Cytomegalovirus-Specific Immunotherapy for Glioblastoma Treatments

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INTRODUCTION

Viral antigens expressed within cancer cells have long been investigated as attractive immunological targets in regard to tumor-specific cancer immunotherapy, including cytotoxic T lymphocyte (CTL) or dendritic cell (DC)-based vaccines, because a viral antigen, as a non-self antigen, can elicit potent antitumor immunity in vivo and ex vivo, compared to tumor-associated antigens. Over the last two decades, numerous studies have investigated the presence of cytomegalovirus (CMV) within glioblastoma or gliomas; however, the results are severely conflicting. While a few researchers have suggested the potential benefits of cytotoxic T lymphocyte or dendritic cell-based vaccines for recurrent or newly diagnosed glioblastoma patients, several studies did not at all agree with the existence of CMV in glioblastoma cells. In this review, we summarized the conflicting results and issues about the detection of CMV in glioblastoma or glioma patients. We also provided the clinical data of published and unpublished clinical trials using CMV-specific immunotherapy for glioblastomas.

Keywords Glioblastoma; Cytomegalovirus; Immunotherapy; Adoptive cell transfer; Cancer vaccines.
al. [13]. Since then, various methods have been utilized to detect human CMV from glioblastoma specimens. Mitchell et al. [14] was the first to detect CMV DNA using polymerase chain reaction (PCR), analyzing glioblastoma specimens and peripheral blood. Western blot, flow cytometry, and next-generation sequencing (NGS) also utilized. Among these methods, IHC is most frequently used to detect human CMV in glioblastoma samples. Based on several studies suggesting the relationship between human CMV and glioblastoma, consensus on the role of human CMV in glioblastoma was made in 2011 [15]. For high sensitivity in detection, a precise method involving cell culture, immunostaining, and RNA/protein extraction from glioblastoma tissue was also proposed by Cobbs et al. [16]. Nevertheless, results of recent studies are conflicting. Detailed results according to the detection method are described in Tables 1-4.

A total of 36 studies have evaluated the presence of proteins in paraffin sections of glioblastomas and/or gliomas using IHC methods and 23 studies suggested the presence of CMV proteins in patient's specimens, while 13 studies did not demonstrate the presence of CMV proteins (Table 1) [1,2,7,10,13,14,17-46]. When using IHC, the median detection rates of CMV protein for gliomas or glioblastoma was 77.5% (range, 2.1% to 100%), and median detection rates for glioblastoma only was 90.5% (range, 2.1% to 100%). The detection rates of CMV proteins seemed higher in glioblastoma than in gliomas [13,17-20,29-36]. Immediate-early proteins (IEs) and phosphoprotein 65 (pp65) are popular targets when using IHC. Among the 36 total studies, 28 studies targeted IEs (17 studies targeted IE-1 specifically) and 16 studies targeted pp65.

In addition, 14 studies utilized ISH to detect CMV DNA or mRNA in paraffin sections of glioblastomas and/or gliomas [1,13,14,17,18,23,27,31,32,38,41-44]. Seven studies showed positive results, while seven studies did not find CMV genomic products (Table 2). When using ISH, the median detection rate of CMV genomic products for gliomas or glioblastoma was 64.9% (range, 5.3% to 100%) [13,17,18,23,31,32,38].

Thirty-one studies utilized PCR to detect CMV genes within tumors, and 16 studies showed positive results (range, 16.4% to 100%), while 15 studies failed to find CMV genome markers (Table 3) [1,2,8,10,12,14,19,25-28,31,33,36,37,39-44,45-55]. Utilizing primers specific for the CMV glycoprotein B (gB) gene was the first attempt to detect CMV by PCR [1]. Primers of gB, IE, and pp65 were utilized in 15, 8, and 4 studies each, respectively.

