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The blood-brain barrier (BBB) is a paradox. On one hand, it protects the brain from what would otherwise be a constant systemic barrage of noxious substances. On the other hand, it prevents, in large measure, the delivery of therapeutic agents to patients with brain tumors. In an ongoing effort to improve the understanding and clinical consequences of the BBB and its disruption, a 3-day meeting was held under the direction of Drs. Edward A. Neuwelt and Nancy Doolittle of Oregon Health and Science University.

Nearly 100 experts from various clinical and basic science disciplines participated in the Eighth Annual Meeting of the Blood-Brain Barrier Disruption Consortium (April 25 through April 27, 2002, at Skamania Lodge in Stevenson, WA). The meeting, "Importance of the Blood-Brain Barrier and Imaging in Future Neuro-Oncology Therapeutics," was partially funded by an R13 meeting grant from the National Institutes of Health. It was presented after an afternoon symposium titled "Mechanisms and Therapeutics of Neurologic Disease: Impact of the Blood-Brain Barrier" that took place in Portland, Oregon, on April 24.

At the April 25–27 meeting, a full range of clinical topics in neuro-oncology was presented, extending from funding opportunities through clinical management and new directions in therapeutics and imaging, which allowed for lively exchanges between the presenters and the audience. The balanced mixture of state-of-the-art clinical protocols and future directions for patient care enabled practicing physicians (neurologic surgeons, neurologists, medical oncologists, radiation oncologists, diagnostic radiologists) to appreciate the ongoing translational efforts bringing new concepts to clinical fruition.

The initial evening of the consortium, opened by Archie Bleyer (MD Anderson Cancer Center), concentrated on pediatric and adolescent brain tumors and provided an introduction to case presentations the next day by Gregory Hornig (Children's Mercy Hospital), Nate Selden (Oregon Health and Science University), and Kenneth Stevens (Oregon Health and Science University), who demonstrated combination therapy (surgery, chemotherapy) and BBB disruption for high grade glioma and primitive neuroectodermal tumors in children.

Dr. Hornig discussed the importance of chemotherapy delivery as a means to decrease the need for radiation. He illustrated this concept by presenting a 2-year-old child enrolled in the Oregon Health and Science University Blood-Brain Barrier Disruption Program who, after completion of a bone marrow transplant, had recurrence of the primative neuroectodermal tumor but subsequently had a dramatic response to intra-arterial delivery of chemotherapy after BBB disruption (Fig 1, A–D). This permitted up to a 100-fold increase in drug delivery to the brain and CSF compared with the same dose when IV administered. Thus, only very focused radiosurgery and not cranial spinal radiation was subsequently administered. The child remained healthy and without recurrence 24 months later.

Raymond Mulhern (St. Jude Children's Hospital) continued the discussion of efficacy versus toxicity with a focus on radiation therapy and neuropsychological testing. He documented a continual decline of patients' intelligence quotient over time after radiation therapy. This decline correlated with diminution of white matter volume, as determined by volumetric measurements based on serial MR images. Altering therapeutic chemotherapy and radiation therapy strategies to diminish these deleterious effects was discussed. It is anticipated that functional MR imaging (cortical activation by using the blood oxygen level dependent technique) will have a role in assessing the effects of these treatment protocols.

Gigi McMillan (Director, We Can Pediatric Brain Tumor Network) presented information from the patient advocate perspective. As the mother of a child with a brain tumor, she brought attention to the significance of the emotional health of the family. She noted that treating physicians and health care providers can ensure continued participation in treatment studies, especially during collection of crucial follow-up data.

