Proceedings of ICBioMed 2024 Workshop: Computational Proteomics in Drug Discovery and Development from Medicinal Plants
DOI: 10.54254/2753-8818/65/2024.LA18094

Application of Immunotherapy in Brain Cancer Treatment

Ziqi Wang

Shanghai World Foreign Language Academy, Shanghai, China

miss.wzq.q@gmail.com

Abstract. Brain cancer is a malignant tumor, characterized by abnormal growth of cells in the brain. The high mortality rate and poor prognosis of brain cancer make it become a notable cancer type. Statistics demonstrate that the incidence of brain cancer is still increasing, hence, studies on immunotherapy of brain cancer, one of the most common and vital therapies in treating cancer, becomes important. This review mainly introduces three kinds of immunotherapy, including vaccines, immune checkpoint inhibitors (ICIs) and Chimeric Antigen Receptor (CAR) T-cell therapy. Even though these treatments share similar basic mechanisms, taking advantage of host immune system, they are different in the way of evoking immune response. Both vaccines and CAR-T utilize the binding between pathogenic substance and immune cell, while the ICIs rely on the release of immune suppression. Most of the immunotherapeutic strategies have shown great efficiency, and the corresponding side effects also exist, which still need to be explored, like the inefficiency caused by the complex tumor microenvironment and the off-target issue risen by the scarcity of tumor-specific antigens. Therefore, novel combinations of different therapies and designs of research may be the new trends of the immunotherapy for brain cancer.

Keywords: Immunotherapy, treatment, brain cancer.

1. Introduction

Comparing with some common cancers such as lung cancer and breast cancer, the incidence of brain cancer is low. However, brain cancer is still a vital public health issue throughout the world for its severe symptoms, poor prognosis and high mortality [1, 2]. Based on estimations from the Global Cancer Observatory (GLOBOCAN) 2020, one of the largest portions of the worldwide illness burden is attributed to brain and central nervous system cancer. The eighth most common cause of Years of Life Lost (YILs) among all cancers in both men and women is brain and central nervous system cancer, according to the 2017 Global Burden of Disease (GBD) Study [2].

Risk factors of brain cancer include genetic and environmental factors. One of the main cause of cancer is gene mutation. Such variation can be inherited or acquired. In addition, medical diagnostic radiation or high-dose ionizing radiation, which is an environmental risk factor, is another identified risk factor of brain cancer. Therefore, people with occupation that may expose to such radiation tend to have a higher incidence of brain cancer than others. Electromagnetic radiation from mobile phones and other wireless devices, infectious agents and living near landfills and high-voltage power lines are some other potential environmental factors [3].

Brian tumors are classified by their microscopic structures and unique molecular characteristics, such as Astrocytoma, Chordoma, CNS Lymphoma. Glioblastoma is the most common type of primary malignant brain tumour in adults. Patients with such type of brain cancer cannot be cured even after

DOI: 10.54254/2753-8818/65/2024.LA18094

surgery and radiotherapy. Brain tumors are also graded into different levels to demonstrate the severity of different types of brain tumors. In general, CNS WHO grade 1 tumors are the least aggressive ones while CNS WHO grade 4 tumors are the most aggressive ones [4].

Focal symptoms appeared during brain tumor clinical presentation depend on several different factors, including location, rate of growth, the overall lesion size and nature. Mechanism of symptom presentation can be divided into tumor and peritumoral factors. Symptoms of brain cancer generally includes edema, hemorrhage, vascular compromise, and obstruction [5].

As shown in Figure 1, both the number of new cases and deaths increase from 1990 to 2019, which has become a trend of the incidence and mortality rate of brain cancer.

