



Prognosis of Glial Tumors with Cytomegalovirus: A Brief Review of Literature



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Abstract

Malignant tumors of central nervous system are categorized with the poor prognosis, with high level of mortality and morbidity. Glioblastomas is one of the most deadly malignant tumor of brain in adults which cost their lives. Role of cytomegalovirus in glioblastoma pathogenesis was proposed decades ago and much work was done to figure out the genetic involvement of CMV leading to poor prognosis of tumor. It has been the topic of ongoing research for some decades now. We have conducted this review article to evaluate the prognosis of glial tumors with cytomegalovirus, after a thorough review of medical literature from PubMed and Google scholar. Currently, many clinical trials and researches has been done to evaluate the treatment of glioblastoma and to see the beneficial effects on the growth of tumor, and significant results has been shown in the treatment of GBM which increases the life expectancy up to 15 months.

Keywords: Glioblastoma; Cytomegalovirus; Gliomas; Pathogenesis; Oncomodulatory function

Abbreviations: HCMV: Human cytomegalovirus; GBM: Glioblastoma Multiform; WHO: World Health Organisation; PCV: Procarbazine; TMZ: Temozolomide; PDGFRA: Platelet-Derived Growth Factor Receptor- α ; IHC: Immunohistochemistry; PCR: Polymerase Chain Reaction; IE1-Immediate Early 1

Introduction

The World Health Organization (WHO) classification system groups gliomas into 4 histological grades defined by increasing degrees of undifferentiation, anaplasia, and aggressiveness [1]. According to WHO grade IV tumors (glioblastoma and its variants), grade III tumors are (anaplastic variants of astrocytoma, oligodendrogliomas and oligoastrocytoma) and grade II are (diffuse astrocytomas, oligodendrogliomas and oligoastrocytomas). In this article we will be focusing on the malignant tumors with their survival rates Table 1 [2]. Human cytomegalovirus (HCMV) is a beta herpes virus infecting 70-90% of general population and continue to live in host after the primary infection [3], it can cause serious complication on

reactivation in fetuses or immune compromised. According to the studies it was to made clear that existence of HCMV components showed no significant correlation with the prognosis of glioma patients. The objective of this study was further emphasis on prevalence, genetic involvement and prognosis of CMV with the gliomas. Here in this review we will be discussing the:

1. Genetic involvement of HCMV in the GBM
2. GBM prognosis with HCMV
3. HCMV role in GBM
4. Therapeutic role of HCMV

Table 1: Classification of Malignant gliomas and survival according to the Surveillance, Epidemiology and the End Result (SEER) Program Registry.

	1-year (Survival Rate%)	5-year (Survival Rate%)
WHO grade IV tumor Glioblastoma and variants	35.5	4.7
WHO grade III tumors		
1.Anaplastic astrocytoma	60.1	25.9
2.Anaplastic oligodendroglioma	81	49.4
3.Anaplastic oligoastrocytomas	NA (not available)	NA (not available)
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Review of Evidence

Literature was searched on engines like Google Scholar, PubMed, Scopus and Embase. MeSH and non-MeSH terms like “Glioblastoma”, “Cytomegalovirus”, “Gliomas”, “Pathogenesis”, “oncomodulatory function” were used to filter out the topic specific data. Two independent reviewers (AL, MN) thoroughly searched titles, keywords and abstract to extract the relevant data. Any disagreement was resolved by the consensus of third independent reviewer (SDA). Collected data was analyzed by two independent reviewers (KAA, SDA) to finalize the list of articles on which the review is conducted. Similarly, any conflict between two reviewers was resolved by a third independent reviewer (MMS). Articles relevant to Gliomas (pathogenesis, association with CMV, clinical prognosis, treatment options) were included in this research. However, articles mainly discussing other primary tumors like lymphoma, suprasellar tumors, and ventricular tumors were excluded from this study. Data search was not confined on the basis of time period, type of article and books or gray literature. Only limitation applied was exclusion of data in language other than English-language.

