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A Study to Evaluate the Efficacy of Dendritic Cell Immunotherapy in Glioblastoma Multiforme

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Abstract

Cancer is the second leading cause of death and continues to grow globally, exerting tremendous physical, emotional and financial strain on individuals and their families. Glioblastoma is the most frequent malignant tumor of the Central nervous system with the worst prognosis. The current conventional treatment of surgery chemo and radiation does not provide complete remission. Dendritic cells (DCs) are the most powerful antigen presenting cells and DC-based vaccination has the potential to target and eliminate GBM cells and enhance the responses of these cells to the existing therapies with minimal damage to the healthy tissues around them. It can enhance recognition of GBM cells by the patients' immune system and activate vast, potent, and long-lasting immune reactions to eliminate them. Dendritic cell immunotherapy aims at inducing an antitumoral immune response seeking to exploit this pivotal role of DC therapeutically. Keeping this in mind, a retrospective study was conducted to evaluate the safety and efficacy of dendritic cell immunotherapy in GBM patients who had recurrence or residual disease post conventional therapy. The outcome of the study has been encouraging proving beneficial for patients with minimum residual tumor burden.

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Introduction

Cancer is the second leading cause of death and continues to grow globally, exerting tremendous physical, emotional, and financial strain on individuals and their families, accounting for approximately 1 in 6 human deaths worldwide. In 2018, approximately 9.6 million deaths were due to cancer [1]. Brain tumours are the leading cause of cancer-related death. Glioblastoma multiforme, also referred to as grade IV astrocytoma, is the most frequent malignant tumour of the central nervous system with the worst prognosis. It is a fast-growing aggressive malignant tumour of the CNS arising from glial cells, constituting 47.7% of all CNS tumours, with an incidence of five cases per 100,000 people [2]. The cause of GBM is unknown; however, it is believed that aging progressively suppresses normal immune surveillance, which contributes to GBM cell initiation and/or outgrowth [3]. Other contributory factors include irradiation and, viral infections such as CMV [4,5]. The mainstay treatment for GBM is neurosurgery, followed by radiotherapy and chemotherapy with temozolamide. However, since GBMs are surrounded by a zone of migrating, infiltrating tumour cells that have a tendency to invade the surrounding tissues, it becomes impossible to remove the tumour entirely, and as a result, GBM has a high recurrence rate at sites distant from the original resection site. Radiotherapy and chemotherapy succeed only in controlling the disease and not in eradicating it. As complete remission is difficult to achieve, intensive research in different domains has been performed to improve the prognosis of glioblastoma multiforme patients. Immunotherapy is one such treatment which has gained momentum over the years. Immunotherapy, also referred to as biological therapy, is the treatment of disease by either activating or suppressing the immune system. It includes restorative immunotherapy, modulating immunotherapy, passive immunotherapy, adoptive immunotherapy, and active specific immunotherapy with vaccines.

Active cell-based immunotherapies have proven to be effective in some cancers, and dendritic cell therapy has shown promising results. Immune effector cells, such as lymphocytes, macrophages, dendritic cells, natural killer cells, and cytotoxic T lymphocytes, work together to defend the body against cancer by targeting abnormal antigens expressed on the surface of tumour cells. Of these, dendritic Cells are the most powerful human antigen-presenting cells and are key to development of T cell response

[6]. DCs are immature cells that reside in most tissues where they sample antigens. When activated by pathological changes, DCs migrate to the draining lymph nodes and present as mature DC peptides. Antigen-specific cytotoxic T lymphocytes and helper T cells recognise these peptides, are activated, proliferate, and differentiate into effector cells which execute various cellular adaptive immune responses, including killing of target cells [6]. DCs are typically not found in the normal brain parenchyma but are instead present in vascular-rich compartments, such as the choroid plexus and meninges, suggesting of a potential migratory pathways of peripheral DCs into the CNS [7]. Under pathological conditions, DCs migrate to the brain and spinal cord through afferent lymphocytes or high endothelial venules. Dendritic cell immunotherapy/vaccination aims to induce an antitumoural immune response by exploiting this pivotal role of DCs therapeutically.

DC-based vaccination therapy was first applied in a clinical trial in 1996 for B-cell lymphoma; however, in 2006, the clinical efficacy of this therapy was proven in hormone-refractory prostate cancer patients [8]. Several immunotherapy strategies based on dendritic cell vaccines have been attempted for GBM and have been shown to be safe and tolerable. In 2009, Ardon et al integrated immunotherapy in the primary standard treatment for eight pilot adult patients (median age 50 years) with GBM, showing excellent quality of life during vaccination with progression-free survival at six months of 75% and median overall survival for all patients was 24 months. Cho Yang (in 2012) conducted a study in patients with newly diagnosed GBM and found that, the OS rate was better than that in control group (18.8%; 15.0 months) [9,10]. Inogés in 2017 conducted a phase II trial of autologous dendritic cell vaccination in newly diagnosed glioblastoma patients, showing its feasibility and safety with an increase in the overall survival of GBM patients [11]. The results of previously published trials and studies have hinted at the efficacy of dendritic cell immunotherapy.

Dendritic cell immunotherapy involves the isolation of CD14+ monocytes from the patient's peripheral blood. These isolated monocytes were cultured in the laboratory with granulocyte macrophage colony-stimulating factor (GM-CSF) and interleukin 4 (IL-4) for 6 days to differentiate into immature dendritic cells. Once immature DCs were obtained, they were matured/activated using tumour-specific antigen/ tumour-associated antigens for 48 hrs. These mature DCs are loaded with whole tumour lysate peptide antigens which are generated from apoptosis or freeze-thawing (necrosis) of GBM cells. They recognise and capture antigens, and present processed peptides (derived from captured antigens) to T cells in the context of major histocompatibility complex (MHC) class I or II. Tumor-loaded DCs with maturation stimuli increased the expression of costimulatory molecules such as CD 83 and CD 86 and the secretion of proinflammatory cytokines, such as IL-12. Each dendritic cell has the ability to target 3000 - 5000 T cells per hour and generate tremendous anticancer immunity. These mature DCs are then injected back into the patient, usually intravenously. Once in the body, they migrate to the tumour site through afferent lymphocytes, where they are able to prime naïve T cells and initiate an adaptive immune response. The CD4+ helper T cells secrete IL-2 to stimulate CD8+ cytotoxic T cells which then secrete IFN-γ and exhibit cytolytic immune responses against GBM cells. They display immune regulatory systems that balance the complex system of inflammatory and inhibitory immune reactions in the tumor microenvironment.

Wheeler CJ in 2004 conducted a study on the clinical responsiveness of GBM to chemotherapy after vaccination. There was increased responsiveness to TMZ chemotherapy after DC vaccination [12]. Considering the promising results from various studies, we performed a randomised retrospective study using whole-lysate peptide dendritic cell vaccination with standard conventional treatment modalities. This study aimed to evaluate the safety and efficacy of dendritic cell vaccination in GBM patients with recurrence or residual disease after conventional therapy.

Methods

A retrospective randomised study was conducted at the Denvax Clinic, Vasant Vihar, in 18 patients diagnosed with glioblastoma who received dendritic Cell Immunotherapy. All confirmed cases of glioblastoma with recurrence or residual disease after conventional therapy were administered dendritic cell immunotherapy.

Preparation of DC Vaccine

In all GBM patients peripheral blood was collected and mixed in cell nute and sent to the laboratory where isolated monocytes were cultured with GM-CSF and IL4 to differentiate into immature DCs. Immature DCs are activated into mature dendrites using tumour-specific antigen. Mature DCs were further loaded with whole tumour lysate peptide antigens. Mature DCs were preserved in liquid nitrogen until use.

The DC vaccine dissolved in 100 ml normal saline was administered via slow intravenous infusion over 30 min. Six consecutive doses were administered at intervals of 2 weeks for total 6 doses. Patient assessment was performed using the following parameters every 3months for one year.

1. Neurological performance status using standardised mental state examination(SMSE). A standardised approach to scoring and interpreting people's cognitive function, provides **a global score for cognitive ability that correlates with daily functioning**.
2. Karnofsky performance status- **an assessment tool for predicting the length of survival in terminally ill patients**. The KPS is an 11 point rating scale which ranges from normal functioning (100) to death (0) in ten point increments.
3. Evidence of tumour response was demonstrated by using Response Assessment in Neuro oncology (RANO Criteria)- Imaging and Clinical status. MRI Spectroscopy was used for imaging.

Primary endpoint was Progression free survival and secondary endpoint was overall survival.

Table 1: Assessment parameters of all patients before treatment and after treatment with immunotherapy

Case	Age / Sex	Karnovsky Score		Standardised Mini Mental State Examination (SMMSE)		RANO Criteria		Induction Of Therapy
		Pre	Post	Pre	Post	Pre	Post	Month/year
1	51y/M	50	90	Severe	Normal	PD	CR	March 2021
2	33y/M	40	70	Severe	Mild	PD	PR	November 2021
3	75y/M	60	80	Moderate	Mild	PD	PR	March 2021
4	84y/M	40	60	Severe	Moderate	PD	SD	April 2021
5	44/M	50	70	Severe	Mild	PD	PR	November 2019
6	44y/M	50	90	Severe	Normal	PD	CR	March 2021
7	45y/F	50	80	Severe	Mild	PD	PR	November 2021
8	57y/F	60	80	Moderate	Mild	PD	PR	November 2021
9	23y/F	40	70	Severe	Moderate	PD	PR	August 2021
10	48y/M	50	60	Severe	Moderate	PD	SD	July 2021
11	48y/M	50	70	Severe	Mild	PD	PR	June 2019
12	44y/M	60	80	Severe	Mild	PD	PR	January 2017
13	46y/M	50	60	Severe	Moderate	PD	SD	October 2019
14	57y/M	60	70	Moderate	Mild	PD	PR	March 2018
15	48y/M	60	90	Moderate	Normal	PD	CR	May 2019
16	53y/M	70	70	Moderate	Moderate	PD	PR	July 2017
17	34y/F	50	60	Severe	Moderate	SD	SD	June 2018
18	32y/F	50	90	Severe	Normal	PD	CR	July 2019

PD-Progressive disease, SD- Stable disease, PR- Partial Response, CR- Complete Response

Results

Nineteen patients were reported to the clinic for Dendritic Cell immunotherapy. One patient was not excluded because the patient had deteriorated and was hospitalised in ICU.

