# Dendritic Cell Vaccines Offer Promising Signals as Glioblastoma Therapy

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Immunotherapy is rapidly emerging as a very attractive and novel therapeutic approach for cancer, including for glioblastoma multiforme (GBM), the most common primary malignant brain tumor in adults.[1]

For patients with this malignancy, the current multimodal therapy of surgery, chemotherapy, and radiotherapy is often ineffective. Consequently, higher rates of tumor recurrence and progression are often the rule with GBM, and the prognosis is very dismal. Patients have a median survival of less than 15 months.[2] Furthermore, by the fifth year of diagnosis, more than 90% of patients are likely to succumb to the disease.[3] Novel and effective alternative therapeutic strategies are therefore essential.

With immunotherapeutic approaches, cancer-specific immune responses can occur through several nonmutually exclusive strategies. These include activation of the immune system with tumor antigens; neutralization of tumor antigens with antibodies; enhancement of immune-stimulatory signaling pathways that promote cytotoxic T-cell activity; or adoptive T-cell tumor-targeting mechanisms.

Most immune-based therapeutic strategies for GBM have focused on the concept of vaccines, with the overwhelming majority of applications based on dendritic cells (DCs). The DC vaccine strategy was pioneered through the development of sipuleucel-T for the treatment of castration-resistant prostate cancer (CRPC). In a landmark study,[4] Kantoff and colleagues demonstrated a significant improvement in overall survival (OS) for patients with CRPC who were treated with sipuleucel-T, helping to establish the foundation and enthusiasm for applicability to other cancers.

## Strong Rationale for DC Vaccines

DCs are particularly attractive in vaccine applications because of their exquisite, efficient ability to present foreign antigens as antigen-presenting cells (APCs) to the immune system, thereby generating an antigen-specific adaptive immune response. With this approach, expanded clones of autologous DCs pulsed with either GBM cell lysates or tumor-derived peptides are used for the vaccine (**Figure 1**). It is anticipated that the DCs will recognize GBM cells bearing applicable antigens, thus leading to destruction of residual GBM tumor cells through adaptive immune-mediated mechanisms.

A major feature of this approach is its personalized cancer care focus, and the potential to target a broad range of tumor antigens. Potential limitations of this strategy include the requirement for surgical resection, as well as the labor-intensive and complex process of vaccine manufacturing.

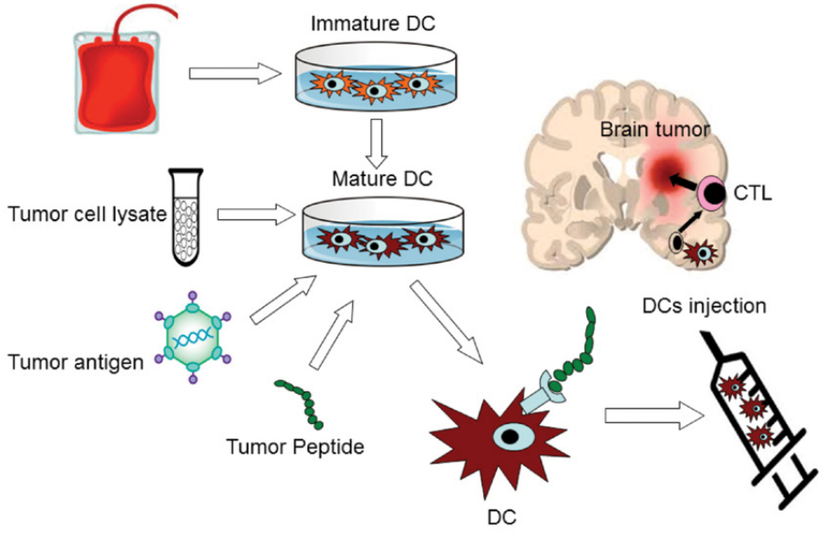
The safety, immunogenic potential, and effectiveness of DC vaccines pulsed with GBM tumor cell lysates or tumor-eluted peptides have been well established in preclinical[5-10] as well as clinical studies.[11-21] The preponderance of evidence suggests that the vaccine strategy is well tolerated, effective, and can improve overall survival in a tumor-specific, immune response–dependent fashion.

### *Lysates*

One of the largest clinical studies of DC vaccines in GBM was conducted by De Vleeschouwer and colleagues.[17] They safely treated 56 patients with recurrent GBM with DCs pulsed with autologous tumor lysate as postsurgical adjuvant therapy. There was a marked tendency toward improvement in both progression-free survival (PFS) and OS within the vaccination group.

Currently, Moffitt Cancer Center is participating in a multicenter phase III randomized double-blinded clinical trial examining the efficacy of a DC vaccine, DCVax-L, derived from autologous DCs pulsed with GBM lysates (NCT00045968).[22] The study, which began in December 2006, seeks to randomize 300 patients with newly diagnosed grade IV GBM in a 2:1 ratio to receive either DCVax-L or placebo. Participants are screened for the

**Figure 1. Typical dendritic cell (DC) vaccine scheme**




Dendritic cells (DCs) obtained from differentiated monocytes in peripheral blood (red icon) are matured and then pulsed with tumor cell lysates, antigens, or peptides. The loaded cells are expanded and injected intradermally into patients, where the vaccine targets cytotoxic T lymphocytes (CTLs).

Illustration courtesy Arnold Etame, MD, PhD

trial before they undergo surgical resection of the tumor; they then receive standard therapy, including radiation and temozolomide, before proceeding to randomization.

