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NEURO-ONCOLOGY ADVANCES

Abstracts

INVITED LECTURES

LS1

PRACTICAL APPLICATION AND UNDERLYING BIOLOGY OF TUMOR TREATING FIELDS

Daniela Bota; Department of Neurology, UC Irvine Medical Center

Glioblastoma (GBM) is the most common and most aggressive form of brain cancer in adults. For decades, the mainstay of therapeutic intervention was based on surgical resection (when safely feasible), followed by radiotherapy (RT). In 2005, data from the landmark EORTC-NCIC trial changed the standard of care treatment for GBM. This phase III trial demonstrated a survival advantage for concomitant and adjuvant temozolomide (TMZ) chemotherapy when added to the standard course of radiation. In the group of patients assigned to radiation plus TMZ, median survival improved from 12.1 months (radiotherapy alone) to 14.6 months, but all the patient finally relapsed on TMZ. In 2015, Tumor Treating Fields (TTF, Optune) became the first FDA-approved device for the treatment of for newly diagnosed GBM. This approval was based on the EF-14 clinical trial results, in which nearly half of the patients treated with Optune in combination with maintenance temozolomide (TMZ) were alive at 2 years compared with 31% of people on TMZ alone.

Optune utilize the natural electrical properties of dividing cancer cells to disrupt mitosis and provide continuous antimitotic action against progression of GBM. TTF-treated tumor cells can exit the process of mitosis aberrantly and release cellular stress signals, such as the endoplasmic reticulum chaperonin calreticulin (CRT) and high mobility group box 1 protein (HMGB1). CRT is important to induce antitumor immune responses because CRT inhibition decreases immunogenicity. HMGB1, an endogenous chromatin-associated protein released from dying tumor cells, also plays a critical role in the activation of HMGB1-mediated toll-like receptor 2 (TLR2) immune signaling. The presence of those signals may facilitate immune activation, and immunogenic induced cell death, and eventually result in tumor destruction.

In this presentation, Daniela Bota, MD, PhD, will review the clinical results of Optune in the treatment of GBM, and will discuss the novel biological mechanisms underlying the effects of Optune in controlling tumor growth and promoting the immune responses in GBM.

Key words: glioblastoma, tumor treating fields, novel mechanisms

SL1

GENETICS OF PEDIATRIC BRAIN TUMORS: RECENT ADVANCES AND FUTURE PERSPECTIVES

David T. W. Jones; German Cancer Research Center (DKFZ), Heidelberg, Germany

The last decade has seen a true revolution in our understanding of the oncogenic mechanisms underlying human tumors, brought about by transformative advances in the technologies available to interrogate the (epi) genetic composition of cancer cells. The dynamic pediatric neuro-oncology community has proven to be very agile in adapting to these changes, and has arguably been at the forefront of some of the most exciting new discoveries in tumor biology in recent years. For example, high-throughput genomic sequencing has revealed highly frequent mutations in histone genes in pediatric glioblastoma; highlighted an ever-expanding role for oncogenic gene fusions in multiple pediatric brain tumor types, and also shed light on novel phenotypic patterns such as chromothripsis (dramatic chromosomal shattering) and somatic hypermutation - the latter being a possible marker for response to novel immunotherapeutic approaches. Epigenetic profiling has also identified a role for 'enhancer hijacking' (whereby genomic rearrangement brings an active enhancer element in close proximity to a proto-oncogene) in multiple pediatric brain tumors, and is even pointing towards a fundamentally new way in which tumors may be molecularly classified.

In coming years, the major challenge will be to harness the power of these discoveries to more accurately diagnose patients and to identify potential therapeutic targets in a more personalized way, so that these major biological advances can also be translated into substantial clinical benefit. Examples such as the dramatic responses observed in childhood brain tumor sufferers to BRAF V600E and NTRK inhibitors demonstrate the promise that such an approach can hold, but it will require a fundamental shift in the way that clinical trials are planned and conducted in order to optimize patient care.