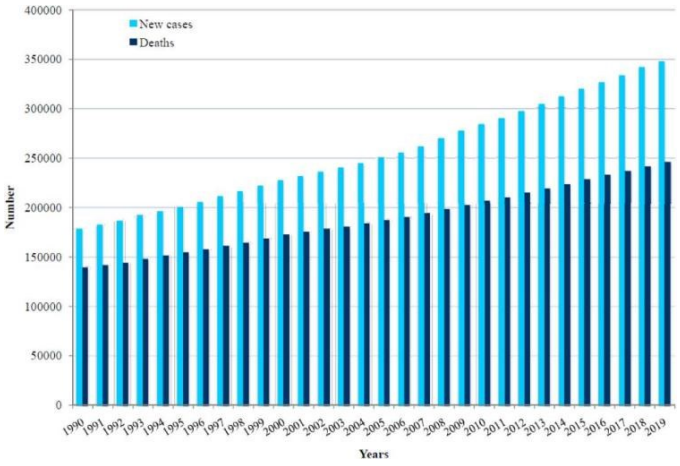
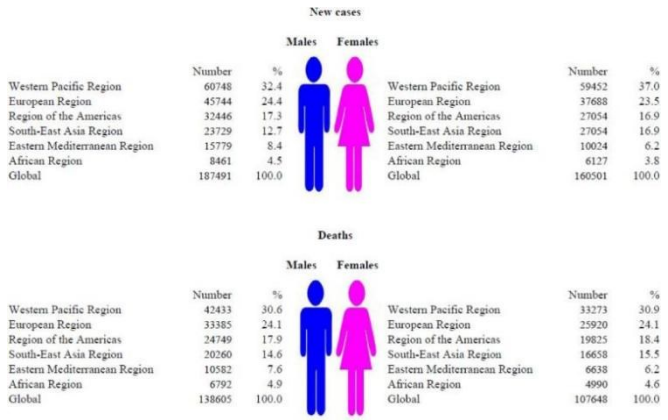


Figure 1. Number of new cases and deaths worldwide in 1990-2019 [2].

In Figure 2, generally, males had higher incidence and mortality rates than females in 2019 in all WHO regions [2].



New cases	Males Number	Males %	Females Number	Females %
Western Pacific Region	60748	32.4	59452	37.0
European Region	45744	24.4	37688	23.5
Region of the Americas	32446	17.3	27054	16.9
South-East Asia Region	23729	12.7	27054	16.9
Eastern Mediterranean Region	15779	8.4	10024	6.2
African Region	8461	4.5	6127	3.8
Global	187491	100.0	160501	100.0

Deaths	Males Number	Males %	Females Number	Females %
Western Pacific Region	42433	30.6	33273	30.9
European Region	33385	24.1	25920	24.1
Region of the Americas	24749	17.9	19825	18.4
South-East Asia Region	20260	14.6	16658	15.5
Eastern Mediterranean Region	10582	7.6	6638	6.2
African Region	6792	4.9	4990	4.6
Global	138605	100.0	107648	100.0

Figure 2. Number of new cases and deaths of brain cancer in WHO regions, by sexes in 2019 [2].

As the incidence and mortality rates of brain cancer have a obvious increasing trend in both sexes worldwide, which makes studies on the treatments of brain cancer more necessary [2]. Among these treatments, immunotherapy shows great efficiency. Nowadays, the immunotherapy of cancer includes ICIs, monoclonal antibodies, cancer vaccines, CAR-T cell therapy, cytokines. Tumors evade the immune system mainly by immunosuppression and chronic inflammation. Therefore, in general, immunotherapy is to activate or inhibit some pathways in the immune system to make the system work normally and prevent the formation of tumors.

DOI: 10.54254/2753-8818/65/2024.LA18094

2. Treatment of brain cancer

As one of the most substantial and effective treatments of brain cancer, immunotherapy now comes into use worldwide, with regimens currently in clinical trials. Several immunotherapies are detailed below, containing vaccines, ICIs and CAR T-Cell therapy. Their mechanism, efficiency and limitations are elucidated thoroughly.

