Brain Tumor Vaccines

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KEYWORDS

• Brain tumor vaccines • Brain tumor immunotherapy • Dendritic cell vaccines • Peptide vaccines

KEY POINTS

- Vaccines are capable of mounting a peripheral immune response that can penetrate the blood brain barrier for the treatment of brain tumors.
- Peptide vaccines against epithelial growth factor receptor variant III, survivin, various heat shock protein complexes, and personalized tumor antigens have been developed for the treatment of glioblastoma.
- Dendritic cell vaccines can be designed against a variety of targets including tumor lysate, known antigens, and messenger RNA to combat high-grade gliomas and have demonstrated robust immune responses.

INTRODUCTION

Vaccines are regarded as one of the most impactful medical advancements because they have had tremendous success reducing morbidity and mortality associated with many infectious diseases. Modern vaccination began with Dr Edward Jenner's experiments to inoculate patients with cowpox—a mild, noncontagious disease—to prevent the far deadlier smallpox. Widespread vaccination led to the complete eradication of smallpox while continued technological advancement has resulted in the development of licensed vaccines for more than 30 diseases, which are estimated to save 2 to 3 million lives each year.[1,2]

Adaptive or acquired immunity is achieved through exposure to a pathogen or vaccination. This arm of the immune system is specific to particular pathogens and can provide long-lasting protection. Fundamentally, vaccines exert their effects by activating a patients' adaptive immune system against a target that resembles a pathogen or toxin. To accomplish successful immune system stimulation, 2 broad categories of vaccines have been developed: live attenuated vaccines and subunit vaccines.[3] Upon interacting with the vaccine, antigen-presenting cells (ie, macrophages, dendritic cells [DC], B cells) recognize the foreign antigens and load them onto major histocompatibility complex (MHC class I or II) for presentation to the adaptive arm of the immune system. Direct MHC I presentation to $CD8^+$ cytotoxic T cells results in a cell-mediated response and the destruction of target cells. MHC II presentation to $CD4^+$ helper T cells can further facilitate a cytotoxic response or stimulate a humoral immunity by activating B cells to produce antibodies. These antibodies can bind pathogens, resulting in neutralization and increased phagocytosis of antibody-bound antigen. Importantly, memory cells are also created and remain dormant until re-exposure to the infectious agent or toxin, resulting in restimulation of the immune cascade and pathogen elimination.[4]

Interest in using the immune system to fight malignancies has exploded in recent years.[5] Immunotherapies such as chimeric antigen receptor T cells prime engineered T cells to kill cancer cells and immune checkpoint inhibitors work to activate the immune system by disinhibiting tumor immune suppression.[6,7] One challenge in using the immune system stems from immune cells' ability to precisely distinguish "self" from "foreign" tissues to prevent autoimmunity. Most antigens expressed by cancers are self-antigens present on normal tissue, which may be slightly immunogenic or nonreactive. Therapeutic cancer vaccines have the potential to increase the immune

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system's antitumor activity by training immune cells to target antigens expressed on cancers. Although vaccination has had tremendous success in preventing infectious disease and virally initiated cancers, namely, liver and cervical cancers caused by hepatitis B virus and human papillomavirus, respectively, vaccination as therapy against established disease has proven much more challenging.[8–10] Immune system evasion is a hallmark of cancers that represents a major hurdle for vaccine development. Cancers actively disguise themselves from immune cells by creating an immunosuppressive tumor microenvironment to dampen the immune system's cancer-fighting potential.[6] However, recent clinical results have shown clinical benefit and established therapeutic cancer vaccination as an attractive platform for further development.

In 2010, the US Food and Drug Administration approved the first therapeutic cancer vaccine (sipuleucel-T) composed of peripheral blood mononuclear cells stimulated against a recombinant fusion protein for the treatment of castration-resistant prostate cancer.[7] Therapeutic vaccines have since been developed for breast cancer, lung cancer, melanoma, pancreatic cancer, colorectal cancer, and renal cancer. These vaccines stimulate the immune system against tumor-associated antigens (TAAs), tumor-specific antigens, or neoantigens on malignant tumor cells. TAAs such as HER2/NEU are often overexpressed in malignancy, but are also expressed at lower levels in some healthy tissues.[11] One example of exploiting this increased expression of these genes in cancer includes the antibody-based immunotoxins against mesothelin, an overexpressed TAA. The treatment of advanced mesothelioma, as well as lung, pancreatic, and ovarian cancers demonstrated cancer regression without appreciable toxicity.[12] Tumor-specific antigens and neoantigens also present attractive targets because they are mutated antigens resulting from genomic instability and represent a unique cancer-specific target. However, these targets are not globally expressed across all tumor cells and are restricted to the subclonal populations within the heterogenous cancer. Previous work demonstrated the safety and immunogenicity of a vaccine targeting 20 predicted personal tumor neoantigens in melanoma, warranting further study.[13]

