Improved Drug Delivery to Brain Tumors

Chair: Arnold I. Freeman, MD, University of Missouri, Kansas, MO

Participants
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O. Michael Colvin, MD, Johns Hopkins Oncology Center, Baltimore, MD
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Andrew Hertler, MD, Louisiana State University, Shreveport, LA
Victor Levin, MD, MD Anderson Cancer Center, Houston, TX
Eric Mayhew, Ph.D., Roswell Park Memorial Institute, Buffalo, NY
David Poplack, MD, National Institutes of Health, Bethesda, MD
Joan Shapiro, Ph.D. Memorial Sloan-Kettering, New York, NY
William Shapiro, MD, Memorial Sloan-Kettering, New York, NY
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Layout and Goals
Sessions:
I. Blood-Brain Barrier and its Physiology
II. Directions of Current Therapy
III. Targeted Therapy in Brain Tumors
IV. Discussion and Summary

The fourth Annual Forbeck Forum probed the problems of treating brain tumors with chemotherapy. Advances in the cure rate of brain cancers have lagged behind most other childhood cancers. Further, the morbidity of this cancer is often devastating. For example, in children cured of medulloblastoma (a brain tumor in the back if the head), there is often a profound loss of intelligence, which may be so severe as to greatly decrease the quality of life. The brain is unique in that it is in a protected environment so that toxins and other products normally present in the blood cannot gain entry into the brain. The blood brain barrier (BBB) is the prime basis for the protected environment. Unfortunately, this also means that many chemotherapeutic drugs cannot gain entry into the central nervous system. There are, however, techniques which can overcome the BBB. For example, certain “lipid-soluble” drugs cross the BBB. Drugs may be administered in very high doses, thereby “forcing their way” into the CNS, or, them may be administered directly into the artery that bathes the part of the brain where the tumor is located. This achieves a high level of drug in the substance of the brain tumor.
Outcome Report

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The first session was chaired by Dr. Josep Fenstermacher and dealt with the basic understanding of the control of drug access to the brain. The thrust of this session was that factors, other than BBB, play a role in drug penetration onto cancer cells. Noted were the capillary density (the number of capillaries per area in the various geographical locations of the brain), the length of the capillary, and the transit time of chemotherapy in the capillaries. Drugs that are highly bound to protein in the blood do not penetrate into the central nervous system. Discussed were mathematical models depicting these problems and pointing toward possible solutions. Also, the benefit of PET scanners to evaluate the metabolism and drug penetration into the brain tumors were evaluated. For example, a patient whose tumor takes up BCNU (an anticancer drug) was shown to have a better response.

The second session was chaired by Dr. William Shapiro and discussed results on recently completed or ongoing studies. These included the use of various drugs in recurrent brain tumors, as well as the use of drugs in a primary adjuvant fashion along with surgery and radiation in an attempt to improve the cure rate. Intra-arterial drug therapy (giving the drug directly into the artery bathing the tumor rather than into a vein), and the benefits of this maneuver, as well as its toxicities, were debated.

At present, standard therapy for high grade gliomas of the brain (the common adult cancer of the brain) is maximal resection, followed by radiation and then BCNU chemotherapy. Unfortunately this program leaves a great deal to be desired. Only 25% of patients with high grade gliomas are alive at 18 months. The smaller the amount of tumor left after surgery, the better the prognosis. It was observed that brain tumors which initially respond to treatment and then recur have become highly resistant to drugs. A new anticancer drug, ACNU (an analog of BCNU), was tested in Japan and has shown that it is effective against brain tumors. The use of bone marrow transplantation in childhood brain tumors was discussed. This technique allows very high doses of drug to be given intravenously. Some impressive responses in far advanced cases were noted.

Dr. John Kemshead chaired the third session which dealt with innovative techniques for the administration of chemotherapy. Intra-arterial chemotherapy was again presented. Discussions included the use of monoclonal antibodies to target drugs, radionucleotides, and toxins, including their use when administered directly into the spinal fluid. Other ideas include discussion of the advantage of using liposomes which are small lipid balls with hollow centers that can be filled with drugs; and the implantation of wafers (containing drugs) directly into the tumor bed (after the tumor has been surgically removed). In this situation, drugs may be directly released into the tumor for long periods of time.

Exciting spinoffs from this meeting included the collaborative evaluation of multidrug resistance in brain tumors and the extension of using wafers in clinical trials.
Quotes from Participants:

“The meeting was exciting for me because I have never attended such a meeting before in which one specific subject is extensively and freely discussed by a small group of people.”
- Yukitaka Ushio, Kumamoto University, Japan

“As a result of the Forum ... I plan to have a one-day symposium at the MD Anderson Cancer Center to discuss issues related to the blood-brain barrier and hopefully to develop new treatments. We are certain that this is precisely the kind of interaction that you envisioned when you developed the Forum concept.”
- Victor Levin, MD, MD Anderson Cancer Center, TX

“The enmeshing of basic laboratory and clinical investigative scientists is, I believe, a critical prerequisite for the development of practical solutions based upon sound scientific rationale. I certainly came away with a number of concrete ideas for exploration and possible implementation in the near future.”
- Jonathan Finley, MB, ChB, Children’s Hospital of Philadelphia

“... good discussions of very difficult problems faced in the treatment of brain tumors. I got several ideas for my future work ...”
- Mirko Diksic, Ph.D., McGill University, Canada