2.1. Therapeutic vaccines

2.1.1. Peptide vaccines. Peptide vaccines, as a polymer of 20-30 amino acids, have great superiority in production, besides, the inoculation process is easy. For brain tumor, it usually caused by mutation in the epidermal growth factor receptor variant III (EGFRvIII) and about 20%-30% population of Glioblastomas (GBMs) contain this specific alternative. Rindopepimut, a peptide vaccine to treat GBM, is linked to an immune adjuvant named keyhole limpet hemocyanin (KLH). Transferring this vaccine into the granulocyte macrophage, then, it could be delivered into the target site precisely. 65 EGFRvIII-mutated GBM patients were examined in a multicenter, phase 2 trial named ACT III for the rindopepimu. This proved that rindopepimu with conventional therapy was well tolerated together. The progression-free survival (PFS) was 66% after 5.5 months. There was a 21.8-month overall survival (OS) rate. These figures led to the recognition of rindopepimut as a breakthrough therapy in February 2015. Moreover, results from a phase 2, double-blind trial that examined rindopepimut in combination with bevacizumab for GBM patients currently receiving treatment were presented at the 2015 American Society of Clinical Oncology (ASCO) meeting. This study showed that rindopepimut was associated with a rise in OS of more than two months, and that anti-EGFRvIII titers were directly connected to survival [6].

However, there is still a drawback to this kind of vaccination. Both the idea of immunologic escape and the variable expression of EGFRvIII within a tumor. Since cancer cells with the EGFRvIII mutation are the targets of rindopepimut, cells expressing wild-type EGFR are subject to selective pressure. ACT III clearly elaborated on this constraint. Following a three-month course of rindopepimut therapy, EGFRvIII vanished in 67% of recurrent GBM cases. Consequently, for peptide vaccines, multipeptides or targeting at homogenously expressed antigens might be required [6].

One of these multipeptide vaccines, IMA950, is made up of 11 human leukocyte antigen-binding tumor-associated peptides. Its acceptable tolerability and the fact that more than 30% of patients in a phase 1 study responded to multiple tumor-associated peptides required additional research [6].

An other tumor antigen with potential for vaccination is the intracellular protein Isocitrate dehydrogenase I (IDH1). It works within the tricarboxylic acid cycle to catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate. However, a point mutation at arginine 132 inside IDH1 results in the production of 2-hydroxyglutarate, an oncometabolite. Furthermore, it exhibits uniform expression across the tumor, in contrast to EGFRvIII. To put it briefly, it is a legitimate avenue for future vaccine development treating brain cancer, but there is still room for advancement in terms of this particular antigen [6].

2.1.2. HSP vaccines. Heat-shock proteins (HSPs) are generated when cells increase quantity under environmental stress. They can also help modulate some aberrant proteins. When exogenous or soluble peptides bind with HSPs, the HSP-antigen complexes will stimulate CD8-positive T cells through cross-presentation. Due to their ability to connect with soluble proteins and generate cytotoxic T-lymphocytes, which trigger immunological responses, HSPs are being investigated as potential delivery systems for therapeutic cancer vaccines. While the quantity of such a vaccination is limited by tumor size, using HSPs may profit from the vaccine's personalized composition [6].

2.1.3. DC vaccines. Dendritic cells (DCs) play a vital role in the priming and consolidation of anti-tumor adaptive immune response. Compared to peptide-based vaccine, the DC-based vaccine is similiar in the way to activate host immune response, by exposing the antigen to immune cells, but different in the way to delivering the antigen. For peptide-based vaccine, the peptide itself could be recognized as

DOI: 10.54254/2753-8818/65/2024.LA18094

an antigen, then promoting the T cell proliferation, while for DC-based vaccine, the antigen is displayed by DCs, which act as a vector. That is, after being harvested in culture and given exposure to tumor lysate or specific tumor antigens, DCs are taken from patients and then returned to them to stimulate a T-cell-mediated response. The result of phase III trial of DCVax-L is published in 2023, demonstrated that the median OS of 64 patients using DCVax-L was 13.2 months while the OS of external control group is 7.8 months. This study can show the great potential of DC vaccines in clinical application [7].

Tumor antigens are thought to be a further method of activating collected DCs in addition to tumor lysate. Phosphoprotein 65 RNA (pp65) of the cytomegalovirus (CMV) is one example of this. Glioblastomas' malignant phenotype can be adjusted by CMV. A 2014 study discovered that T cells from GBM patients may lyse autologous GBM cells in an antigen-specific manner, multiply clonally 10–20 times, and become stimulated in vitro when exposed to CMV pp65-loaded, autologous DCs. Ongoing clinical research is being done on CMV pp65 DC [6].

