

Vaccine Immunotherapy for Patients with Glioblastoma Multiforme

By

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Note: The author of this paper is not an M.D. The contents of this paper are based on the listed references and are offered for educational and informational purposes only. This article is meant to bring attention to a timely treatment therapy concept that should be considered; it is not meant to be a complete literature review for either immunotherapy or vaccine therapy. Patients should refer to their health care provider for medical advice. Special acknowledgement and thanks are made to Meng-Yin Yang et al., 2006, and Ben A. Williams, 2007, for their recent reviews of this subject.

Background

As anyone familiar with glioblastoma multiforme (GBM) unfortunately knows too well, currently available treatments seldom provide anything more than temporary respite and tumor growth inevitably recurs. One area showing considerable promise is that using the patient's immune system as an instrument for cancer therapy. An immune response directed against cells bearing tumor markers or antigens could provide a specific and effective mechanism for killing the unresectable, infiltrating residual tumor; thus halting the inevitable recurrence. While the theory is "elegant and persuasive", a substantial clinical breakthrough has yet to be made and most clinical investigations have not yet translated into FDA-approved therapies for brain tumor patients (1).

Some of the factors limiting success thus far include the following (1, 2, 3, 4, and 5):

- Different people have different tumors with different collections of antigens/proteins, so generic vaccines will not be effective (unless targeted against GBM-specific molecular pathways common to all patients) and patient-specific ones will be required.
- A paucity of well-defined, tumor-specific antigens exists (most of the surface antigens for GBM cells are the same as those of "normal" host cells).
- The human central nervous system (CNS) is immunologically quiescent.
 - Absence of organized lymph tissue and traditional lymphatic drainage from the brain decrease the immunologic responsiveness of the CNS.
 - The tight blood-brain barrier hinders the transport of many types of immunoreactive molecules and immune cells into the brain.
 - High concentrations of immunoregulatory factors interfere with inflammatory responses within the CNS.
 - Danger exists when stimulating inflammatory responses within the CNS.

- There is a lack of cellular major histocompatibility complex (MHC) expression on normal cells within the CNS, which limits activation and migration of armed T cells.
- Ineffective antigen-processing events (6, 7) dampen both humoral and cellular immune responses.

Nevertheless, a great deal of promising immunotherapy-related research has been conducted over the past 10 years and continues today. The major areas of immune investigation have been focused on the following approaches: **passive immunotherapy** (introducing target (tumor)-specific monoclonal antibodies [mAb] into the patient) (1, 8, 9); **radioactive antibody targeting** (tagging a target-specific mAb with a radioisotope to deliver high-dose radiation to malignant cells) (1, 10-16); **coupled targeted immunotoxins** (with interleukin and other growth factors) (1, 17-25); **adoptive immunotherapy** (transferring the patient's own immune cells [or other immune cells] that have been stimulated outside the body with tumor antigens) (1, 26, 27); **lymphokine-activated killer cells** (specific case of adoptive immunotherapy using "trained" peripheral blood lymphocytes to lyse natural killer-resistant tumor targets at the site of the tumor) (1, 28, 29); **cytotoxic T lymphocytes** (another specific case of adoptive immunotherapy using tumor cells to stimulate T cells and accelerate/activate the patient's own cellular mediated resistance) (1, 30-35), and **active immunotherapy** (1, 36-38). This article will focus on active immunotherapy – the administration of the tumor antigenic material to induce a primary immune response, e.g. to "vaccinate" a patient against their own tumor.

Active Immunotherapy

Because most tumor antigens are poor stimulators of the immune system, active immunotherapy usually includes the use of adjuvants to enhance the immune response by prolonging the time of exposure to antigen and by increasing the activity of antigen presenting cells (APCs) which are essential in the activation of the body's cellular mediated resistance process (1). The most common approaches include the use of dendritic cell (DC)-based, cytokine immunogene, and bacterial/viral tumor vaccine therapies.

Dendritic cell-based vaccines

DCs are the most effective APCs in the body as evidenced by their abilities to stimulate leukocyte reactions and to prime naïve T lymphocytes. This strategy involves exposure in the laboratory of the patient's dendritic cells to their tumor antigen in combination with various stimulating factors, followed by an injection of these "primed" DCs into the patient to stimulate an internal immune response. Although soluble antigen is naturally released by tumor cells in later stages with the development of necrotic areas, such tumors are past the threshold when they can be checked by a patient's natural immune reaction. This strategy accelerates the body's natural process; hopefully inducing tumor destruction in the earliest stages of growth (1).