Researchers also utilized NGS to detect CMV genes within tumors based on their own samples, as well as public database. The most common data source is The Cancer Genome Atlas (TCGA) and National Center for Biotechnology Information (NCBI). Out of eight studies, four studies downloaded NGS

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**Table 1. Cytomegalovirus detection by immunohistochemistry**

| Study | Target | Glioblastoma (%) | Gliomas (%) |
|-------|--------|------------------|-------------|
| Cobbs et al. [13] | pp65 | 8/8 (100) | 10/11 (90.9) |
| | IE1 | 22/22 (100) | 27/27 (100) |
| | p52/76 kDa | 8/8 (100) | 10/10 (100) |
| Lau et al. [1] | pp65 | 0/8 (0.0) | 0/22 (0.0) |
| Sabatier et al. [17] | IE1 | 9/97 (9.3) | 9/132 (6.8) |
| Poltermann et al. [2] | pp65, IE1, EA | 0/22 (0.0) | 0/38 (0.0) |
| Mitchell et al. [14] | pp65 | 30/33 (90.9) | 1/0 (0.0) |
| | IE1 | 4/45 (93.3) | |
| Scherer et al. [18] | IE1 | 21/21 (100) | 44/50 (88) |
| Slinger et al. [21] | US28, IE | 20/21 (95.2) | |
| Lucas et al. [22] | pp65 | 25/49 (51.0) | |
| | IE1 | 8/49 (16.3) | |
| Ghazi et al. [23] | pp65 | 5/11 (45.5) | |
| | IE1 | 10/11 (90.9) | |
| Rahbar et al. [24] | IE | 7/90 (80.2) | |
| | LA | 7/60 (83.3) | |
| Rahbar et al. [25] | IE | 74/75 (98.7) | |
| | LA | 70/75 (93.3) | |
| Baumgarten et al. [26] | pp65, EA, IE | 2/91 (2.1) | |
datasets from the TCGA Cancer Genomics Hub repository (CGHub, now migrated to Genomic Data Commons; https://portal.gdc.cancer.gov) and three studies from NCBI Sequence Read Archive (SRA; https://www.ncbi.nlm.nih.gov/sra) or Gene Expression Omnibus (GEO; https://www.ncbi.nlm.nih.gov/geo/) (Table 4) [3-6,9,11,37,56]. Unlike other methods, all studies using NGS failed to demonstrate the presence of CMV genes. There was only one positive case from a study, but it may be explained by the contamination of CMV protomer gene

### Table 1. Cytomegalovirus detection by immunohistochemistry (continued)

| Study          | Target Glioblastoma (%) | Gliomas (%) |
|----------------|-------------------------|-------------|
| Holdhoff et al. [41] | pp65, IE 0/95 (0.0) | 0/97 (0.0) |
| Hu et al. [34] | IE2 25/25 (100)         |             |
| Yang et al. [42] | IE1/2 0/116 (0.0) | 53/53 (100) |
| Zavala-Vega et al. [46] | IE1 0/7 (0.0) |             |
| Qin et al. [35] | IE 17/20 (85.0) | 31/40 (77.5) |
| Loit et al. [43] | IE 0/42 (0.0) |             |
| Maleki et al. [36] | pp65 16/45 (35.6) | 24/97 (24.7) |
| Wen et al. [45] | IE1/2 0/116 (0.0) | 76/116 (67.9) |

pp, phosphoprotein; IE, immediate-early antigen; EA, early antigen; LA, late antigen; US, unique short region; UL, unique long region; gB, glycoprotein B