Due to autologous DCs' poor penetration of lymph nodes and insufficient ability to activate lymphocytes, an issue for this therapy is boosting DC migration and lymphocyte activation to achieve stronger antitumor effects. Preconditioning the vaccination site by fully utilizing the immune system's "memory" component is one way to address this. In this manner, a systemic, immune-driven attack by administering recall antigens to the patients. Circulating recall antigen-specific memory lymphocytes that are already there and ready to go are what this attack depends on. Undoubtedly, such a strengthened immune system might produce the perfect environment for DCs. A research illustrated that, comparing with patients obtained the monotherapy of DC vaccine, who had OS of 18.5 months, 12 newly diagnosed GBM patients who got a tetanus booster, which is a recall antigen, prior to receiving DCs that were pulsed with the CMV pp55 had better DC homing to lymph nodes and better OS of 36.6 months, which demonstrated the effectiveness of such a solution [6].

2.2. Immune checkpoint inhibitors (ICIs)

Since one of the main causes of cancer is immunosuppression, which is done when tumor cells bind their immune checkpoints, whose function is to prevent the immune system from responding too strong to harm the healthy cell in the body, with the receptors on T cells. This sends an “off” signal to T cells or NK cells and makes T cells unaware of the proliferation of tumor cells. Tumors then escape immune-driven destruction. Such mechanism suppresses the respond of immune system to the abnormal accumulation of tumor cells, limiting a host’s ability to kill tumors, and then cause cancer. ICIs target the T cell receptors (TCRs) or the immune checkpoints on the tumor cell, block the pathway of immunosuppression and keep the immune system activated.

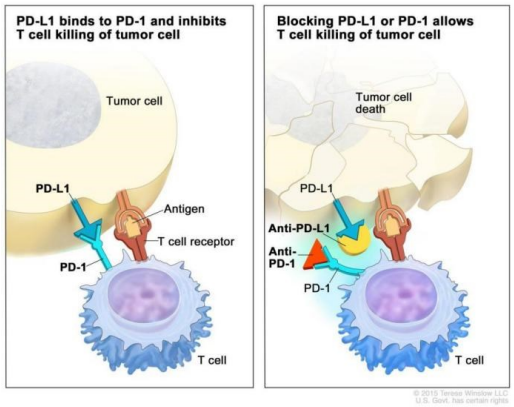


Figure 3. The mechanism of Anti-PD-1/PD-L1 inhibitors [8].

As shown in Figure 3, PD-1/PD-L1 is one of the most common pathways which the inhibitors target. Anti-PD-1/PD-L1 inhibitors are checkpoint inhibitors that block PD-1 and PD-L1 interactions and activities.

DOI: 10.54254/2753-8818/65/2024.LA18094

In addition to PD-1/PD-L1 pathway, CDLA-4 and CD86 or CD80 are also other pathways in which suppression in the immune system happen commonly. Nivolumab (anti-PD-1), pembrolizumab (anti-PD-1) and ipilimumab (anti-CTLA-4) are some checkpoints inhibitors that play important roles in the treatment of advanced cancer. However, they also have some side effects. For example, ipilimumab may cause severe pneumonitis, colitis and hypophysitis. Immune toxicity caused by these inhibitors limits their use to patients due to the possible severe effects on patients with pre-existing autoimmune disorders [6]. Moreover, resistance of the inhibitors will definitely limit the effect of them, which makes this another challenge the researchers need to overcome in the future.

Nowadays, ICIs are vital for curing malignancies, such as primary brain tumors. In Checkmate-143. researchers tested the feasibility of combining nivolumab with ipilimumab in treating recurrent GBM, and compared such combination therapy with nivolumab alone therapy. The result showed that the combination therpay can increase the OS rate, rise to 80% from 75% which is the OS rate of nivolumab alone therapy. Nevertheless, half of the patients had to stop the treatment early due to intolerability, and 80% of patients who received such combination therapy experienced three or four side events [6]. Therefore, such combination therapy of ICIs still require more development to become mature.

