might stratify the risk better than the current criteria have also been evaluated. Despite the discordance among the results of previous studies, CDKN2A/2B homozygous deletions have been shown prognostic significance in high-grade IDH-mutant astrocytomas and microvascular proliferation stratifies IDH-mutant gliomas lacking a CDKN2A homozygous deletion, suggesting that the integration of molecular information and traditional histological findings is still essential for achieving maximum risk stratification of adult cases of IDH-mutant diffuse gliomas. The grading scheme for adult IDH-mutant as well as wild-type gliomas should therefore be revised in the next WHO update.

SL3

PRIMARY CNS LYMPHOMA: CURRENT CONCEPTS AND THERAPEUTIC PERSPECTIVES

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The lecture will summaries current standards of disease staging and treatment of Primary Central Nervous System Lymphoma (PCNSL). Concepts underlying the current first-line treatment regimen will be presented and current controversies in the treatment of PCNSL, including choice of induction regimen, choice of consolidation, and the roles of surgery/radiation/intrathecal therapy, will be discussed. In additional, the presentation will summarize novel insights into the pathophysiology of PCNSL, particularly the B-cell receptor signaling pathway (BCR). Results of completed and ongoing clinical trials targeting the BCR will be presented. The treatment standards in the recurrent setting will be summarized and additional novel therapeutic avenues, eg. immune checkpoint inhibition will be discussed. Furthermore, novel combinational clinical trials in recurrent/refractory setting will be discussed. Moreover, the diagnostic and prognostic value of novel, genomic testing and their integration into clinical trial development and clinical decision making will be discussed.

Key words: -Primary Central Nervous System Lymphoma, chemotherapy regimen, salvage therapy, B-cell receptor signaling pathway

S5-KL-1

CURRENT TREATMENT FOR DLBCL AND PROPHYLAXIS AND TREATMENT FOR SECONDARY CNS LYMPHOMA.

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Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of lymphoma, comprising 30% of all lymphoma cases. More than 60% of patients can be cured with current standard treatment, R-CHOP. On the other hand, prognosis of patients with relapsed or refractory DLBCL is disappointing with less than 10% being cured with salvage chemotherapy followed by high-dose chemotherapy with autologous stem cell transplantation. Prognosis of patients with central nervous system (CNS) relapse is especially poor because of a limited treatment option. Thus, evaluating risks of CNS relapse at diagnosis and administering prophylaxis including intrathecal methotrexate (MTX) or systemic high-dose MTX concurrently with R-CHOP or as consolidation therapy in high-risk patients are often-used approach. Clinically, higher risk according to the International Prognostic Index and extranodal involvement in organs such as kidney, adrenal gland, breast, testis, or bone marrow are considered to be high-risk for CNS relapse. Recently, CNS-International Prognostic Index has been proposed to integrate aforementioned risk factors. Moreover, patients with intravascular large B-cell lymphoma, CD5+ DLBCL, double hit lymphoma are reported as high-risk for CNS relapse. Further, the MYD88 L265P mutation, a common mutation in primary CNS DLBCL (PCNSL) is also common in DLBCL of testis or breast, which are the sites associated with CNS relapse.

Strategies for CNS prophylaxis have not established yet, and it is still unclear whether intrathecal MTX or high-dose MTX can prevent CNS relapse. Moreover, treatment for secondary CNS relapse have not been established. In particular, for those with both CNS and extra-CNS lesions, effective treatment options are very limited. The role of novel agents such as BTK inhibitors, lenalidomide, and immune check point inhibitors, whose efficacy have been shown for PCNSL, should be investigated further in the management of secondary CNS lymphoma.

Key words: Secondary CNS lymphoma, prophylaxis

S5-KL-1

CANCER GENOMIC MEDICINE: FROM BENCH TO CLINIC

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Over the last two decades, genomic technology such as microarray and next generation sequencing (NGS) enabled comprehensive analysis of cancer genome. International cancer genome consortium, established in 2007, completed the analysis of 25,000 cases and has brought discovery of novel cancer driver genes and improved our understanding cancer biology. For example, discovery of IDH1/2 mutation in various cancers created a new concept, 2-hydroxyglutarate as Oncometabolite. The mutational signature patterns allow us to predict how the individual cancer was developed. Anti-cancer drugs, such as alkylating agents, occasionally modify the bases and introduce mutations through mispairing in replication.

