Vol 3 | Issue 1 | Pages 61-64

Journal of Brain Disorders
ISSN: 2578-6571

Research Article

DOI: 10.36959/524/332

Immunotherapy for Glioma

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Summary

Glioma is the most common intracranial malignancy in the central system. At present, the treatment method of glioma is mainly surgical resection combined with chemotherapy and radiotherapy, but the malignancy degree of high-grade glioma is high, and the median survival period of patients is still short. This treatment method has failed to give greater benefit to patients. In recent years, with the deepening understanding of the molecular biology and tumor microenvironment, the research of glioma immunotherapy has also been rapidly developed, providing many new directions for the treatment of glioma. A review of glioma immunotherapy is now given.

Preface

Glioma is a tumor originating from brain glial cells, and is the most common primary malignant central nervous system tumor. According to the WHO 2016 CNS tumor classification criteria, low grade glioma mainly refers to diffuse astroglioma, oligodendroglioma, oligodendroastrocytoma; high grade glioma mainly refers to anaplastic astrocytoma, anaplastic oligodendroglioma, glioblastoma, and diffuse neutral glioma [1]. Among them, glioblastoma is the intracranial tumor with the highest incidence, the largest degree of malignancy and the worst prognosis, accounting for about 46.6% of the malignant intracranial tumors [2]. For low-grade gliomas, surgical treatment with maximal safe tumor resection significantly improved patient outcomes, with a 10-year survival rate of 47% and a median survival of 11.6 years [3]; For high-grade gliomas, the comprehensive treatment of surgery combined with radiotherapy and chemotherapy is the standard therapy, but the prognosis is still unsatisfactory, and the median survival after standardized treatment of adult malignant glioblasts (GBM) is only 14.2 months, with an average 5-year survival rate of < 5% [4]. In recent years, with the brain immune system, glioma tumor microenvironment, molecular biology, experts at home and abroad on glioma immunotherapy conducted many research, in order to provide more new ideas for glioma treatment, try our best to extend patient survival, improve patient quality of survival, bring more benefits for it. This article now reviews the immunotherapy of glioma.

Overview of Glioma Immunotherapy

Tumor immunotherapy is a treatment that obtains or enhances anti-tumor immune effects by mobilizing host immune defense mechanisms or administering certain bio-active substances. Over the years, the BBB has been thought to have tight connectivity and the CNS lacks classical lymphatic drainage with the immune privilege that the brain is refractory to ectopic tissue or only to produce limited rejection [5]. At the same time, some studies have found that the glioma tumor microenvironment has a significant inhibitory effect on the immune response. Glioma cells secrete a large number of chemokines, cytokines, cytokines, and growth factors that promote the infiltration of astrocytes, pericytes, endothelial cells, circulating progenitors, and a series of immune cells, such as microglia, peripheral macrophages, myeloid inhibitory cells (MDSC), leukocytes, CD4 + T cells, and T regulatory lymphocytes (Tregs) [6]. These cells regulate and participate in glioma proliferation, invasion, and drug resistance in the microenvironment. They produce interactions unable to activate effector T cells and produce durable antitumor immune responses [7]. However, scientists have been in recent decades studying the role of the brain immune system, and relevant research results have revised these concepts. Recently, findings in the CNS lymphatic system confirm that intracranial tumors can elicit potent antitumor immune effects [8]. Animal models have demonstrated that tumor-derived antigens can be drained into the neck lymph nodes from the CSF to stimulate specific T cells, and that T-cell amplification can penetrate the blood-brain barrier to migrate to the CNS, targeting the killing of tumor cells to cause an antitumor response [9]. The immune

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Accepted: May 29, 2022

Published online: May 31, 2022

Citation: Li Zhang, Xiao Qi Xie, Chen Yi, et al. (2022) Immunotherapy for Glioma. J Brain Disord 3(1):61-64

system can also communicate with the brain parenchyma through cerebrospinal fluid and interstitial fluid to transport antigens and immune cells [10]. The deepening understanding of the brain immune system, glioma tumor microenvironment and molecular biology provides many investigable targets for glioma immunotherapy. At present, the immunotherapy for gliomas includes tumor vaccines, immune checkpoint inhibitors, adoptive cell therapy, oncolytic virus therapy, etc.

Tumor Vaccine

Tumor vaccine is active immunotherapy, refers to the use of tumor cells or tumor antigen substances to be immune to the body, enabling the host immune system to produce an immune response against tumor antigens. Currently, tumor vaccines against gliomas include dendritic cell (DC) vaccines, polypeptide vaccines, and heat shock protein (HSPs) vaccines. DC is the most functional APC in the body, which can be sensitized and activated *in vitro* with different forms of tumor antigen (tumor complete cellular antigen, tumor cell lysates, etc.), and then re-immunized or retransmitted to the patient, so as to more effectively induce the body to produce specific CTL and memory cells, and enhance the anti-tumor response [11]. In a phase I clinical trial of a sensitized DC vaccine (named ICT-107) loaded with multiple antigens of six epitopes, AIM-2, MAGE1, Trp-2, gp100, HER2, and IL-13Ra2), It was found that the vaccine was strongly responsive to gp100 and HER 2 in the newly diagnosed glioblastoma, Extended the median overall survival period (38.4 months), This trial demonstrated the survival benefits of DC vaccines, But a randomized phase II trial showed no significant improvement in OS [12,13]. Furthermore, a recent phase III trial demonstrated that the autologous tumor lysis vaccine DCVaxL combined with standard treatment prolonged survival in patients with newly diagnosed glioblastoma than standard treatment alone (median overall survival, 23.1vs15-17 months) [14]. It can be seen that DC vaccine is promising in glioma immunotherapy and needs further in-depth research. Peptide vaccines are vaccines synthesized by chemistry following the amino acid sequence of a segment of antigen epitope in the tumor antigen gene. The synthetic polypeptide vaccine can directly bind to the MHC molecules on the APC surface and activate the T cells, thus inducing an antitumor immune response. Glioma polypeptide vaccines mostly use tumor-specific antigens (TSA) as targets, such as the epidermal growth factor receptor (E GFR) vIII and isocitrate dehydrogenase (IDH)-1 (R321h) [15,16]. EGFRvIII is a mutant fragment of the epidermal growth factor receptor (EGFR), the most common mutation found in the classical GBM, resulting in the constitutive activation of the EGFR, expressed in 25% to 30% of the GBM, and associated with the shorter survival of the GBM [17,18].

Rinodopepimut is a vaccine directed against EGFRvIII. Two Rindopepimut efficacy studies on EGFRvIII reported the minimum month age of 23.6-26 in patients with GBM [19,20]. The strong specific response and promising OS rate of EGFRvIII were further confirmed in the ACT III trial [21]. However, an interim analysis of a phase III trial of Rindopepimut combined with temozolomide for newly diagnosed glioblastoma (ACT IV expressing EGFRvIII) concluded that the ACT-IV trial should be terminated because the primary end point of the trial (improved overall survival) is unlikely to be reached. Trial analysis of approximately half of the patients lost EGFRvIII expression, suggesting that unstable EGFRvIII expression in glioblastoma amplified by EGFR affected efficacy [22]. Heat shock proteins have molecular chaperone activity that can inhibit temperature, oxygen, and ion-induced biomololecular degeneration [23]. It was found that HSP-96 can bind tumor-associated antigens, and that the HSP-96-peptide complex (HSPPC-96) can be ingested by antigen-presenting cells, thus effectively mediating class I and II MHC-mediated presentation of tumor polypeptides and producing a robust tumor-specific immune response [24]. In 2014, a phase II clinical trial of the HSPPC-96 vaccine against GBM completed the phase 1 trial. Tumor resection of relapsed GBM patients and extracted HSPPC-96 antigen from resected glioma tissue to synthesize an individualized anti-glioma vaccine, bringing m PFS and m OS to 19.1 and 42.6 weeks, respectively [25].

Overstep Cell Therapy

Adoptive cell therapy is performed by isolating autologous or allogeneic immune effector cells, activated *in vitro* and retransmitted, to directly kill or stimulate the body's anti-tumor immune response. Currently, the host cells with antitumor activity that can be utilized by ACT are mainly NK, LAK, T, and CAR-T cells, and their amplification and activation are beneficial to exert the antitumor effects [26,27]. Current CAR-T cell therapy against GBM mainly targets three specific antigens: The human epidermal growth factor receptors EGFRvIII, (HER)2, and IL13Rα2. In a phase I clinical trial, 10 relapsed GBM patients were treated with autologous EGFRvIII-specific CAR T cells, with one patient followed up over 18 months along with residual stable focal disease. The absence of any extraumtumor toxicity or cytokine release syndrome was found in these patients, demonstrating that systemic infusion of EGFRvIII-CAR T cells was feasible and safe. While the presence of CAR T cells at the tumor site demonstrates that systemically infused T cells can be activated and recruited to the brain [28]. Another phase I clinical trial of the tumor-associated antigen, human epidermal growth factor receptor-2 (HER2), reported the results of treating 17 GBM patients with HER2-specific CAR T cells. The results showed that the median overall survival was 11.1 months after first T cell injection was 11.1 months and 24.5 months after diagnosis throughout the study; and 8 of 17 patients (1 partially effective, 7 stable) had no serious adverse events after dose-escalation therapy and clinical benefit observation. This suggests that the infusion of virus-specific T cells (VSTs) modified by the HER2-specific chimeric antigen receptor (CAR) is safe and provides clinical benefit in patients with progressive glioblastoma. However, we also found that CAR T cells did not expand and maintained low levels in the periphery [29]. Further studies are therefore necessary to improve the methods for the survival and expansion of CAR T cells *in vivo*.

Oncolytic Virus Therapy

Oncolytic viruses can selectively replicate and kill cancer cells with their own biological affinity or through genetic

modification without harming normal cells. In addition to having the properties of directly dissolving tumors, oncolytic viruses can also induce effective antiviral and antitumor immune responses [30]. DNX-2401 is a tumor-selective, replication-competent oncolytic adenovirus. In 2018, a phase I clinical trial of DNX-2401 for relapsed high-grade gliomas showed a prolonged survival in 20% of 25 patients in the treatment group treated with viral therapy alone and a tumor reduction of over 95% in 3 patients [31]. G207 is a mutated, genetically engineered type 1 herpes simplex virus oncolytic virus. In 2014, phase I clinical trials were conducted in nine patients with relapsed GBM. The patient was vaccinated with G207 once at the tumor strengthening site, followed by a focal radiotherapy (5Gy). The results of this study suggest that G207 is well tolerated and is safe. Meanwhile, six of these nine patients had stable or partial remission at least one time point, with a median OS of 7.5 months. This study demonstrated the safety and clinical efficacy potential of a single-agent oncolytic herpes simplex virus combined with radiation therapy in patients with malignant glioma [32]. The treatment of oncolytic herpes simplex virus (e. g., G207) for human gliomas warrants further investigation. PVSRIPO is a genetically modified poliovirus-rhinovirus chimera. Preliminary data released at the ASCO Annual Meeting 2015 showed that among 24 patients treated with PVSRIPO (42% had received bevacizumab previously), the 2-year overall survival was 24% and the median overall survival for all of the doses of PVSRIPO was 12.5 months; the latest results reported in 2016 showed that three patients (13%) remained alive at year 3 [33].

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DOI: 10.36959/524/332