2.3. Chimeric Antigen Receptor (CAR) T-Cell therapy

In CAR-T cell therapy, T cells from the patients will be taken out, genetically engineered and then infused back into the patients. This engineering add CAR, a synthetic receptor, to the T cells. Such receptors can target specific antigen, which can be more effective than TCRs.

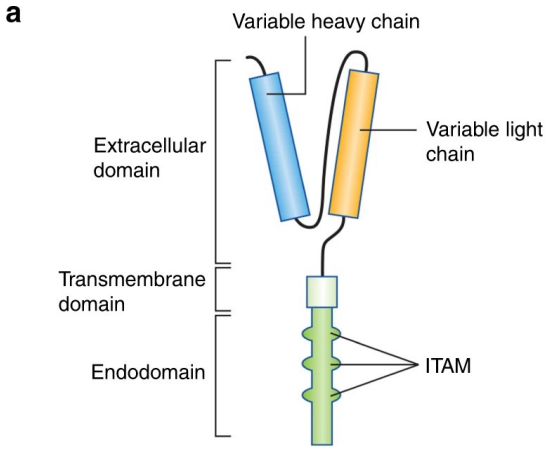


Figure 4. Structure of CARs [9].

CARs consist of three basic parts, as shown in Figure 4. The intracellular domain, being the fundamental structural element of the majority of CARs, takes charge of signal transduction whereas the extracellular domain recognizes antigens. The transmembrane domain is responsible for surface expression and stability of the receptor.

DOI: 10.54254/2753-8818/65/2024.LA18094

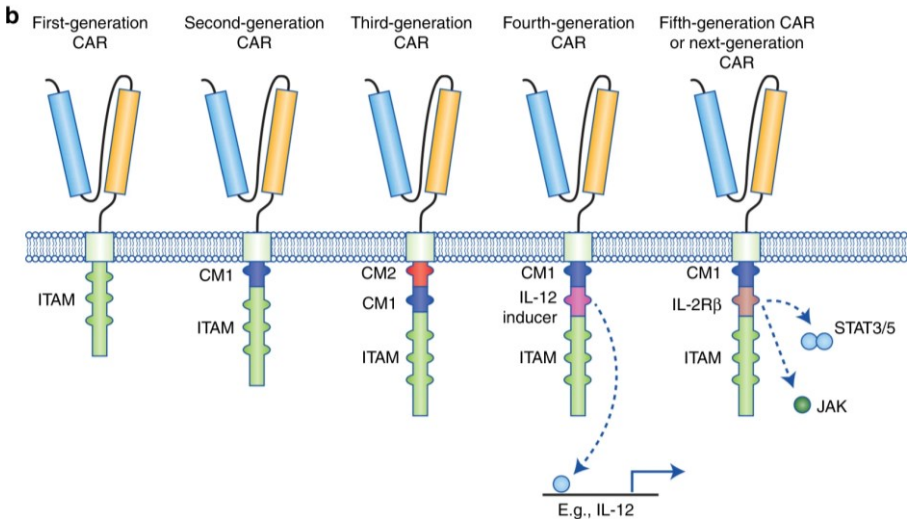


Figure 5. Structure of CARs of different generations during the development [9].

As demonstrated in Figure 5, by adding more intracellular signaling sequences of an extra co-stimulatory domain, CARs can develop to a more effective generation.

Additionally, solid tumors like gliomas can be treated with CAR-T cell therapy. Antigens that are lowly expressed in normal tissue and abundantly expressed in tumor tissues are known as tumor-associated antigens (TAAs). They can play important roles in treating solid tumor by using CAR-T cell therapy. Mucin-1, B7H3, Human epidermal growth factor receptor 2 (HER2), Epidermal growth factor receptor (EGFR) are some examples of TAAs [10].

