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, 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 heterogeneous 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 University, City of Hope National Medical Center, and the University of California, San Francisco.

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University in Columbus, University of Minnesota in Minneapolis, Cleveland Clinic Foundation in Ohio, University of Kentucky Hospital in Lexington, Centre Hospital Universitaire de Sherbrook in Canada, and Hadassah University in Jerusalem, Israel.

Osmotic Opening of the Blood-Brain Barrier

The technique of BBBD used by the BBBD consortium involves an osmotic process. Intra-arterial infusion of hypertonic solution of mannitol (25%) into a carotid or vertebral artery produces a transient and reversible disruption in the BBB by causing endothelial cell shrinkage associated with the hypertonic environment, thus opening the endothelial tight junctions. The first phase I clinical trial involving BBBD began in 1979; since then, Neuwelt and collaborators consistently have been able to demonstrate significant enhancement of chemotherapeutic agents, proteins, and even viral vectors to the brain.

BBBD currently is used in the clinical setting to increase the delivery of chemotherapeutic agents for the treatment of brain tumors in humans. As of June 2003, more than 6,200 BBBD procedures in more than 520 patients have been performed at OHSU. The most impressive results have been achieved in adults with primary CNS lymphoma (PCNSL). Studies show that out of 74 patients with PCNSL who underwent intra-arterial chemotherapy in conjunction with BBBD, 48 achieved complete response (65%) after one year of treatment. The estimated five-year survival was 42%, and the median survival was 41 months (Kraemer, Fortin, Doolittle, & Neuwelt, 2001; McAllister et al., 2000). These results can be compared with those in other published studies, which report a 42-month median survival rate with a 22.3% five-year survival for 31 patients with PCNSL treated with cranial radiotherapy and methotrexate and high-dose cytarabine chemotherapy (Abrey, DeAngelis, & Yahalom, 1998; DeAngelis, 1999).

BBBD and chemotherapy also have been administered to children and young adults with rewarding results. Thirty-four patients with histologically confirmed germ cell tumors (n = 9), PCNSL (n = 9), or primitive neuroectodermal tumors (n = 16) were treated with intra-arterial chemotherapy with BBBD at OHSU from August 1981–April 1995. Eighty-two percent of the patients had an objective response to treatment, including 62% with complete response and 20% with partial response. For most patients, cognitive functioning was maintained or improved at follow-up (Dahlborg et al., 1998). These results compare favorably with other studies of embryonal CNS tumors treated with chemotherapy given without radiotherapy, which report an objective response of 48% (Heideman et al., 1995).

Enhanced chemotherapy delivery via BBBD is used as palliative therapy for malignant glioma and is compared to the more traditional radiotherapy treatment. In a study of 78 patients with malignant gliomas, 57 received cranial irradiation before referral for intra-arterial chemotherapy in conjunction with BBBD. They were compared to 21 patients who received BBBD chemotherapy without previous radiotherapy. Only 8 of the 21 patients treated with BBBD required subsequent radiotherapy for tumor progression. Kroll and Neuwelt (1998) reported that both groups had a median survival of 17 months from the time of diagnosis and suggested that the quality of survival, based on neuropsychological assessments, may have been enhanced by avoiding or postponing cranial irradiation.

Although CNS metastases occur 10 times more frequently than primary brain tumors, available treatment options are limited, and chemotherapy use in this area has been studied poorly. Newton et al. (2003) have reported preliminary data using BBBD in conjunction with intra-arterial infusion of carboplatin with IV etoposide for brain metastasis. Thirty out of 24 patients (54%) achieved objective responses per magnetic resonance imaging (MRI) scan. Six patients (25%) achieved a complete response with time to progression of 65.8 weeks, six patients (25%) achieved a partial response with time to progression of 25 weeks, and one patient (4%) achieved a minor response with time to progression of 14.2 weeks.

