Brain Tumor Therapy: New Lights on the Horizon

“Although the world is full of suffering, it is full also of the overcoming of it.” Helen Keller 1880-1968

For the more than 100,000 Americans each year who are diagnosed with a malignant brain tumor, there is today new hope. The last few years have brought new concepts, new technology, and new weapons in the battle against brain tumors. There is, as never before, new light at the end of old tunnels. For this feature edition of Cancer Control, some of the brightest lights in the field of neuro-oncology have shared their experiences, contributions, and knowledge to point to new methods to control malignancy in the brain. Survival for patients with malignant brain tumors, formerly a death sentence, is being extended by the combination of better neuroimaging, surgical, pharmacological, and biological approaches. Ultimately, the discoveries of the molecular mechanisms that control malignancy in the brain will be translated into practical therapies to tame the tiger and significantly increase survival.

Stuart Grossman, MD, Joy Fisher, MA, Steven Piantadosi, MD, PhD, and Henry Brem, MD, discuss the organization, objectives, and activities of the NCI-sponsored consortium, “New Approaches to Brain Tumor Therapy” (NABTT). Because no one individual or even one institution can likely overcome the challenges posed by brain tumors, the NIH a few years ago requested grants from CNS brain tumor consortia. The NABTT CNS Consortium is one of two multicenter, cooperative groups actively engaged in novel therapeutic approaches. Headquartered at The Johns Hopkins Oncology Center, the current membership includes Emory University, Henry Ford Hospital, Massachusetts General Hospital, Moffitt Cancer Center, University of Alabama, University of Pennsylvania, University of Texas (San Antonio), and Wake Forest University. The mandate is to stimulate advances in the treatment of patients with high-grade astrocytomas by joining institutions with a large number of brain tumor patients, a record of excellence in clinical research, and access to exciting new approaches for these patients. The NABTT institutions conduct toxicity, safety, and efficacy (phase I/II) trials for patients with newly diagnosed and recurrent glioblastomas. Since 1993, 31 clinical protocols have been written for the Consortium. One hundred and seventy-eight patients have been entered on NABTT therapeutic protocols, and 669 have registered for nontherapeutic protocols. In 1996, the member institutions treated 2,116 patients with primary brain tumors, a sizeable percentage of the national total. The NABTT Consortia has evaluated agents such as a-aminocamptothecan (9 A-C) and paclitaxel. NABTT investigators first noted that anticonvulsants have a major effect on the pharmacology of several chemotherapeutic drugs by activation of hepatic enzymes.

Michael Lev, MD, and Fred Hochberg, MD, describe the novel use of perfusion magnetic resonance (MR) imaging to assess brain tumor responses to new therapies. “Functional” imaging techniques that can differentiate tumor from normal brain tissue based on diverse physiological parameters are an exciting area of clinical investigation. The newer technologies go beyond conventional MR imaging, which is the gold standard for anatomic mapping, and provide maps of tumor perfusion that will be especially important to monitor the effects of newer compounds such as thalidomide, marimastat, and penicillamine that inhibit tumor angiogenesis. Mapping of blood volume reflects activity of brain tumors pretreatment and posttreatment. MR perfusion techniques are likely to be at least as sensitive and specific as radiolucide-based techniques, and they offer the added advantages of higher intrinsic resolution, convenient co-registration with conventional MR imaging, and time-and cost-effective imaging in a patient population already receiving frequent follow-up MR imaging scans.

Frederick Lang, MD, David Wildrick, PhD, and Raymond Sawaya, MD, present the MD. Anderson experience of the current management of cerebral metastases, focusing on the role of surgery. With recent advances in surgical technology, it is now possible to obtain local control and increase survival and quality of life in patients with single and multiple (up to four tumors) brain metastases. This sweeping article considers patient selection criteria, surgical approaches, intraoperative adjuncts, whole-brain irradiation postoperatively, and the place of stereotactic radiosurgery. The preference is for surgical eradication wherever possible and safe. Radiosurgery can be used as an alternative for smaller or inacessible tumors. Today, tumors previously considered to be inoperable are completely resectable using modern techniques such as microneurosurgery, image-guided neuronavigation devices, complex skull base exposures, metabolic mapping, functional MRI, and intraoperative cortical mapping. The current experience at Moffitt supports this approach, with many patients going home on the first or second day after surgery with total resection of the tumor, minimal or no morbidity, reduction in corticosteroid dependence, and improvement in neurological function and quality of life.