This talk will highlight some of the most striking developments in the field, and look at the challenges that remain before these can lead to improved patient outcomes.

Key words: Genomics, Pediatric, Epigenetics

AS1-KL-1

DEVELOPMENT OF HIGH-DOSE CHEMOTHERAPY INCLUDING THIOTEPA COMBINED WITH AUTOLOGOUS PERIPHERAL BLOOD STEM CELL RESCUE

Junichi Hara; Children's Medical Center, Osaka City General Hospital

Thiotepa is a classic alkylating agent that was launched in 1958 in Japan. We have consistently developed thiotepa-containing HDC since 1992, inspired by the fact that thiotepa was used as an alternative to melphalan as a high-dose chemotherapy (HDC) drug for neuroblastoma in the United States. Thiotepa is considered to be a drug suitable for brain tumor treatment because of its good BBB permeability, equal concentration in cerebrospinal fluid and blood, and the characteristics of alkylating agents that enhance the effect by log ratio of dose. Melphalan, which is also an alkylating agent as a central agent of HDC, has a strong antitumor effect, so we planned to use both at the maximum tolerated dose for each. Therefore, in order to reduce toxicity, it was decided to divide it into two doses at weekly intervals and to administer thiotepa for 24 hours in order to prevent hepatic sinus obstruction syndrome (SOS). Since 1993, a dose determination study was conducted, and the doses of thiotepa and melphalan were determined to be 800 mg/m2 and 280 mg/m2, respectively. Autologous peripheral blood stem cell transplantation using this regimen was performed as a consolidation therapy for metastatic pediatric medulloblastoma in 28 and 15 patients, respectively, in 2 series. Five-year progression-free survival rates of 82.1 ± 7.2% and 92.9 ± 6.9% were obtained. After that, the supply was stopped in 2009. This time, a domestic study was conducted with the dose of melphalan reduced to 210 mg/m2, and this year, a new indication (pretreatment for autologous hematopoietic stem cell transplantation in childhood malignant solid tumors) was acquired and launched. By this dose reduction, reduced gastrointestinal toxicity such as mucosal damage is expected. The JCCG clinical trials incorporating HDC will be conducted in medulloblastoma, ATRT, and refractory germ cell tumors.

Key words: thiotepa, melphalan, high-dose chemotherapy

AS2-1

TREATMENT OF BENIGN INTRA-AXIAL BRAIN TUMORS IN CHILDREN ASSOCIATED WITH EPILEPSY

Takeshi Matsuo; Department of Neurosurgery, Tokyo Metropolitan Neurological Hospital

Low grade neuro-epithelial tumors presenting early-onset epilepsy as the major neurological symptom have recently been categorized as low-grade epilepsy-associated neuro-epithelial tumors, LEAT. Ganglioglioma and dysembryoplastic neuroepithelial tumors consist up to 60% of LEAT. Common characteristics of LEAT being early onset seizure, younger than the age of 15, and temporal lobe localization, its criteria do not include histological or genetic features; LEAT is an independent classification, unrelated to WHO classification.

Treatment for epilepsy associated with LEAT includes medication and surgery. As for drug therapy, most tumor-related seizures are controlled well with anti-epileptic drugs for focal epilepsy such as sodium channel blocker. On the other hand, those who are drug-resistant are candidates for surgical therapy. Because epileptogenic zone mostly exists not in tumor itself but in the marginal brain tissue, pure tumor resection without resection of peripheral epileptogenic zone sometimes fails to achieve satisfactory seizure outcome. Concept of epilepsy surgery is indispensable in pre-operative evaluation and in planning surgical strategy. Related association fibers in addition to five zones, epileptogenic zone, seizure onset zone, irritative zone, symptomatogenic zone and functional deficit zone should be taken into consideration.

Long-term survival is expected in children who underwent total resection of benign tumors. Therefore, good seizure control is crucial in improving activities of daily lives.