Genetic Involvement of HCMV in GBM

HCMV association with the gliomas is a heavy debate and link between them is still controversial. Many researches and papers are submitted on this topic from the late 1900s and in the early 2000s the presence and role of HCMV was reported and uptill now work is been done to lower the incidence rate. In 2002, Cobbs et al. was the first person to report the presence of HCMV in high grade gliomas [4]. He suggested in his research that maximum of the glial tumors were associated with HCMV and it play vital role in the pathogenesis of tumor .In his study with use of immunohistochemistry (IHC) of formalin fixed paraffin-embedded tissue he was able to identify immediate early 1 (IE1) protein, pp65,p52/76-kDa early DNA binding protein and early protein, he was surprised to found the proteins both in cytoplasm

and nuclei of tumor but not in the normal brain tissue. Further in the early 2000s,work was done to see the pathogenesis and to confirm the studies about the presence of HCMV when, in 2008 Scheurer et al. [5] with the use of (IHC) and was able to detect HCMV (IE1) protein in 100% of glioblastomas and 82% of low-grade gliomas from the paraffin-embedded tissues. The author validated the findings of Cobbs and colleagues that HCMV IE1 and other virus specific oligonucleotides can be detected by these methods but there was no sign of virus in the necrotic area or outside the tumor margins [4-6]. Upto the present time studies have identified the presence of HCMV proteins IE1, US28, pp65, gB, HCMV IL-10, and pp28 and the HCMV genes IE1 and gB with the use of, immunohistochemistry, in situ hybridization, electron microscopy, polymerase chain reaction (PCR) coupled with DNA sequencing, enzyme-linked immunosorbent assay, and flow cytometry [3,4,6-11], among them the most studied protein has been IE1. Unpublished data presented by T. F. Kowalik proved difficult to arrange the HCMV genome found from the sample of human glioblastoma individually, it may be due to discontinuous or fragmented genomes. Using the combined PCR-DNA sequencing methodology,94% samples of CMV genomic DNA was detected, it’s a method that show polymorphisms in specific area of glioblastoma encoding the tegument protein pp65 [12], it was summarized that HCMV genomes associated with glioblastoma are tumor specific and it can vary in different population. After the study of results, it was concluded that there is sufficient presence of HCMV protein in gliomas and their sequences and viral genome are present in the malignant gliomas [9-13].

GBM Prognosis with CMV

There was no prognostic role of HCMV in GBM was found, whether the IHC staining showing positive IE1 or pp65 staining or the patient had HCMV DNA in tumor tissue or blood [14,15]. According to the research it was reported that there is increased

survival rate for the low grade tumors (IE1 IHC positive<25%) compared with high grade tumors (13 vs 33 months, p = 0.036) but there was no disease free survival rate was found [16], but it is still controversial and debatable that whether the relationship between increased number of positive IHC cells was caused by increased viral reactivation which was due to immunosuppressive tumor, oncomodulatory properties of HCMV causing more aggressive phenotype or an artifact of intra-tumoral variability in staining.

Role of HCMV in GBM

Many reviews and articles were published to know the pathogenesis of HCMV and how it acts on the cell cycle interfering with the cell proliferation, amplification, its angiogenesis. According to a recent study done clarify that platelet-derived growth factor receptor- α (PDGFRA) is the key element which was needed to for the entry of HCMV in the cell which further activate the PI(3) K/Akt pathway causing the inhibition of apoptosis [17], tumors with amplification of PDGFRA had higher rate of HCMV infections. An increased human telomerase activity in cell with HCMV infection or positive IE1 activity was thought of increase cell survival [18]. From another study it was made clear that HCMV pp71 protein co-localizes with the stem cell factor of GBMs, and causes capillary formation resulting in angiogenesis [19].

Onco-Modulatory Factors

The idea of oncomodulation and CMV was initially introduced by Cinatl et al. [20] in 1996, that HCMV can alter the function of cancer cell without being directly involved in malignant transformation. Further it was updated that even the DNA of CMV was not even retained in the cell and lately the antigens of HCMV started to decline [21]. Malignant tumors like GBM express certain factors and receptors (e.g: CD-133 & Mdm-2 receptor expression) which enhances the survival capability of tumor and assist its growth under any stressor [22,23].