Prakash Sampath, MD, and Henry Brem, MD, review the development, current usage, and future possibilities of slow-release polymer, chemotherapeutic implants for local control and treatment of malignant brain tumors. The BCNU-impregnated wafer (Gliadel) is the first new therapy approved by the Food and Drug Administration in 23 years for patients with gliomas. Prospective, randomized, multi-institutional, placebo-controlled studies have shown improved survival in patients with both newly diagnosed and recurrent glioblastomas. Studies currently underway are evaluating the use of the BCNU wafers in patients with cerebral metastases, pediatric brain tumors, and adult primary brain tumors using a high concentration (20%) of BCNU. The wafer is considered an exciting platform for local drug delivery of agents that are possibly more powerful than BCNU, including paclitaxel, cyclophosphamide derivatives, platinum-based drugs (carboplatin and cisplatin), and antiangiogenesis compounds.

Akio Morita, MD, Laligam Sekhar, MD, and Donald Wright, MD, review the current concepts in the management of tumors of the skull base. Recent advances in the surgical techniques involving cranial base approaches have made surgical intervention safer and curative resection more likely. In the management of benign tumors, surgical resection remains the gold standard for treatment. While immediate complications are still significant, long-term outcomes in most cases are excellent. Simply put, the tumor is better located in the hands of the pathologist than in the brain of the patient. Modern techniques, many of which were developed by Sekhar and colleagues, allow the surgeon to individually tailor therapy based on removal of the tumor using sophisticated technology, integrated when indicated, with radiosurgery, fractionated radiotherapy, and chemotherapy. The treatment plan takes into consideration the biological aggressiveness of the tumor, its location, and the patient’s symptoms.

Tom Mikkelsen, MD, provides an overview of a most promising area of cancer therapeutics, with tremendous importance for the future management of brain tumors. Classic cytotoxic therapy generally has been insufficient to control the growth and spread of malignant brain tumors. Local therapies such as surgery, polymers, and radiosurgery can control the focal lesion, but malignant gliomas inevitably recur due to the invasion and angiogenic response of isolated tumor cells beyond the reach of the surgeon. The explosion in our understanding of growth factors, proteolytic enzymes, and signal transduction mechanisms from basic research during the past 15 years has led to a variety of new compounds available to inhibit angiogenesis and invasiveness. Several protease inhibitors, angiostatic agents, and signal transduction inhibitors are currently in clinical trials. These agents by their nature are cytostatic rather than cytotoxic and may have less toxicity than classical chemotherapeutic agents. The results of clinical trials in the next decade will determine whether this new class of pharmacological treatments is as effective as monotherapy or whether cytostatic therapy will be synergistic with radiation and chemotherapy to achieve maximal efficacy.

Finally, Herbert Engelland, MD, provides a look into the future using antisense technology to block gene expression of key molecular components of the malignant phenotype to suppress the growth of malignant brain tumors. Antisense oligodeoxynucleotides are “smart bombs” that specifically block the expression of targeted
oncogenes (c-myc, c-myb, c-sis, c-erb), growth factors (bFGF, VEGF, PDGF, TGF-beta, TNF-alpha), signal transduction enzymes (PKC-alpha), or proteases (urokinase). Antisense oligodeoxynucleotides successfully prevent glioblastoma gene expression in vitro. While potential obstacles to their clinical use still exist, these do not seem insurmountable. Upcoming clinical trials are expected to provide information regarding the safety and efficacy of antisense oligodeoxynucleotides against malignant brain tumors.

Steven Brem, MD, FACS
Professor of Neurosurgery University of South Florida, Tampa, Fla
Program Leader, Neuro-oncology and Chief, Neurosurgery H. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla