

antimitotic effects of TTFIELDS discerned the positive combinatorial potential of TTFIELDS with other agents targeting the division process. Subsequent to elucidation of anti-mitotic effects, other downstream effects of TTFIELDS include induction of endoplasmic reticulum stress, up-regulation of autophagy and cell death, thus driving immunogenic cell death. Indeed, in several preclinical models, combining TTFIELDS with immunotherapeutics demonstrated enhanced efficacy. Recently, additional novel effects of TTFIELDS were characterized, including inhibition of DNA damage repair responses and induction of transient and reversible permeabilization of the blood brain barrier (BBB). These new findings offer potentially innovative means to optimize treatment outcomes by combining TTFIELDS with radiation therapy and DNA damaging agents, as well as improved delivery of impermeant agents across the BBB. These scientific findings were instrumental in advancing the clinical pipeline of TTFIELDS, which includes conduct of ongoing trials combining TTFIELDS with a variety of modalities, in approved indications and in other solid malignant tumor types. The aim of this talk is to describe TTFIELDS' preclinical research activities and tools, and to specify how these study outcomes have defined and advanced the clinical pipeline.

SS-4

#### HIGH DOSE CHEMOTHERAPY WITH AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR CNS LYMPHOMA

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High-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HDT-ASCT) is listed as a consolidation therapy option for primary central nervous system (CNS) lymphoma in the guidelines of western countries. The advantages of HDT-ASCT for primary CNS lymphoma as consolidation are believed to be high rates of long-term remission and lower neurotoxicity, even though its eligibility is limited to younger fit patients. In the Japanese guideline, HDT-ASCT for primary CNS lymphoma is however not recommended in daily practice, mainly because thiotepa was unavailable since 2011. The Japanese registry data for hematopoietic transplantation have shown that primary CNS lymphoma patients were treated with various HDT regimens and thiotepa-containing HDT was associated with better progression free survival (P=.019), lower relapse (P=.042) and a trend toward a survival benefit (Kondo E et al, Biol Blood Marrow Transplant 2019). A pharmacokinetic study of thiotepa (DSP-1958) in HDT-ASCT for lymphoma was conducted in 2017, and thiotepa was approved for HDT-ASCT in lymphoma this March, meaning that optimal HDT regimen for CNS lymphoma is now available in Japan. The treatment strategy of CNS lymphoma needs further development to improve survival and reduce toxicity.

SS-5

#### CURRENT MANAGEMENT OF PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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Primary CNS Lymphomas (PCNSLs) is a highly aggressive malignant tumor with poor prognosis and increasing incidence in elderly patients. High-dose methotrexate (HD-MTX) followed by whole-brain radiation therapy (WBRT) improves survival in PCNSLs. Several HD-MTX-based regimens, in combination with alkylating agents and rituximab, have been developed that can achieve high and durable complete response rates in patients with newly diagnosed PCNSL. In Japan, the R-MPV regimen using rituximab, HD-MTX, procarbazine, and vincristine has been recognized as the standard treatment for initial induction for newly diagnosed PCNSL. The optimal consolidative therapy for patients with disease responsive to induction chemotherapy is not yet defined. WBRT at standard dose (30–45 Gy) has a risk of neurotoxicity. To minimize the effects of delayed neurotoxicity, high-dose chemotherapy supported by autologous stem cell transplantation, reduced dose WBRT (23.4Gy), non-myeloablative chemotherapy, and maintenance chemotherapy have been addressed in large randomized trials. Gene expression profiling has provided insights into the pathogenesis of PCNSL. Recent insight into the pathophysiology of PCNSL has led to the investigation of targeted agents in the treatment of recurrent disease. In March 2020, Tirabrutinib (TIR), a second-generation oral Bruton's tyrosine kinase inhibitor, was approved for relapsed or refractory PCNSL based on the results of the phase I/II study in Japan. Seventeen of 44 patients treated with TIR at 480 mg fasted QD, an approved dose, had overall response rate of 52.9%, median progression-free survival of 5.8 months, and time to response as short as 0.92 months. The most common adverse event at any grade was rash (32%). The skin-related disorders were manageable with

appropriate skin treatments. However, greater attention and management is needed the case of more rare adverse events such as severe skin-related disorders and pneumocystis pneumonia. This lecture aims to present the recent development in treatment for PCNSL.

