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Adverse Reaction Mechanism and Optimization Strategy of Therapeutic Vaccines for Glioblastoma

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Abstract. This paper focuses on glioblastoma therapeutic cancer vaccines as the research subject, introducing the mechanisms of action and side effects of therapeutic vaccines. Regarding local, systemic, nervous, and immune-related adverse reactions occurring in vaccine clinical applications, the article analyzes the core causes and solutions for adverse reactions from four aspects: improper antigen selection, imbalance in immune activation levels, the immunosuppressive tumor microenvironment of the glioblastoma, and the overlap of side effects from multimodal combination therapies. At the same time, the paper looks ahead to the development direction of this field, pointing out that personalized vaccine development, combined application of vaccines with immune checkpoint inhibitors, and conducting larger-scale clinical trials are future research priorities. Therapeutic vaccines are an important means of precision treatment for glioblastoma, but they still face limitations such as adverse reactions. Balancing anti-tumor efficacy with therapeutic safety is the core key to future vaccine optimization and clinical translation

Keywords: Glioblastoma, Cancer vaccine, Adverse reaction, Optimization strategy

1. Introduction

Glioblastoma (GBM) is a very aggressive type of primary malignant brain tumour. Gliomas account for about 81% of all cases of adult malignant brain tumours. Among them, glioblastoma is the most malignant type and is classified as a grade 4 glioma according to the World Health Organization (WHO) classification system; it has the most severe clinical and pathological characteristics. A Grade 4 indicates a very high proliferation rate of the tumour and significant invasion of adjacent healthy brain tissue; it is highly likely to spread quickly. This will severely restrict the chances of full surgical removal and greatly increase the difficulty of developing effective treatment plans. Glioblastoma was previously known as glioblastoma multiforme; although it is no longer the official name now, the same type of tumour is still referred to as such [1].

Currently, the causes of most glioblastomas are unknown. Therefore, this kind of brain cancer may be caused by alterations in the DNA of brain cells. The above modifications are generally referred to as mutations by professionals. Damage to DNA can inhibit normal cell division and apoptosis, thus promoting the development of cancer. A considerable number of cancer cells can gather to form tumours. As the tumours grow, they have spread to the surrounding brain tissue and

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caused symptoms and other diseases. Most glioblastomas are not hereditary diseases, and it is infrequent for multiple family members to be ill.

Immunotherapy is not very effective for glioblastoma because of the blood-brain barrier; it cannot deliver immune drugs and immune cells to the tumour. At the same time, the microenvironment of brain tumours is highly immunosuppressive, has few tumour mutations and limited identifiable antigens, and is thus unable to trigger an effective immune response. Tumors are also highly heterogeneous, prone to immune evasion, and may have reduced overall immune function. Therefore, the therapeutic effect of this treatment is much weaker than that of melanoma and lung cancer.

Therefore, therapeutic vaccines have attracted the attention of scientists for active immunisation. They hope to stimulate the patient's own tumour-reactive T cells by presenting tumour antigens and thus form a long-lasting anti-tumour immune memory. This strategy has the advantages of the immune window period during the small residual lesion stage after surgery and chemoradiotherapy, and compensates for the pre-existing anti-tumor immunity in GBM by amplifying tumor-specific T cell clones. Therefore, this paper focuses on the application of therapeutic vaccines in glioblastoma to explore their prospects and problems as an immunotherapy strategy for malignant brain tumors, and to offer a new therapeutic path for this extremely poor prognosis and refractory tumor.

2. Mechanism of therapeutic vaccines

The first is the absorption and metabolism of tumour antigens. After the vaccine delivers specific tumour antigens in the body, dendritic cells (core antigen-presenting cells) actively recognise and capture free tumour antigens, then break down and process them within the cell. Then, they cut the intact antigen proteins into shorter antigen peptide fragments and display these processed antigen fragments on the cell membrane surface of dendritic cells for subsequent immune recognition.

The second is antigen presentation and T cell activation. Dendritic cells present processed tumour antigens to the initial T lymphocytes in the body within immune lymphoid tissue by means of specific presentation, and at the same time provide costimulatory signals to enable the immune system to recognise tumour characteristics of glioblastoma [2].

The third is the activation of T cells. Dendritic cells present these antigens to T cells at this time. Activated T cells can take one of two forms: CD8+ cytotoxic T lymphocytes, which directly kill cancer cells; CD4+ helper T lymphocytes, which support and enhance the immune response [2].

In the presence of many immune cells working together, glioblastoma cells have been accurately targeted for lysis and eliminated in the first wave of targeted anti-cancer immune destruction.

A main advantage of cancer vaccines is that they can induce a secondary immune response via antigen diffusion. Tumor destruction releases more antigens, and antigen-presenting cells (APCs) can also cross-present new antigens to activate T cells. This secondary response can recognise antigens other than those of the original vaccine and, thus, reduce antigen escape and extend anti-tumour immunity [3].

3. Clinical applications

Peptide vaccines have become an important platform for GBM vaccine research due to their easy preparation, controllable cost, and easy quality control. These vaccines typically consist of short or long peptides of tumor-associated antigens combined with immune adjuvants, delivered via subcutaneous or intradermal injection. The ETAPA trial represents a new approach in peptide vaccine design. The Phase I trial evaluated the P30-EPS vaccine, a chimeric peptide vaccine that

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links three class I tumor-associated antigens (CMV pp65, Survivin, EphA2) to the generic class II tetanus toxoid epitope P30. The innovation of this design is the broad recruitment of CD4+ T cell assistance by introducing a universal CD4+ coepitope, thereby enhancing cytotoxic T cell responses. Eighteen newly diagnosed MGMT non-methylated GBM patients received seven doses, showing that the vaccine was well tolerated in all patients with grade 2 ≤adverse reactions. Eleven patients developed antigen-specific IFN-γ responses, with the 400 μg dose group showing stronger recall responses. Longitudinal TCR sequencing showed that vaccine-associated clones amplified after booster immunization, including newly emerging low-frequency clones and persistent dominant clones, suggesting the formation of immune memory [4].

EGFRvIII is a classic case in the field of GBM peptide vaccines. EGFRvIII is a common mutant epidermal growth factor receptor in GBM, characterized by tumor-specific expression. Patients receiving this vaccine had a median progression-free survival of 15.2 months, compared to only 6.3 months in the control group; median overall survival was 23.6 months, compared to just 15.0 months in the control group. Testing of recurrent tumor samples showed that most recurrent lesions no longer expressed EGFRvIII antigens, demonstrating that the vaccine-induced immune response can effectively clear EGFRvIII-positive tumor cells. These results indicate that the vaccine can elicit a specific immune response with anti-tumor biological activity. Although it effectively clears tumor cells, studies have clearly pointed out that its clinical efficacy is clearly limited: most recurrent tumors achieve immune escape by losing the EGFRvIII antigen

The basic principle of the dendritic cell (DC) vaccine is to differentiate from the patient's peripheral blood mononuclear cells to obtain DC, then deliver it to the patient after in vitro loading with tumor antigens, leveraging DC's strong antigen-presenting ability to initiate tumor-specific T cell responses. The DC-ATA vaccine represents a significant advancement in this field. A single-arm phase 2 trial evaluated the efficacy of AV-GBM-1 (autologous dendritic cell-loaded autophagocytic tumor antigen) in treating newly diagnosed glioblastoma. Fifty-seven patients vaccinated after receiving standard chemoradiotherapy had a median progression-free survival of 10.7 months, a 57% increase from the historical control of 6.8 months, a median overall survival of 16.0 months, and a 3-year progression-free survival rate of 12.1%. Multivariate analysis showed that completion of 8 vaccinations, MGMT promoter methylation, dexamethasone dose of ≤2 mg, and administration of ≥ 6 cycles of temozolomide were independent prognostic factors. All 7 patients with 3 years of progression, age < 60, dexamethasone ≤ 2 mg, and no bevacizumab were used. The study suggested vaccine safety and feasibility, but overall survival benefit was limited; extending vaccination may further improve survival [5].

4. Adverse reactions

The most common side effects of therapeutic cancer vaccines are localised adverse reactions. Pain, redness of the skin, swelling, itching and other skin diseases may occur at the injection site. These symptoms are mostly caused by activation of local immune cells and activation of inflammatory signaling pathways after vaccination. Most of the adverse reactions at the injection site in clinical trials for glioblastoma vaccines are mild and resolve on their own within a short time [6].

Although most local reactions in patients are not serious, they show that the body has produced an immune response to the vaccine. The degree of harm from a vaccine is affected by the kind of vaccine, its components, additions and so on. Therefore, local toxic reactions need to be considered in the optimisation of vaccine formulations; however, compared with neurological complications, the clinical risk of local side effects is generally lower.

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Systemic side effects of therapeutic cancer vaccines can also occur, such as fatigue, fever, headache, nausea, chills and flu-like symptoms. The above-mentioned system reactions are usually triggered by systemic immune activation and the release of large amounts of inflammatory cytokines. Most are mild to moderate and can be managed clinically by treating symptoms. In some cases, there are more serious side effects. Severe allergic reactions have occasionally been reported in the clinical trials of personalized cancer vaccines.

5. Causes of adverse reactions and improvement strategies

5.1. Selection of tumor antigens

The first reason for the low efficiency and safety of therapeutic vaccines is the choice of tumour antigens. Tumour-associated antigens are highly expressed in cancer cells but may also be present at low levels in normal tissues. Targeting these antigens may lead to non-specific immune reactions and thus fail to identify tumours effectively. New Antigens are a solution to this problem. These antigens are results of gene mutations in tumour cells that are absent in normal cells and thus more specific to tumours. Tumours are very heterogeneous; not all mutations produce antigens that can activate T cells effectively, so selecting suitable new antigens is still a difficult technical problem.

Early vaccines focused on tumor-associated antigens (TAAs). Although these antigens are highly expressed in tumour cells, they may also be present in normal tissues and lack complete tumour specificity; therefore, there is a risk of non-specific immune reactions. Tumor-specific neoantigens are generated by somatic mutations in cancer cells and rarely occur in normal cells; thus, they provide more specific targets for T cell-mediated immune responses [7].

Personalized neoantigen vaccines have been shown in research on glioblastoma to induce immune responses in $CD4^+$ and $CD8^+$ T cells. Glioblastoma generally has a small number of tumour mutations and therefore a limited quantity of neoantigens for screening. Some tumours have a small number of mutation sites and insufficient mutant peptides for efficient presentation by major histocompatibility complexes (MHCs), so the selection of vaccine targets is limited [8].

5.2. Intensity of immune activation

Another reason for the reduced toxicity of vaccines is a weaker immune response. Vaccines need to provoke an adequate immune response to overcome the immunosuppressive effect of tumours; however, too strong an activation of the immune system may lead to inflammation and an increased risk of adverse reactions. Therefore, optimisation of immune activation is not necessarily the best way. A good vaccine should provoke a strong and prolonged anti-tumour response with minimal off-target systemic inflammation. Vaccine dose, type of adjuvant, antigen formulation and vaccination schedule all affect the strength and duration of immune response.

Antigen design optimisation and the regulation of immune activation levels also need to be optimised. Therapeutic vaccines need to induce a strong anti-tumour immune response; otherwise, excessive activation of the immune system may cause inflammation and increased toxicity. Therefore, an ideal vaccine should not provoke a powerful immune response but rather cause regulated and specific immune activation to achieve anti-tumour effects [8].

Intensity of immune activation is affected by antigen dose, adjuvant type, delivery vector and vaccination schedule. Reasonable Optimisation of these parameters can enhance T-cell responses and reduce unnecessary systemic inflammation. Another reason for reduced vaccine effectiveness is the use of glucocorticoids. Patients with glioblastoma are often on dexamethasone and other drugs to

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manage cerebral oedema and neurological disorders; these immunosuppressive drugs may reduce the efficacy of vaccines. Dexamethasone has been used in previous studies to reduce the immunogenicity of personalised neoantigen vaccines. Therefore, the future treatment plan will need to control the neurological symptoms and maintain the anti-tumour immune effect simultaneously [9].

5.3. Tumor microenvironment

Another problem in the treatment of glioblastoma is the tumour microenvironment. This tumour is in an immunosuppressive microenvironment rich in regulatory T cells, tumour-associated macrophages, myeloid-derived suppressor cells and other immunosuppressive signalling molecules. These substances suppress T cell activation and reduce vaccine efficacy. Therefore, there is a dilemma in the treatment approach: to counteract the inhibitory effects of the tumour microenvironment, researchers need to strengthen immune activation; however, enhanced immune stimulation also increases the risk of inflammatory toxicity. Therefore, when developing safer vaccines, the biological characteristics of the glioblastoma microenvironment must be fully considered [10].

5.4. Combination targeted therapy

In addition, therapeutic vaccines are also being used in conjunction with chemotherapy, radiation therapy, immune checkpoint inhibitors, etc. Combination therapy can overcome tumour resistance and enhance anti-tumour effects by multiple pathways, but predicting and controlling adverse reactions also increase the difficulty of prediction and management for adverse reactions. For example, symptoms of abnormal blood indicators and physical fatigue may be due to chemotherapy rather than the vaccine; nerve damage caused by radiotherapy may also be related to vaccine-induced inflammation. Therefore, the future clinical trials should set up strict control groups and improve adverse reaction monitoring systems to distinguish between side effects caused by different treatments.

Therefore, more and more research has begun to employ multi-antigen combination-target strategies. Due to the high tumour heterogeneity of glioblastoma, different sub-populations of tumour cells often express different antigens. Vaccines that only target a single antigen may fail to kill antigen-negative cells and thus be immune-evasive. In combination with tumour-associated antigens, tumour-specific neoantigens and other potential targets, the range of tumour cells recognised by the immune system can be expanded to enhance therapeutic effect. However, increasing the number of antigens does not necessarily lead to better efficacy and safety. All candidate antigens need to be evaluated for tumour specificity, immunogenicity and expression in normal tissues; thus, in antigen screening, both coverage and safety must be achieved [8].

Based on this, the design of personalised vaccines has been developed to improve treatment efficacy. Personalised vaccines are not the same as the old-fashioned vaccines; they are based on the molecular features of a person's cancer cells. With the development of next-generation sequencing technology, researchers can find mutation locations in patients' tumours and predict immunogenic neoantigens. Personalized vaccines can improve tumour targeting and reduce ineffective immune activation; by combining several patient-specific antigens, they may also address tumour heterogeneity and lower the risk of immune escape.

Early clinical trials have shown that personalised neoantigen vaccines are immunogenic and have not caused serious treatment-related adverse events. However, the current research sample size is

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small, and their long-term safety and clinical effectiveness have not been verified. Personalised vaccines also have the problems of tumour sequencing, neoantigen prediction, vaccine production and quality control, and are thus time-consuming and expensive. For patients with rapidly progressing glioblastoma, it is still a problem how to complete personalised vaccine preparation in time [7].

6. Future Outlook

Personalized therapeutic vaccines are widely regarded as one of the most promising directions in glioblastoma immunotherapy. With continuous advances in tumor gene sequencing technology and bioinformatics tools, researchers are expected to more efficiently screen individually specific neoantigens from each patient's tumor tissue and design customized vaccines that precisely target the unique molecular characteristics of individual tumors.

7. Conclusion

Therapeutic vaccines are promising new treatments for brain tumours, particularly glioblastoma. The special features of these therapies are that they can stimulate the patient's own immune system to recognise and fight against cancer cells in the body. Based on the present clinical data, most vaccine-related adverse reactions are mild and manageable, such as a local reaction at the injection site, general fatigue, fever, etc. Neurological damage, such as cerebral oedema and seizures, can also occur; therefore, close monitoring of these changes in the brain is required to prevent severe harm to the brain.

Many reasons are responsible for the occurrence of adverse vaccine reactions, such as selection and optimisation of antigens, degree of immune activation, immunosuppression in the tumour microenvironment, and combination therapy with other treatments. Therefore, improving therapeutic vaccines cannot be limited to enhancing immune activation capacity. Future research will be conducted in the following directions: develop highly specific new antigen targets, apply the concept of personalised vaccine design, achieve precise and controllable immune activation strength, and enhance toxic response monitoring systems.

In the end, whether therapeutic vaccines can effectively treat brain tumours in people will depend on finding a suitable combination of anti-tumour effect and medication safety. Large-scale, standardised clinical trials and new developments in personalised immunotherapy technology are currently underway to determine if therapeutic vaccines will be safe and effective enough for inclusion in the standard treatment of glioblastoma in the future.

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