Summary of the Juvenile Pilocytic Astrocytoma Workshop: "Towards Biologic Based Therapies"

Introduction:

written by Jeanne Young, President, The Childhood Brain Tumor Foundation, Workshop Administrator

On Monday, May 22, 2006 the Childhood Brain Tumor Foundation (CBTF), Germantown, MD, and the Children's National Medical Center's (CNMC) Department of Neurology, Washington, DC, Co-Sponsored the Juvenile Pilocytic Astrocytoma Workshop: "Towards Biologic Based Therapies". This full day, Professional Workshop was conducted at the North Bethesda Marriott Conference Center and included worldwide JPA experts, both researchers and clinicians, from varied disciplines including: oncology, neurosurgery, neuropathology, neuroscience, radiology, neuro-radiology and radiation oncology.

Workshop Agenda: To clearly identify AND accelerate the pace of the most promising research directions for finding kinder/gentler treatments and 100% cure for JPA.

Workshop Format: The workshop intended to bring together the world experts in the field of brain tumor research AND for the first time focusing their efforts as a group on identifying the most promising research directions to accelerate more effective treatments and a cure for this under researched disease. Participants delivered both speaker presentations and participated in round table discussions.

Juvenile Pilocytic Astrocytoma Defined: Juvenile Pilocytic Astrocytoma (JPA) is the most common childhood brain tumor, and it appears in both children and adults. These tumors can be life threatening depending on tumor location. JPA can be located near centers of the brain associated with vital functions, emotion, thought, movement, sensory development, etc. As with many tumors, children may also experience long-term, permanent neurological impairments and side effects both from the tumor and as a result of the treatments that are utilized in order to arrest/eradicate the tumor growth.

Workshop Participants: All physicians voluntarily donated their time to speak and participate at the workshop. We are very grateful for their valuable time and contributions.

--Roger J. Packer, MD, Children's National Medical Center (CNMC) - Workshop Director, Executive Director of Neuroscience and Behavioral Medicine
--David H. Gutmann, MD, Ph.D., Washington University - Workshop Co-Director; Director of Neuro-Oncology and the Neurofibromatosis Program
--Mark W. Kieran, MD, Ph.D., Dana-Farber Cancer Institute - Workshop Co-Director, Assistant Professor of Pediatrics, Harvard Medical School

--Eric Bouffett, MD, Hospital for Sick Children, (Toronto), Director of Pediatric Brain Tumor Program
--Derek Bruce, MD, CNMC (DC); Professor of Surgery, Division of Neurological Surgery
--Peter C. Burger, MD, Johns Hopkins Hospital (Baltimore); Professor of Neuro-Pathology and Oncology
--Vittorio Gallo, MD, Ph.D., CNMC; Professor, Dept. of Pediatrics and Pharmacology
--Jacques Grill, MD, Ph.D., Institut Gustave-Roussey, France; Pediatric Department
--Tobey J. MacDonald, MD, CNMC; Clinical Director of Pediatric Neuro-Oncology
--Robert McKinstry, III, MD, Ph.D., Washington University, (Washington); pediatric neuroradiologist and Associate Professor at Washington University School of Medicine
--Thomas E. Merchant, DO, Ph.D., St. Jude Medical Center, (Tennessee); Chief of Radiation Oncology

--Giorgio Perilongo, MD, University of Padua, (Italy); Director of Paediatric Haematology-Oncology
--Joshua Rubin, MD, Washington University; Professor of Pediatrics and Neurology

--Raymond Sze, MD, CNMC; Chief, Diagnostic Imaging & Radiology, Associate Professor of Radiology
--Uri Tabori, MD, Hospital for Sick Children, (Toronto); Clinical Research Fellow, Division of Hematology/Oncology
--L. Gilbert Vézina, MD, CNMC, Director of Neuro-Radiology, Professor of Radiology and Pediatrics
--Jeffrey Wisoff, MD, New York University (New York). Associate Professor of Neurosurgery and Pediatrics

Nancy Tarbel, MD, Massachusetts General Hospital, was unable to attend due to unforeseen circumstances, her speech presented by Dr. Thomas Merchant.

Executive Summary

written by Dr. Roger J. Packer, Workshop Director and Co-Directors, Drs. David H. Guttmann and Mark W. Kieran

Primary Avenues for Research and Progress:

1. Identification and validation of molecular therapeutic changes in juvenile pilocytic astrocytomas that might serve as targets for therapeutic drug design..

2. Development of biologically-based therapies based on the identified molecular targets and their translation expeditiously into clinical management by well-developed clinical studies

3. Further development and implementation of preclinical model systems that serve as initial "filters" for identified biologically-based therapies.

4. Development of more informative neuroimaging techniques, including molecular imaging, to determine the efficacy of biologically-based interventions, disease status of the child, and the need for continued therapy.

5. Development of a cross-disciplinary multi-institutional collaborative program involving basic scientists and clinicians to accelerate the pace of discovery and evaluation of new therapies to treat juvenile pilocytic astrocytomas.