Although improvements have been made in the design and production of therapeutic vaccines, further developments are required to induce robust $CD4^+$ and $CD8^+$ effector function against tumor cells while avoiding induction of autoimmunity, immune reaction–like cytokine storm, or on-target off-tumor toxicity. Additionally, the efficacy of cancer vaccines and immunotherapy in general correlates with tumor mutational burden and microsatellite instability; as mutations increase, antigenic targets for the immune system to activate against also expands.[14] Innovations in cellular engineering have enabled adoptive cell therapy, where patients' own immune cells are isolated and either engineered or stimulated ex vivo to enhance their cancer-fighting capabilities.[15] DC vaccines are one type of adoptive therapy in which isolated DCs are stimulated with tumor markers ex vivo and reintroduced to the patient to activate cytotoxic and humoral immunity and importantly have the ability to target multiple antigens in parallel to enhance antitumor effects.[16]

Gliomas represent approximately 81% of newly diagnosed malignant primary brain tumors and glioblastomas are the most aggressive type, with less than 3% of patients surviving 5 years and a mean survival of less than 15 months.[17] Despite an increasingly comprehensive understanding of the molecular drivers of glioblastoma, targeted therapies have remained largely ineffective in improving prognosis beyond standard therapy of surgical resection, radiation, and chemotherapy.[18] Because of this poor prognosis, novel innovative treatments are needed such as cancer vaccines, which have the potential to overcome the challenges faced by previous treatments. However, vaccine development must still address challenges resulting from rapid growth, tumor heterogeneity, low tumor mutational burden, and immunosuppression in brain cancers.[19] Under physiologic conditions, the brain parenchyma is tightly shielded from the systemic immune system via the blood–brain barrier and minimal lymphatic vessels for antigen presenting cells to traffic to lymph nodes.[20] Additionally, microglia, brain resident macrophages, establish the bulk of the immune cell population, but have lower antigen-presenting capacity than other cells of the macrophage lineage.[21] Another important consideration for brain tumors is the recruitment of myeloid and lymphoid cells that play an integral role in supporting malignant growth. Tumor-associated macrophages represent the most abundant stromal cell type in glioblastoma, constituting 30% of the tumor mass and skew toward the immunosuppressive M2 phenotype, which inhibits $CD4^+$ and $CD8^+$ T-cell functions while inducing T regulatory cell differentiation.[22] T regulatory cells secrete IL-10 to contribute to immunosuppression and tumor-infiltrating lymphocytes display high levels of programmed death 1, CTLA-4, LAG3, TIM3, TIGIT, and CD39, which all indicate T-cell exhaustion.[23,24] These factors

contribute to an immunosuppressive environment, or immunologically cold tumors, which generally demonstrate a poor response to immunostimulatory therapies such as therapeutic cancer vaccines.[20]

Advancements in neuro-oncology, including the discovery of new therapeutic targets, the development of mechanisms to increase tumor sensitivity to current immunotherapies, and an improvement in the tumor-specific pathway targeting have opened the doors to developing therapeutic vaccines for brain tumors.

PEPTIDE VACCINES

After the cloning of the first human TAA gene in the early 1990s, peptide vaccines were developed to stimulate patient's immune system against both TAAs and neoantigens.[25] Peptide vaccines offer the potential to induce T-cell–based killing and antibody production against foreign tumor antigens. They are generally made of amino acid sequences of various lengths attached to an immunogenic adjuvant to increase immunogenicity.[26] The administration of a synthetic or naturally occurring polypeptide vaccine results in uptake, processing, and presentation via MHC I on APCs, or direct insertion into MHC II, which ultimately leads to the activation of the adaptive immune response against the administered antigen. Through antigen-presenting cells interaction with naïve lymphocytes, $CD8^+$ T cells directly targeting cancer cells or $CD4^+$ T cells boosting antitumor immunity are activated as cancer-fighting agents (Fig. 1).[27,28]

One of the first protein-based vaccines was against epithelial growth factor receptor variant III (EGFRvIII), a cell membrane receptor unique to cancer cells. The EGFRvIII tumor-specific antigen results from a frame deletion mutation of exons 2 to 7 in the extracellular domain of EGFR, which creates a unique glycine residue between exons 1 and 8 that can be exploited therapeutically.[29–32] It is an attractive target for a peptide vaccine because it is expressed in breast, ovarian, and lung malignancies in addition to approximately 24% to 67% of glioblastoma cases, and it is absent in normal tissue.[33] The EGFRvIII peptide vaccine aims to stimulate a patient's immune system against EGFRvIII-positive glioblastoma cells. Phase I/II trials of CDX-110 (rindopepimut), a 14-mer peptide conjugated to the keyhole limpet hemocyanin (an immunostimulatory carrier protein) peptide vaccine injected intradermally, demonstrated safety,

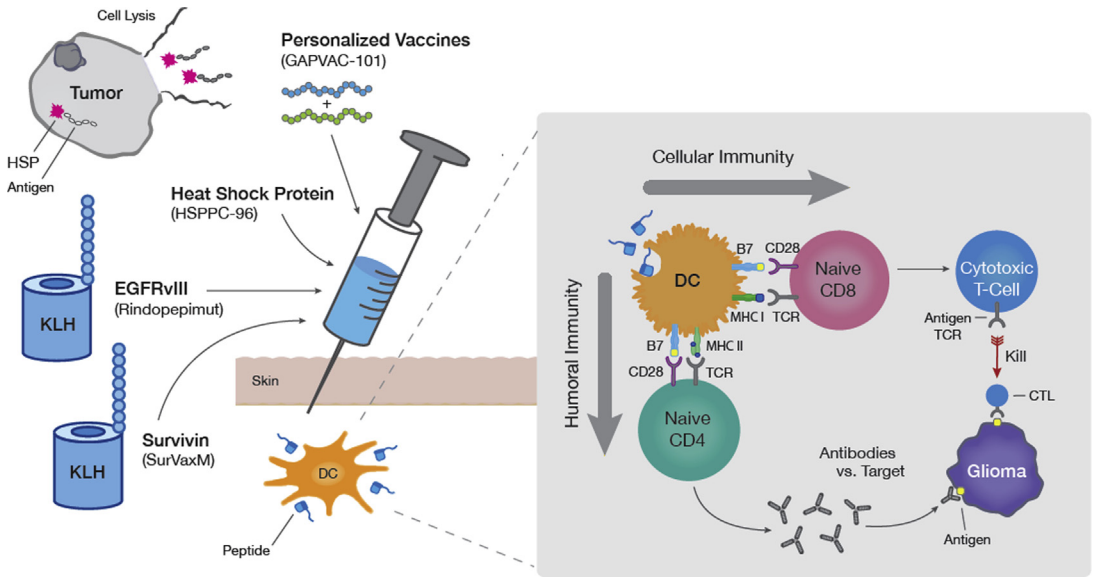

Fig. 1. Peptide and HSP vaccines. Peptides can be conjugated to immunogenic haptens (ie, keyhole limpet hemocyanin [KLH]) linked to EGFRvIII peptide (PEPvIII-KLH) rindopepimut or survivin peptide (Survivin-KLH, SurVaxM) for vaccine preparation and administered intradermally. Mixture of personalized peptide antigen vaccines (GAPVAC-101[APVAC1:unmutated + APVAC2:neoantigens]) based on patient tumor specific profile. Heat shock peptide-proteins complex-96 (HSPPC-96) is extracted from patient's tumor samples, purified, and injected in a similar manner as peptide vaccines. The antigen(s) recognized by antigen presentation cells (DCs) and presented to helper T-cells ($CD4^+$) and cytotoxic T-cell lymphocytes (CTL, $CD8^+$). Activated B-cells then produce antibodies to the peptide.

a tumor-specific immune response, and improved survival compared with matched control patients. However, the phase III double-blind randomized control trial (ACT IV) unfortunately showed no significant difference between the control and vaccine groups, and the trial was discontinued.[34–37] In the vaccine group, patients expressed increased EGFRvIII antibody production and the majority of resected recurrent tumors were negative for EGFRvIII. These data suggested that the EGFRvIII peptide vaccine successfully targeted EGFRvIII positive tumor cells but in the process selected for EGFRvIII negative or low expressing tumor cells. Therefore, in a heterogenous tumor such as glioblastoma, single antigen therapy may have very limited success rate despite measurable positive immune response.

Peptide vaccines have also been developed for additional glioma specific mutations including variants of the isocitrate dehydrogenase type 1 (IDH1) and histone-3 genes. IDH1 mutations most often occur at the Arg132 residue in the catalytic pocket, promoting malignant transformation and genomic hypermethylation.[38,39] More than 70% of diffuse grade II and III gliomas contain the IDH1(R132H) mutation, which is an immunogenic epitope that can be targeted via peptide vaccination.[40] Preclinical data demonstrated that IDH1(R132H) peptide vaccines are presented on MHC II and induce mutation-specific $CD4^+$ T-cell activation and antibody production.[41] Multiple phase I trials have been launched to determine vaccine safety (NCT02454634, NCT02193347).[42] Similarly, in aggressive midline gliomas, K27M mutations in the histone-3 gene result in methylation pattern alterations and subsequent changes in gene expression.[43] Preclinical work demonstrated that H3K27M peptide vaccines are presented via MHC I and elicit mutation-specific $CD4^+$ and $CD8^+$ immune responses in MHC-humanized mice.[44] A phase I clinical trial evaluating a synthetic peptide targeting the H3.3.K27 M protein is underway (NCT02960230).

Another target for peptide vaccination is survivin, a tumor-associated antigen that is a membrane inhibitor of apoptosis and regulator of the cell cycle. Its expression is absent in terminally differentiated tissues but present in various cancer types, including glioblastoma.[45] A peptide vaccine targeting survivin is currently under investigation. The vaccine uses a 15-mer survivin peptide linked to keyhole limpet hemocyanin (SurVaxM) to stimulate an immunogenic response. Early clinical trial data demonstrated antibody production and T-cell response to survivin vaccine. A phase I trial of recurrent malignant glioma patients with surviving-positive tumors were given subcutaneous SurVaxM with sargramostim, a bone marrow stimulant, at 2-week intervals. SurVaxM administration was well tolerated. 6 of 8 immunologically evaluable patients demonstrated IgG production against the survivin peptide and increased survivin responsive $CD4^+$ and $CD8^+$ T cells. The median overall survival was 86.6 weeks from study entry with 7 of the 9 patients surviving more than 12 months.[46] An early phase II trial is underway for patients newly diagnosed with glioblastoma with restricted HLA types (HLA-A*02/03/11/24 haplotype) (https://clinicaltrials.gov/ct2/show/NCT02455557). The data so far are optimistic with a 12-month overall survival of 94.2%.[47]

To overcome the challenges associated with single antigen therapies, peptide vaccines targeting multiple glioblastoma antigens have been developed as personalized therapeutic vaccines. This new strategy seeks to exploit multiple antigens to overcome the low mutational burden involving around 30 to 50 nonsynonymous mutations and the immunosuppressive environment of glioblastoma.[48] A recent study demonstrated that a multiepitope, personalized neoantigen-based vaccine based on patient's tumor transcriptomes and immunopeptidomes is feasible for patients with glioblastoma. This phase I/Ib study compared resected glioblastoma tissue with healthy tissue via whole-exome sequencing and RNA sequencing data to determine neoantigens. From these data and using patient-specific HLA allotype assessment, peptides with high predicted HLA binding affinity were designed and synthesized. The neoantigen peptide vaccine library was administered after radiotherapy and stimulated a neoantigen-specific T-cell response in patients with an increased concentration of circulating and tumor-infiltrating T cells in vaccine treated patients. While demonstrating that personalized neoantigens can favorably alter the immune landscape in a glioblastoma, tumor-infiltrating T cells after vaccination expressed multiple co-inhibitory receptors, consistent with an exhaustion phenotype.[49] An additional study, the phase I trial GAPVAC-101 of the Glioma Actively Personalized Vaccine Consortium, used both unmutated antigens and neoepitopes in an effort to increase immune cell activity against the limited glioblastoma target space. This study similarly demonstrated feasibility with an activation of $CD8^+$ T cells and the development of a sustained response via memory T cells using the unmutated APVAC1 antigen panel or a predominantly $CD4^+$ T-cell response using the APVAC2 neoantigen vaccine.[50]

