

Could we Benefit from Varicella Zoster Vaccines as Immune Adjuvants in Glial Tumor Treatment?

Meric A Altinoz^{1*} and İlhan Elmaci^{1,2}

¹Neuroacademy Research Group, Istanbul, Turkey

²Department of Neurosurgery, Memorial Hospital, Istanbul, Turkey

*Corresponding Author: Meric A Altinoz, Neuroacademy Research Group, Kagithane, Istanbul, Turkey.

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Abstract

Glioblastoma is the most frequent malignant brain tumor of adults and has a very grave prognosis. Therefore, development of novel strategies in glioblastoma treatment is an urgent necessity. Several epidemiological studies have shown that a history of varicella zoster infection (chickenpox or shingles) and/or immunopositivity against varicella zoster significantly protect against risk of high grade glial tumors. Varicella zoster is a neurotropic α -herpesvirus which can infect the central nervous system. Because of its neurotropism and its capability to exert decades-long latency across the neuraxis, Varicella zoster is especially outstanding to investigate in regard to development and/or prevention of glial tumors. Indeed, Varicella Zoster-stimulated peripheral blood mononuclear cells from Varicella Zoster-seropositive individuals could recognize and kill HLA class I-matched glioma cells, but not matched astrocytes. It was proposed that the protective effect of prior Varicella Zoster infection against the incidence of glioma may be mediated by cytotoxic T lymphocytes that recognize epitopes shared by Varicella Zoster virus and glioma cells. In this manuscript, we bring the available together and conclude that anti-Varicella Zoster vaccines strongly deserve to be investigated in animal models, whether they can stimulate immunity and decrease growth of intracranially implanted glioma cells.

Keywords: Glioblastoma; High Grade Glial Tumor; Varicella Zoster; Chickenpox; Shingles; Vaccine

Introduction

Glioblastoma (GBM) has the highest incidence among primary brain tumors, second only to meningioma [1]. The prognosis of GBM is extremely bad, with a 5-year survival rate of < 4% from the time of diagnosis [1]. This grave nature of GBMs indicates a crucial need to discover novel strategies for their treatment. Anecdotal case reports and small case series showed significant tumor regression following injection with rabies virus vaccine (RV-V) in patients with GBM [1]. As will be outlined below, several and consistent epidemiological reports also suggest that a history of Varicella Zoster Virus (VZV) infection and/or immunopositivity against VZV-antigens have a significantly protective effect against GBM. Hence, in this theoretical review article, we propose that VZV-vaccines may be novel immunoadjuvants in GBM treatment. Varicella zoster virus (VZV) is one of eight herpesviruses infecting humans and causes chickenpox (varicella) in teens and young adults and herpes zoster (shingles) in older. VZV is also known by different names, including chickenpox virus, varicella virus, zoster virus, and human herpesvirus type 3 (HHV-3). VZV is a neurotropic α -herpesvirus which can infect the central nervous system, with an annual incidence rate of 1.02 - 1.8 cases per 100,000 [2]. Other important neurological complications of VZV infection include postherpetic neuralgia, zoster multiplex and inflammation of cerebral arteries which may lead to stroke [3]. VZV initially infects the respiratory mucosa and then progresses into viremia, during which the virus is transported to and replicates in the skin. Prior to the employment of routine VZV vaccination in the 1990s, chickenpox was an extremely common childhood illness, affecting over 90% of individuals. After acute infection, the virus establishes life-long latency in the cranial nerve and dorsal root ganglia, and may later exert recrudescence in

about 10 - 20% of VZV-infected individuals, causing shingles. Viral recrudescence can also result in encephalitis and myelitis. Because of its neurotropism and its capability to exert decades-long latency across the neuraxis, VZV is especially outstanding to investigate in regard to development and/or prevention of glial tumors.

VZV shares a considerable genome homology to herpes simplex viruses and its single, linear double-stranded DNA is 125,000 nt long including 71 open reading frames, 68 of which encode proteins and thus may provide immune targets. VZV-envelope glycoproteins (gB, gC, gE, gH, gI, gK, gL) correspond with those in HSV. Spherical VZV virions include a 100 nm nucleocapsid of 162 hexameric and pentameric capsomeres. The capsid is surrounded by loosely associated proteins known as the tegument, which exert critical roles in initiating the virus reproduction. The tegument is covered by a lipid envelope studded with glycoproteins on the external surface of the virion. A live attenuated VZV Oka/Merck strain vaccine was approved in 1995 by the US Food and Drug Administration (FDA) and is currently marketed in the United States under the trade name Varivax[®]. In 2006, the FDA approved Zostavax[®] for the prevention of shingles, which is a more concentrated formulation of the Varivax[®], developed to stimulate immunity in older adults whose immunity to VZV declines with advancing age. A systematic review by the Cochrane Library shows that Zostavax[®] reduces the incidence of shingles by about 50% [4].

