alkylating agent which having good aqueous solubility and GIT absorption, is used to be given in the oral dosage form. If the agent is known to be highly sensitive to moisture, due to its hygroscopic nature, the drug is encapsulated within the shells of capsule.

CONCLUSION

GBM has limited treatment options. The current standard of care enhances the survival of patients but does not cure or prevent recurrences. Glioblastoma remains a challenging disease to treat even with the recent advances. The above treatment choices work as a tool to improve patients' quality of life and extend progression of free survival. This review does not discuss all therapeutic approaches to GBM; it attempts to highlight the severity of disease and its symptoms, how it may be diagnose or its general treatment.

REFERENCES

1. Angelis L.M. De, Brain tumors, The New England Journal of medicine, 2001; 344:114-123.
2. Levin V. And Prados M.. Biology and treatment of malignant gliomas, in Seminars in Oncology. 2000; 27, 123-126.
3. Giglio P., Chemotherapy for glioblastoma: Past present and future, Glioblastoma. 2002; 203-216
4. Jellinger K., Glioblastoma multiforme: morphology and biology, Acta neurochirurgica, 1978; 42:5-32.
5. Jones RV., Rees J.H., Smirniotopoulos J.G., and Wong K., Glioblastoma multiforme: radiologicpathologic correlation. Radiographics, 1999; 16(6):1413-1438.

6. Stupp R., Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. Engl J Med, 2005; 352(10):987-996.
7. Kitange G., Smith J. et. al. Genetic alterations and chemotherapeutic response in human diffuse gliomas, Expert Review of Anticancer Therapy, 2001;1(4):595-605.