### Table 2. Cytomegalovirus detection by in situ hybridization

| Study          | Target Results (glioblastoma) | Results (glioma) |
|----------------|-------------------------------|------------------|
| Cobbs et al. [13] | HCMV mRNA 8/8 (100) | 10/10 (100) |
| Lau et al. [1] | HCMV mRNA 4/4 (100) | 6/6 (100) |
| Sabatier et al. [17] | HCMV DNA 7/9* | 7/132 (5.3) |
| Mitchell et al. [14] | HCMV DNA 16/16* | 0/22 (0.0) |
| Scheurer et al. [18] | HCMV DNA 21/21 (100) | 44/50 (88) |
| Ghazi et al. [23] | HCMV DNA 8/9 (88.9) |             |
| Yamashita et al. [27] | HCMV DNA 0/10 (0.0) |             |
| Wakefield et al. [38] | HCMV DNA 13/16 (81.3) |             |
| Stangherlin et al. [31] | HCMV mRNA 2/10 (20.0) | 19/52 (36.5) |
| Xing et al. [32] | HCMV DNA 28/43 (65.1) | 43/79 (54.4) |
| Holdhoff et al. [41] | HCMV DNA 0/30 (0.0) | 0/30 (0.0) |
| Yang et al. [42] | HCMV DNA 0/116 (0.0) |             |
| Loit et al. [43] | HCMV DNA 0/10 (0.0) |             |
| Limam et al. [44] | HCMV DNA 0/55† | 0/60† |

*Among IHC+positive patients; †Among PCR+positive patients. HCMV, human cytomegalovirus

### Table 3. Cytomegalovirus detection by polymerase chain reaction

| Study          | Target Results (glioblastoma) | Results (glioma) |
|----------------|-------------------------------|------------------|
| Lau et al. [1] | gB 0/8 (0.0) | 0/22 (0.0) |
| Poltermann et al. [2] | gB, IE1 0/23 (0.0) | 0/40 (0.0) |
| Mitchell et al. [14] | gB 21/34 (61.7) | IE1 8/34 (23.5) |
| Bhattacharjee et al. [47] | IE1 16/17 (94.1) |             |
| Ranganathan et al. [48] | UL17, UL27, UL55, UL69, UL82, UL96, UL111A, UL122, US11, US28 | 75/75 (100) |
| Rahbar et al. [25] | IE 5/5 (100) |             |
| Matalf et al. [49] | pp71 10/15 (66.7) | 11/17 (64.7) |
| Baumgarten et al. [26] | HCMV DNA 0/10 (0.0) |             |
| Ding et al. [19] | gB 12/19 (63.1) | 35/67 (52.2) |
| Mohammad et al. [51] | miR-UL112-3p 20/36 (56.8) |             |
| Yamashita et al. [27] | gB, IE 0/59 (0.0) |             |
| dos Santos et al. [50] | pp65 21/22 (95.5) | gB 20/22 (90.9) |
| Bianchi et al. [28] | gB 17/34 (50.0) | 21/47 (44.7) |
| Tang et al. [37] | UL34, UL80.5 0/32 (0.0) |             |
| Stangherlin et al. [31] | pp65 9/10 (90.0) | 38/52 (73.1) |
| Taha et al. [10] | HCMV DNA 0/32 (0.0) |             |
| Lin et al. [8] | gB 0/45 (0.0) | 0/63 (0.0) |
| Malekpour Afshar et al. [52] | HCMV DNA 75/75 (100) |             |
| Bahador et al. [39] | pp65 26/159 (16.4) | IE1 12/119 (10.1) |
| Garcia-Martinez et al. [40] | HCMV DNA 3/122 (2.5) |             |
| Han et al. [33] | gB 30/95 (31.6) | 48/150 (32.0) |
| Holdhoff et al. [41] | US17 4/61 (6.6) | 4/71 (5.6) |
| Strojnik et al. [12] | gB 0/33 (0.0) | 0/45 (0.0) |
| Zavala-Vega et al. [46] | IE 7/7 (100) | gB 5/7 (71.4) |
| Yang et al. [42] | UL73 9/116 (7.8) | UL144 0/116 (0.0) |
| Loit et al. [43] | HCMV DNA 1/29 (3.4) |             |
| Adnan et al. [53] | gB 1/112 (0.9) |             |
| Limam et al. [44] | IE2 55/82 (67.1) | 60/112 (53.6) |
| Goerig et al. [54] | HCMV DNA 12/44 (27.3) | 28/118 (23.7) |
| Maleki et al. [36] | pp65 44/45 (97.8) | 68/79 (70.1) |
| Ghaffari et al. [55] | gB 3/42 (7.1) |             |