The glioma mouse model Mut3, a study was done which shows mice with mutation in TP53 and Nf1 genes shown decreased glioma-associated survival from MCMV infection by STAT-3 associated mechanism [24]. There are three mechanisms by which signal transducer and activator of transcription-3 can activate HCMV:

- i. Secretion of interleukin-6 by HCMV-infected cells via the interleukin-6R–Janus kinase–STAT3 pathway.
- ii. Expression of the constitutively active HCMV chemokine receptor US28, which phosphorylates STAT3.
- iii. HCMV glycoprotein B signaling through the PDGFRA–Janus kinase–STAT3 axis [25,26].
- iv. Increased signaling of STAT3 activity leads to cell cycle progression, but this cycle is dysregulated in GBM lead to mutation of TP53, loss of PTEN gene causes the inhibition tyrosine kinases receptor (Ras) and similarly loss of Nf1 function affects the function of phosphoinositide-3-kinase.

Therapeutic Role of CMV

Malignant cancers spread by two ways. Initially, tumor cells spread through the hematogenous and lymphatic route and metastasize to another organ. Then, secondly it invades the local intra-organ where it forms a new tumor. In case of gbm distant metastasis most commonly occur through cerebral spinal fluid flow [27,28]. According to a research we have found that patient with gbm have median survival rate of only 15 months [29,30]. The treatment currently designed for gbm is initially surgery when feasible, then radiation followed by chemotherapy temozolomide [29]. Some additional therapeutic options are also available like angiogenesis inhibitors in combination with chemotherapeutic agents, active and passive immunotherapy but all these treatments failed due to the invasive nature of gbm as it crosses the blood-brain barrier. Tabular presentation of glioma classification is given in Table 2 [31-34].

Table 2: Summary for the current treatment for malignant gliomas.

Tumors	Treatment
1. Glioblastoma (WHO grade IV)	Maximal surgical resection, radiotherapy, plus concomitant and adjuvant TMZ
2. Anaplastic astrocytomas (WHO grade III)	Maximal surgical resection (can go for radiotherapy, plus concomitant plus adjuvant TMZ or TMZ alone) there is no accepted standard therapy.
3. Anaplastic oligodendrogliomas and anaplastic oligoastrocytomas (WHO grade III)	Maximal surgical resection (can do radiotherapy alone, TMZ or PCV with or without radiotherapy, radiotherapy with concomitant and adjuvant TMZ or radiotherapy plus adjuvant TMZ (any of the options can be taken there is no standard treatment option.
4. Recurrent tumors	Reoperation in selected patients, carmustine wafers, conventional chemotherapy (lomustein, PCV, carmustine) bevacizumab plus irinotecan, experimental therapies

Surgical resection is the first most step-in malignant gliomas, but it is not helpful in completely removing the tumor because its invasive nature and it help in decreasing the symptoms and also helps molecular study of the mass. Currently, the surgical procedure has improvised and ensure safety of the patient because the extent of the tumor infiltrate can be located with the

advances such as MRI-guided neuronavigation, intraoperative MRI, functional MRI, intraoperative mapping [35]. Radiotherapy is the essential part in the treatment, from the researches it was made clear that radiotherapy after surgery has shown a marked increase in the patient survival from 3 to 4 months up to 7 to 12 months [36,37]. Chemotherapy also plays its role in increasing

the survival rate according to two meta-analysis adjuvant chemotherapy increases the survival 6-10% in 1-year survival rate [38,39].

Conclusion

Malignant gliomas have been the topic of interest from the early 1900s and still work has been going on this, although it's still incurable disease but now proper and improvised treatment option has introduced for the better understanding of its complex molecular biology, microenvironment and immunologic interactions with the host. Several treatment options have been introduced with the promising survival rate of 15 months. Still work is going on for better progression and improving the future of patients.

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