Journal of Vaccines, Immunology and Immunopathology
Lichtor T. J Vaccines Immunol 9: 1117.
www.doi.org/10.29011/2575-789X.0001117
www.gavinpublishers.com

Review Article

Immunotherapy in the Treatment of a Brain Tumor

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Citation: Lichtor T (2024) Immunotherapy in the Treatment of a Brain Tumor. J Vaccines Immunol 9: 1117. DOI: 10.29011/2575-789X.0001117

Received Date: 24 April, 2024; **Accepted Date**: 02 May, 2024; **Published Date**: 06 May, 2024

Abstract

Treatment options for brain tumors include surgical resection, cranial irradiation and systemic or local chemotherapy. These treatments all have serious adverse side effects and provide relatively minimal survival benefits for most brain tumors. Antigenic differences between normal and malignant cells of the cancer patient form the rationale for clinical immunotherapeutic strategies. Cytokines such as IL-15 or IL-2 that stimulate an antitumor immune response have been shown to have high potential for use in immunotherapy against various tumors. In this review, studies with either a poxvirus genetically engineered to secrete IL-15, or allogeneic fibroblasts engineered to secrete IL-2 are shown to be an effective treatment strategy in prolonging survival in mice with malignant intracerebral tumors upon injection of the treatment cells into the brain. Future studies with these treatment strategies in patients with intracerebral tumors are urgently needed.

Introduction

Limitations of current brain tumor treatments

The ability to diagnose and surgically treat brain tumors has improved with recent technical advances [1]. However, the standard treatment modalities following surgical resection including cranial irradiation and systemic or local chemotherapy each have serious adverse side effects. The few long-term survivors are often left with cognitive deficits and other disabilities [2,3]. Novel therapies are urgently needed.

Principles of brain tumor immunology

Antigenic differences between normal and malignant cells from tumors form the rationale for clinical immunotherapeutic strategies. Different strategies have been attempted to enhance the anti-tumor immune responses in mice and patients with intracerebral neoplasms. Dendritic cell treatments represent one immunotherapeutic approach that has demonstrated promise in animal models, but clinical trials involving dendritic cells have documented relatively short benefits, which are limited to a minority of treated patients with brain tumors [4]. In many aggressive tumors, such as gliomas, progression is enabled by local immunosuppression driven by the accumulation of regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC) [5]. The lack of response to treatment in glioma patients may be attributed to the immunosuppressive T cells (regulatory T cells) that normally prevent anti-tumor immunity when the immune response is evoked [6].

The use of IL-2 has been a significant force in cancer immunotherapy (7). However, the application of IL-2 in the treatment of a variety of tumors is limited by toxicity and the expansion of regulatory T cells. To overcome these limitations and improve response rates, other agents, which stimulate T cells such as IL-15, have been in clinical development. IL-15 has been shown to have particularly high potential for use in immunotherapy against various tumors [7], and IL-15 unlike IL-2 does not stimulate regulatory T cells [8].

Potential application of oncolytic viruses in brain tumor therapy

Oncolytic viruses, either engineered or in nature, may selectively infect and lyse tumor cells while avoiding infection of normal cells [9]. Once oncolytic viruses infect tumor cells, they may contribute

to the anti-tumor response by a direct cytotoxic effect on tumor cells and consequent release of tumor-associated antigens, which can stimulate anti-tumor immune responses [10]. When the virus is engineered to express an immunostimulatory cytokine [11], it also becomes a vector for local expression of potent immune-activating agents, attracting immune cells into the tumor microenvironment.

Development of Potential Treatments

Cytokine expression in tumors is one strategy used to stimulate potent activation of the immune system resulting in antitumor immune responses. The use of cytokines has become more common in treatment of patients with high grade gliomas, particularly with IL-2 and IL-15 [12,13]. A potential advantage of IL-15 is that there is less activation of immune inhibitory Tregs associated with this cytokine. Preliminary results, however, have not demonstrated efficacy for prolonging survival in patients with brain tumors using various cytokines including IL-2 or IL-15 [14].

Several treatment strategies involving cytokine expressing treatment cells have recently been reviewed [15]. Prolongation in survival was found with mice bearing an intracerebral glioma treated intracerebrally with an oncolytic poxvirus expressing the IL15Rα-IL15 fusion protein as the T cell activating stimulus in combination with a prostaglandin synthesis inhibitor to block immunosuppression (celecoxib) supplemented by adoptive T-cell therapy (tumor-specific CD8+ T cells). Rapamycin was also used to enhance the spread and replication of the oncolytic virus [16-18]. The rationale for this treatment is that the oncolytic poxvirus could lead to a direct cytotoxic effect on glioma cells and consequent release of potential tumor antigens, which may stimulate a stronger anti-tumor immune response. When the virus is engineered to express a cytokine, it becomes a vector for local expression of potent immune-activating agents. In this study IL15 was chosen because it activates and maintains the function of NK and CD8+ T cells [19] with less activation of Tregs [20,21]. Systemic inflammation that occurs upon parenteral delivery of this cytokine has not been observed following introduction of IL15 into the brain.

Another immunologic strategy was studied using a vaccine prepared by transfer of a cDNA expression library derived from tumor cells into an allogeneic mouse fibroblast cell line expressing a cytokine such as IL-2. These cells have been found to have great potential in the development of an antitumor immune response and prolongation of survival in mice with an intracerebral tumor following intracerebral injection of the treatment cells [15, 22]. The allogeneic fibroblasts transfected with tumor DNA stimulate the expression of tumor antigens. The transferred DNA integrates spontaneously into the genome of the recipient cells and replicates as the cells divide. This strategy results in the development of immunity to antigens that characterize the patient's tumor. Only small amounts of tumor tissue are required enabling treatment at an early stage of the disease, when tumor tissue is available in only limited amounts and the tumor is most susceptible to immune based therapy. A novel enrichment strategy has also been developed to increase the proportion of immunotherapeutic cells in the vaccine.

Conclusion

To be successful, every remaining tumor cell in the patient must be eliminated. It is unlikely that a single form of therapy can achieve this goal. However, immunotherapy in combination with surgery, radiation therapy and chemotherapy will likely find a place in the treatment of patients with brain tumors. The development of DNA-based tumor vaccines is a novel strategy that does not require antigen identification or protein purification and yet can elicit a robust and long-lasting activation of the immune response, which results in tumor rejection. The enrichment strategy enables the generation of more highly immunogenic pools of transfected cells with enhanced immunotherapeutic properties. The DNA-based vaccines have great potential for further development of cancer immunotherapy in general and specifically for treatment of malignant brain tumors. The use of oncolytic viruses engineered to secrete cytokines remains another potential treatment option for patients with brain tumors and requires further study regarding the potential of this treatment option.

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