KNL-1

#### PATHOLOGIC DIAGNOSIS OF BRAIN TUMORS IN THE MOLECULAR ERA

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The WHO Classification of CNS Tumors, first published in 1979, was revised four times during the recent four decades. The revision was based on the refinement of tumor entities and introduction of new entities, which were facilitated by the development of new investigative techniques, such as immunohistochemistry and molecular cytogenetics. More sophisticated approaches including NGS and methylation analysis will introduce more molecularly defined entities in the next WHO Classification. The molecular analyses are a very powerful tool for brain tumor research. They have disclosed molecular mechanisms of several tumors and discovered unrecognized tumor entities till then. More precise biologic behavior could be estimated by molecular profiles. Furthermore, the development of novel molecular-targeted therapies will be expected. In the clinical practice, brain tumors should be diagnosed stepwise. First, clinical and image information is mandatory. Histopathologic and immunohistochemical findings should be evaluated within the clinical context. For molecularly defined tumors, genetic analyses are necessary. Following the stepwise procedures, the risk of falling in pit-falls may be decreased. In the molecular era, the integrated diagnosis, combined histopathologic and molecular information, of brain tumors is necessary. Recently, the Japanese Society of Pathology (JSP) has started the project which foster next-generation pathologists interested in rare cancers including brain tumors. In addition, some molecular information could be gained through the consultation system run by JSP and the National Cancer Center Japan. To adapt the next, more detailed molecular classification, it may be necessary that the cancer genome panel test become available within the national health insurance system.

MS-1

#### SURGICAL STRATEGY FOR BRAIN TUMOR BASED ON MOLECULAR AND FUNCTIONAL CONNECTOMICS PROFILES

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It is reported that the development of new perioperative motor deficits was associated with decreased overall survival despite similar extent of resection and adjuvant therapy. The maximum safe resection without any neurological deficits is required to improve overall survival in patients with brain tumor. Surgery is performed with various modalities, such as neuro-monitoring, photodynamic diagnosis, neuro-navigation, awake craniotomy, intraoperative MRI, and so on. Above all, awake craniotomy technique is now the standard procedure to achieve the maximum safe resection in patients with brain tumor. It is well known that before any treatment, gliomas generate globally (and not only focally) altered functional connectomics profiles, with various patterns of neural reorganization allowing different levels of cognitive compensation. Therefore, perioperative cortical mapping and elucidation of functional network, neuroplasticity and reorganization are important for brain tumor surgery. On the other hand, recent studies have proposed several gene signatures as biomarkers for different grades of gliomas from various perspectives. Then, we aimed to identify these biomarkers in pre-operative and/or intra-operative periods, using liquid biopsy, immunostaining and various PCR methods including rapid genotyping assay. In this presentation, we would like to demonstrate our surgical strategy based on molecular and functional connectomics profiles.

MS-2

#### MINIMALLY INVASIVE GLIOMA SURGERY WITH NAVIGATION SYSTEM AND TUBULAR RETRACTOR

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Navigation systems are reliable and safe for neurological surgery. Navigation is an attractive and innovative therapeutic option. Recently, endo and exoscopic surgeries have been gradually increasing in neurosurgery. We are currently trialing to use 4K and 8K systems to improve the accuracy and safety of our surgical procedures. Surgeries for deep-seated tumors are challenging because of the difficulty in creating a corridor and observing the interface between lesions and the normal area. In total, 315 patients underwent surgery at Okayama University between 2017 and 2019. Among them, we experienced 92 glioma surgeries using navigation systems. Preopera-