Epidemiological Evidence Indicating Lowered Risk of GBM With History of VZV-Infection and/or Immunopositivity Against VZV

The first epidemiological studies, which demonstrated association of VZV-infection with reduced risk of glioma, were published in 1997 [5,6]. The authors questioned adults with glioma (n = 462) and age-, sex-, and ethnicity-matched controls (n = 443) about their histories of chickenpox or shingles [5,6]. They revealed that the cases were significantly less likely than controls to report a history of either chickenpox (odds ratio, OR = 0.4) or shingles (OR = 0.5) [5,6]. To achieve serologic support for these results, the authors performed double-blind ELISA assays for IgG antibodies to VZV among 167 self-reporting subjects for whom blood samples were available. Among those reporting a positive history, cases were less likely than controls to be positive for anti-VZV IgG (71 % vs. 85%) and an OR of 0.6 was obtained using either serologic data or reported history of chickenpox in this subgroup of subjects [5,6]. The authors proposed that either adults with glioma were less likely than controls to have had prior VZV infection or to have an adequate IgG response to VZV.

In 2001, the same group reported their results regarding immunopositivity to four common herpesviruses (VZV, herpes simplex, cytomegalovirus, and Epstein Barr) among 134 cases and 165 controls that represent all subjects for whom blood specimens were available [7]. This report added results for IgG antibodies to VZV among 56 cases and 76 controls to their previous results published for 78 adult glioma cases and 89 controls. After adjustment for age, White versus non-White ethnicity, and gender, GBM cases were less likely than controls to have IgG antibodies to VZV (OR = 0.4) [7]. Furthermore, cases with lower grade of gliomas were as likely as controls to have anti-VZV antibodies. Moreover, GBM cases were also somewhat more likely to have antibodies to herpes simplex virus and cytomegalovirus, suggesting that a general immune depression from the brain tumor or treatments may not account for the lower prevalence of antibodies against VZV [7]. Since VZV infection usually occurs early in life and since the study was statistically adjusted for age, the authors concluded that it is unlikely that age differences between cases and controls caused these findings. To explain their findings, they proposed two different theories. The first is that, if a virus or viruses with some cross-reactivity to VZV involve in triggering gliomagenesis, individuals with stronger immunity to VZV might be less susceptible to glioma. Their second theory is that latent VZV infection itself might afford some protection against GBM formation via a mechanism involving that malignant conversion of glial cells might increase their susceptibility to the infection and cytolytic reactions elicited by VZV [7].

In 2005, the same group reported their results regarding the associations of IgG antibodies to VZV and three other herpesviruses among 229 adults with glioma and 289 controls [8]. The authors underlined that none of the cases in their current report were included in the previous report and, thus, represented an independent series. Cases were less likely than controls to report a history of chickenpox (the age-, gender-, and ethnicity-adjusted OR = 0.59), and they also had lower levels of IgG to VZV (for being in the highest quartile vs. the lowest quartile: the age-, gender-, and ethnicity-adjusted OR = 0.41). The inverse association with anti-VZV IgG was most pronounced for

GBM cases versus controls and there was no significant association between VZV and lower grade gliomas [8]. Furthermore, the inverse ORs for the fourth versus the first quartile of anti-VZV IgG for cases of any histology versus controls declined slightly yet remained statistically significant, when subjects were excluded from analysis who were taking medicines that might decrease anti-VZV IgG levels [8].

