v. 4, n. 94, 2024

International Journal of Health Science

Acceptance date: 25/10/2024

CLINICAL IMPACT OF IMMUNOTHERAPY IN THE TREATMENT OF GLIOBLASTOMA: SYSTEMATIC REVIEW OF THERAPEUTIC APPROACHES AND RESULTS

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Abstract: Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor in adults, with a median survival of only 15 months, even with conventional treatment that includes surgical resection, chemotherapy and radiotherapy. In recent years, immunotherapy has emerged as a promising approach to treating tumors, including GBM, with the possibility of targeting the immune system to fight tumor cells. This systematic review aims to evaluate clinical trials that have investigated the use of immunotherapies in the treatment of GBM, focusing on three main aspects: safety profile, adverse effects and tolerability, especially in combination with chemotherapy and radiotherapy. Six clinical trials published between 2019 and 2024 were selected, totaling 6,215 patients. Therapeutic approaches ranged from dendritic cells, CAR-T cells, immune checkpoint inhibitors and personalized vaccines. The results indicated that immunotherapies have an acceptable safety profile, with manageable adverse effects such as fatigue, fever and, in some cases, cytokine release syndrome and neurotoxicity, especially in CAR-T therapies. Treatment tolerability was high, with most patients managing to complete the therapeutic protocols without significant interruptions. However, the efficacy of these therapies still faces limitations, such as tumour heterogeneity and immune evasion, highlighting the need for new studies exploring the personalization of treatments and the use of specific biomarkers. We conclude that immunotherapies represent a significant advance in the treatment of GBM, but more controlled, long-term clinical trials are needed to conclusively validate their efficacy and safety.

Keywords: Glioblastoma multiforme, immunotherapy, CAR-T cells

INTRODUCTION

Glioblastoma multiforme (GBM) is the most common and aggressive type of primary brain tumor in adults, representing between 60 and 70% of gliomas and around 15% of all primary malignant brain tumors (1). Characterized by rapid progression and a high recurrence rate, GBM has an average survival of only 15 months, even with the use of conventional treatments such as surgical resection, radiotherapy and chemotherapy with temozolomide (2) (3). One of the main challenges in the management of GBM is the genetic and molecular heterogeneity of the tumor, as well as the presence of glioma stem cells (GSCs), which are highly resistant to conventional therapies (4). These cells contribute significantly to tumor recurrence due to their ability to repair DNA damage and evade the immune system (5)(6). However, the treatment of GBM with immunotherapies faces additional challenges due to the unique barriers imposed by the central nervous system (CNS), such as the blood-brain barrier and the immunosuppressive tumor microenvironment, which limit the effectiveness of these interventions (7). Despite these obstacles, several immunotherapy strategies have been investigated for GBM, including the use of CAR-T cells, tumor vaccines and immune checkpoint inhibitors (8). CAR-T cell therapies, which have demonstrated success in the treatment of hematological malignancies, are being adapted for solid tumors, such as GBM, with the aim of targeting specific immune responses against tumor antigens, such as EGFRvIII (9). Tumor vaccines, especially those based on dendritic cells, have also been explored as a way of activating the immune system to attack specific tumor cells (10). In addition, immune checkpoint inhibitors, such as those that block the PD-1/PD-L1 pathway, are being evaluated in combination with standard therapies, such as radiotherapy and chemotherapy, to potentiate the immune response and overcome the immunosuppression promoted by the tumor (11).

OBJECTIVES

The aim of this systematic review is to evaluate clinical trials on the use of immunotherapies in the treatment of glioblastoma multiforme (GBM), focusing on three main aspects: safety profile, adverse effects and tolerability, especially in combination with chemotherapy and radiotherapy. The review aims to identify the main adverse effects observed, analyze the safety of immunological therapies and assess the tolerability of patients during treatment, taking into account the impact of these interventions on quality of life.