However, because of the complicated tumor microenvironment, lack of particular antigens, and off-target effects, using CAR-T cells for solid tumor therapy still presents some difficulties. There's off-tumor toxicity which remains a challenge of using TAAs for CAR-T cell therapy in solid tumors. TAAs are overexpressed in tumor cells, but still express at low density in normal cells. Hence, such therapy may also kill the normal cells and may have really harmful side effects to the patients. Therefore, CAR-T cells need to be able to distinguish between cancer cells and normal cells maybe by sensing the density of antigens. In addition, lack of public tumor neoantigens and tumor-antigen heterogeneity, which leads to immunologic escape and tumor recurrence, are also challenges this therapy is now facing, requiring to be improve in the future.

3. Discussion

In the future, different combinations of those therapies will definitely become a main direction for development. For example, a clinical trial, which is still being tested, combine ATL-DC, a kind of DC vaccine with ICI pembrolizumab. Such combination aims to activate the synergistic effect of the systemic antitumor response, which is able to make such treatment more effective than monotherapies used before. Now it has been found that newly invented adjuvants can engage in innate immune activation pathways to improve the effectiveness of the therapies. This is a goal and the abbreviated way to reach the goal which other research and studies in the future might focus on. In addition, novel designs of the clinical trial can also contribute to improve the immunotherapies. In these trials, researchers are able to select more clinical results from a greater range. Moreover, designs that have more cooperation between clinical institutions are also helpful for the improvement of the therapy. These designs can be done by setting a more dispersive subgroup for research [7]. The previously described difficulties with CAR-T cell therapy can be addressed with the use of dual CAR and tandem CAR, as well as enhanced recognition ability of TAA binding domain in CARs. While the interaction between the CAR and its binding target influences the tumor-killing effect, proliferation capacity, and the persistence of the

DOI: 10.54254/2753-8818/65/2024.LA18094

response, dual CAR and tandem CAR can moderate off-target effects and achieve precise treatment. They represent trends that may be sequentially developed in the future.

4. Conclusion

To summarize the above, the three main immunotherapies for brain cancer are therapeutic vaccines, ICIs and CAR-T cell therapy, all of these treatments aim to stimulate the host immune response to fight against the tumor cells. Although some of these treatments have been tested to be safe and effective, they still have limitations. For vaccines, they may be relatively easy for researchers to produce and manage or some of them even achieve personal customization. However, the limitations are immunologic escape, the heterogeneous expression of antigenic EGFRvIII in a tumor and the restricted amount of generated vaccine. ICIs can effectively prevent immonosuppression, but the side effect still obvious like the overactivation of immune response. CAR-T cell therapy can improve the immune attack, whereas the complicated tumor microenvironment, lack of particular antigens, and off-target effects are the challenges of this therapy.

References

[1] Taphoorn, Martin J. B. , et al. "An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients." European Journal of Cancer 46.6(2010):1033-1040.

[2] Ilic, I. , and M. Ilic . "International patterns and trends in the brain cancer incidence and mortality: An observational study based on the global burden of disease." Heliyon 9(2023).

[3] Gomes, J. , A. A. Zayadi , and A. Guzman . "Occupational and Environmental Risk Factors of Adult Primary Brain Cancers: A Systematic Review." International Journal of Occupational & Environmental Medicine 2.2(2011):82.

[4] https://braintumor.org/

[5] Alentorn, Agusti , Khê Hoang-Xuan, and T. Mikkelsen . "Presenting signs and symptoms in brain tumors. " Elsevier Health Sciences (2016).

[6] Anastasie, et al. "Immunotherapy approaches in the treatment of malignant brain tumors." Cancer (2016).

[7] Zhao, B., Wu, J., Li, H. et al. Recent advances and future challenges of tumor vaccination therapy for recurrent glioblastoma. Cell Commun Signal 21, 74 (2023). https://doi.org/10.1186/s12964-023-01098-0

[8] https://www.cancer.gov/

[9] https://www.nature.com/

[10] Amorós-Pérez B, Rivas-Pardo B, Gómez del Moral M, Subiza JL, Martínez-Naves E. State of the Art in CAR-T Cell Therapy for Solid Tumors: Is There a Sweeter Future? Cells. 2024; 13(9): 725. https://doi.org/10.3390/cells13090725