Currently we are aware that cancer is a genetic disease, where accumulation of genetic and epigenetic alterations in the genome leads to cellular transformation, and that mutation in each patient is unique. To realize the personalized oncology, clinical sequencing test was developed. This year a couple of NGS-based cancer panel tests have been approved for reimbursement by nation-wide healthcare system in Japan.

In this seminar I will discuss the future improvement in genomic oncology.

Key words: cancer genome, genomic oncology, mutation signature

EL2

CHANGES IN JAPANESE ACADEMIC CLINICAL TRIALS AND FRAMEWORKS FOR PLANNING CLINICAL TRIALS

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After the enforcement of the Japanese Clinical Trials Act, the number of investigator-initiated registration-directed trials (IIRDT, Chiken) is increasing while the number of non-registration academic trials is decreasing. Pharmaceutical companies tend to make an investment in IIRDT because the data derived from IIRDT can be utilized for new drug application for PMDA, which means the goals and return are clear for industries. On the other hand, the reason of the decrease of non-registration academic trials is the burden of cost and procedures specified in the Clinical Trials Act. In order to start academic trials, certain amount of research budget is indispensable due to the cost for certified review board and clinical trial insurance. Also, even minor changes of site information in jRCT should be submitted to certified review board and the hospital directors of all participating sites, which is one of the most serious burden for investigators. Confirmation of COI declaration in participating sites is another burden for investigators/sites. Under these circumstances, the number of non-registration academic trials will be decreasing for the time being.

In the Clinical Trials Act era, investigators must prepare some budget to start clinical trials. In order to obtain public funding, social/scientific value and scientific validity are substantially important. To express the social value sufficiently, the purpose of the trial should focus not on the researcher's interest but on the contribution for patients. In terms of scientific validity, the framework of PICO is useful; PICO means Patient, Intervention, Control and Outcome. Utilization of this framework and the consistency of these four factors are essential to make the trial design sound.

Key words; Clinical Trials Act, Chiken, Clinical Trial Design

ANGIOGENESIS/INVASION (ANGI)

ANGI-01

ALTERATION IN IMMUNE REGULATORY CELLS BEFORE AND AFTER TREATMENT BY STUPP REGIMEN WITH OR WITHOUT BEVACIZUMAB FOR GLIOBLASTOMA

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BACKGROUND: In our previous study, bevacizumab (Bev), a humanized anti- vascular endothelial growth factor monoclonal antibody, downregulated the expression of programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) immune checkpoint molecules, suppressed the infiltration of immunosuppressing cells such as regulatory T cells (Tregs) and tumor-associated macrophages (TAMs), and induces cytotoxic T lymphocytes (CTL) infiltration. To explore the possibility that inhibition of immunosuppressive cell infiltration and induction of CTL were attributed to not only Bev alone but also radiation (RT) or temozolomide (TMZ), we re-evaluated those alterations in the tumor tissue obtained from patients before and after the treatment using Stupp regimen (RT concomitant with TMZ) without Bev therapy. MATERIALS & METHODS: We analyzed 10 tumor tissues from 5 patients with GBMs, which were paired samples of pre- and post- standard chemoradiotherapy (Stupp regimen: RT plus concomitant and adjuvant TMZ). Immunohistochemical analyses were performed on formalin-fixed, paraffin-embedded tissue of 10 tumors. The sections were stained with anti-Ki-67, anti-VEGF-A, anti-VEGFR1, anti-VEGFR2, anti-CD34, anti-HIF1 alpha, anti-CA9, anti-nestin, anti-PD-1, anti-PD-L1, anti-CD4, anti-CD8, anti-Foxp3, and anti-CD163 antibodies. All expressions were assessed by authors with blinded clinical information. RESULTS: Immunohistochemical analyses demonstrated that the expres-