Clinical trials involving chemotherapy with a focus on dose intensity was the concentration of the next session. The challenges and problems of conducting randomized clinical trials in brain tumors were discussed from the perspective of a statistician, Dale Kraemer (Oregon Health and Science University). The rare occurrence of some tumors, difficulties with patient recruitment, and biases in selection and referrals were all mentioned as problems in designing randomized clinical trials. The need for a standardized tumor response definition was discussed. Leslie Muldoon (Oregon Health and Science University) emphasized work on preclinical chemo-protection studies in which increased chemo-protection could allow for a greater dose and therefore result in increased cytotoxicity to a tumor. For example, Nancy Doolittle described the potential use of sodium thiosulfate infusion 4 hours after BBB disruption, when BBB permeability has returned to baseline, as a protective agent for carboplatin-based high frequency hearing loss and possibly as a prevention of thrombocytopenia when administered in high doses, 4 or 8

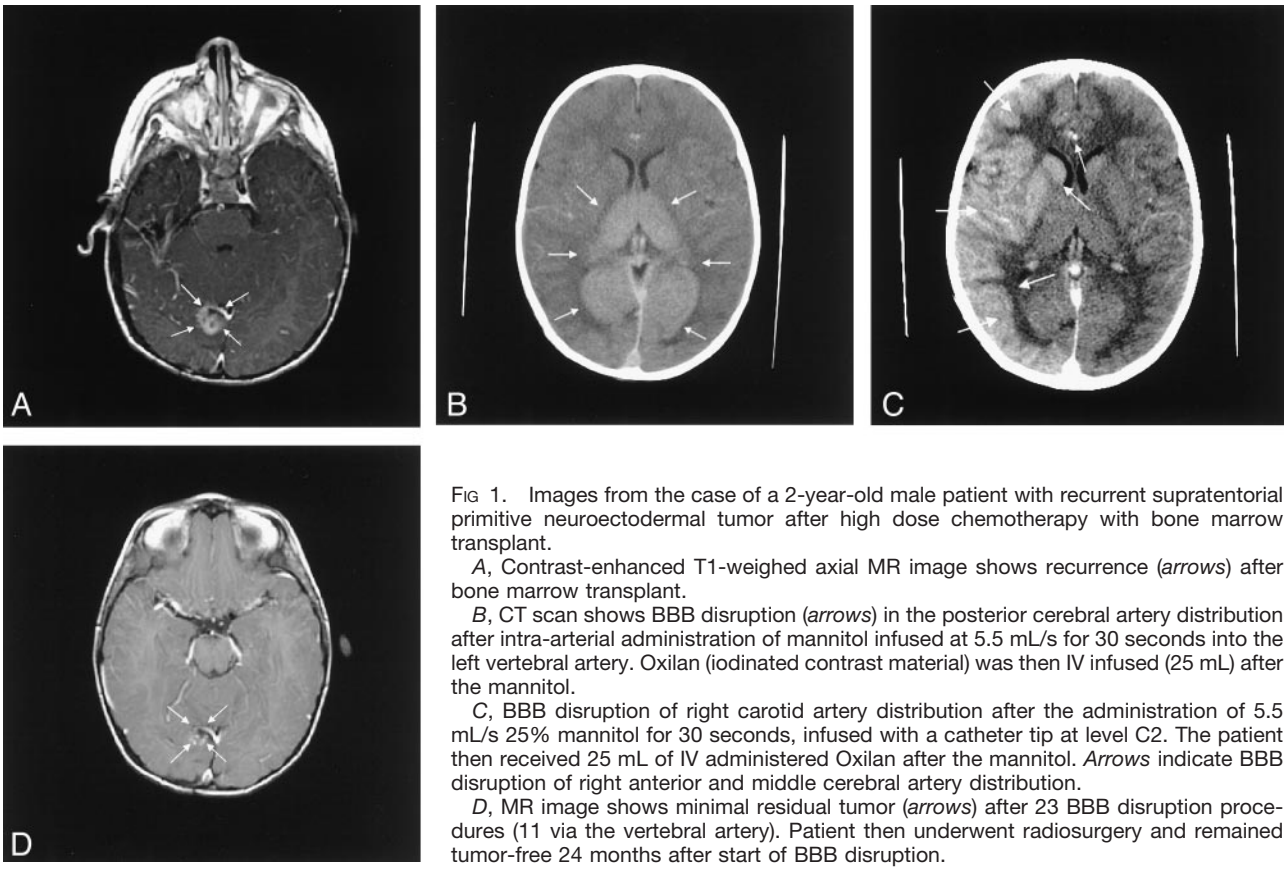


FIG 1. Images from the case of a 2-year-old male patient with recurrent supratentorial primitive neuroectodermal tumor after high dose chemotherapy with bone marrow transplant.