pp, phosphoprotein; IE, immediate-early antigen; EA, early antigen; LA, late antigen; US, unique short region; UL, unique long region; gB, glycoprotein B; HCMV, human cytomegalovirus
In IHC, paraffin blocks of fresh brain autopsy specimens must be sectioned in 6 μm slices. Application of pepsin or trypsin at 37°C for 4–6 min and of citrate at 85°C–90°C for 2–4 min followed by washing in a 45°C–50°C water bath for 2.5 hour should be performed carefully to avoid damage to viral antigens. Han et al. [33], following the methodology of Cobbs et al. [16], showed a high detection rate using IHC (82.1% and 68.4% in glioblastoma for IE-1 and pp65, respectively). In contrast, some studies utilizing thin formalin-fixed paraffin-embedded tissue sections (3–4 μm) or an automated immunostainer demonstrated low detection rates [36,43,44]. Yang et al. [42] failed to detect IE protein in 116 samples using the methodology of Cobbs et al. [16]. The low detection limit of IHC, small sample size, and measurement error may explain the false negative results as well [26]. Second, the blood positivity of the CMV may also contribute to the detection results for human CMV. Over the past several decades, several viruses have turned out to elicit oncogenesis. Including human papillomavirus that causes cervical cancer and hepatitis C virus that causes liver cancer, oncogenic viruses are responsible for 10% to 15% of human cancers [57]. These viruses directly affect healthy cells and cause cancer transformation through spreading its nucleic acids. Meanwhile, other viruses, including human CMV, are known to cause cancer in a more indirect manner, which is known as onco-modulatory effect. In other words, human CMV infection, unlike oncovirus, is known to enhance malignancy via formation of tumor-related microenvironment [58].

Human CMV has recently been suggested to have a onco-modulatory role in several brain malignancies including glioma, medulloblastoma, and neuroblastoma [59,60]. Onco-modulatory effects are defined as contributing to increase the extent of malignancy. In detail, human CMV infection induced the cells to be more vulnerable to carcinogenic materials due to lack of adhesion molecules in neurons, which are more aggravated when CMV re-activation occurred more frequently [58,60]. In addition, human CMV-infected glioma cells showed stem-like characteristics with increased IE protein expression [34,39,45,61]. Several studies suggest specific onco-modulatory roles of CMV-infected glioma. These roles include self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis, deregulation of cellular energetics, avoiding immune destruction, tumor-promoting inflammation, and genome instability and mutation [58,59].

Controversy of detection results

The difference between studies may be explained by several reasons. First, CMV proteins and nucleotides could be readily detected if the entire protocol is optimized as suggested [15,16]. In IHC, paraffin blocks of fresh brain autopsy specimens must be sectioned in 6 μm slices. Application of pepsin or trypsin at 37°C for 4–6 min and of citrate at 85°C–90°C for 2–4 min followed by washing in a 45°C–50°C water bath for 2.5 hour should be performed carefully to avoid damage to viral antigens. Han et al. [33], following the methodology of Cobbs et al. [16], showed a high detection rate using IHC (82.1% and 68.4% in glioblastoma for IE-1 and pp65, respectively). In contrast, some studies utilizing thin formalin-fixed paraffin-embedded tissue sections (3–4 μm) or an automated immunostainer demonstrated low detection rates [36,43,44]. Yang et al. [42] failed to detect IE protein in 116 samples using the methodology of Cobbs et al. [16]. The low detection limit of IHC, small sample size, and measurement error may explain the false negative results as well [26]. Second, the blood positivity of the CMV may also contribute to the detection results for human CMV. Over the past several decades, several viruses have turned out to elicit oncogenesis. Including human papillomavirus that causes cervical cancer and hepatitis C virus that causes liver cancer, oncogenic viruses are responsible for 10% to 15% of human cancers [57]. These viruses directly affect healthy cells and cause cancer transformation through spreading its nucleic acids. Meanwhile, other viruses, including human CMV, are known to cause cancer in a more indirect manner, which is known as onco-modulatory effect. In other words, human CMV infection, unlike oncovirus, is known to enhance malignancy via formation of tumor-related microenvironment [58].