The Blood-Brain Barrier Disruption Procedure

The BBBD procedure has been described previously (Doolittle, Petrillo, Bell, Cummings & Erikson, 1998; Neuwelt & Dahlborg, 1989) and is explained here with updated modifications. The BBBD procedure is performed in an angiography suite, and patients are under general anesthesia. Patients are treated on two consecutive days every four weeks for one year. The monthly hospital course is summarized in Figure 1. The treatment consists of a multiple-drug regimen with some of the chemotherapy given via IV prior to the osmotic opening of the BBB to allow time for the respective agents to be metabolized and delivered in their bioactive form to the tumor while the barrier is open. The intra-arterial chemotherapy is infused directly after the opening of the BBB. The IV and intra-arterial chemotherapy drugs are infused rapidly over 10 minutes each. The IV chemotherapy is infused via an implanted port. All patients are hydrated for a minimum of six hours prior to the chemotherapy and receive anticonvulsants. A urinary catheter is placed to facilitate fluid balance management.

A femoral artery is catheterized, and a selected intracranial artery is cannulated under fluoroscopy. A solution of 25% mannitol, which osmotically opens the BBB, is infused through the catheter, followed by the intra-arterial chemotherapy. Next, a nonionic contrast dye is administered via IV and a computed tomography (CT) scan is completed. Because the barrier opening is transient, a CT scan must be obtained as soon as possible and no later than one hour following the disruption so the degree of disruption can be visualized and documented. The CT scan result will determine the rate of mannitol infusion for future disruptions. After exubation, patients return to the oncology unit.

Tumor response to treatment is assessed prior to each monthly treatment by MRI scan with and without gadolinium contrast. The degree of enhancement and the volume of the tumor are compared to the prior month’s scan and the baseline scan. The response to the treatment is rated as complete response, par-
Partial response is a reduction greater than or equal to 50% of the tumor volume determined by MRI. Stable disease is defined as no change, an increase by less than 25% of the tumor volume, or a decrease by less than 50% of the tumor volume. Progressive disease is defined as greater than 25% increase in size of the tumor or appearance of a new lesion. Disease progression response leads to a change in treatment modalities.

Treatment Regimens

The chemotherapy regimen is dependent on tumor histology and history of prior chemotherapy. Patients with high- and low-grade gliomas, primitive neuroectodermal tumors, germ cell tumors, and cancer metastases to the brain usually are treated with a carboplatin tri-drug regimen, including intra-arterial carboplatin, IV cyclophosphamide, and IV etoposide phosphate (see Figure 2). Because of high-frequency hearing loss when carboplatin is given intra-arterially in conjunction with BBBD (Williams et al., 1995), IV infusion of high-dose (20 mg/m²) sodium thiosulfate (STS) is given for hearing protection four hours after the carboplatin. Patients with previously impaired hearing receive a second bolus (16 mg/m²) eight hours after the carboplatin infusion (Doolittle, Muldoon, et al., 2001).

Patients with PCNSL receive a methotrexate tri-drug regimen, including intra-arterial methotrexate, IV cyclophosphamide, and IV etoposide phosphate (see Figure 2). To ensure renal protection, sodium bicarbonate is added to the IV fluid and titrated to achieve a urine pH greater than 6.5, and a leucovorin rescue is initiated 36 hours following the first dose of methotrexate; patients receive 80 mg via IV followed by a standardized 30 mg oral dose every six hours for a total of 20 doses. Prophylactic subcutaneous enoxaparin (40 mg per day for 10 days) is given to all patients with CNS lymphomas, starting six hours after completion of the second BBBD, based on their historically higher risk for developing a deep vein thrombosis (Goldschmidt, Linetsky, Shalom, Varon, & Siegal, 2003).

