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Anti-Tumour Treatment

Active immunotherapy using dendritic cells in the treatment of glioblastoma multiforme

Amade Bregy [a], Theresa M. Wong [a], Ashish H. Shah [a], John M. Goldberg [b], Ricardo J. Komotar [a,*]

[a] University of Miami Miller School of Medicine, Department of Neurological Surgery, Miami, FL, USA
[b] University of Miami Miller School of Medicine, Division of Pediatric Hematology Oncology, Department of Pediatrics, Miami, FL, USA

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ABSTRACT

Objective: Glioblastoma multiforme, the most common malignant brain tumor still has a dismal prognosis with conventional treatment. Therefore, it is necessary to explore new and/or adjuvant treatment options to improve patient outcomes. Active immunotherapy is a new area of research that may be a successful treatment option. The focus is on vaccines that consist of antigen presenting cells (APCs) loaded with tumor antigen. We have conducted a systematic review of prospective studies, case reports and clinical trials. The goal of this study was to examine the efficacy and safety in terms of complications, median overall survival (OS), progression free survival (PFS) and quality of life.

Methods: A PubMed search was performed to include all relevant studies that reported the characteristics, outcomes and complications of patients with GBM treated with active immunotherapy using dendritic cells. Reported parameters were immune response, radiological findings, median PFS and median OS. Complications were categorized based on association with the craniotomy or with the vaccine itself.

Results: A total of 21 studies with 403 patients were included in our review. Vaccination with dendritic cells (DCs) loaded with autologous tumor cells resulted in increased median OS in patients with recurrent GBM (71.6–138.0 wks) as well as those newly diagnosed (65.0-230.4 wks) compared to average survival of 58.4 wks.

Conclusions: Active immunotherapy, specifically with autologous DCs loaded with autologous tumor cells, seems to have the potential of increasing median OS and prolonged tumor PFS with minimal complications. Larger clinical trials are needed to show the potential benefits of active immunotherapy.

Introduction

In the year 2012, The National Cancer Institute (NCI) reported that 22,910 adults would be diagnosed with brain or other central nervous system (CNS) tumors; 15% of these tumors are diagnosed as glioblastoma multiforme (GBM). With a yearly incidence of 2.5 in 100,000,[1] GBM is the most common and lethal type of brain tumor with a median overall survival (OS) of three months without standard treatment.[2] Currently the accepted conventional treatment for GBM is maximal surgical resection of the tumor followed by radiation with 60 Gy of fractionated radiation therapy and chemotherapy with temozolomide.[3] This offers a median OS of 14.6 month,[4] a prognosis that still remains dismal. Current research points to immunotherapy as a non-surgical adjuvant treatment option with minimal risk of side effects.

The principle of immunotherapy for cancer is based on stimulating the body's own immune system in order to amplify both a humoral and cytotoxic immune response to target tumor cells.[5] Immunotherapy works either by boosting the immune system entirely or by training the immune system to attack the tumor based on specific antigenicity.[6]

In the initial stages of this research, immunotherapy was not considered to be an effective treatment option due to the blood brain barrier (BBB) as well as the absence of the conventional lymphatic drainage system.[7] The BBB serves as a boundary that separates the peripheral circulation and the CNS, which inherently prevents immune reactions other than those from microglia from occurring in the brain.[8] Additionally with the absence of the conventional lymphatic vessels and low levels of circulating T-cells in the brain, it is difficult to understand how activated peripheral immune cells would be able to cross the BBB and target a tumor in the brain.[7] Previous literature has established the theory of two-way communication between the CNS and peripheral circulation by either a humoral immune response or nervous transmission.[9] The latter relies on afferent or efferent nerve fibers of the CNS to create an autoimmune link across the BBB. This link is exemplified by the

* Corresponding author. Address: University of Miami, Department of Neurological Surgery, 1095 NW 14th Terrace, 2nd Floor, Miami, FL, USA. Tel.: +1 (305) 243 2427.
E-mail address: rkomotar@med.miami.edu (R.J. Komotar).