sion levels of immune regulatory molecules such as Foxp3, CD163, PD-1, PD-L1, CD4, and CD8 were not significantly changed after the treatment using the Stupp regimen, compared with combinational usage of Bev. In addition, expressions of VEGF/VEGFR, hypoxic markers, and stem cell marker were not altered before and after Stupp regimen, either. Bev persistently inhibited immune suppressive cells and immune checkpoint molecules via down-regulation of VEGF pathway. In contrast, Stupp regimen did not affect immune regulations and tumor microenvironment. CONCLUSION: These results suggested that immunosupportive effect was caused by Bev administration, leading to the novel combinational treatment strategies, in addition to Stupp regimen.

ANGI-05

PATHOGENESIS OF RESISTANCE (MIMICRY AND CO-OPTION) TO ANTI-ANGIOGENIC TREATMENT FOR GLIOBLASTOMA

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PURPOSE: Vessel co-option and vascular mimicry are important resistant factors with ant-angiogenic treatment for glioblastoma, but those precise evaluation is not clear. We had three types of glioblastoma surgically removed specimens treated with / without bevacizumab (Bev). Using these samples, pathogenesis of co-option and mimicry was morphometrically clarified. MATERIALS / METHODS: Three types of glioblastoma specimens were analyzed; 1) Bev naive (N group, n 14), 2) Bev effective that was treated preoperative neoadjuvant Bev (E group, n 5), 3) Bev refractory that recurred with continuous Bev treatment for paired E group (R group, n 5). Vascular density was defined as a number of type IV collagen covered lumen. Vascular mimicry was measured as a ratio of CD34 negative / type IV collagen positive lumen. Vessel co-option was graded to 3 degrees (-), (+), (++) at tumor margin. RESULTS: (1)Vascular density was significantly lower with E group ($p<0.01$) and R gr up ($p<0.02$) compared to N group. (2)Mimicry was significantly higher with R group compared to N and E group ($p<0.01$). Between paired samples, refractory case was constantly higher than effective sample. (3) Co-option was increases with R group compared to N group. DISCUSSION/CONCLUSION: The effect of Bev for glioblastoma was investigated on three points (vascular density, vascular mimicry and vessel co-option) and two pathogeneses were clarified. In Bev refractory case, density was decreased, but mimicry and co-option were increased compared to Bev naive case. In Bev effective case, density was decreased, but mimicry and co-option were unchanged. Anti-angiogenic treatment for initial and Bev refractory glioblastoma should consider targeting co-option and mimicry in addition to Bev.

CELL BIOLOGY/METABOLISM/STEM CELLS (CBMS)

CBMS-01

AGE-DEPENDENT GLIOBLASTOMA PROGRESSION SUPPRESSED BY NAD+

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The rise in population aging worldwide is causing an unparalleled increase in death from many cancers, including glioblastoma (GBM). Here, we have explored the impact of aging and rejuvenation on GBM tumorigenesis. Compared with old GBM, young GBM displayed elevated neuronal/synaptic signaling via brain-derived neurotrophic factor (BDNF) and SLIT and NTRK like-family member 6 (SLITRK6), promoting favorable survival rates. These effects were attributed to the rise in nicotinamide adenine dinucleotide (NAD+) levels, as brain rejuvenation by parabiosis or administration of nicotinamide mononucleotide (NMN) in mice elicited a younger phenotype with activated neuronal/synaptic signaling and improved outcomes. Our data indicate that age-associated NAD+ loss contributes to the highly aggressive GBM in the elderly. These findings have therapeutic implications in GBM and provide mechanistic insights into the exacerbation of GBM tumorigenesis with age.