Other chemotherapeutic regimens are available or substituted in situations of relapsed disease with prior exposure to chemotherapy or in cases of tumor progression during the course of BBBD treatment. In addition, all patients receive 8 mg ondansetron via IV immediately following each BBBD. Because STS has a high emetogenic potential, patients receiving high-dose STS are premedicated with a regimen of steroids, diphenhydramine, and lorazepam one hour before each STS bolus. Finally, all patients are treated with steroids, usually dexamethasone 24 mg per day, to control brain edema induced by the procedure and, in the case of lymphoma, by tumor lysis. The steroids are tapered off as tolerated over one week.

Forty-eight hours after completion of chemotherapy, patients begin to receive daily subcutaneous injections of filgrastim (300 or 480 mcg, depending on body weight) until their absolute neutrophil count is greater than 2,500/mm³. Pegfilgrastim (6 mg onetime injection, 48 hours after chemotherapy) may be used when insurance coverage and/or treatment protocol permit. Epoetin alfa (20,000–60,000 U) is administered routinely once a week for hemoglobin less than 11 g/dl.

Carboplatin Tri-Drug Regimen
- Etoposide phosphate, administered via IV, 200 mg/m² per day each day, for a total dose of 400 mg/m²
- Cyclophosphamide, administered via IV, 330 mg/m² per day each day, for a total dose of 660 mg/m²
- Carboplatin, administered intra-arterially, 200 mg/m² per day each day, for a total dose of 400 mg/m²
- Sodium thiosulfate, 20 mg/m² administered via IV, four hours after carboplatin, as needed, second bolus of 16 mg/m², eight hours after carboplatin

Methotrexate Tri-Drug Regimen
- Etoposide phosphate, administered via IV, 150 mg/m² per day each day, for a total dose of 300 mg/m²
- Cyclophosphamide, administered via IV, 500 mg/m² per day each day, for a total dose of 1 gm/m²
- Methotrexate, administered intra-arterially, 2.5 gm per day, for a total dose of 5 gm
- Leucovorin, 80 mg given via IV 36 hours after first methotrexate infusion, followed by 50 mg by mouth every six hours for 20 doses
- Sodium bicarbonate added to IV fluid and titrated for a urine pH > 6.5

Adverse Events and Complications

BBBD is an invasive procedure performed under general anesthesia with all the risks associated with this type of treatment. The chemotherapy-induced side effects are typical, including nausea, vomiting, neuropenia, thrombocytopenia, anemia, and fatigue. Some of the more specific events include deep vein thrombosis and transient neurologic deficits, such as unilateral motor weakness, aphasia, or diplopia, which may occur immediately following the procedure. Neurologic symptoms are treated with IV dexamethasone and resolve 24–48 hours after BBBD. Seizures are associated with 7% of BBBD procedures. These usually are unifocal in nature and occur during the procedure when a patient is under general anesthesia. Intraprocedural seizures are managed with a barbiturate (thiopental) given by the anesthesiologist. All patients receive phe nobarbital or their current anticonvulsant the night before the procedure and also receive lorazepam preoperatively.

In a review of data accumulated from March 1994–November 1997 at OHSU and participating centers, Doolittle et al. (2000) reported the recorded complications for 221 patients or 2,464 treatments with intra-arterial chemotherapy with or without BBBD. Asymptomatic subintimal tear occurred in 11 patients (5%), pulmonary embolism occurred in 6 patients (3%), deep vein thrombosis occurred in 33 patients (15%), and renal toxicity occurred in 4 patients (2%). In addition, 12 patients (5%) experienced obtundation over 48 hours, and 3 patients (1%) suffered a stroke. Finally, one patient died from brain herniation less than 48 hours after treatment.

An unexpected complication secondary to infusion of carboplatin in conjunction with BBBD has been high-frequency hearing loss. Approximately 79% of patients receiving carboplatin in conjunction with BBBD were affected (Williams et al., 1995). Since May 1995, STS has been introduced as an agent to reduce the ototoxicity of carboplatin. Clinical studies using delayed high-dose STS showed a clear protective effect against carboplatin-induced hearing loss when carboplatin is administered in conjunction with BBBD (Doolittle, Muldoon, et al., 2001).