Key words: LEAT, epilepsy surgery, focal resection

AS2-2

NEUROCOGNITIVE AND PSYCHOSOCIAL DISORDERS IN CHILDREN WITH BRAIN TUMORS

Manabu Yoshihashi; Department of pediatrics, Kanagawa rehabilitation hospital

The survival rate of children with brain tumors has been improving in the recent times. However, treatment outcomes should also include improved functional prognosis, considering motor dysfunction and sensory disorders, such as vision, and neurocognitive and psychosocial disorders, such as impaired intelligence, memory disorders, impaired attention, and impaired social behavior. In children with brain tumors, neurocognitive and psychosocial disorders easily occur due to various factors such as effect of the tumor, complications such as hydrocephalus, and impact of surgical treatment or radiotherapy. In addition, neurocognitive and psychosocial disorders are associated with decreasing quality of life (QoL) of pediatric patients with brain tumors.

When assessing neurocognitive and psychosocial disorders, objective assessments such as a neuropsychological assessment that includes an academic achievement test and an intelligence test, and subjective assessments such as observing behaviors need to be included. However, limited pediatric neuropsychological tests available in Japan.

Little evidence is available on the direct intervention methods that aim to improve neurocognitive and psychosocial disorders. Medical management for epilepsy, hydrocephalus, and endocrine disorders is performed while carefully considering cognitive function even in patients with neurocognitive and psychosocial disorders. Patients' symptoms and QoL can be improved through cognitive rehabilitation, environmental adjustments such as an intervention in their educational environment, and family support. To integrate these medical and social models, a multidisciplinary team approach is required.

There is limited data on the assessment and intervention methods available for neurocognitive and psychosocial disorders of children with brain tumors. Currently, only a few facilities are equipped to provide expert treatment. The Neuropsychological Assessment Subcommittee (Brain Tumor Committee, the Japanese Children's Cancer Group (JCCG)) aims to standardize the evaluation of neurocognitive and psychosocial disorders and intervention methods. These will be presented in line with the medical care provided at our hospital.

Key words: neurocognitive and psychosocial disorder, brain tumor, child

MS1

TOWARD ESTABLISHMENT OF ROUTINE MOLECULAR DIAGNOSTICS FOR ADULT GLIOMAS UNDER THE NATIONAL HEALTH INSURANCE

Koichi Ichimura; Division of Brain Tumor Translational Research, National Cancer Center Japan

Molecular diagnosis is now an official part of the diagnosis of brain tumors. Since WHO2016 incorporated the status of IDH mutation and 1p/19q codeletion as a part of the definition for oligodendrogliomas, astrocytomas and glioblastomas, molecular tests have become an essential part of the clinical management of adult gliomas. However, these tests are not covered by the National Health Insurance in Japan, and the cost and the limited availability of tests are prohibitive to perform molecular tests in most hospitals where brain tumor patients are treated. In 2015, the Committee for Molecular Diagnosis of Brain Tumor was established within the Japan Society for Neuro-Oncology in order to develop a standardized molecular tests for adult gliomas under the National Health Insurance. For the detection of 1p/19q codeletion, FISH is the most commonly used method. However, the widely available commercial FISH probe is located within 1p36, the regions where partial deletion often occurs in glioblastoma. This could lead to miss-judgement of 1p/19q codeletion which may result in miss-diagnosis. We have designed a novel FISH probes located in the region of 1p and 19q where partial deletions are rarely found, and are developing them as an in vitro diagnostic tests. Our ultimate aim is to establish a standardized molecular tests for adult gliomas under the National Health Insurance.

