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Glioblastoma Multiforme

Authors

Tejaswi Kanderi[1]; Vikas Gupta[2].

Affiliations

[1] UPMC Pinnacle
[2] South Carolina Department of Mental Health

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Introduction

Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults accounting for 45.2% of malignant primary brain and CNS tumors. GBM remains an incurable disease with a median survival of 15 months.[1] Only 5.5 % of patients survived five years post-diagnosis.[2] GBMs comprises primary and secondary subtypes that evolve through different genetic pathways affecting patients at different ages with differences in outcomes.[3]

Primary GBMs account for 80% of GBMs and occur in older patients with a mean age of 62 yrs while secondary GBMs occur from lower-grade astrocytoma or oligodendroglioma in younger patients with a mean age of 45 years. Secondary GBMs are usually located in the frontal lobe, have a lesser degree of necrosis, and carry a better prognosis than primary GBMs.

The World Health Organization defines GBM as a grade IV cancer characterized as malignant, mitotically active, and predisposed to necrosis. GBM has a very poor prognosis.

Etiology

Many genetic and environmental factors have been studied in glioblastoma multiforme, but no risk factor that accounts for a large proportion of GBM has been identified. So like many other cancers, GBM is sporadic, although a study showed a high prevalence (17%) of prior therapeutic irradiation among patients with GBM.[4] The latency between irradiation and the development of GBM varies from a few years to several decades. Some studies showed the risk of GBM with decreased susceptibility to allergy, immune factors, immune genes, and some single nucleotide polymorphisms detected by genome-wide association studies.[5]

Studies have shown a low risk of gliomas with allergies and atopic diseases.[6] Also, in the short term, less than 10 yrs use of anti-inflammatory medications is associated with a protective effect on GBM.[7] There is no substantial evidence of GBM association with lifestyle factors like smoking, alcohol consumption, drug use, or exposure to N-Nitroso compounds.[8] Studies have shown that the use of mobile phones doesn't increase the risk of development of GBM; however, association with long term use needs further confirmation.[9]

Epidemiology

Based on the 2013 CBTRUS (Central Brain Tumour Registry of the United States) report, the average annual age-adjusted incidence rate (IR) of GBM is 3.19/100,000 population. This is the highest incidence rate among malignant brain and CNS tumors. GBM is primarily diagnosed in adults with a median age of 64 years. It is very rare in children. The incidence increases with age with a peak at 75-84 years of age and a drop after 85 years. The number of cases is expected to increase, given the increasing aging population in the United States.

GBMs are reported more in men; the incidence rate in men is 1.57 % more than that of women.[10] The frequency of

primary GBMs is more in men, and secondary is more common in women.[11] The incidence of GBM is more in whites, followed by blacks.GBMs are commonly seen in the supratentorial region but very rarely found in the cerebellum and spinal cord.

Pathophysiology

Malignant cells have abnormal proliferation, growth, and angiogenesis due to mutations.[12] GBM is found to have many genetic and epigenetic mutations. The mutations are important to identify and classify in order to understand the tumor behavior and treatment resistance throughout the clinical course. Due to the presence of different triggering mutations in addition to key mutations in the GBM stem cells, glioblastoma multiforme is classified into primary tumors arising from neural stem cell precursors and secondary tumors arising from mutations in mature neural cells like astrocytes. Alteration in genetic information, causing expression and suppression of genes compared to their physiological levels in healthy brain cells, lead to both cellular and extracellular matrix changes resulting in a multiform number of biochemical forms. Hence, the name multiforme due to the extent of genotypic diversity.[13]

Histopathology

GBM has typical features of malignant tumors like atypical cells, nuclear hyperchromasia, increased mitotic figures, angiogenesis, and necrotic areas GBM has high vascularity.[14] It is also reported that newly formed vessels may contain multiple Weibel-Palade bodies, which are normally absent in the brain endothelial cells. Vessels may contain thrombi that lead to endothelial damage and proliferation.