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### Table 4. Cytomegalovirus detection by next generation sequencing

| Study | Data source | Results (glioblastoma) | Results (glioma) |
|-------|-------------|------------------------|-----------------|
| Khoury et al. [3] | TCGA | 0/167 (0.0) | 0/215 (0.0) |
| Tang et al. [4] | TCGA | 0/167 (0.0) | 0/215 (0.0) |
| Cimino et al. [5] | GPS at Washington University | 0/21 (0.0) | |
| Cosset et al. [6] | Geneva University Hospitals | 0/20 (0.0) | 0/26 (0.0) |
| Tang et al. [37] | TCGA | 1/34 (2.9) | 0/701 (0.0) |
| Strong et al. [9] | TCGA | 0/170 (0.0) | 0/701 (0.0) |
| TCGA WGS | 0/61 (0.0) | 0/61 (0.0) |
| NCBI | 0/92 (0.0) | 0/92 (0.0) |
| LCRC, BioServe | 0/3 (0.0) | 0/3 (0.0) |
| Johnson et al. [11] | NCBI | 0/5 (0.0) | |
| Yuan et al. [56] | NCBI | 0/111 (0.0) | |

TCGA, The Cancer Genome Atlas; GPS, Genomics and Pathology Services; TCGA WGS, The Cancer Genome Atlas Whole Genome Sequencing; NCBI, National Center for Biotechnology Information; LCRC, Louisiana Cancer Research Center
clinical experiences of 25 patients treated with CTL [63]. The group that received CTL before progression demonstrated longer overall survival (23 versus 14 months) than those who received CTL after progression.

Three studies reported the clinical outcomes of autologous CMV-specific DC-based vaccines for newly diagnosed glioblastoma patients. The first study, using a CMV-DC vaccine published in 2015, included 12 patients with newly diagnosed glioblastoma. The study showed better overall survival and progression-free survival (with hazard ratios of 0.620 in overall survival) [64]. Also, in the group treated with pp65-pulsed DC vaccine with tetanus and diphtheria toxoid (Td), increasing migration of DC toward lymph node was found than in a group treated with an unpulsed DC vaccine. A second study published in 2018 included 15 patients with newly diagnosed glioblastoma who received an autologous CMV-specific CTL and pp65 pulsed CMV-DC vaccine [65]. Patients treated with CTL therapy followed by CMV-DC vaccine showed better overall survival and progression free survival (13.4 month overall survival and 8.1 month progression-free survival after recurrence). These two studies suggested that the pp65-specific DC vaccine was associated with increased CMV-specific T cell frequency as well as survival outcomes, when combined with Td toxin or autologous CTL. Another study using a CMV-specific DC vaccine combined with the standard of care including concomitant chemoradiation followed by dose-intensified temozolomide, enrolled 14 patients with newly diagnosed glioblastoma [66]. When the patients were treated with pp65-specific DC vaccine with granulocyte macrophage-colony stimulating factor (GM-CSF) after temozolomide, the median overall survival was 41.1 months and progression-free survival 25.3 months. Table 5 summarizes the published results of clinical trials of CMV-specific immunotherapy for glioblastoma [62-66].

Unpublished clinical trials
Unpublished clinical trials of CMV-specific immunotherapy include various combinational strategies. In detail, among four

Table 5. Published clinical trials of CMV-specific immunotherapy for glioblastoma