Another type of peptide vaccine that has garnered interest for their immunogenic properties are heat shock proteins (HSPs). HSPs are produced by cells in response to stressful conditions and provide a physiologic link between the innate and adaptive immune systems through chaperoning antigens to APCs like DCs. During cell stress, HSPs are expressed intracellularly and bind misfolded proteins to prevent aggregation. HSPs loaded with protein may be released into circulation and bind to CD91 receptors on APCs to initiate both MCH I and II presentation.[51] In malignancy, HSPs bind to tumor specific neoantigens to activate both innate and adaptive immunity against patient-specific cancer mutations. To leverage this physiologic role of HSP, tumor cells are lysed and the HSPs of interest are isolated for intradermal vaccines. To date, HSP–antigen complexes have been used in a variety of cancer types including melanoma,[52,53] renal cell carcinoma,[54] colorectal cancer,[55] and glioblastoma,[55,56] and have been well-tolerated with a low toxicity. Despite optimistic findings in early phase clinical trials, a larger phase II randomized trial treating recurrent patients with glioblastoma with HSP peptide complex 96 (HSPPC-96) failed to show survival benefit when compared with bevacizumab alone (overall survival 7.5 vs 10.7).[57] However, experiments measuring INF-γ release demonstrated increased tumor-specific peripheral blood mononuclear cells after exposure to autologous tumor lysate.[58] Because the data for patients with newly diagnosed glioma continue to demonstrate increased survival when programmed death ligand 1 is upregulated on myeloid cells, a phase II trial of HSPPC-96 with patients newly diagnosed with glioblastoma with and without programmed death 1 inhibitor pembrolizumab (NCT03018288) is underway.[59]

DENDRITIC CELL VACCINES

Different from peptide vaccines, which rely on a host's ability to direct pathogens to APCs, DC vaccines are directly primed against specific targets to mount a robust immune response against tumor cells. DCs are professional APCs capable of activating adaptive immunity through the presentation of epitopes that can be harnessed to combat tumor cells. Most autologous DC vaccines are made from DCs extracted from patients through leukapheresis and exposed ex vivo to tumor-associated antigens (peptides or messenger RNA) of choice. The cells are then

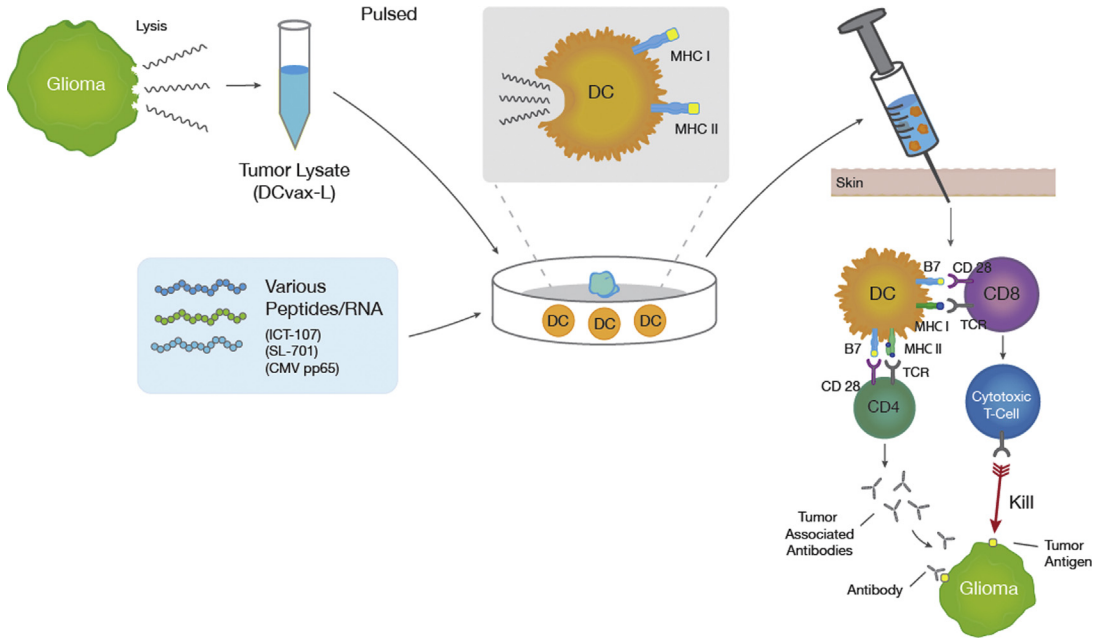

Fig. 2. DC vaccines. DCs isolated from peripheral blood leukapheresis are pulsed against tumor associated antigen, messenger RNA, or lysate, that is, *ICT107*: HER2, TRP-2, gp100, MAGE-1, IL13Ra2 and AIM-2, *SL701*: ILRa2, ephA2, surviving, *DCVax-L* (autologous tumor lysate), or *CMV pp65*. Primed DCs are then administered as a vaccine to patients peripherally. Following injection, DCs then recruit CTLs and stimulate antibody production against tumor epitopes. Activated cytotoxic T-cells and antibodies cross the blood brain barrier and target tumor cells with the surface receptor.