One of the critical lessons from initial clinical trial efforts with DC vaccines was correlating therapeutic benefits with immunogenicity. The first attempt to establish vaccine efficacy with immunogenicity on the DC platform occurred in a clinical trial by Wheeler and colleagues.[18] When they treated 32 patients with GBM using DCs pulsed with GBM lysate, they clearly identified T-cell responsiveness as a variable that strongly correlated with a prolonged survival and prolonged disease progression time in the vaccinated cohort. Subsequent clinical studies have similarly assessed and confirmed correlation between immunogenicity and therapeutic benefit for such patients. Markers of immune responsiveness could facilitate optimal stratification of patients in the future.

*Peptides*

Synthetic peptides derived from tumor-associated antigens also have been employed in DC vaccines. The ease of manufacturing substantial amounts makes this approach attractive.

For GBMs in particular, the mutated epidermal growth factor receptor variant III (EGFRvIII) is a highly immunogenic target with surface expression in 30% to 40% of GBM.[23] In preclinical orthotopic GBM models, a synthetic peptide derived from a segment of EGFRvIII demonstrated immunogenicity, significant antitumor activity, inhibition of formation of tumor in 70% of vaccinated animals, and ultimately resulted in long-term survivors.[24] In a subsequent clinical study of newly diagnosed GBMs, the same research group was able to demonstrate EGFRvIII-specific immune responses secondary to vaccination using DCs pulsed with the synthetic peptide derived from a segment of EGFRvIII.[25] Median PFS of 6.8 months and median OS of 18.7 months relative to onset of vaccination were realized, representing a significant improvement compared with match controls. Several additional clinical trials are under way examining EGFRvIII as a vaccine target.

In order to broaden the antigen coverage of DC vaccines, another approach has been to pulse DCs simultaneously with a panel of several tumor-associated antigen peptide. Using DCs directed against a panel of six glioma-associated antigen peptides, Phuphanich and colleagues demonstrated an overall median survival of 38.4 months in newly diagnosed patients with GBM who expressed at least three of the six antigens in a phase I clinical trial.[26] Within the series of 15 patients, five patients demonstrated postvaccination T-cell responsiveness as evidenced by CD8-positive and interferon-gamma production. Based on these encouraging findings, placebo-controlled, randomized phase III studies using this six-peptide panel are under way.

*Stem Cells*

In addition, the strategy of employing DCs to target tumors antigens can be extrapolated to targeting cancer stem cells that serve as the ultimate drivers of therapeutic resistance and tumor propagation. There is preclinical evidence that DC vaccines can target the tumor stem cell–resistant clones if pulsed with stem cell–specific antigens.[27, 28] In a recent clinical study involving seven GBM patients treated with DC pulsed with mRNA from cancer stem cells, the investigators demonstrated the safety, feasibility, and potential for such an approach to positively influence PFS.[29] Additional studies are warranted for further validation of this approach.

**Evidence for Moving Forward**

In summary, DC vaccine strategies have demonstrable clinical feasibility, safety, and efficacy in a subset of patients with GBM. Efforts at identifying humoral factors that correlate with vaccine efficacy as well as strategies that enhance T-cell responsiveness secondary to vaccination could have a significant impact. The theoretical risk of unintended autoimmune reactions to this vaccine strategy remains extremely low. Several clinical trials are under way looking at whole-tumor cell lysates, tumor-eluted peptides, synthetic tumor-associated peptides, and nucleic acids with exciting prospects. Our center is involved with some of these endeavors, notably the whole-cell lysate approach for patients with newly diagnosed GBM in a phase III clinical trial format.

Full references accompany article at **www.OncLive.com**

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### New Myelofibrosis Inhibitor Explored

**Rami S. Komrokji, MD,** discusses an analysis of pacritinib for the treatment of myelofibrosis. Currently, only one JAK2 inhibitor, ruxolitinib, is approved for the treatment of myelofibrosis. Komrokji is the clinical director of Hematologic Malignancies at Moffitt Cancer Center.

*Rami S. Komrokji, MD*

Pacritinib, a dual JAK2/FLT3 inhibitor, was evaluated in an integrated analysis from two phase I/II clinical trials. The analysis found that pacritinib was well tolerated with no instances of major adverse events in myelofibrosis, regardless of a patient's baseline platelet counts. http://goo.gl/NV2g1x

### TKI Options in RCC Examined

**Shilpa Gupta, MD,** discusses factors that influence choices about which tyrosine kinase inhibitor to prescribe for the treatment of patients with metastatic renal cell carcinoma. Three FDA-approved agents target vascular endothelial growth factor in this tumor type, noted Gupta, a genitourinary oncologist at the Moffitt Cancer Center.

*Shilpa Gupta, MD*

The side effect profile of the drug must be considered, along with the patient's age, functional status, and any comorbidities. http://goo.gl/S76Kg8

### Risk Levels Factor Into Melanoma Imaging

**Jeffrey S. Weber, MD, PhD,** believes the type of imaging used in determining the extent of disease in patients with melanoma should be risk adjusted. Patients with stage IIIB/C or resected stage IV melanoma should be staged using a PET-CT scan and an MRI of the brain and spinal cord, since results could change the treatment administered.

*Jeffrey S. Weber, MD, PhD*

Weber, director of the Donald A. Adam Comprehensive Melanoma Research Center at the Moffitt Cancer Center, discussed imaging and other topics recently during an *OncLive* Peer Exchange® roundtable that focused on clinical advances and practical considerations in the treatment of patients with metastatic melanoma. http://goo.gl/ksq8Aj