| Study                  | Disease                        | Arms                                                                 | Phase | Numbers of patients | Survival outcomes | Clinical trial number |
|------------------------|--------------------------------|----------------------------------------------------------------------|-------|--------------------|-------------------|-----------------------|
| Schuessler et al. [62] | Recurrent glioblastoma         | Autologous CMV-specific CTL                                          | 1     | 19                 | OS: >57 weeks     | ACTRN12609000338268   |
|                        |                                |                                                                      |       |                    | (range, 19 to 346 weeks) |                       |
|                        |                                |                                                                      |       |                    | PFS: >35 weeks     |                       |
|                        |                                |                                                                      |       |                    | (range 15.4 to 254 weeks) |                       |
| Mitchell et al. [64]   | Newly diagnosed glioblastoma   | Arm1: autologous CMV-DC vaccine (unpulsed)                          | 1     | 12                 | (Arm1) OS: 18.5 months, PFS: 10.8 months | NCT00639639 |
|                        |                                | Arm2: autologous CMV-DC vaccine (pp65 pulsed) with Td               |       |                    | (Arm2) HR for OS=0.620, p=0.023, HR for PFS=0.845, p=0.027 |                       |
|                        |                                |                                                                      |       |                    | (Compared to OS and PFS of Arm1) |                       |
| Batich et al. [66]     | Newly diagnosed glioblastoma   | Arm1: resection and temozolomide therapy                             | 1     | 14                 | (Arm2) OS: 19.2 months, PFS: 8.0 months | NCT00639639 |
|                        |                                | Arm 2: autologous CMV-DC vaccine (pp65 pulsed) with GM-CSF, after resection and temozolomide therapy |       |                    | (Arm2) OS: 41.1 months, PFS: 25.3 months |                       |
| Reap et al. [65]       | Newly diagnosed glioblastoma   | Arm1: autologous CMV-specific CTL with saline                       | 1     | 15                 | (Arm2) OS: 13.4 months, PFS: 8.1 months | NCT00693095 |
|                        |                                | Arm2: autologous CMV-specific CTL with autologous CMV-DC vaccine (pp65 pulsed) |       |                    |                                                                      |                       |
| Smith et al. [63]      | Newly diagnosed glioblastoma   | Autologous CMV-specific CTL                                          | 1     | 25                 | OS: 23 months (range, 7 to 65 months) | ACTRN12615000656538 |
|                        |                                |                                                                      |       |                    |                                                                      |                       |

CMV, cytomegalovirus; CTL, cytotoxic T lymphocyte; DC, dendritic cell; GM-CSF, granulocyte macrophage-colony stimulating factor; OS, overall survival; PFS, progression-free survival; Td, tetanus and diphtheria toxoid
## Table 6. Unpublished clinical trials of CMV-specific immunotherapy for glioblastoma

| Treatment modality | Recruitment status | Disease | Phase | Number of patients | Results | Estimated primary completion date | Clinical trial number |
|--------------------|--------------------|---------|-------|--------------------|---------|-----------------------------------|-----------------------|
| Autologous CMV-DC vaccine + anti-PD-1 mab (nivolumab) | Completed | Recurrent glioblastoma, malignant glioma | 1 | 6 | Arm1: anti-PD-1, Arm2: anti-PD-1 with CMV-DC overall survival – months (8.0, 5.7 to 8.3 / 15.3, 4.7 to N/A), progression free survival – months (4.3, 2.1 to 5.3 / 6.3, 4.7 to 10.7) | September, 2017 | NCT02529072 |
| Autologous CMV-DC vaccine + Td, GM-CSF adjuvant | Completed | Recurrent and pediatric glioblastoma, malignant glioma | 1 | 11 | Not reported | November, 2019 | NCT03615404 |
| CMV-peptide vaccine (PEP-CMV) + Td preconditioning, booster | Terminated | Newly diagnosed glioblastoma | 1 | 27 | Not reported | June, 2020 | NCT02864368 |
| Allogenic CMV-specific CTL + fludarabine, cyclophosphamide | Terminated | Glioblastoma | 1 | 25 | Not applicable | October, 2010 | NCT00990496 |
| Autologous CMV-specific CTL | Terminated | Glioblastoma | 1 | 2 | Not applicable | January, 2012 | NCT01205334 |
| CMV-peptide vaccine (PEP-CMV) | Terminated | Newly diagnosed glioblastoma | 1 | 150 | Not applicable | January, 2014 | NCT01854099 |
| Autologous CMV-specific CTL (HER2-CAR) | Completed | Recurrent and newly diagnosed glioblastoma | 1 | 16 | Not applicable | June, 2014 | NCT01109095 |
| Autologous CMV-DC vaccine + Basiliximab | Completed | Newly diagnosed glioblastoma | 1 | 34 | Not applicable | July, 2016 | NCT00626483 (two-arm phase I for 2017 Clin Cancer Res) |
| Autologous CMV-DC vaccine + Td, Basiliximab, and saline | Completed | Newly diagnosed glioblastoma | 2 | 100 | Not applicable | October, 2020 | NCT03667281 |
| VBI-1901 vaccine* + GM-CSF | Active, not recruiting | Recurrent glioblastoma | 1, 2 | 38 | Not applicable | March, 2022 | NCT03382977 |
| Autologous CMV-specific CTL | Completed | Recurrent and newly diagnosed glioblastoma, malignant glioma | 1 | 65 | Not applicable | June, 2022 | NCT02661282 |
| MT-201 vaccine† | Not yet recruiting | Newly diagnosed glioblastoma | 1 | 27 | Not applicable | December, 2022 | NCT04741984 |
| Autologous CMV-DC vaccine + GM-CSF | Recruiting | Newly diagnosed glioblastoma | 1 | 10 | Not applicable | May, 2023 | NCT04963413 |
| Autologous CMV-DC vaccine + GM-CSF; Td, and saline | Recruiting | Newly diagnosed glioblastoma, malignant glioma | 2 | 175 | Not applicable | June, 2023 | NCT02465268 |
| Autologous CMV-DC vaccine + GM-CSF; and Td | Recruiting | Newly diagnosed glioblastoma | 2 | 48 | Not applicable | December, 2023 | NCT038927222 |
| Autologous CMV-DC vaccine + Td, and Varilimumab | Recruiting | Newly diagnosed glioblastoma | 2 | 112 | Not applicable | March, 2025 | NCT03688178 |

