Oncolytic Viruses
Treatment and implications for patients with gliomas

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BACKGROUND: Oncolytic viral therapies are increasingly being explored for the treatment of diverse cancer types, most notably melanoma. However, advances in the treatment of high-grade gliomas, and specifically glioblastoma multiforme (GBM), are the result of novel oncolytic viral therapies. Delta-24-RGD is one such therapy that has demonstrated promising results in phase 1 trials.

OBJECTIVES: The objective of this article is to provide an overview of Delta-24-RGD, highlighting considerations for nurses in diverse clinical, research, and advanced practice roles.

METHODS: A high-level overview of the pathophysiology of the Delta-24-RGD virus as it relates to GBM is presented. A case study is used to illustrate the course of care for a patient receiving this therapy.

FINDINGS: Delta-24-RGD has demonstrated remarkable clinical efficacy in the near to complete regression of GBM activity. Nurses may increasingly be caring for patients who are undergoing such therapy or have received it in the past. Understanding the mechanism of action, safe-handling implications, and expected patient care needs and treatment sequelae is important.

KEYWORDS
glioblastoma multiforme; gliomas; Delta-24-RGD; oncolytic; melanoma

Glioblastoma multiforme (GBM) is a malignant high-grade glioma, emerging from astrocytes that comprise the supportive tissues of the brain (American Brain Tumor Association, 2014). GBM is more prevalent in men than women and accounts for about 3% of pediatric brain tumors (American Brain Tumor Association, 2014). About 24,000 new cases of brain and other nervous system tumors are estimated to occur in 2016 (National Cancer Institute, 2016), of which GBM is estimated to account for about 52% (American Association of Neurologic Surgeons, 2015). The hallmark of GBM, characterized by the World Health Organization (WHO) as a grade 4 tumor, is proliferative vascularization, whereby the tumor stimulates angiogenesis, the formation of its own blood vessels, via the overexpression of hypoxia inducible factor alpha and vascular endothelial growth factor (Cohen & Colman, 2015). These blood vessels are incompetent, or “leaky,” and IV contrast seeps out into the brain and marks the tumors with enhancement on magnetic resonance imaging (MRI). GBM malignancy stems from the way the tumor infiltrates in and among healthy brain cells; this infiltrative nature contributes to treatment resistance and makes them incurable by surgery alone (Cohen & Colman, 2015). With treatment, the median survival is 14–16 months, with a five-year survival rate of less than 5% (Neagu & Reardon, 2015).

The standard of care treatment for glioblastoma is surgery with the goal of obtaining the most complete gross total resection as is safely possible. The location of the tumor is a key factor in surgical resection because maintaining optimal function after surgery is of paramount importance. The surgery is followed by a total 60 Gy radiation for 30 fractions (daily treatment for 30 days) and concurrent temozolomide (Temodar®), followed by 6–12 months of adjuvant temozolomide until recurrence (Neagu & Reardon, 2015). Serial MRI of the brain is used to reassess tumor status and progression, typically characterized by increased enhancement around the tumor bed, at which time progression to clinical trial may be indicated. Davis (2016) presents a detailed overview of glioblastoma and its treatment. Near or gross total resection is optimal for long-term survival; however, the survival rate has remained unchanged with the current standard of care for treatment (Lacroix et al., 2001).

The challenge inherent in the treatment of high-grade gliomas is treating the tumor and protecting healthy functioning brain cells, with the goal to preserve the patient’s function. Oncolytic viruses are being used to treat high-grade gliomas with this goal in mind (Neagu & Reardon, 2015; Vecil & Lang, 2003). One oncolytic virus, the Delta-24-tripeptide arginylglycylaspartic acid (RGD) virus, is a genetically altered virus derived from the adenovirus and is currently being evaluated in phase 1 studies for the treatment
of GBM (Alonso et al., 2008; Lang et al., 2014). In addition to its capacity to target malignant cells while sparing healthy cells, this virus is also thought to potentially stimulate the body’s immune response via a tumor antigen which may activate immune-mediated antitumor cytotoxicity (Jiang et al., 2014, 2015). Research is being conducted in this area with the goal of using this additional mechanism (body’s immune response) in conjunction with the viral attack on the tumor to work together to kill the tumor.

At the University of Texas MD Anderson Cancer Center, a National Cancer Institute–designated comprehensive cancer center, the neurosurgery department performed approximately 757 surgical resections and biopsies in 2015, of which 152 were resections for GBM. In this context, interprofessional teams are actively implementing research related to Delta-24-RGD. This article presents the pathophysiology, mechanism of action, and nursing considerations related to treatment of GBM with the Delta-24-RGD virus.