In a 1999 Phase I trial, twelve (7 newly diagnosed, 5 recurrent) high-grade glioma patients received three separate vaccinations spaced two weeks apart in addition to standard of care which included external beam radiation therapy. Robust infiltration of T cells was detected in tumor specimens and median survival was 455 days (compared to 257 days for a control population (1, 2, and 39). Other Phase I DC-based clinical trials have been conducted (40-46) and shown promising results (median overall survival: 133 weeks; median overall survival 23.4 months; and 50% 2-year survival rate [41]), and in 2004, it was reported that the use of temodar after vaccination treatment improved outcomes relative to the vaccine alone (47). Proof of clinical benefit is still being established in Phase II clinical trials, which were started in 2002 (48).

Cytokine immunogene therapy

In 2000, a new strategy, the cytokine immunogene therapy, was reported (49). To prepare this type of vaccine, genes are transferred into a fibroblast cell line that causes the cells to produce cytokines, potent proteins known to stimulate the immune system. These cells are subsequently injected into the tumor bed, resulting in the development of an antitumor immune response. Glick et al. found that mice with a primary intracerebral glioma, melanoma, or breast cancer treated with this cytokine-secreting vaccine survived significantly longer than untreated mice. Additionally the vaccine was found to stimulate a systemic antitumor immune response, as shown by immunocytotoxic studies, histopathological examination, and delayed immune memory responses. Their results showed that immunogene therapy was a promising new targeted therapy for the treatment of intracerebral malignant tumors (49).

In 2006, Glick et al. further demonstrated the efficacy of this potential therapy using intratumoral injection of interleukin-2-secreting cells as a treatment or protective vaccine in young mice. They demonstrated a significant prolongation of survival in animals harboring gliomas. Furthermore, long term survivors demonstrated immune memory, as evidenced by prolonged survival when rechallenged with tumor cells. Most impressive of all, 78% of long term survivors did not develop a tumor when rechallenged (50). While limited use of this therapy has been reported in humans (51, 52), studies continue. It is hoped that these findings and those like them will lead in the near future to more extensive clinical trials for the treatment of gliomas using this concept.

Bacterial and viral tumor vaccines

Live bacteria and/or viruses may also serve as a basis for active immunotherapies against brain tumors (1, 48) as their infections and the resulting damage can provide signals that attract APCs and initiate the cellular immune response (53). Studies have been conducted using *Listeria monocytogenes* (54-57), reovirus (2, 58), and reengineered polio virus (2, 59) in animals, and *Salmonella typhimurium* (1, 60), New Castle virus (1, 61), and herpes virus (2, 62) in humans. Four patients with advanced high-grade glioma, treated with the New Castle Disease Virus

vaccine (MTH-68/H) had purported survival times of 5-9 years (61). More recently, Steiner et al., reported the results of a pilot clinical trial using patient tumor cell cultures infected with New Castle Disease Virus, followed by gamma irradiation. 39% had a 2 year survival rate compared to 11% in the controls (63). The use of a modified herpes virus was reported in Scotland in 2000. Four of nine patients were alive at the time of the report; 14-24 months after treatment (2, 64).

GBM-specific molecular pathway vaccines

One of the challenges mentioned earlier in using vaccines directed at tumors is that different people have different tumors with different collections of antigens/proteins; thus generic vaccines will not be effective. However, if a vaccine could be developed that was targeted to a metabolic pathway specific only to GBMs, that vaccine could be used “off the shelf” without modification for individual patients (2). Recently, a vaccine was developed that targets the epidermal growth factor, Variant III, which occurs in a high percentage of GBMs (but not all) but is rarely seen in anything other than GBM tumors. Patients received an initial set of 3 vaccinations at two-week intervals, standard temodar plus radiation, and monthly vaccines thereafter. Median time to tumor progression for 23 patients was 12.1 months, compared to a median time of 7.1 months for patients receiving the same treatment without vaccination. Median survival in the vaccinated patients had not been reached at the time of the report (65). A subsequent trial was completed in which the vaccine was given only to patients who were screened in advance for the mutant receptor before admission into the clinical trial. Median survival was 29 months, one of the best clinical outcomes thus far reported (Celdex Pharmaceuticals Report, June 2007).

Status

While these various strategies hold much promise, various challenges remain (1):

- The use of corticosteroids, almost always a part of the standard care for brain tumor patients, is known to suppress the immune response. Therefore, its use must be considered when contemplating any of these immunotherapy strategies and is another reason that active immunotherapy should be used early, rather than late in a treatment protocol.
- Due to the need for highly patient-selective treatments, the patient accrual on clinical trials is slower, the potential market for an approved product is lower, and the development times to FDA approval are prolonged.
- There are significant manufacturing challenges facing the clinical development of such therapeutics.

When one considers the above it becomes easier to understand why it is generally accepted that simultaneous targeting of several components of the neoplastic process will provide the maximal chances of tumor control. The use of active immunotherapy, in combination with traditional

surgery, radiation, chemotherapy, and molecularly targeted biological agents should prove to be synergistic and of low toxicity. The combined use of conventional treatments within the context of clinical trials of immunotherapy will allow for the evaluation of efficacy yet retain the ethical requirements for human investigation (1).

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