Implications for Practice

The multidisciplinary BBBD team includes advanced practice nurses (APNs), oncology nurses, neurosurgeons, neurologists, neuroradiologists, anesthesiologists, hematologists-oncologists, medical psychologists, ophthalmologists, pharmacists, physical therapists, social workers, and administrative assistants. The role of nurses is essential and central to the success of the treatment as well as the well-being of patients and their families.

APNs are involved from the initial visit when treatment options are discussed and a plan of care is established. Patients and their families are presented with a detailed explanation of the BBBD procedure, risks, and potential adverse effects of BBBD and chemotherapy. Once a patient has decided to en-
ter the program, an APN follows the patient and family closely.

At the monthly hospital admission, the APN meets with each patient and completes a physical examination and neurologic assessment and reviews laboratory data. They discuss the events of the previous month, including assessing the severity of treatment side effects and evaluating the patient’s well-being, coping abilities, quality of life, and educational needs. Medications and medication schedules are reviewed and adjusted as needed. The role of the APN in collaboration with the physicians includes the workup and documentation for hospital admission, coordination of the BBBD procedure, and management of all aspects of patient care, including referrals to other medical disciplines, hospital discharge, and discharge teaching.

After the BBBD procedure, patients will experience large fluctuations in fluid balance and electrolytes, mostly because of the diuretic effect of mannitol and STS. The BBBD team relies on the knowledge and skills of oncology nurses to meticulously track fluid intake and output. A running total is begun during the first BBBD procedure and maintained for the next 48 hours. The goal is to maintain patients’ fluid balance within –250 ml and +500 ml. These patients must not be fluid overloaded, which could put them at risk for elevated intracranial pressure. They also must maintain an adequate urine output of at least 50 ml per hour for proper elimination of chemotherapy agents to prevent renal injury. In addition, a urine pH greater than 6.5 must be maintained if the patient has received methotrexate. Oncology nurses are responsible for hourly evaluation of the patient’s status, including vital signs, neurologic status, fluid balance, need for antiemetics, and overall well-being. Specialized training, which includes quartered educational in-services, and protocol-based guidelines help nurses to recognize the signs and symptoms of increased intracranial pressure, seizures, and neurologic deterioration and facilitate prompt intervention by the medical team.

Following hospital discharge, laboratory studies are performed biweekly. In addition, patients are instructed to check their temperature daily to detect any sign of possible infection. This is important particularly in view of the myelosuppressive effect of chemotherapy. An APN is in contact with patients by telephone at least once a week. The frequency of calls is increased while patients are receiving filgrastim and/or leucovorin to ensure patient compliance and provide guidance as needed. The APN is responsible for closely monitoring patients’ white blood cell counts and quickly identifying any evidence of neutropenic fever for initiation of antibiotic therapy. Platelet counts also are followed closely to prevent bleeding and evaluate the need for a platelet transfusion. Hemoglobin levels are assessed to evaluate the need for supplemental injections of epoetin alfa or adjustment of the dose. In addition, an APN continually evaluates patients for signs and symptoms that would indicate disease progression, evidence of increased intracranial pressure, or increases in seizure activity.

Future Directions

New clinical trials have been developed by the BBBD consortium using thiols as chemoprotectants with the goal of decreasing the incidence of dose reduction of carboplatin because of myelosuppression and ultimately permitting dose escalation of this drug. A phase II clinical study currently is open for subjects with high-grade glioma that involves treatment with intra-arterial carboplatin-based chemotherapy (without BBBD). Subjects are randomized to treatment with or without delayed STS, which may act as a potential protectant against severe thrombocytopenia (Doolittle, Tyson, et al., 2001).

N-acetylcysteine is another thiol of great interest as a potential bone marrow and hearing chemoprotectant. A phase I dose escalation study of N-acetylcysteine in conjunction with carboplatin-based BBBD currently is open for patient accrual at OHSU.