Two patterns of necrotic regions are observed, one is a large necrotic area in the center resulting in insufficient blood supply, other is multiple small foci surrounded by pseudopalisading. The first is typically observed in primary glioblastoma, while the second is seen in both primary and secondary variety.[9]

WHO classification categorizes GBM according to histopathology and molecular patterns. According to histopathology, astrocytomas contain glial fibrillary acidic protein (GFAP). Loss of its expression indicates increasing malignancy and denotes undifferentiated tumor cells. Molecular pattern includes IDH-mutant and IDH-wild type detected by Immunohistochemistry (IHC).

Tumors are classified morphologically by WHO as grade I–IV. Grade I includes benign tumors; grade II includes relatively benign tumors; grade III includes low-grade malignant tumors, and grade IV represents aggressive malignant tumors. Grade IV tumors usually have a median survival of 6–12 months. Glioblastoma multiforme is classified as grade IV.

History and Physical

It is very important to gather a detailed history of symptoms in patients with glioblastoma multiforme. Symptoms depend on the location and size of the tumor and similar to symptoms produced by any benign or malignant brain tumors. GBM typically presents with progressive neurological symptoms over days to weeks. Headache is the most common symptom followed by seizures, focal neurological deficits, and symptoms associated with raised intracranial pressure like nausea, vomiting, blurry vision, and altered mental status. Due to nonspecific symptoms, which can also occur in infectious, inflammatory, or other disease processes, physicians should have a high suspicion of malignancy.[9]

Evaluation

The diagnostic mode of imaging for GBM is contrast-enhanced magnetic resonance imaging. Studies have shown that in the majority of cases, tumor diameter is between 5-10 cm at diagnosis.[9] The tumor usually involves corpus callosum and grows into occipital and temporal lobes bilaterally, resulting in a butterfly pattern on imaging, thus the name “butterfly glioma.”[15]

An intraoperatively removed tumor is required for definitive diagnosis through a histopathological exam.[16] In cases where tumor resection is not possible, or if metastatic GBM is suspected, fine-needle aspiration biopsy is performed on accessible sites.[17]

Testing to assess for the presence or absence of GFAP, IDH mutation status, and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status is usually recommended. MGMT methylation status is useful to predict response to specific chemotherapeutic agents.

Treatment / Management

Formulating a treatment plan includes a multidisciplinary team including surgical, medical, and radiation oncologists. The recommended modality of treatment is maximal surgical resection followed by chemoradiotherapy.

According to NCCN guidelines, patients are divided into age >70 and age < 70. Each category is further divided into good and poor performance status to form a treatment plan accordingly. For patients with age > 70 and poor performance status, hypofractionated radiotherapy can be given rather than the standard 6-week course with concurrent chemotherapy.

Treatment slightly varies in patients with methylated MGMT status as they are shown to have maximal benefit from temozolomide, an alkylating agent. So radiotherapy alone is not recommended in these patients, whereas radiotherapy alone is recommended at times for unmethylated patients.

Differential Diagnosis

Differentials for abnormal imaging findings similar to GBM include infectious causes like a bacterial or viral abscess, inflammatory conditions, demyelinating conditions like multiple sclerosis, vascular malformations, sub-acute ischemic or hemorrhagic strokes, benign tumors, and rare artifacts.

Surgical Oncology

The goal of surgery is the maximum safe resection to preserve neurological function with improved survival. Since GBM infiltrates surrounding structures, gross total resection is not always possible.[9] Data from Surveillance, Epidemiology, and End Results (SEER) suggest gross total resection and subtotal resection is associated with improved survival compared to biopsy alone or no surgical intervention. The decision regarding subtotal resection vs. stereotactic biopsy vs. palliative surgery depends on location, age, comorbidities, and goals of care.

Most of the time, surgical resection is useful for definitive diagnosis and treatment. Postoperatively a repeat imaging should be done in 24 to 48 hours to assess the extent of resection.

