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A Review On – Glioblastoma Multiform

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Abstract: Glioblastoma multiform disease and pathological conditions are known from two decades. The two genetic pathways de novo (primary) glioblastomas and secondary glioblastomas with the genes coding for them is also well known. Adjuvant therapy radiation and chemotherapy is used for the treatment of glioblastoma multiform. Different types of radiation therapies like, external beam radiation therapy (EBRT), stereotactic brachytherapy, stereotactic radiosurgery, boron neutron capture therapy (BNCT**)** used to treat GBM. In chemotherapy temozolamide, glidel wafers, dexomethazone, talampanel, nitrosourease, different platins and etoposides are used. The article gives an insight to the current therapies and research work being done in this area.
Key words: Glioblastoma Multiform.

Introduction:

Glioblastoma multiforme (GBM) is the most common grade IV astrocytoma. Astrocytoma is one of three distinct types of gliomas in the brain, although mixed cell types occur as well. GBMs are highly malignant, infiltrate the brain extensively and at times may become enormous before turning symptomatic. GBM is an anaplastic, highly cellular tumor with poorly differentiated, round, or pleomorphic cells, occasional multinucleated cells, nuclear atypia, and anaplasia. Variants of the tumor include gliosarcoma, multifocal GBM, or gliomatosis cerebri (in which the entire brain may be infiltrated with tumor cells). These variants, however, do not alter the prognosis of the tumor. Multifocal metastasis of GBM, including far distant spinal drop metastasis in patients treated with antiangiogenic chemotherapy[1] is extremely rare but is increasing. Two reasons for the metastasis are an antiangiogenic therapy – induced activation of glioma invasion[2] and the fact that patients are living longer[3]. Several authors have reported a true increase in the incidence of brain tumors, especially among the elderly, and many have attributed the observed changes to developments in diagnostic imaging or changes in the classification system[4].

The overall prognosis for GBM has changed little in the past 2 decades, despite major improvements in neuroimaging, neurosurgery, radiation treatment techniques, adjuvant chemotherapy, and supportive care. Few patients with GBM survive longer than 3 years and only a handful survive 5 years. Glioblastoma multiforme (GBM), like other brain tumors, produces symptoms by a combination of focal neurologic deficits from compression and infiltration of the surrounding brain, vascular compromise, and raised intracranial pressure.

Symptoms include headaches (30-50%), headaches are nonspecific and indistinguishable from tension headache, as the tumor enlarges it may have features of increased intracranial pressure, seizures (30-60%). Many different grading systems exist for gliomas. The current WHO classification of gliomas is based on the presence or absence of 4 histologic criteria: (1) nuclear atypia, (2) mitoses, (3) endothelial proliferation, and (4) necrosis.

Two genetic pathways have been delineated in its development: de novo (primary) glioblastomas and secondary glioblastomas. **De novo glioblastomas** are most common. De novo GBM develops in older patients and demonstrates a high rate of epidermal growth factor receptor (EGFR) overexpression, phosphatase and tensin homologue deleted on chromosome 10 (PTEN) mutations, and p16INK4A deletions. In contrast, **secondary GBM** develops in younger patients and develops from a malignant transformation of a previously diagnosed low-grade tumor. TP53 and retinoblastoma gene (RB) mutations are more common in the development of secondary glioblastomas. Researchers reviewed 16 published studies that looked at cell phone use and the risk of brain cancers and concluded that using cell phones for more than 10 years gives a consistent pattern of increased risk of at least 2 types of brain cancer such as acoustic neuroma and gliomas. The risk is significantly higher for the ipsilateral exposure (tumor on the same side of the brain as cell phone exposure)[5].

In GBM, surgery is always an incomplete debulking, since it is a highly infiltrating tumor and cannot be resected completely. The extent of surgical resection depends on location and eloquence of the brain areas. However, a recent trial using 5-aminolevulinic acid showed a significantly higher rate of complete resection (65% gross total resection) of enhancing tumor on postoperative MRI performed within 72 hours of surgery versus 35% in the conventional surgery arm. Further analysis of the data has demonstrated that patients who underwent gross total resection, regardless of the treatment arm, had superior survival to those who received subtotal resection[6].

Therapy:

After surgery, combination of radiation therapy (RT) with temozolomide followed by adjuvant temozolomide therapy remains the most effective adjuvant therapy for the treatment of patients with GBM. In a phase 3 clinical trial organized by European Organization for Research and Treatment of Cancer and the National Cancer Institute of Canada showed modest improvement of overall survival 14.6 months compared with 12 months in the RT arm[7]. The standard of care for RT in GBM is focal, fractionated external beam RT. New techniques and technologies continue to be evaluated, but none has clearly shown to be superior to standard EBRT. Different methods of administering radiation therapy are available. **i) External beam radiation therapy (EBRT)**: The standard dose of external beam radiotherapy is 60 Gy in single daily fractions of 1.7-2 Gy, 5 times a week. This is applied to a limited field that includes the enhancing volume on CT scans with a 2-3 cm margin or a 1-2 cm margin beyond T2-weighted MR images. **ii) Stereotactic brachytherapy:** In patients who have recurrence after conventional radiotherapy, repeat resection of the tumor and brachytherapy may be indicated. Excellent candidates are patients with unifocal, well-defined, supratentorial tumors less than 5 cm in diameter that do not involve the corpus callosum, brain stem, or ependymal surfaces. Brachytherapy involves using stereotactic techniques to accurately place catheters containing radioactive isotopes within brain tumors, without tumoricidal effect to normal brain tissues. Typically, brachytherapy delivers an additional 50-60 Gy of radiation, bringing the total dose of radiation up to 110-120 Gy. **iii) Stereotactic radiosurgery:** Stereotactic radiosurgery is a technique used to treat small (< 4 cm), radiographically well-defined lesions with a single high-dose fraction of ionizing radiation in stereotactically directed narrow beams. Radiosurgery has the advantage over brachytherapy in being noninvasive, allowing treatment of patients with tumors in surgically inaccessible or eloquent areas of the brain or serious coexisting medical illnesses. **iv) Boron neutron capture therapy (BNCT):** This modality of treatment is still investigational, not widely available, and costly. The value still is not proven. Recently, patients treated with intra-arterial polyhedral borane anion and focused thermal neutron irradiation and reported a 5-year survival rate of 50% with few complications[8]. Boron neutron capture therapy for newly diagnosed or recurrent high-grade gliomas still is being evaluated.

Case studies:

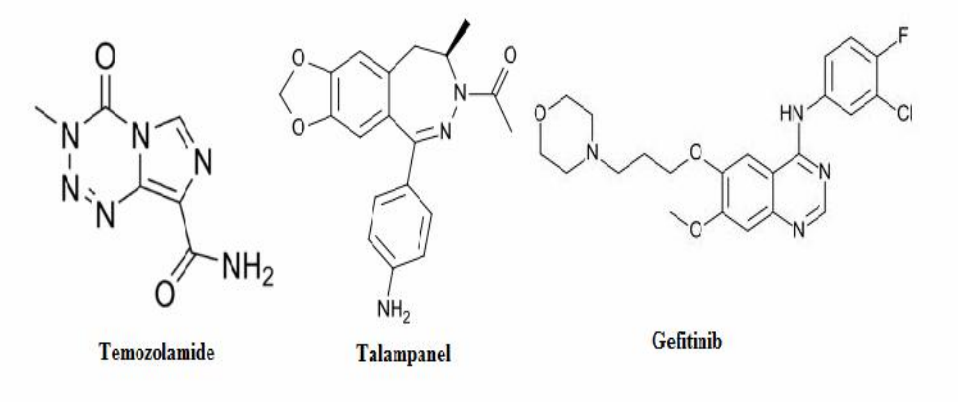
A phase III randomized trial combining low-dose chemotherapy using the oral **alkylating agent temozolomide** concurrently with radiation, followed by an additional 6 months of adjuvant temozolomide showed statistically

significant survival benefit over radiation alone. The median survival was 14.6 months with radiation therapy plus temozolomide and 12.1 months with radiation therapy alone. The treatment was well tolerated with minimal additional toxicity. Another phase III randomized trial that included 240 patients compared surgery with implantation of **polymer wafers with BCNU** (Gliadel wafers) into the tumor bed demonstrated significant prolongation of survival compared with a placebo wafer. Both groups received radiation therapy. The median survival was 13.9 months in the group treated with Gliadel wafers and 11.6 months in the group treated with placebo[9]. A safety and efficacy study by using adjunct combination therapy with BCNU wafers and permanent iodine-125 seeds resulted in favorable survival in patients with recurrent GBM. The median survival was 69 weeks and the median progression-free survival was 47 weeks. The incidence of brain necrosis appeared to be higher than with either therapy alone. However, the necrosis was manageable with surgery or hyperbaric oxygen therapy and did not affect the survival[10]. A posthoc analysis in a subset of patients in a phase III trial, patients whose tumors had methylation of the promoter region of the methylguanine methyltransferase (MGMT) gene survived longer and derived greater benefit from the addition of temozolomide therapy to RT than those whose tumors were not methylated[11].

Extensive research is taking place on newer therapeutic options example, immunotherapy, antiangiogenesis[12], biologic therapy, growth factor and second messenger inhibition, gene therapy. For tumor recurrence, various conventional chemotherapeutic agents, including **nitrosoureas**, BCNU and CCNU, and chemotherapies such as **cisplatin, carboplatin, etoposide,** are used. Selected patients may benefit from tumor resection. Patients with recurrent GBM are encouraged to participate in approved clinical trials to develop effective regimens.