*VBI-1901 vaccine refers to an enveloped virus-like particle vaccine targeting CMV antigens, gB and pp65; †MT-201 vaccine refers to a pp65 monocyte vaccine in which monocytes are isolated from patients' leukapheresis. CMV, cytomegalovirus; DC, dendritic cell; CTL, cytotoxic T lymphocyte; GM-CSF, granulocyte macrophage-colony stimulating factor; Td, tetanus and diphtheria toxoid; CAR, chimeric antigen receptor; HER-2, human epidermal growth factor receptor 2; PD-1, programmed cell death protein 1
clinical trials using CMV-specific CTL therapy (NCT00990496, NCT01205334, NCT01109095, NCT02661282), one recent trial applied CMV-specific CTL with an engineered HER-2 chimeric antigen receptor (NCT01109095). Clinical trials using CMV-specific DC-based vaccines with various adjuvants such as GM-CSF (NCT04963413), ’Id toxin (NCT03615404, NCT02465268, NCT03927222), or cancer drugs including IL-2 receptor antagonist (NCT00626483, NCT02366728), anti-CD27 antibody (NCT03688178), and anti-CD-P1 inhibitor (NCT02529072) are currently being investigated. Another type of CMV-specific vaccine including enveloped virus-like particle vaccine (VBI-1901), or pp65-specific monocyte vaccine are also being investigated (NCT03382977, NCT04741984). The summary of unpublished clinical trials of CMV-specific immunotherapy for glioblastoma is contained in Table 6.

CONCLUSION

As one of the novel immunotherapeutic strategies, clinical approaches using CMV-specific CTL and/or DC-vaccines have been tested. However, there are some limitations of previous studies. First, numerous studies have tried to evaluate the presence of CMV within glioblastoma; however, consolidative results for the presence of CMV within glioblastoma are needed. Second, the onco-modulatory role of CMV for gliomagenesis is unknown. Third, clinical trials have suggested positive clinical outcomes, but additional larger and randomized studies are needed. As viral antigens can elicit one of the most powerful immune reponses, the presence of viral antigens within tumor cells can be an attractive immuno-therapeutic target for various cancer types. Therefore, further translational studies are needed to support the presence of CMV and the onco-modulatory role in gliomagenesis.

Ethics Statement

Not applicable

Availability of Data and Material

All data generated or analyzed during the study are included in this published article.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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