Key words: IDH mutation; 1p/19q codeletion; in vitro diagnostics

MS2

BRAIN TUMORS AND EPILEPSY

Toshihiko Iuchi; Division of Neurological Surgery, Chiba Cancer Center, Chiba, Japan

A brain tumor is one of the major causes of epilepsy, and glioma patients frequently exhibit seizures. Epileptic seizure, one of the features of glioma, is also known to be correlated with better outcome of patients. One of the reasons why patients with seizures have a good prognosis is that oligodendroglial tumors tends to cause epilepsy. However, even if limited to glioblastomas, the prognosis with epilepsy is still better than the others. Recently, the association between IDH mutations and epilepsy had been reported. IDH is an enzyme which converts isocitrate to alpha-ketoglutarate, but when this enzyme is mutated, 2-hydroxyglutarate (2HG) is produced instead of alpha-ketoglutarate. The molecular structure of 2HG is similar to glutamate, and it had been also reported that 2HG binds to the NMDA receptor. Indeed, in our cases, the IDH-mutation rate was higher in cases with epilepsy than the others. From our study of gene expression profiles, it was also clarified that the expressions of neuron-related genes were higher in cases with epileptic seizures, suggesting that many tumors classified as proneural type were included in this subset. As described, epilepsy phenotype is important, even in daily practice, because it predict the molecular status of gliomas and estimates the prognosis of the patients.

On the other hand, control of the seizures is important to keep patients' QoL and to provide effective treatment. In this seminar, the control of epilepsy during and early after surgery, and how to manage status epilepticus will be reviewed.

SS1-KL-1

APPLICATION OF AI TECHNOLOGIES FOR MEDICAL CARE

Ryuji Hamamoto; Division of Molecular Modification and Cancer Biology, National Cancer Center Research Institute, Japan

On the basis of progress of the Machine Learning algorithm mainly on the Deep Learning, improvement of the GPU performance, the large-scale public database such as TCGA is available, big attention recently gathers in the AI technology. While large countries such as the United States or China vigorously promote AI research and development by a national policy, Cabinet Office, Government of Japan, also emphasized the importance of AI technologies in the 5th Science and Technology Basic Plan in 2016. As for the AI development, it is wrestled relatively for a long time; the word "Artificial Intelligence" was firstly used in the Dartmouth workshop in 1956. However, the AI development has not been promoted smoothly until now and repeats the active state period and the period of depression. As the current active state period of AI is called as the third AI boom, the most different point of this boom and the other booms is that AI technologies have already been involved in our social life such as the AI-based face authentication device in this period. Indeed, The US Food and Drug Administration (FDA) has already authorized around 30 AI-based medical instruments, and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan also authorized the first AI-based medical instrument last year. Therefore, now is the important time that we need to consider deeply for the creation of an affluent society, which enables coexistence of human being and AI. In this lecture, I particularly focus on medical imaging analysis using AI technologies and, would like to lecture on an action to the medical care application of the AI technology based on the experience that promoted medical AI research as the leader of two national projects relevant to medical AI called CREST and PRISM, and RIKEN AIP center.

Key words: AI, deep learning, medical image analysis

SL2

ADVANCES IN MOLECULAR BIOLOGY AND GENETICS IN GLIOMA RESEARCH AND THERAPY

Webster K. Cavenee; Ludwig Institute for Cancer Research, University of California San Diego

The most recent version of the *WHO Classification of Tumours of the Central Nervous System* includes, for the first time, the joint consideration of tumor pathology with tumor genetics as measured in various ways. This has come decades after the first recognition of genetic lesions in tumor genomes as discerned by cytogenetics and more than 30 years after the first reports of specific and recurrent genetic abnormalities in human tumors, particularly gliomas. This information is vitally important because it is now being used not just for tumor diagnosis but also to indicate specific therapies. In this lecture, I will review the increasingly precise methodologies being employed, the resultant genetic lesions being uncovered and the increasing import of such information for therapeutic selection.

Key words: Glioblastoma Genetics Characterization

LS2

METASTATIC BRAIN TUMORS / MENINGIOMAS: CURRENT CONCEPTS AND THERAPEUTIC PERSPECTIVES

Matthias Preusser; Department of Medicine I, Medical University of Vienna

Non-glial brain tumors are the most common neoplasms affecting the central nervous system. Brain metastases are a heterogenous complication of