METHODOLOGY

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, with a focus on identifying and analyzing clinical trials that evaluated immunotherapies in the treatment of glioblastoma multiforme (GBM), as well as systematic reviews relevant to the topic. Prospective and retrospective clinical trials published between 2019 and 2024 investigating the safety profile, adverse events and tolerability of immunotherapies in GBM patients, including CAR-T cells, tumor vaccines and immune checkpoint inhibitors, were included. Systematic reviews were also included to provide a comprehensive overview of therapeutic approaches. Exclusion criteria included editorials, case reports, case series and narrative reviews. The searches were carried out in the PubMed database. To identify the clinical trials, the search term "Glioblastoma multiforme AND neurosurgery AND clinical trial" was used, filtering for publications from the last five years (2019-2024), resulting in a

International Journal of Health Science ISSN 2764-0159 DOI https://doi.org/10.22533/at.ed.159491241410949

total of 145 clinical trials. From these, 6 clinical trials were selected for inclusion in the review. For systematic reviews, the search term used was: "Glioblastoma multiforme AND neurosurgery AND systematic review", with the same time filter, resulting in 217 studies. Of these, 5 systematic reviews were included in the review. The studies were selected in two stages. In the first, two independent reviewers assessed the titles and abstracts to determine eligibility. In the second stage, the selected articles were reviewed in full text, and any discrepancies were resolved by a third reviewer. The information extracted included the authors, year of publication, type of immunotherapy, number of patients, therapeutic interventions, primary outcomes (safety profile, adverse events) and treatment tolerability. Given the high degree of heterogeneity in the included studies, the analysis was carried out qualitatively. The risk of bias was assessed using the Cochrane tool for randomized clinical trials and the ROBINS-I tool (Risk of Bias in Non--Randomized Studies - of Interventions) for non-randomized studies.

RESULTS

145 clinical trials were found in the initial search, of which 6 were selected for this systematic review, totaling 6215 patients. All studies focused on the efficacy and safety of immunotherapies in the treatment of glioblastoma multiforme (GBM), with therapeutic approaches ranging from dendritic cells, CAR-T cells, immune checkpoint inhibitors and personalized vaccines.

SECURITY PROFILE

The autologous dendritic cell vaccine was considered safe, with most adverse events classified as mild to moderate, including fatigue and headache. No serious or fatal vaccine-related adverse events were reported in patients with newly diagnosed and recurrent GBM (1). Oncolytic immunotherapies were well tolerated, with mild to moderate adverse effects, such as fever and flu-like symptoms, which were adequately managed. There were no reports of serious or fatal adverse effects (2). CAR-T therapy targeting EGFRvIII and IL13Rα2 showed more severe adverse events compared to other therapies. Cytokine release syndrome (CRS) was observed in around 25% of patients, but was controlled with the use of IL-6 blockers and corticosteroids. Neurotoxicity was also recorded in approximately 10% of patients, but was adequately managed with no therapy-related deaths (3). Therapy with depatuxizumab mafodotin demonstrated an acceptable safety profile. Ocular toxicity was one of the main adverse effects, with some patients requiring ophthalmologic follow-up, but without discontinuation of therapy for the majority (4). Off-the-shelf CAR-T therapy also presented some cases of serious adverse events, including neurotoxicity and CRS, but less frequently. CRS was moderate in most cases and adequately controlled. Neurotoxicity was observed in a small number of patients, but was controlled without fatal complications (5). Intracerebral administration of immune checkpoint inhibitors demonstrated an acceptable safety profile, with some autoimmune reactions treated with corticosteroids without serious complications. Combination with radiotherapy did not result in a significant increase in toxicity (6). The safety profile of the immunotherapies reviewed, including CAR-T, dendritic cell vaccines and checkpoint inhibitors, was considered acceptable in most studies, with serious adverse events such as CRS and neurotoxicity being rare and manageable. Most patients tolerated the therapies without fatal complications, and the most frequent side effects were classified as mild to moderate. The combination of immunotherapy with traditional treatments, such as radiotherapy, also proved viable from a safety point of view.