*A*, Contrast-enhanced T1-weighed axial MR image shows recurrence (*arrows*) after bone marrow transplant.

*B*, CT scan shows BBB disruption (*arrows*) in the posterior cerebral artery distribution after intra-arterial administration of mannitol infused at 5.5 mL/s for 30 seconds into the left vertebral artery. Oxilan (iodinated contrast material) was then IV infused (25 mL) after the mannitol.

*C*, BBB disruption of right carotid artery distribution after the administration of 5.5 mL/s 25% mannitol for 30 seconds, infused with a catheter tip at level C2. The patient then received 25 mL of IV administered Oxilan after the mannitol. *Arrows* indicate BBB disruption of right anterior and middle cerebral artery distribution.

*D*, MR image shows minimal residual tumor (*arrows*) after 23 BBB disruption procedures (11 via the vertebral artery). Patient then underwent radiosurgery and remained tumor-free 24 months after start of BBB disruption.

hours after carboplatin delivery. An update of a phase I clinical trial, currently being conducted at Oregon Health and Science University, using *N*-acetylcysteine administered in the descending aorta before BBB disruption carboplatin-based chemotherapy was presented.

Funding opportunities for general neuro-oncology clinical trials and for trials involving BBB disruption specifically were of great interest to the audience because many funding agencies encourage trials that assess the efficacy of various clinical protocols. Representatives of the National Institutes of Health and the Veterans Affairs, including Roy Wu, John Hoffman, Brian Wojcik, Tom Jacobs, Katie Woodbury-Harris, and Paul Hoffman, presented various opportunities available through their respective funding agencies. After John Hoffman (Chief of Molecular Imaging at the National Institutes of Health) described funding opportunities in molecular imaging, Tom Jacobs of the National Institute of Neurologic Disorders and Stroke (NINDS) discussed funding opportunities in neuro-oncology clinical trials, including RO1s (research projects that have the most flexible funding mechanism), PO1s (program projects that are a combination of at least three phase I and II trials or research studies), and K23/24s (mentored and mid-career awards). Katie Woodbury-Harris, also of NINDS, spoke of the clinical trials group and the process in place at NINDS to establish pilot clinical trials; it was emphasized that these were not to be mini phase III trials. Veterans Affairs funding for neuro-oncology research is currently small. However, Paul Hoffman emphasized that the Veterans Affairs Administration wants to become a greater sponsor of this type of investigation. The National Institutes of Health (web site, www.nih.gov) lists program announcements, grant availability, ongoing trials, and instructions regarding how to apply for grants. The National Institutes of Health Specialized Program of Research Excellence (http://spores.mci.nih.gov) is designed to fund large scale translational research in cancer and is organ site-specific. Because of this specialization, the program requires that a clinical scientist and a basic scientist participate in each grant-funded project. It was made clear that the program mechanism actively seeks pilot projects, de-emphasizing the submission of preliminary data as part of the proposal. The greatest problem areas regarding grant submission, which most members of the audience understood, were unclear relationships between laboratory work and clinical studies, deficiencies in statistical power, inadequacies in writing style and proofreading, and failure to follow instructions for submission.