delivered either peripherally or intracranially to the patient to generate a cell-mediated and humoral immune response against various targets (Fig. 2). DC vaccines are capable of stimulating T cells to cross the blood–brain barrier. Additionally, they have a low toxicity profile. The ability of DCs to target multiple antigens provides an advantage compared with single antigen therapies when treating tumors with heterogeneous cell populations.

DCs pulsed with known antigens demonstrated an increased overall survival and immune response in preclinical models and clinical trials. In an early phase I study of multiple-peptide pulsed DC vaccine (ICT-107), in patients with newly diagnosed glioma with HLA-A1 or HLA-A2 and at least 1 TAA (HER2, TRP-2, gp100, MAGE-1, IL13-Rα2, or AIM-2) were given 3 intradermal doses of DCs pulsed with TAA along with standard chemotherapy and radiation. At an average follow-up of 40.1 months, 6 of 16 patients with newly diagnosed glioblastomas had no evidence of tumor recurrence. Overall, the phase I trial showed promise with an increased (median progression-free survival of 16.9 months and a median overall survival of 38.4 months).[60] In a randomized phase II multicenter trial (NCT01280552, n = 124), patients receiving the DCs pulsed with TAAs had greater progression-free survival without a significant improvement to overall survival (progression-free survival of 11.2 months vs 9.0 months [$P = .011$] and overall survival of 18.3 months vs 16.7 months [$P = .64$]).[61] Based on this trial, an HLA-A2 patient subpopulation was identified to have a significantly increased overall survival and increased responder rates for a phase III trial (STING, NCT02546102). Unfortunately, STING for HLA-A2 newly diagnosed glioma was terminated owing to an inability to secure funding. With the success of the multiple peptide vaccine, another autologous DC vaccine pulsed with known TAAs—IL13-Rα2, EphrinA2 and Survivin (trade name: SL701)—was developed. Currently, SL701 with or without Avastin (bevacizumab) is under phase II investigation (NCT02078648).[62]

Human cytomegalovirus (CMV) proteins are another interesting target being studied for DC vaccines. Some reports suggest that human CMV is frequently expressed in glioblastomas but absent in surrounding normal tissue.[63–65] CMV pp65 is a major CMV structural tegument protein found in a subset of glioblastoma cells. DCs pulsed with messenger RNA for pp65 generated T cells against CMV pp65. Early phase I trials for patients newly diagnosed with glioblastoma treated with DC pulsed with CMV pp65 messenger RNA demonstrated increased survival, safety, and significant immune response against pp65.[66,67] Larger phase II studies of DC-pp65 have since demonstrated reproducibility of previous clinical trial data with, an overall survival of 37.7 and 38.3 months in the ATTAC-GM and ATTAC-Td studies, respectively. The most recent study also demonstrated increased DC migration to the draining lymph nodes bilaterally.[68] Further trials will be conducted to examine CMV pp65 vaccine's efficacy alone or in combination with varlilumab for the activation of $CD27^+$ lymphocytes (NCT03688178, NCT02465268).