ADVERSE EFFECTS

Most patients treated with the autologous dendritic cell vaccine experienced mild adverse effects, such as fatigue and headache. There was no need for significant interventions to control the adverse effects, which were considered manageable. No serious adverse events were directly related to the vaccine (1). Oncolytic immunotherapies have been associated with fever and mild to moderate flu-like symptoms, often attributed to the immune response induced by the therapy. These side effects have been managed with symptomatic drugs, and no serious adverse effects have been reported (2). Cytokine release syndrome (CRS) was the main adverse effect observed in CAR-T therapies, occurring in around 25% of patients. CRS was of moderate severity in most cases and controlled with IL-6 blockers and corticosteroids. Neurotoxicity was recorded in approximately 10% of patients, but was managed appropriately, without the need for definitive discontinuation of therapy (3). Ocular toxicity was the most significant adverse effect of therapy with depatuxizumab mafodotin. Some patients required ophthalmological follow-up during treatment. However, the majority of patients continued therapy without the need for interruption, indicating that ocular toxicity was manageable (4). Off-the-shelf CAR-T therapy was associated with adverse effects such as neurotoxicity and CRS. CRS was mostly moderate, and neurotoxicity occurred in a small number of patients. Both effects were managed effectively, without the need to interrupt treatment in most cases (5). Autoimmune reactions, such as dermatitis and colitis, have been observed in patients treated with immune checkpoint inhibitors. These reactions were treated with corticosteroids and did not result in serious complications or treatment interruption. The combination of checkpoint inhibitors with radiotherapy did not significantly increase adverse events (6). The adverse effects reported in the clinical trials reviewed were mostly mild to moderate and included fatigue, headache, fever and flu-like symptoms. Cytokine release syndrome (CRS) and neurotoxicity were the most serious adverse effects, particularly in CAR-T therapies, but both were successfully controlled. Ocular toxicity was observed in therapy with depatuxizumab mafodotin, but was manageable. In general, adverse effects were manageable and did not compromise treatment continuity in most patients.

TOLERABILITY

The dendritic cell vaccine was well tolerated by most patients, with few cases of treatment interruption. Mild adverse events, such as fatigue and headache, did not compromise treatment continuity, and most patients completed the protocol without significant complications (1). Oncolytic immunotherapies showed high tolerability, with patients generally completing the treatment protocol without major complications. Mild side effects, such as fever and flu-like symptoms, were easily managed, and there were no treatment interruptions due to adverse events (2). Despite the occurrence of cytokine release syndrome (CRS) and neurotoxicity, most patients treated with CAR-T therapies were able to complete their treatment. CRS was controlled with medication, allowing patients to continue therapy without major interruptions (3). depatuxizumab mafodotin-related ocular toxicity was adequately managed in most cases, allowing patients to continue treatment. The tolerability of the therapy was considered good, with most patients completing treatment without serious interruptions (4). Off-the-shelf CAR--T therapy was well tolerated by most patients, despite cases of neurotoxicity and CRS. These adverse effects were controlled, and patients were able to complete treatment without ma-

jor complications (5). Intracerebral administration of immune checkpoint inhibitors was well tolerated by patients, with few severe autoimmune reactions. The combination with radiotherapy did not compromise tolerability, and patients were able to complete treatment without significant interruptions (6). Overall, the immunotherapeutic approaches reviewed showed good tolerability, with most patients completing treatment without serious interruptions. Adverse effects, such as CRS and neurotoxicity, were manageable, allowing patients to continue treatment. The therapies reviewed were considered feasible in terms of tolerability, with low rates of discontinuation due to adverse events.

DISCUSSION

The clinical trials reviewed on the use of immune therapies, such as dendritic cells (DCV) and CAR-T, demonstrate promising immune responses in the treatment of glioblastoma multiforme (GBM). However, the clinical efficacy of these approaches is often limited by the presence of a highly immunosuppressive tumor microenvironment and physical barriers, such as the blood-brain barrier, which restrict the penetration of immunotherapeutic cells into tumor tissue (1-6). The immunosuppressive microenvironment in GBM is sustained by various mechanisms, such as the presence of tumor-associated macrophages (TAMs) and regulatory T cells, which create an unfavorable environment for the activation of immune cells. These elements limit the effectiveness of therapies such as CAR-T and dendritic cell vaccines, which depend on a robust immune response to be effective. Another recurring challenge was the variability in patient responses, even within a single protocol. The genetic and molecular heterogeneity of GBM results in different tumor antigen profiles, which compromises the efficacy of targeted therapies, such as CAR-T cells, which target EGFRvIII and IL-13Rα2(3,5). In addition, the phenomenon of "immune escape", in which tumors lose target antigens after starting therapy, reduces the long-term efficacy of these approaches (3). This reinforces the need for more personalized treatments, based on continuous monitoring of tumor biomarkers that allow therapies to be adjusted according to changes in the tumor's antigenic profile. Studies have indicated that patients with high antigen expression, such as IL13Rα2, tend to respond better to targeted CAR-T therapies (5). However, the lack of reliable biomarkers to predict individual response remains a critical barrier (3,5). The development and validation of biomarkers is essential to identify which patients are most likely to benefit from specific immunotherapeutic approaches, thus enhancing treatment personalization. The combination of immunotherapy with traditional treatments, such as radiotherapy and temozolomide, has shown promise in some trials. Radiotherapy can increase the immunogenicity of tumor cells, promoting a more robust anti-tumor response, and the "abscopal effect" has been observed as a therapeutic opportunity that increases the immune response in non-irradiated areas (6). However, more studies are needed to optimize the synergy between these modalities and determine the best administration protocols. The safety of immune therapies was widely considered acceptable in the trials reviewed, although serious adverse events such as cytokine release syndrome (CRS) and neurotoxicity have been observed in patients treated with CAR-T cells (3,5). The need for close monitoring and appropriate preventive strategies to mitigate these adverse effects is evident, especially in therapies that involve modulating the immune system. Despite the advances, a common limitation of the studies was the small number of patients and the absence of control groups in some trials, which

makes it difficult to generalize the results (1-6). Phase III clinical trials, with larger numbers of participants and standardized protocols, are needed to provide more robust data on the safety and efficacy of immunotherapies. Personalization of treatments, based on molecular and immunological profiles, may be the key to improving clinical outcomes in the treatment of GBM (9,10). This review highlights the potential of immunotherapies in the treatment of GBM, but also emphasizes the need for future studies exploring new biomarkers, therapeutic combination strategies and ways of overcoming the immunosuppressive microenvironment, so that these therapies can reach their full potential in clinical practice.

CONCLUSION

This systematic review emphasized the remarkable progress in the use of immunotherapies in the treatment of glioblastoma multiforme (GBM), highlighting therapies with dendritic cells, CAR-T and immune checkpoint inhibitors. Despite advances, clinical results are impacted by significant challenges, such as tumor heterogeneity, immune evasion mechanisms and the loss of target antigens, factors that limit the durability of therapeutic responses. CAR-T cell therapies, particularly targeting the EGFRvIII and IL13Rα2 antigens, have demonstrated robust immune responses. However, these treatments still face difficulties in combating the immunosuppressive microenvironment of GBM, which reduces their long-term efficacy. The review also indicated that immunotherapy can be safely integrated into standard GBM treatment, including temozolomide and radiotherapy, without a significant increase in toxicity. To maximize the benefits of immunotherapies, it will be crucial to develop biomarkers that can better stratify patients, allowing treatments to be personalized according to tumor and immunological profiles. This would increase the likelihood of identifying patients who are more likely to respond positively to immunotherapies. The challenges of tumor resistance and variability in responses remain, and for these therapies to reach their full potential, phase III clinical trials are needed, with larger samples and tighter control. The future of immunotherapy in GBM is promising, but its success is tied to constant innovation and research, especially with regard to the combination of different immunotherapies, such as CAR-T and checkpoint inhibitors. By exploring these combined approaches, it is possible that these therapies will become central components of the clinical management of GBM, providing better outcomes for patients.

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