**Delta-24-RGD Virus**

The Delta-24-RGD oncolytic virus, currently known as DNX-2401, is a genetically altered adenovirus. The name Delta 24 comes from the description of the genetic alteration, D, or delta, for “deleted” and 24 for the 24 BP deletion of the viral EiA, a control protein active in viral reproduction. This deletion is thought to be the pathophysiologic mechanism by which the virus is able to attack tumor cells while remaining unable to penetrate normal cells (Jiang et al., 2014). Similar to viruses such as polio or HIV, adenovirus—the cause of the common cold—is less virulent and, therefore, thought to be potentially less harmful to the patient. The adenovirus normally binds to the coxsackie–adenovirus receptor through interaction between its viral protein pentagon base and alpha integrins, which are transmembrane receptors facilitating cell-to-cell interaction, allowing the adenovirus to enter the cell through receptor-mediated endocytosis (Fueyo et al., 2003; Jiang et al., 2015; Wollmann, Ozduman, & van den Pol, 2012). This process provides the key with which to enter tumor cells. The virus further contains the RGD, which facilitates cellular attachment via integrins, cell surface proteins that act as receptors for the virus (Fueyo et al., 2003). Once the virus has entered and attached to the tumor cell, it initiates replication, causing the malignant cell to lyse and release viral particles into the surrounding area. These viral particles then seek out more brain tumor cells, and the process begins again. Via oncotropism, a process by which the virus seeks out and destroys tumor cells and leaves healthy brain cells unharmed, Delta-24-RGD is able to infiltrate malignant cells while leaving normal surrounding cells unharmed. Delta-24-RGD is therefore referred to as a “smart bomb” because of its ability to enter tumor cells and destroy them from within. This process, seen in Figure 1, is optimal to support the preservation of healthy brain cells and function.

In addition, the adenovirus may activate immune-mediated antitumoral cytotoxicity (Jiang et al., 2015). At the author’s institution, the oncolytic virus is injected directly into the tumor during a stereotactic biopsy of a brain tumor, or injected with stereotactic guidance into the tumor directly through a burr hole (Lang et al., 2014). Patients at the author’s institution have presented with what appears to be an inflammatory response prior to the tumor shrinking (Lang et al., 2014). A review of the tumor in one symptomatic patient, who required tumor resection after injection with the virus, revealed macrophages and cluster of differentiation (CD8) T cells with only rare tumor cells. In addition, three responders had a 10- to 1,000-fold increase in interleukin-12p70, which is involved with introducing cell-mediated immunity (Lang et al., 2014). These three responders had complete sustained responses for a number of years prior to recurrence. In the setting of high-grade gliomas, considering longevity is usually measured in months; using years as a measure of response is considered a remarkable and exciting finding. With such promising findings, trials will continue to expand in this area, requiring clinical, research, and advanced practice nurses to be familiar with and knowledgeable of the management of patients undergoing oncolytic viral therapy with Delta-24-RGD.

**Research Considerations Regarding Screening and Eligibility for Treatment**

Patients eligible for treatment with Delta-24-RGD are currently required to have progression of disease as a first or second recurrence following standard of care treatment. The incidence of...
ONCOLYTIC VIRUSES

GBM, 3.2 per 100,000 individuals (Davis, 2016), and the number of patients eligible for clinical trial enrollment after progression can make identifying patients for such clinical trials challenging. At the author’s institution, patients are evaluated for potential study participation by the neurosurgery department when standard of care treatment has failed and a new or recurrent lesion is discovered.

To ensure the quality of research data, optimal patient screening and selective study enrollment according to strict inclusion/exclusion criteria is imperative (Gross, Mallory, Heiat, & Krumholz, 2002). Specific enrollment criteria for the Delta-24-RGD trials include screening the patient to ensure no active infection is present, because this may elicit a systemic immune response that may be harmful to the patient. In addition, patients who have recently had a vaccination, and may have a reaction to that vaccination, should be carefully evaluated. Participants must be screened for the previous use of agents, such as bevacizumab (Avastin®) or other chemotherapies that can decrease blood counts, to reduce the risks for intra- and postoperative complications during the Delta-24-RGD intratumoral administration.