Because DCs can mount an immune response to a series of known antigens, DCs exposed to unknown antigens through autologous tumor lysates could also generate systemic immune responses against a variety of tumor cells, with a possible benefit to overall survival. DCs pulsed with autologous human tumor lysate that is, either acid-eluted or freeze-thawed (DCVax-L) provide a patient-specific vaccine based on a patient's resected tumor and covers a wide array of epitopes. In a phase I trial, 12 patients (5 recurrent and 7 newly diagnosed patients) treated with DCVax-L showed an improved median progression-free survival (median progression-free survival of 19.9 months vs 8.2 months) and overall survival (median overall survival of 35.8 months vs 18.3 months) compared with historic controls with 50% survival at 2 years and 2 patients still alive at the time of publication (>58.0 and >48.4 months).[69] These patients are still alive today, over 16 years since the conclusion of this initial Phase I trial. Six of the 12 patients developed a systemic cytotoxic T-lymphocyte response on in vitro lysis assays, 4 of the 8 patients had tumor-infiltrating lymphocytes on reresection, and 1 patient showed objective MRI changes after injection. This phase I trial showed safety, bioactivity, and feasibility, and led to a randomized, multi-institute, double-blind, placebo-controlled phase III clinical trial (NCT00045968) of DCVax-L. The phase III trial compared chemoradiation (n = 99) with DCVax-L plus chemoradiation (n = 232) for patients newly diagnosed with glioblastoma in a 2:1 randomization, with crossover upon progression.[70] Because datalock was just recently completed at the time of this writing, the data remain blinded for this trial. However, a recent interim update showed that the overall survival seems to be favorable (intention-to-treat median overall survival of 23.1 months; 2-year survival rate of 46.2%; 3-year survival rate of 25.4%) and continues to be well-tolerated with low levels of adverse events. Also, as expected, the overall survival correlated with the extent of

the resection.[51] In contrast, DC lysate In order to further enhance the efficacy of DCVax-L, a phase II randomized trial for recurrent glioma patients treated in combination with with DCVax-L in combination with with programmed death 1 blockade (NCT03014804) is underway.

SUMMARY

Glioblastoma treatments are in dire need of additional therapeutic options. Peptide and DC vaccines have demonstrated safety as potential treatments for brain tumors. A few treatments including SurVaxM and DCVax-L show early promising results with data from DCVax-L pending evaluation of phase III data. Cancer vaccines activate robust antitumor responses through immunostimulation against cancer antigens or transfusion of DCs stimulated ex vivo against tumor antigens to initiate adaptive immunity. Importantly, vaccines have shown the ability to induce antitumor T-cell trafficking and antibody production across the blood–brain barrier. GAPVAC-101 and DCVax-L also have the benefit of activating an immune response against multiple cancer antigens, and DCVax-L in particular can target unknown antigens by pulsing the cells with autologous tumor lysate, thereby potentially overcoming the problem of tumor heterogeneity. Recent results have demonstrated the potential for cancer vaccines to become an important therapeutic option in addition to surgery, radiation, and chemotherapy.

Although tumor vaccines have shown potential, there are still many opportunities to improve their cancer fighting capabilities. Activated T cells that migrate to the tumor face a harshly immunosuppressive environment and previous studies have demonstrated that vaccine-stimulated T cells exhibit many of the classic exhaustion markers once they engage with the cancer. To overcome these challenges, combination therapies incorporating both tumor vaccines and checkpoint inhibitors or immunostimulants are currently underway. Furthermore, vaccines targeting single antigens create selection pressure for tumor cells expressing the antigen at lower levels, which leads to therapeutic resistance. Vaccines targeting a broader cancer antigen landscape have been developed, but their efficacy must be validated and reproduced in larger studies. There have also been great strides made in using patient-specific tumor transcriptome or proteome data to develop personalize vaccines. This strategy can identify personalized neoantigens to combat the heterogenous glioblastoma tumor population, but the efficacy of targeting predicted neoantigens in glioblastoma is only theoretical and further research is needed to determine their effectiveness.

CLINICS CARE POINTS

- Brain tumor vaccines tested to date have generally been well-tolerated, with the most common side effects being moderate injection site reactions. However, severe adverse events, including toxic epidermal necrolysis, have been reported.
- Steroids diminish the general immune response to immunotherapy. In a small early phase clinical trial using neoantigen peptide vaccines, patients who received dexamethasone did not respond to therapy. Patients receiving brain tumor vaccines should be on minimal doses of steroids.
- Preliminary evidence on SurVaxM peptide has shown a median overall survival of 86.6 weeks and 2 phase I studies on multiepitope, personalized vaccines have shown potential in inducing T-cell responses in glioblastoma.
- An interim analysis of the intent-to-treat population in a phase III DCVax-L study demonstrated a median overall survival of 23.1 months from the surgery and a median overall survival of patients with methylated MGMT of 34.7 months from surgery; both represent a significant increase when compared with that of standard of care treatment.
- The benefits derived from therapeutic vaccines are often observed at later time points after treatment when compared with other therapy types. This factor is often demonstrated in the tail of survival curves.

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