Comments:

The Juvenile Pilocytic Astrocytoma Workshop on May 22, 2006 focused multiple investigators on the topic of juvenile pilocytic astrocytomas (JPAs). Although the workshop was divided into four sessions, it became clear by the end of the sessions that much of the work that investigators are already doing was complementary, and overall themes could be developed. A major gap in developing more effective therapies for JPAs is the lack of funds directed to this disease entity and a paucity of collaborative high-volume cross-disciplinary research studies. Importantly, there was a general consensus that the different research programs would welcome the opportunity to work together to develop a comprehensive approach to JPA.

Session One

Session One outlined what is currently known about the clinical characteristics, neuropathologic features, and outcome of children with juvenile pilocytic astrocytomas. After surgery, most children with tumors which are amenable to gross total resection fare well. There is a significant subset of patients whose lesions are not amenable to total resections, without placing the child at grave risk for long-term neurologic sequelae, especially deep-seated lesions. Surgery for those children does not result in long-term disease control. A subset of children with JPAs, probably 30 to 40%, will develop progressive disease after initial treatment, and treatment for those with progressive disease is less than optimal. Of those children with progressive disease after initial treatment, 25 to 50% will ultimately die of their disease.

The second major theme from the opening session was that neuroimaging investigations to assess the response to therapy are inadequate. Newer techniques, which are currently available, but which have not been uniformly applied, including diffusion-weighted imaging and dynamic contrast enhancement of tumor permeability, hold significant promise. Similar studies on other astrocytomas have shown that diffusion-weighted imaging may predict response to therapy, but research has not yet proven effective in gauging JPA tumor growth. In addition, some imaging modalities may also result in better pre-operative planning. An area which has not been explored in this patient population is the molecular imaging of JPAs and with the increasing identification of molecular targets and markers of disease progression and disease stabilization (including apoptosis); molecular imaging is an exciting future avenue of research, but has not yet been widely evaluated.

Session Two

The neurobiology of pilocytic astrocytomas is being actively explored in multiple centers. The major message from this session is that considerable progress has been made in defining key growth control pathways, genetic changes, and preclinical small animal models. The converging evidence from a number of laboratories suggests that a limited number of critical growth control pathways raises the possibility that therapeutic, biologically-based therapies could be highly effective in JPAs. In addition to an increased understanding of the molecular basis for juvenile pilocytic astrocytoma development and growth, the Workshop highlighted other ways to understand mechanisms controlling tumor growth such as maintenance of telomeres and the tumor microenvironment. In this regard, the study of JPA arising in neurofibromatosis type 1 may provide a portal for understanding the molecular pathogenesis of sporadic JPAs, and provide considerable insights into the therapies for sporadic, non-NF1-associated JPAs. There is exciting work in progress aimed at identifying factors which control tumor growth, and might result in tumor cessation or regression. Work on telomere maintenance, viral etiologies and the effects of the tumor microenvironment on tumor growth may unravel some of these issues. Lastly, the availability of small animal preclinical models of low-grade pediatric brain tumors will provide first line screens for biological agents with greatest promise prior to human clinical study.

Sessions Three and Four

The afternoon sessions outlined the progress that has been made in surgery, radiation therapy, and chemotherapy. Although surgery can be made safer or more exact, and radiation therapy has become increasingly sophisticated, it is unlikely that these techniques will cure many more children with juvenile pilocytic astrocytomas. The incorporation of state-of-the-art surgical and radiotherapy techniques will likely make treatment safer and incrementally improve outcome.

Similarly, significant work has been done with various chemotherapeutic agents. Carboplatin and vincristine remains the gold standard, however, a significant number of children who receive initial chemotherapy will progress. Although better chemotherapeutic approaches are needed, it seems unlikely that these agents will result in a quantum leap in disease control. In this regard, biologic agents that target specific molecular aberrations in juvenile pilocytic astrocytomas may prove to be more effective either alone or in combination with other agents or more standard forms of treatment, including radiotherapy and chemotherapy.

As noted in the initial objectives listed in the Executive Summary, it is believed that all of these themes can be merged into one major direction for the management of JPAs that take advantage of the cross-disciplinary expertise and collaborative spirit of this small community of researchers and clinicians.

Next Steps:

written by Jeanne Young, President of The Childhood Brain Tumor Foundation

This unprecedented gathering of worldwide experts in the area of JPA research was an unmitigated success according to all participants. Several scientists commented that they rarely have an opportunity to focus their attention on one disease and welcomed the collaborative nature of this initiative.

A copy of the Executive Summary will be provided to the National Institutes of Health to draw attention to the unique challenges of this most common childhood brain tumor and examine the possibilities for future research.

The Executive Summary of the JPA Workshop will also be posted on the www.Fightjpa.org and www.childhoodbraintumor.org Web sites. You may reprint and distribute this article, and include it in any non profit newsletters or on line sites, by notifying www.fightjpa.org and using the following acknowledgment:

This article was written for the Childhood Brain Tumor Foundation, Germantown,MD, www.childhoodbraintumor.org and the Fight JPA Initiative, founded at www.fightjpa.org.