Research Nursing and Advanced Practice Considerations

History and Physical

A complete and thorough history should be obtained when considering the patient’s eligibility for this trial. This includes assessment related to the exclusion criteria, such as infection and recent immunization, outlined previously. The patient should also be screened for active infections by serum, urine, and nasal swabs. After treatment, infection monitoring should continue and include viral polymerase chain reaction testing. Assessment for history of seizure activity, presenting symptoms, and symptom history is vital for providing a baseline evaluation and assessing for serious treatment-related adverse events.

Baseline physical examination should include complete assessment by system, including neurologic, cardiac, pulmonary, and gastrointestinal examination, because resulting inflammatory response to treatment can attack any body tissue. Even a mild change in the patient’s neurologic examination must be documented and taken into consideration. Familiarization with the anatomy and function of the brain, specifically those areas with tumor involvement, is critical to assessing for mild symptoms or status changes that can occur post-treatment. Ongoing evaluation of the patient’s treatment history and physical examinations is important in discovering subtle changes as early as possible.

Pharmacologic Considerations

Caution must be used when prescribing glucocorticosteroids in patients who are receiving immune-modulated therapies. With glioblastoma, as the tumor dies and the body’s immune response attacks the tumor, swelling can occur that causes alterations in the patient’s functioning or other deleterious side effects. Although steroids often are the standard of care treatment to reduce swelling, they can also suppress the immune response that is fundamental to the therapeutic efficacy of this treatment. In addition, long-term use of steroids can result in elevated blood sugars, which may increase the risk of infection and decrease the body’s ability to heal after surgery (Sturdza et al., 2008). Larger doses of steroids may cause alterations in the patient’s sleep patterns, which can result in a lower seizure threshold (Sturdza et al., 2008). In addition, steroids are known to increase the patient’s appetite and weight, and increase the volume of fluid in a patient’s body, resulting in elevated blood pressure (Sturdza et al., 2008). Steroids also have been known to induce alterations in a patient’s behavior, sometimes rendering them less compliant with protocol activities (Sturdza et al., 2008). In addition, steroids are known to decrease proximal muscle mass, making them at greater risk for falls and injury. Therefore, careful consideration and monitoring should be given to prescribing steroids for the management of side effects post-treatment.

Perioperative Care

The patient who is screened and deemed eligible and subsequently enrolled in this protocol receives treatment in the operating room via stereotactic injection of the virus directly into the tumor. At the author’s institution, the procedure typically requires only an overnight stay for observation. The lighter form of anesthesia using a more “friendly” laryngeal mask over the epiglottis to protect the airway is sufficient rather than general anesthesia with endotracheal intubation.

Once the virus has been injected, the patient remains in full contact isolation in the perioperative period. Because this is a genetically altered virus with a minor risk for shedding, it is important to educate nursing staff about safe handling of blood and body fluids of the patient. However, little or no viral shedding has been

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observed to date. Similar to considerations for other viral-based therapies, patients should avoid the immunocompromised population, young children, and older adults (Hoffner, Iodice, & Gasal, 2016). Standard use of personal protective equipment (PPE), including mask, gown, and gloves, should be observed. Special consideration should be given to educating the patient and caregiver about minimizing the risk of infection. PPE should be provided or ordered and, if a biohazard container is not available, discarded dressings should be bagged, sealed, and thrown out per usual.

Protocol and safety measures must be followed, and contact isolation should be maintained until the patient is discharged. Isolation for the patient can contribute to emotional distress, which should be addressed through reinforcement of teaching and continual assessment and support by nursing staff. Once discharged, the patient is primarily managed in the outpatient setting, with regular physical assessments and sampling of bodily fluids. This includes blood, urine, saliva, and nasal swabs. The nursing staff is educated to use caution with the collection of these samples and to use universal precautions.

Providing Emotional Care for the Patient

Completion of treatment can have significant psychosocial sequelae for patients. Most notably, during what is described as the re-entry period, immediately following treatment completion, patients can feel at a loss or abandoned without the safety net of continual monitoring (Stanton, Rowland, & Ganz, 2015). Concerns related to mood, personality changes, and cognitive functioning associated with high-grade gliomas and their treatment are frequently reported by patients or caregivers (Catt, Chalmers, & Fallowfield, 2008). Further existential distress related to loneliness, anxiety, and fear of death can be prominent in this population (Adelbratt & Strang, 2000; Catt et al., 2008). One of the most challenging aspects of caring for patients with brain tumors under active surveillance is supporting them as they await the results of their surveillance MRI, which can contribute to significant uncertainty (Lin et al., 2012). Patients should be provided with support, the opportunity to express fears and concerns, and evidence-based education about what to expect in the interim period. Waiting for test results can often be just as stressful, if not more stressful, for patients than the disease itself, and patients may question their treatment decisions.