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vagus nerve, which has been found to direct communication between the brain and the immune system.[10,11] Signals that originate in the brain are transmitted through the vagus nerve as an action potential. This ultimately leads to the release of cytokines, which then mounts an inflammatory immune response. On the other hand, humoral immunity relies on immunoglobulin as the main mediator across the BBB to increase response to foreign antigens (tumors). An example of this type of transmission is the vaccine induced experimental model of autoimmune encephalomyelitis (EAE).[9] In these studies, activated CD4+ T-cells have been observed circulating in the periphery and then infiltrating the CNS to induce EAE.[12] Therefore, in analogy immunotherapy may be a plausible treatment option where activated immune cells after exposure to a peripheral antigens from the vaccine are transported through the bloodstream and can cross the BBB. However, the exact mechanism by which this occurs is not fully understood.[7,13,14]

The primary focus of this paper is to describe mechanisms and findings of active immunotherapy using dendritic cells (DCs) as the antigen presenting cells (APCs). This type of treatment is based on training the body's immune system to create an antitumoral response.[15] In this type of therapy, APCs are sensitized with a tumor specific antigen and administered as a vaccine either by intradermal or subcutaneous injection. This results in the generation of appropriate T-cells that mount an antitumor response. Active immunotherapy is not only applicable in treating the initial tumor, but it may also induce a memory immune response, that offers protection to the body from future tumor recurrences.

In order to assess the safety and efficacy of active immunotherapy using DCs as APCs, we have conducted a systematic review of the literature to help establish a general consensus on the safety of active immunotherapy as well as to define a paradigm for treatment protocols (increased median OS, progression free survival (PFS) and the quality of life of the patients).

Materials and methods

Study selection

Using the MeSH database system of PubMed, a literature search was performed between the years 1992 and 2013 for all articles containing the terms *glioblastoma* and *immunotherapy ((“Glioblastoma”[Mesh]) AND “Immunotherapy”[Mesh]).* The articles were limited to English with humans as the only subjects of this study. Additionally, the article types were limited to case reports, clinical trials and randomized controlled trials while reviews, editorials and commentaries were excluded. The initial inclusion criteria focused mainly on immunotherapy as an adjuvant treatment for

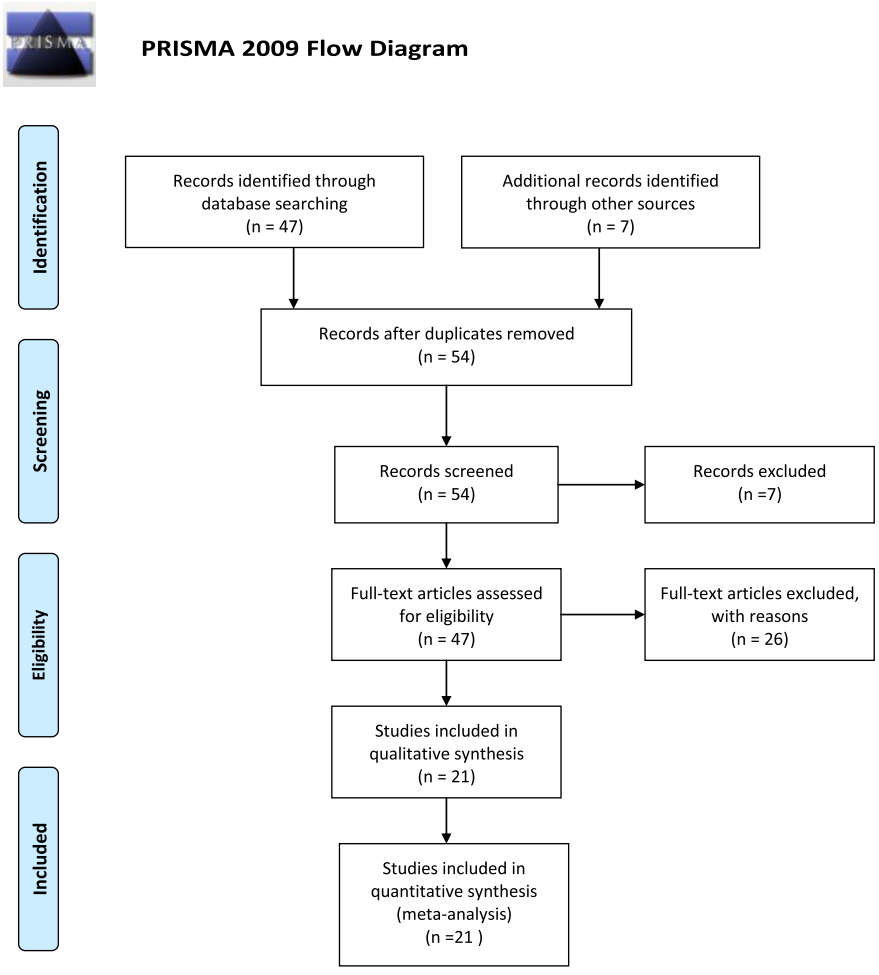

Fig. 1. The PRISMA figure illustrates the systematic process that was conducted to locate case reports, clinical trials and prospective studies that we analyzed in this review.