Radiation Oncology

The goal of radiotherapy is to deliver radiation to the tumor and to a margin of radiographically normal tissue to limit the recurrence. The radiation dose is 50-60 Gy delivered over a period of six weeks in fractions of 2 Gy.[18] [19][20] The two most common methods of delivering radiotherapy include three-dimensional conformal RT (3D-CRT) and intensity-modulated RT (IMRT).

According to NCCN guidelines, hypofractionated radiotherapy can be recommended in patients with poor performance status or Age >70 irrespective of performance status or methylated status of MGMT promoter either with or without chemotherapy.

Clinical trials are ongoing regarding the role of irradiation in patients with recurrent glioblastoma. More evidence is needed regarding dose, frequency, fractionation, and prior treatments, etc.[21]

Pertinent Studies and Ongoing Trials

Studies have shown patients who had RT doses of 50 to 60 Gy had longer median survival than those who received lower postoperative RT doses.[18][19] Studies have also shown marginal or no benefit of brachytherapy for high-grade gliomas given their infiltrative nature.[21][22] Studies testing the efficacy of proton and neutron therapy are under process.

Radiation sensitizers are the compounds given along with radiotherapy with an idea to increase its therapeutic effect. None of these compounds is approved for GBM at present.

Toxicity and Side Effect Management

Side effects of radiation therapy include radiation dermatitis, neurocognitive toxicity, and endocrinopathies in the future.

Patients receiving concurrent chemotherapy with radiotherapy are at increased risk for leucopenia, thrombocytopenia, and hepatotoxicity. Weekly CBC with differential and liver function tests are recommended. Severe thrombocytopenia can result in withholding of radiotherapy until blood counts are stabilized. Due to lymphopenia especially affecting CD4 count, pneumocystis pneumonia prophylaxis should be administered to all patients receiving daily chemotherapy while on radiotherapy.

Medical Oncology

The tumor specimens will be tested for O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation and isocitrate dehydrogenase (IDH) mutation (type 1 or type 2). The presence of methylation of the MGMT promoter predicts improved survival and benefit from chemotherapy with alkylating agents.[23] The presence of IDH 1/2 mutation doesn't guide directly towards specific treatment, but most IDH 1/2 mutant GBM has methylation of MGMT promotor guiding therapy indirectly. Also, IDH 1/2 mutation denotes improved prognosis and eligibility for clinical trials.

According to NCCN guidelines, patients with newly diagnosed MGMT-methylated glioblastoma, age 70 years or younger, should be treated with temozolomide and radiotherapy. Trails have shown increased overall survival at 2 and 5 years on continued follow up in a group who received radiotherapy with concurrent daily temozolomide followed by six monthly cycles of adjuvant temozolomide. Results are similar in patients with age >60 and poor prognostic factors.[24][25][26] Trials were conducted with a combined regimen of temozolomide and lomustine with radiation therapy as an alternative option in MGMT-methylated GBM, which resulted in inconclusive results.[27]

Treatment is similar in MGMT-unmethylated glioblastoma, age 70 years or younger; however, these patients derive less benefit from temozolomide when compared to the methylated group. Standard therapy with temozolomide and radiotherapy is recommended if MGMT status is unknown due to benefit from temozolomide with tolerable side effect profile along with the lack of available alternatives for unmethylated tumors.

In patients with age 70 years or older with good performance status, temozolomide and radiotherapy are recommended, But a hypofractionated radiation course can be done rather than the standard course. Twelve cycles of adjuvant temozolomide are recommended with hypofractionated radiotherapy rather than six cycles in such patients (I, A recommendation).[28] In patients with age 70 years or older with poor performance status, single modality, either temozolomide or radiotherapy, can be considered to avoid side effects and toxicities. In such cases, MGMT methylation status can be helpful in deciding between chemo and radiotherapy.[29]

No strong evidence exists for alternatives to temozolomide for MGMT- unmethylated tumors, although trials have been conducted using a combination of bevacizumab/irinotecan in the past.[30]

Temozolomide is given orally daily during radiation therapy. Adjuvant treatment starts four weeks after radiotherapy, and it is given for six cycles, daily for five days in a 28-day cycle. Side effects include leucopenia, thrombocytopenia, hepatotoxicity, nausea, constipation, fatigue, etc. Regular CBC should be done, and therapy should be held if absolute

neutrophil count (ANC) falls below 1500/microL or platelets fall below 100,000/microL.

Prophylaxis for Pneumocystis pneumonia (PCP) should be given to all patients receiving concomitant chemoradiotherapy due to the high risk of CD4 T cell depletion by temozolomide.

Magnetic resonance imaging (MRI) with contrast is recommended within one month after completing radiotherapy and then frequently every two months during adjuvant temozolomide to assess the disease status. Further recommendations, according to NCCN, includes MRI every two to four months for two to three years, and less frequently after that.

Treatment recommendation guidelines:

Class of recommendation: Class I A, Age> 70- radiotherapy plus concomitant therapy with temozolomide followed by adjuvant temozolomide with six cycles.

Age< 65-70, hypofractionated radiotherapy plus concomitant therapy with temozolomide followed by adjuvant temozolomide with 12 cycles.

It also recommended considering age and performance status while making clinical decisions in GBM patients.[28]

Prognosis

Various clinical factors are shown to affect survival like age, performance status, MGMT methylation status, and IDH1/2 mutation status. Young age, good performance status, MGMT methylation, IDH 1/2 mutant variety confers to have improved survival compared to their counterparts.[31]

Complications

In addition to complications from chemotherapy and radiotherapy that are discussed above, the disease process itself has complications like recurrence. GBM is usually associated with pseudoprogression, which is a sub-acute worsening of MRI findings that occur within three months after the completion of chemoradiotherapy. It is a treatment-related effect. It is important to distinguish between pseudoprogression and the true progression of the disease to avoid abrupt discontinuation of treatment. The key feature to distinguish is that pseudoprogression is usually asymptomatic. Treatment should be continued if pseudoprogression is suspected unless the patient is symptomatic or worsening of clinical features occur.

Consultations

A multidisciplinary team, including physicians from fields of neurology, neurosurgery, surgical, medical, and radiation oncology, is recommended. Also, given a poor prognosis, palliative care involvement is recommended from the early stages of diagnosis.

Deterrence and Patient Education

Glioblastoma multiforme is an aggressive and most common primary brain cancer. It develops from a type of brain cell called the glial cell. As the tumor grows, it causes pressure on surrounding brain cells resulting in symptoms like headache, seizures, memory problems, personality changes, vision, language difficulty, weakness, and paralysis. Some of the symptoms may mimic a stroke.

It is unknown what causes GBM. Studies reported that a history of radiation treatment in early life could increase the risk of getting it.

GBM is diagnosed by CT/MRI, followed by biopsy for confirmation. If the imaging shows the typical appearance and other characteristics, then the suspicion of GBM is high. In such cases, surgical resection is preferred after extensive discussion with the patient, family, and medical and surgical oncology teams.

The mainstay of treatment includes radiotherapy and chemotherapy after surgical resection. Given its aggressive nature, even with maximal therapy, GBM has poor overall survival and a high rate of recurrence. Survival rate ranges from one to two years in most patients. Due to high recurrence, frequent follow-ups with repeat imaging are recommended even after completion of treatment.

Research is going on regarding the use of various new medications. Patients with GBM can participate in clinical trials.

Enhancing Healthcare Team Outcomes

An interdisciplinary team involving nurses, palliative care, care coordinators is extremely important in addition to medical, surgical, and radiation oncologists in the management of patients with GBM. Primary care physicians and neurologists most commonly refer patients with this condition.

Due to the aggressive nature of the tumor, palliative care should be initiated as soon as the diagnosis is made. It is important to determine the goals of care and wishes of patients throughout the continuum of care. Discussions about prognosis need to be done with patients and families to set expectations about the disease. The overall goal is to maintain the patient's quality of life as long as possible with adequate management of symptoms. Nevertheless, discussion regarding newer therapies and clinical trials should be done in eligible patients.[32]

Questions

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