In 2011, Sjöström, *et al.* reported results of their study in regard to the associations of prediagnostic immunity to VZV, cytomegalovirus (CMV), adenovirus (Ad), and Epstein-Barr virus (EBV) including the nuclear antigen (EBNA1) with glioma risk [9]. They performed analyses on plasma samples from 197 adult cases with glioma and 394 controls collected from Sweden and Denmark. Since samples from glioma cases could be influenced by treatments such as steroids and chemotherapy, studies on prediagnostic immunity against viruses added further value to determine real associations between anti-viral immunity and risk of glioma. They found that low VZV IgG levels were significantly more common in glioma cases than the controls (OR = 0.68) for the fourth compared with the first quartile ($p = 0.06$ for trend). Furthermore, the results became more significant when evaluating cases with blood sampling at least 2 years before diagnosis (OR = 0.63) ($p = 0.03$) [9]. Moreover, no association with glioma risk was observed for CMV, EBV, and adenovirus. These results further supported the findings that VZV-infections may provide a protective role against glial tumors by showing that the levels of anti-VZV antibodies in glioma patients are lower before than immunosuppressive treatments. In the same year, McCarthy, *et al.* published data pooled from 7 case-control studies (5 US and 2 Scandinavian) [10]. Unconditional logistic regression was used to determine ORs adjusted for age, gender, and study site. They analyzed data on 617 cases and 1260 controls. Having had chicken pox was associated with a decreased risk of oligodendroglioma (OR = 0.6) and anaplastic oligodendroglioma (OR = 0.5) in the US studies [10].

Lee, *et al.* measured antibodies against ten VZV-related proteins, selected for high immunogenicity or determined function in 143 glioma cases and 131 healthy controls [11]. Glioma cases exerted significantly lower seroreactivity in comparison to controls for six antigens, including proteins IE63 (OR = 0.26, comparing lowest quartile to highest), and the VZV-unique protein ORF2p (OR = 0.44, lowest quartile to highest). In their final model, anti-IE63 reactivity was the most significant parameter associated with glioma status ($p < 0.0001$). IE63 is an immediate early protein involved in transcriptional activation during viral replication and is the only protein proven to be essential for latency [11]. IE63 is also required for viral immune evasion by downregulation of IFN- α induced host antiviral response. Immunological characterization of this protein may help in discovery of mechanisms behind the different immune responses of glioma patients from controls. The authors also observed strong correlations of gE and gH with glioma, especially in men and in patients who reported more than 2 allergies [11].

Of the seven membrane glycoproteins, gE is the most highly expressed and in infected host cell membranes, gE plays an essential role in cell fusion and viral propagation and is indispensable for viral infectivity. Moreover, gH contains an immunodominant complement-independent neutralization epitope, where directed antibodies can effectively block viral entry and spread [11]. They did not find any significant association of gI, except for a borderline association in women. Another glycoprotein, gK which may also be essential for syncytia formation and viral growth, was insignificant in the parsimonious model but was significantly associated in women. ORF2p and ORF20p were significant both in the parsimonious model and stratified analyses, while ORF12p was significant only in stratified analyses [11]. Antibodies to IE63, gE, gH and ORF12p were very significant in men, whereas those to gK, ORF2p and ORF20p were so in women. These findings are not easily explicable, but the authors attributed these changes to the fact that women are more prone to T helper2 type cytokine profiles related to humoral immunity [11].

Lastly in 2016, Amirian, *et al.* reported their results about the association of VZV infection with glioma risk by utilizing data from the Glioma International Case-Control Study (GICC), which is a multisite consortium study with information on 4533 cases and 4171 controls collected across five countries [12]. Using two-stage random-effects restricted maximum likelihood modeling and after adjusting for age and sex, they revealed that a positive history of chickenpox was associated with a 21% lower glioma risk. The protective effect of chickenpox was stronger for high-grade glioma, particularly among those under age 40 [12]. These recent findings, which represent the results of the largest study to date on this topic, confirmed the inverse associations on VZV and glioma.