A clinical trial for patients with anaplastic oligodendroglioma, aggressive oligodendroglioma, or oligoastrocytoma is being developed. The chemotherapy regimen will consist of carboplatin, melphalan, and etoposide phosphate in conjunction with BBBD, and patients will receive delayed high-dose STS for hearing protection.

Members of the BBBD consortium also are exploring the area of CNS immunotherapy, concentrating on immunotoxin therapy for glioblastoma multiforme. In a 2003 presentation, Walter Hall, MD, from the University of Minnesota shared the progress of his research, describing immunotoxins as potential “smart bombs” that use cytokines, which stop protein synthesis by binding to the cell membrane and then enter into the tumor cell. Hall’s research results showed significant decreased tumor size and increased survival time in a mouse glioblastoma multiforme model using a recombinant form of diphertheria toxin therapy (Li et al., 2002).

A great deal of research has surrounded the antitumor effects of monoclonal antibodies. Rituximab, a monoclonal antibody to the CD20 antigen that is present in 95% of patients with B-cell lymphoma, has been added to the carboplatin-based chemotherapy regimen for BBBD treatment of relapsed PCNSL (Tyson et al., 2003). Combination of radiopharmaceuticals and BBBD drug delivery is of great interest. At the time of this writing, approval is being requested for the use of ibritumomab, a radioisotope conjugated to the CD20 antigen, in a phase I study in conjunction with BBBD. Ibritumomab has been approved recently by the U.S. Food and Drug Administration for the treatment of systemic non-Hodgkin lymphoma.

Trastuzumab is a monoclonal antibody of great interest that could be added to a chemotherapy regimen with BBBD to treat metastatic breast disease to the brain. With the increasing incidence of metastatic disease, researchers will need to develop treatment protocols specific for CNS metastatic disease from organs such as the breast and lungs, as well as for melanoma.

The BBBD consortium actively is developing treatment protocols for the pediatric population because of the high incidence of brain tumors in children. In the Consortium’s experience, children have tolerated the BBBD treatments well, with no significant cognitive impairment (Dahlborg et al., 1998).

Conclusions

BBBD is an innovative, safe, and effective way to deliver chemotherapy to brain tumors while minimizing toxicities. Since 1979, adults and children with chemotherapy-sensitive brain tumors have been treated with encouraging results and acceptable quality of life. BBBD offers exciting possibilities for the delivery of new agents such as monoclonal antibodies, immunotoxins, and gene therapy across the BBB for the treatment of numerous CNS diseases. The promising role of thiols as chemoprotectants continues to be explored with the goal of maintaining consistent chemotherapeutic dose intensity and, ultimately, dose escalation. Within a multidisciplinary team, APNs play a vital role in the coordination of the BBBD procedure and the comprehensive management of patients during their treatment course and follow-up. APNs from the entire BBBD consortium are involved actively in data collection and publication. They also are involved in the development of clinical protocols with the goal of achieving more effective treatments for patients with malignant brain tumors while maintaining good quality of life.

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- The survival of patients with malignant central nervous system lesions has been poor because of the relative ineffectiveness of chemotherapy and neurotoxicity associated with radiation therapy.
- The blood-brain barrier (BBB) hinders the transport of drugs and other materials into the brain tissue.
- By disrupting the BBB, exposure to chemotherapy can increase up to 100-fold without significant increase in neurotoxicity.
- BBB disruption (BBBD) is an osmotic process in which a hypertonic solution (mannitol 25%) is infused intra-arterially into a carotid or vertebral artery to produce a transient and reversible disruption of the BBB.
- The BBBD procedure is performed in an angiography suite with a patient under general anesthesia.
- Treatment-related side effects include nausea, vomiting, myelosuppression, and, less commonly, deep vein thrombosis and transient neurologic deficits.

For more information on this topic, visit the following Web sites.

American Brain Tumor Association
www.abta.org
Brain Tumor Society
www.tbts.org

Links can be found at www.ons.org.

Rapid Recap

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