The median patient age was 48years. The Karnofsky Performance Score (KPS) was 90–100 in 22.2%, 80 in 22.2%, 70 in 33.3% and 60 in 22.2%. Standardised mini-mental state examination (cognitive function) improved in all patients after treatment with immunotherapy. Complete response was observed in 22.2% patients, partial response was 55.5% and stable disease in22.2% patients. No disease progression was observed in any of the patients treated with immunotherapy. No adverse events or toxicities attributable to immunotherapy were observed.

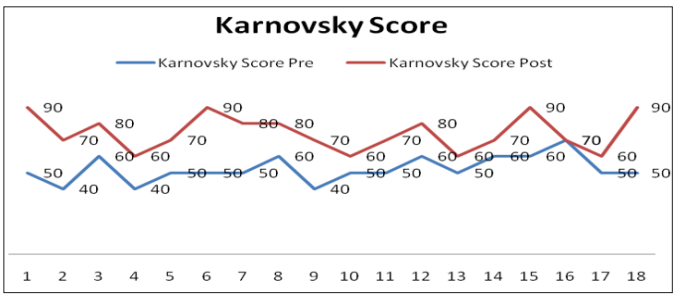

Figure 1: Karnovsky score Analysis of all patients before and after treatment with Dendritic cell immunotherapy

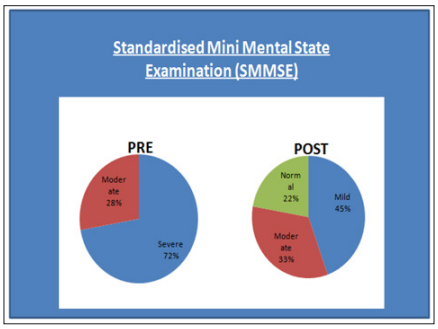

Figure 2: Standardised mini mental state examination analysis of all patients before and after treatment with DC immunotherapy

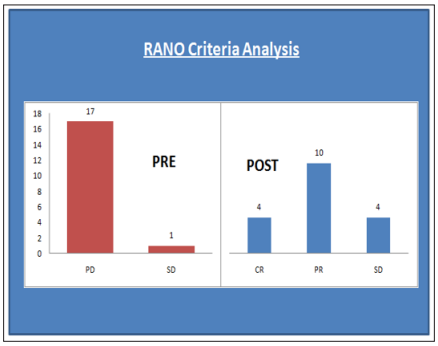

Figure 3: RANO Criteria analysis of all patients before and after treatment with DC immunotherapy

Discussion

Currently dendritic cell therapy is not a part of the standard of care. However, it has been attempted in recurrent settings and has shown to be feasible and safe in previous trials. Glioblastoma multiforme (type IV) is known to have 5.1 months survival despite conventional treatment modalities including surgery, chemotherapy and radiotherapy [13]. Post-conventional treatment and, immunotherapy has been proven to be effective in numerous experimental models of cancer. Mutating cancer cells fail to recognize the immune vicinity and are likely to become cancerous [14]. Failure of the immunological response to five-step mutation is considered a hallmark of cancer development. Cytotoxic T-cell (CTL) responses are rarely generated in cancerous tissue [14]. The generation of parallel immunity plays an important role in the establishment of solid tumours. Immature dendritic cells are often found in and around tumour cells but they cannot elicit CTL response [14]. The mainstay of cancer regression is an effective CTL response. This was possible with the generation of mature DCs in the present study. After activation by DCs, effector T cells cross the blood-brain barrier and exert their effector function in the brain, with a contribution of luminal antigen presentation by endothelial cells to identify the specific site for effector T cells to enter the brain parenchyma and a final tuning of T cell effector functions by the brain microenvironment. We succeeded in establishing the safety and efficacy of DC therapy, and the Karnovsy performance status and tumour response have been encouraging. However, the overall survival data are yet to be established as most of the cases are still in treatment or follow-up. The clinical and neurological improvements were comparable with those reported in other studies. We reasoned that this might help prime the immune system and allow a faster immune response build-up after subsequent doses. Moreover, the effort to keep vaccinating patients even after progression could be important for the improvement of the overall survival, and we plan to have larger clinical trials combined with conventional therapies to make immunotherapy with dendritic cell immunotherapy a standard practice in the near future.

Conclusion

Our results suggest that the addition of autologous DC immunotherapy to conventional treatment in cases of GBM is feasible both clinically and radiologically, well tolerated, and may be possibly beneficial for patients with minimum residual tumour burden. Our findings further underscore the importance of a proper assessment of the potential of adjuvant DC immunotherapy in patients with GBM, and as a fourth oncological treatment modality, integrated in the conventional therapy for these patients in particular.

Conflict of Interests

The authors declare that they have no conflict of interests.

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