A session on neuro-imaging of brain tumors commenced with an update on the advances in MR imaging of brain tumors by Robert Quencer from the University of Miami. State-of-the-art MR imaging to determine the chemical profiles, physical chemical data, and hemodynamic information regarding brain tumors was described and illustrated with single-voxel and multi-voxel MR spectroscopy, including chemical shift imaging (spectroscopic imaging), diffusion imaging plus apparent diffusion coefficient maps, and

blood perfusion information. It is clear that imaging of brain tumors has advanced beyond simple anatomic-pathologic displays on MR images and now stands at the forefront for assessment of tumors and the efficacy of treatment schemes. Future applications will move beyond proton spectroscopy to multinuclear (phosphorus-sodium) spectroscopic imaging. Diffusion imaging will, with higher and higher gradient applications, map out and separate slow and fast components of water diffusion. These techniques will provide greater insights into brain tumor pathology and treatments.

The use of iron-based contrast agents, the physiology of iron, and the current status of Feridex and Combidex (smaller particle size) were discussed by Paula Jacobs of Advanced Magnetics. Specific note was made of the use of these agents in nodal and abdominal imaging and in a multiple sclerosis model. In general, iron oxide particles showed uptake in cells with normal phagocytic activity. The exciting potential value of the clinical use of Combidex as a contrast agent in the CNS was described by Peter Varallyay (Oregon Health and Science University), and its projected use included better delineation of tumors, the more accurate assessment of residual tumor, and the theoretical advantage of monitoring like-sized viral particles used to treat brain tumors. To detect exactly where the dextran-coated Combidex goes, which is not possible with other contrast agents, the use of iron stains and anti-dextran antibodies shows Combidex accumulation in microglia and reactive glia, as well as in capillary walls.

An update by John Hoffman (Veterans Affairs) on the status of positron emission tomography of brain tumors included a fundamental description of the detector requirement for positron emission tomography and the use of F-18, N-13, 0–15, C-11, and Rb-82. The ability of positron emission tomography to distinguish tumor from necrosis and predict survival and prognosis was discussed. Dramatic short-term growth of a rat gliosarcoma and its evaluation with MR imaging was shown by Brian Ross (University of Michigan). He discussed the diffusion-weighted imaging findings in this tumor and showed the difference between native tumor (restricted diffusion) versus treated tumor (less restricted diffusion). Importantly, the apparent diffusion coefficient maps showed differences with various treatment strategies (eg, gene therapy plus radiation therapy versus gene therapy plus chemotherapy with 5FU).

A future imaging quest will be to devise a means of imaging apoptosis, perhaps facilitated by the use of nanoparticles. Paul Wang (Oregon Health and Science University) showed the MR imaging consequences of radiation therapy, which was administered for the treatment of astrocytomas and oligodendrogliomas. In the final presentation in this imaging session, Tali Siegal (Haddasah University, Israel) presented MR imaging studies of patients with radiation necrosis and correlated those findings with the patients' clinical statuses. In cases in which relative cerebral blood volume maps were used, there was no elevation of relative cerebral blood volume levels in radiation necrosis (this is clearly different from what is expected in tumors). It was concluded that this technique could complement routine MR imaging in the analysis of tumor versus radiation effects. MR spectroscopy was of less value; it detected low levels of all metabolites in radiation necrosis except, of course, for lipids, which are present in necrosis. As was pointed out, however, in approximately one-third of cases, there is a combination of radiation necrosis and tumor. Positron emission tomography and thallium single-photon emission CT were unreliable in distinguishing these two because of large numbers of false-positive studies. It was concluded that multimodality imaging, specifically combination studies (MR imaging, MR spectroscopy, perfusion MR imaging, and positron emission tomography) will yield the best possibility of distinguishing residual tumor from radiation necrosis.

In the session on head and neck cancer, Frank Ondrey (University of Minnesota) discussed "surrogate end points" (ie, what one should look for histologically or during physical examination that will determine the reversal of malignancy, including malignant genes and tissue markers for therapy effectiveness). Ed Neuwelt spoke of the possibility of intracarotid chemotherapy with sodium thiosulfate protection for head and neck cancer and posed the question of whether the BBB Consortium, the members of which were there in attendance, was interested in developing a multi-institutional intra-arterial chemotherapy-radiation protocol with IV administered sodium thiosulfate rescue.

Walter Hall (University of Minnesota) gave an update on CNS immunotherapy, concentrating on immunotoxin therapy for glioblastoma multiforme. Immunotoxins are potential "smart bombs" that use cytokines, which stop protein synthesis by binding to the cell membrane and then entering into the tumor cell. In a mouse glioblastoma multiforme model, MR imaging was used to follow the effectiveness of a recombinant form of diphtheria toxin therapy, diphtheria toxin amino terminal therapy. With this treatment, decreased tumor size and increased survival time was shown.

Advances in brain tumor vaccines were described by Linda Liau (University of California, Los Angeles). Principles of tumoral and cellular immunity were mentioned; work on dendritic cell-based tumor vaccines was emphasized. The dendritic cells come from bone marrow precursor cells; they activate T cells, and the T cells search out and destroy foreign particles. This has been termed *dendritic cell-based cancer immunotherapy*, and the preclinical animal studies showed that this therapy generated an immunoresponse. Clinically, in a phase I trial, the adverse effects of this therapy were assessed in 10 patients with glioblastomas multiforme. It was pointed out in the subsequent discussions that dendritic cells are usually administered systemically but if they are instilled directly into the brain, they might drain down the ol-

factory nerves to the cervical lymph nodes and activate T cells there.

Combinations of radiation therapy plus immunoconjugate treatment with BBB disruption drug delivery in a tumor model were described by Leslie Muldoon; immunoconjugates bound to chemotherapy via labile linkages was a treatment scheme that was both well tolerated at low doses and efficacious, particularly when delivery was enhanced with BBB disruption.

Gregory Wiseman of the Mayo Clinic discussed therapeutic radionuclides conjugated to the CD20 antigen, used in the treatment of systemic non-Hodgkin's lymphoma. He described the "crossfire effect" in which radioisotope kills cells around the attached cell. The responses of varying grades of systemic lymphoma to Zevalin, which is conjugated Y-90 (for therapy) or In-111 (for imaging), were noted. It was concluded that this novel cancer therapeutic method, which can be completed within 1 week on an outpatient basis, can be an effective treatment.

After the presentation on systemic lymphoma therapy, the discussion switched to possible therapy of primary CNS lymphoma and the advantage of this technique if the safety of CNS delivery can be resolved. With the 90% deposit of radiation energy within a 5-mm radius, actual entrance into abnormal cells is not necessary. The future direction for the treatment of relapsing primary CNS lymphoma was presented by Rose Marie Tyson (Oregon Health and Science University). Intra-arterially administered mannitol (BBB disruption) will be used to increase delivery of chemotherapeutic agents for cytoreduction, while holding administration of enhanced delivery of Zevalin (yttrium-labeled antibody) until after CNS tumor burden is minimized with chemotherapy.

The possibility of a phase III trial in primary CNS lymphoma was raised by Tracy Batchelor (Harvard University). Two questions that need to be addressed are the roles of chemotherapy and whole brain radiation therapy in cases of primary CNS lymphoma. As was pointed out, primary CNS lymphoma is a relatively rare disease accounting nationwide for 1200 cases per year. The problem is how to enroll a significant number of patients to provide such a trial with statistical power. An important issue to address is neurocognitive outcomes in patients treated with either technique. Surely, functional MR imaging (cortical activation) and other advanced MR imaging techniques, such as diffusion-weighted imaging and MR spectroscopy, could lend independent objectivity to the assessment of cognition in these treated patients.

The value of a multidisciplinary approach and exchange of information is exemplified by these ongoing meetings on the BBB (Doolittle ND, Anderson CP, Bleyer WA, et al. *Neuro-oncol* 2001;3:46–54 and Doolittle ND, Abrey LE, Ferrari N, et al. *Clin Cancer Res* 2002;8:1702–1709). Investigators of different specialties and their exchanges of ideas and experiences help add to the growing hope for improved outcomes in the treatment of primary malignant and metastatic brain tumors.

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