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# Osmotic Blood-Brain Barrier Modification for the Treatment of Malignant Brain Tumors

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The American Cancer Society estimated that in the United States, more than 18,400 cases of primary malignant brain tumors will be diagnosed in 2004. From these, 12,690 deaths are expected to occur (Jemal et al., 2004). The 2000 Central Brain Tumor Registry of the United States (CBTRUS) predicted that 39,550 new cases of primary benign and malignant brain tumors would be diagnosed in 2002. Metastases to the brain from a systemic primary cancer are even more common, with an estimated 100,000 new cases each year (CBTRUS, 2000). In adults, the most common brain metastases originate from lung cancer (34%), breast cancer (21%), and melanoma (12%) (Chidel, Suh, & Barnett, 2000). Primary brain tumors affect people of all ages, with peak incidences of certain tumor types, such as pilocytic astrocytomas and medulloblastomas, in early childhood and others, such as meningiomas and glioblastomas, in later adulthood.

Although treatment approaches with new chemotherapeutic agents have improved the outcomes of cancer treatment for systemic diseases, survival for malignant central nervous system (CNS) lesions has been poor. Chemotherapy has been relatively ineffective, and radiation therapy has caused neurotoxicity, often leaving patients with serious cognitive impairments (Crossen, Garwood, Glatstein, & Neuwelt, 1994). Limited penetration of cytotoxic drugs across the blood-brain barrier (BBB) and intrinsic tumor cell resistance are believed to be partially responsible for treatment failures (Bart et al., 2000). Issues involving drug delivery to tumors, including blood flow, drug concentration, and time of exposure,

The blood-brain barrier (BBB) is a physiologic barrier that protects the brain from toxic substances, including most of the chemotherapeutic agents used today. The BBB may be partly responsible for the poor efficacy of chemotherapy for malignant primary or metastatic brain tumors. A technique of osmotic modification of the BBB, known as BBB disruption (BBBD), is used to increase the delivery of chemotherapy to the brain. This article discusses the technique of osmotic opening of the BBB, the national BBBD program, the role of nurses in the care and management of patients undergoing BBBD treatment, outcomes of this technique with a variety of brain tumors, and the future directions of the BBBD program.

**Key Words:** brain neoplasms, blood-brain barrier

are believed to be compounded for tumors in the CNS because of the BBB.

## The Blood-Brain Barrier

The BBB, together with the blood-cerebrospinal fluid (CSF) barrier, maintains brain homeostasis. The BBB hinders the transportation of drugs and other materials from blood into brain tissue. The BBB consists of capillary endothelial cells that lack fenestrations and are connected by continuous tight junctions. Special transport systems are available at brain capillaries for glucose, amino acids, amines, purines, nucleosides, and organic acids; all other materials must cross between endothelial cells (paracellular route) or across cytoplasm (transcellular route) to move from capillary blood to tissue extracellular fluid.

The normal BBB prevents the passage of ionized water-soluble drugs with a molecular mass greater than 180 daltons; most chemotherapeutic agents have a molecular mass from 200–1,200 daltons, and only highly lipid-soluble drugs cross the BBB freely (Neuwelt, 2004). An alternative approach for

drug delivery to the brain is by intrathecal injection into the subarachnoid space and the CSF. However, drug distribution within the CSF and from the CSF to the brain can be slow and unpredictable because the brain has little extracellular space (Hollenberg & Brody, 1998).

Neuwelt and collaborators have demonstrated that intra-arterial delivery of drugs can increase exposure of the tumor to the cytotoxic drug 10-fold. By disrupting the BBB, the investigators were able to increase the exposure up to 100-fold without a significant increase in neurotoxicity (Kroll & Neuwelt, 1998). Although the integrity of the

BBB becomes heterogenous and permeable in the presence of a tumor, as evidenced by contrast enhancement on neuroimaging studies, the permeability appears to be highly variable and decreases as the tumor responds to the treatment, further accentuating the delivery problem (Ott et al., 1991).

The technique of BBB disruption (BBBD) was pioneered by Edward Neuwelt, MD, at Oregon Health and Science University (OHSU) in Portland. Today, a multisite consortium exists for the treatment of patients with brain tumors using osmotic BBBD. OHSU is the coordinating center for the consortium. Additional participating centers are the University of Oklahoma in Oklahoma City, University of Missouri in Kansas City, James Cancer Hospital of the Ohio State

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