A phase II trial of continuous dose-intense **temozolomide** in recurrent malignant glioma concluded that for patients with recurrent GBM, rechallenging with 50 $mg/m^2/d$ continuous dose-intense temozolomide is a valuable option. Patients with recurrence after a treatment-free interval or patients experiencing progression during the first 6 cycles of conventional adjuvant temozolomide therapy benefit the most[13]. This care includes treatment of cerebral edema with a potent glucocorticosteroid. **Dexamethasone** is most commonly used because of its potent impact on edema and minimal mineralocorticoid effects. Steroid therapy often requires prophylactic use of H-2 blockers to prevent gastrointestinal side effects. A recent animal study in rats investigated the use of monoclonal antibodies 8H9 as interstitial infusion showed significant volumetric response and prolonged survival (54 d for untreated rats vs 120 d for treated rats) as a potential target therapy for high-grade gliomas[14]. Over expression of EphA7 was predictive of adverse outcomes in patients with primary and recurrent glioblastoma multiforme, independent of microvascular density (MVD) expression. Moreover, high density of both MVD and EphA7 expression predicted the disease outcome more accurately than EphA7 alone[15]. Nuclear FABP7 was preferentially expressed in infiltrative gliomas only and associated with poor prognosis in EGFR-over expressing glioblastoma. The study suggested that FABP7 immunoreactivity could be used to monitor the EGFR-overexpressed GBM progression[16].

Studies are focusing attention on identifying **molecular markers** similar to anaplastic oligodendroglioma to predict response or resistance to specific treatments. One such interest is the expression of MGMT (O^6 - methylguanine–DNA methyltransferase) gene. The protein product of this gene, 06 alkyl guanine DNA-alkyl-transferase (AGAT), is shown to be a major mechanism for tumor resistance to alkylating agents. Recent clinical trials for malignant gliomas now often include determination of MGMT expression status. Several other molecular markers, such as epidermal growth factor receptor, platelet-derived growth factor receptor, vascular endothelial growth factor receptor, loss of chromosome 10, mutation or loss of the p53 gene, expression of the YKL-40 gene, loss or mutation of PTEN gene, are being investigated. Studies are focusing on new targets such as receptor blockade. Glutamatergic system alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor-blocker talampanel may be beneficial in this disease. In a recent study, **talampanel** was added to the standard radiation and temozolomide in adults with newly diagnosed glioblastoma to estimate the overall survival as well as talampanel toxicity as a secondary measure. The study concluded that talampanel was well tolerated and compared with European Organization for Research and Treatment of Cancer (EORTC) data, median survival seemed superior). Therefore, talampanel can be added to radiation therapy and temozolomide without significant additional toxicity[17, 18].



Regulatory T cells, Tregs, are a subset of lymphocytes that have immunosuppressive attributes. They are elevated in blood of glioblastoma patients and within this tumor's tissue itself. Indoleamine 2,3-dioxygenase (IDO), converts tryptophan to kynurenine. IDO activity enhances Treg formation by pathways that are unknown. Experimentally, inhibition of IDO decreases Treg function and number in rodents. The common anti-viral agent **acyclovir** inhibits IDO. Acyclovir may thereby decrease Treg function in glioblastoma. If it can be confirmed that Treg counts are elevated in glioblastoma patients' tumor tissue, and if we can document acyclovir's lowering of tissue Treg counts by a small trial of acyclovir in pre-operative glioblastoma patients, a trial of acyclovir effect on survival should be done given the current poor prognosis of glioblastoma and the well-established safety and low side effect burden of acyclovir[19]. The potential effects of **anti-integrin** strategies in cancer therapeutics are threefold: antiangiogenesis; anti-invasion; and anti-tumor. In addition, integrin inhibitors have been shown to augment the effect of radiation and may augment that of other therapies, including cytotoxins, cell signaling inhibitors, immunotherapies, vascular targeting agents and antiangiogenics[20]. As a result of their diverse activities in many biochemical processes that are related to a variety of pathologies other than cancer, anti-integrin compounds have been under development for several indications and four are currently FDA approved for noncancerous indications. Drug design often focuses on developing compounds or biologics against specific integrin subtypes or extracellular domains that are known to have increased expression in the disease of interest. Three types of integrin inhibitors are being evaluated in preclinical or clinical cancer trials[21]. Radiosensitizers, such as newer chemotherapeutic agents[22], targeted molecular agents,[23, 24] and antiangiogenic agents may increase the therapeutic effect of radiotherapy[25]. A small proportion of glioblastomas responds to **gefitinib or erlotinib** (tyrosine kinase inhibitors). The simultaneous presence in glioblastoma cells of mutant EGFR and *PTEN* was associated with responsiveness to tyrosine kinase inhibitors, whereas increased p-akt predicts a decreased effect[26,27]. Other targets include PDGFR, VEGFR, mTOR, farnesyltransferase, and PI3K.

Conclusion:

Phosphatase and tensin homologue Chromosome 10 (PTEN) mutations, p16INK4A deletions, TP53 and retinoblastoma gene mutations are the indicators to identify glioblastoma. PDGFR, VEGFR, PI3K, tyrosine kinase, farnesyltransferase are the important targets. For the survival in this disease condition adjuvant therapy of different types of radiations with chemotherapy is succesful to survive for 4 to 5 years. Talampanel with standard radiation therapy have also shown good results. Current studies indicates tyrosine kinase inhibitors gefitinib or erlotinib respond to small glioblastomas. With the chemotherapy also the antiviral agents like acyclovir showed good results to improve the immunity in glioblastomic patients.

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