VZV-Specific Lymphocytes Exert Cytotoxicity Against GBM Cells *Ex Vivo*

Canniff, *et al.* tested several possibilities to reveal the association between anti-VZV immunity and lower risk of gliomas. Reactivated VZV preferentially infects and kills gliomas compared to normal astrocytes; and VZV-specific cytotoxic T lymphocytes (CTL) cross-react with gliomas [13]. They demonstrated that VZV stimulated peripheral blood mononuclear cells from VZV-seropositive individuals recognized and killed HLA class I-matched glioma cells (mean \pm SE decrease in viability of $26 \pm 12\%$, $p = 0.04$), but not matched astrocytes [13]. VZV infection of the glioma cells did not influence the T cell-mediated killing. During asymptomatic reactivations, VZV may invade the CNS, which is strongly evidenced by studies that found VZV DNA in the cerebrospinal fluid of patients with clinically unsuspected VZV infection [13]. Symptomatic VZV reactivation, which clinically presents as herpes zoster; a painful vesicular rash of dermatomal distribution, is commonly accompanied by VZV invasion of the CNS including parenchymal lesions. Based on these grounds, the authors have concluded that the protective effect of prior VZV infection against the incidence of glioma may be mediated by cytotoxic T lymphocytes (CTLs) that recognize epitopes shared by VZV and glioma cells [13]. Specific CTLs may recognize brain tissue if they encounter cross-reactive epitopes or if they are equipped with dual T cell receptors, one for the virus and another that is tissue specific. The authors also noted that the effector cells in our assays were bulk peripheral blood monocytes (PBMC) which contain 20% to 40% CD8+ conventional CTLs [13]. Additionally, VZV-specific CD8+ T cells account for < 5% of the total CD8+ cells in young adults. Assuming that 5% of the VZV-stimulated PBMC used in the glioma cytotoxic assays were VZV-specific CTL, the effector-to-target ratio was 1 VZV-CTL to 2 glioma cells, which suggests that few VZV-specific T cells are needed to lyse glioma cells [13].

Conclusions

It is currently unclear if re-exposure to VZV antigens, such as it may occur during VZV reactivations, boosts the brain resident memory T cells. It would be also essential to illuminate if the VZV-specific memory T cells in the CNS could be expanded through vaccination or other interventions. Two types of research can be employed to reveal the potency of VZV-vaccines as potential immune adjuvants in management of GBM. At first, VZV vaccines may be tested in immunologically-humanized mouse, whether they could stimulate immunity and block growth of intracranially implanted human GBM cells. At second, epitop similarities between VZV surface antigens and GBM cells shall be revealed. Currently existing strong evidence which indicates lower incidence of GBM in patients with anti-VZV immunity would pave the way to develop a novel and likely efficient immune modality in treatment of these grave tumors.

Bibliography

1. Altinoz MA, *et al.* "Rabies virus vaccine as an immune adjuvant against cancers and glioblastoma: new studies may resurrect a neglected potential". *Clinical and Translational Oncology* (2017).
2. Becerra JC, *et al.* "Infection of the central nervous system caused by varicella zoster virus reactivation: a retrospective case series study". *International Journal of Infectious Diseases* 17.7 (2013): e529-e534.
3. Nagel MA, *et al.* "The varicella zoster virus vasculopathies: clinical, CSF, imaging, and virologic features". *Neurology* 70.11 (2008): 853-860.
4. Gagliardi AM, *et al.* "Vaccines for preventing herpes zoster in older adults". *Cochrane Database of Systematic Reviews* 10 (2016): CD008858.
5. Wrensch M, *et al.* "Familial and personal medical history of cancer and nervous system conditions among adults with glioma and controls". *American Journal of Epidemiology* 145.7 (1997): 581-593.
6. Wrensch M, *et al.* "Does prior infection with varicella-zoster virus influence risk of adult glioma?" *American Journal of Epidemiology* 145.7 (1997): 594-597.

7. Wrensch M., *et al.* "Prevalence of antibodies to four herpesviruses among adults with glioma and controls". *American Journal of Epidemiology* 154.2 (2001): 161-165.
8. Wrensch M., *et al.* "History of chickenpox and shingles and prevalence of antibodies to varicella-zoster virus and three other herpesviruses among adults with glioma and controls". *American Journal of Epidemiology* 161.10 (2005): 929-938.
9. Sjöström S., *et al.* "Human immunoglobulin G levels of viruses and associated glioma risk". *Cancer Causes Control* 22.9 (2011): 1259-1266.
10. McCarthy BJ., *et al.* "Risk factors for oligodendroglial tumors: a pooled international study". *Neuro-Oncology* 13.2 (2011): 242-250.
11. Lee ST., *et al.* "Interaction of allergy history and antibodies to specific varicella-zoster virus proteins on glioma risk". *International Journal of Cancer* 134.9 (2014): 2199-2210.
12. Amirian ES., *et al.* "History of chickenpox in glioma risk: a report from the glioma international case-control study (GICC)". *Cancer Medicine* 5.6 (2016): 1352-1358.
13. Canniff J., *et al.* "Cytotoxicity of glioblastoma cells mediated ex vivo by varicella-zoster virus-specific T cells". *Journal of Neurovirology* 17.5 (2011): 448-454.

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