Case Study

A 53-year-old woman presented with severe headache, nausea, vomiting, lethargy, and confusion. She sought medical attention at her local emergency department and an MRI of the brain was performed, which revealed a large enhancing, centrally necrotic right occipital lesion. Near gross total surgical resection revealed GBM, grade 4. She received concurrent chemotherapy with temozolomide and radiation therapy consisting of 60 Gy in 30 fractions. She had an MRI of the brain one month after the completion of therapy, and the enhancing lesion had returned. She presented to the clinic for discussion of surgical treatment options, including the oncolytic virus protocol. She was screened for eligibility and elected to proceed with injection of the virus. She underwent a stereotactic biopsy for the purpose of determining whether the enhancement seen on MRI was truly recurrent tumor or a treatment-related artifact, such as radiation necrosis. The stereotactic biopsy was performed in the operating room and the pathology report returned intraoperatively, confirming tumor, at which time the oncolytic injection was performed, consistent with the research protocol. She received the virus by injection into the tumor and was then closely monitored for signs and symptoms of infection, viral shedding, and neurologic and hemodynamic changes. Her nursing care was carefully documented to include all protocol requirements, to ensure that the data would be complete, and to provide optimal care during this time. She was provided with emotionally supportive care and encouragement during the isolation phase. The nursing team was careful to follow universal precautions when handling bodily fluids. She was also closely monitored after discharge and instructed to report any new symptoms. Care was taken to make sure she understood the signs and symptoms to monitor and report and had emergency contact information, including on weekends, when the clinic was closed. She was also followed, per protocol requirements, with serial MRIs of the brain, which, over time, revealed a significant improvement in the enhancement in the tumor. During this time, her medical record was maintained with attention to detail, to ensure the clinical data was complete and accurate.

Future Directions

Delivering the oncolytic virus into the tumor by means of direct injection is problematic in that it requires surgical delivery and essentially blind injection by a sharp instrument. The risks of bleeding are present, in addition to the risks of the surgery itself. Research is underway to deliver the oncolytic virus by means of mesenchymal stem cell transfusion. The virus is attached to the stem cells, which are harvested from the bone marrow. Because most primary brain tumors do not metastasize to the bone marrow, it is a rational choice. In addition, cells would be autologously harvested, reducing the risk of rejection. Mesenchymal stem cells have been shown to home, or be attracted to, areas of injury, and these stem cells have been successfully delivered to brain tumors in this way in laboratory mice. This would eliminate the need to directly

IMPLICATIONS FOR PRACTICE

- Educate healthcare providers about oncolytic viruses, which are the current and evolving treatment for diverse cancer types, including high-grade gliomas.
- Understand that oncolytic viruses have two mechanisms of action, including direct cell death and as an immunotherapeutic agent. Because of this, they have unique toxicities.
- Encourage safe, evidence-based nursing practice among nurses caring for patients undergoing these treatments.
inject the brain tumor, potentially decreasing risks to the patient. Such mechanisms are being explored in the laboratory setting and may be eligible for phase 1 testing in the near future.

**Conclusion**

Oncolytic viruses have been shown to be effective in infiltrating tumor cells and leaving healthy brain cells unharmed, and eliciting an antitumoral immune response. Nursing care for patients receiving oncolytic viral therapies should include consideration of detailed assessment, safe handling of blood and body fluids related to the minimal potential for viral shedding, and psycho-emotional support for patients and caregivers during and following treatment. Ensuring consistent and accurate documentation among all providers is also crucial to preserving the quality and integrity of what remains clinical trial-driven data. Providing evidence-based education for nurses in diverse roles and settings is important to support safe and effective patient care. Ultimately, oncolytic viral therapies, such as Delta-24-RGD, offer new and exciting treatment mechanisms that are contributing to enhanced survival for patients with previously limited treatment options and survival outcomes. As such therapies continue to emerge, nurses will continue to be at the forefront of providing education and clinical care to these patient populations.

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The author gratefully acknowledges Frederick Lang Jr., MD, FACS, FAANS, for assistance with scientific and literature review and guidance.

The author takes full responsibility for this content and did not receive honoraria or disclose any relevant financial relationships. The article has been reviewed by independent peer reviewers to ensure that it is objective and free from bias. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Oncology Nursing Society.

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