CBMS-02

CROSSTALK WITH ASTROCYTES ESTABLISHES TUMOR EDGE IN GLIOBLASTOMA

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Clinical outcomes for patients with glioblastoma (GBM) are extremely poor due to inevitable tumor recurrence even after extensive treatments. These recurrences are thought to manifest from cells located within the tumor edge. Despite this, the precise molecular mechanism governing GBM spatial phenotypic heterogeneity (e.g. edge vs. core) and subsequent tumor recurrence remains poorly elucidated. Here, using patient-derived GBM core and edge tissues, we analyzed transcriptional and metabolic signatures in an effort to determine how GBM facilitates the edge phenotype and its associated recurrence-initiating cells (RICs). In so doing, we unexpectedly identified CD38 as an essential protein in the formation of the edge phenotype and found a CD38-driven interaction between edge GBM cells and neighboring astrocytes that communally develops a GBM edge that is unresectable by surgery and retains RICs. These findings have profound implications for future clinical therapies and provide new mechanistic insights into both tumor progression and recurrence.

CBMS-03

PHOSPHORYLATION STATE OF OLIG2 REGULATES PROLIFERATION OF GLIOMA STEM CELLS.

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The Cancer Genome Atlas project described a robust gene expression-based molecular classification of glioblastoma with the functional and biological significance of the subclasses yet to be determined. Here, we show that a comprehensive analysis of a panel of glioma initiating cell (GIC) lines can identify a group of stem cells with high OLIGg2 expression as in Proneural-like GBM subtype. In vitro differentiation studies showed that proneural GIC lines possess the potential to differentiate into astrocytic, neuronal, and oligodendrocytic lineages, whereas mesenchymal GICs exhibited limited potential for neural lineage differentiation following retinoic acid induction. A considerable decline of OLIG2 in proneural GIC lines was observed following retinoic acid treatment. We also showed that OLIG2 is a functional marker associated with cell proliferation in Olig2-high GIC lines. In addition, OLIG2 inhibition disrupted cell-cycle control mechanism by decreasing CDK2 and CDK4 and elevating apoptosis-related molecules. Mechanistic investigations revealed molecular interactions between CDK2/CDK4 and OLIG2. Inhibition of CDK2/CDK4 activity disrupted OLIG2-CDK2/CDK4 interactions and attenuated OLIG2 protein stability. Further investigation on these mechanisms may lead to novel targeted therapy on GBMs with high OLIG2 expression.

CBMS-04

SIGNIFICANT ROLE OF HYPOXIA IN THE EXPRESSION AND FUNCTION OF OSTEOPONTIN IN CD44-HIGHLY EXPRESSED GLIOMA STEM-LIKE CELLS IN TUMOR PROGRESSION OF GLIOBLASTOMA

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The poor prognosis of glioblastoma multiforme (GBM) may be due to the surviving glioma stem-like cells (GSCs) in the tumor periphery after tumor resection. We demonstrated that CD44-expressed GSCs existed much more in the tumor periphery of high invasive (HI) type GBM than low invasive (LI) type GBM. The HI type was significantly associated with worse outcome, but how GSCs with high CD44 expression relate to tumor progression remains unknown. In this study, we investigated effects of hypoxia on CD44-directed signal pathways, leading to tumor invasion and proliferation in GBM. We focused on the CD44 ligand osteopontin (OPN) because it is known hypoxia affects the interaction of CD44 and OPN which promotes stemness and proliferation of cancer stem cells. We examined mRNA expressions of hypoxia inducible factor (HIF)-1a, HIF-2a, CD44 and OPN in tumor tissues of GBM and investigated effects of hypoxia (1%O2:severe or 5%O2:moderate) on the expression of these molecules using cultured GSCs that were established from tumor tissues showing high CD44 expression in the periphery of GBMs. In addition, we analyzed the effects of OPN on invasive, migratory and proliferative activities of GSCs under the hypoxic conditions. OPN was much higher expressed in the tumor periphery of LI type GBM than HI type GBM. Severe hypoxia significantly increased the expressions of HIF-1a and CD44 but did not OPN. On the other hands, moderate hypoxia promoted the expressions of HIF-2a and OPN. Knockdown of HIF-2a significantly inhibited OPN expression. In addition, the more OPN was expressed in the cultured GSCs under moderate hypoxia, the more the GSCs proliferated and decreased their invasive and migratory activities. In conclusion, GSCs existing in the tumor periphery of GBM can migrate or proliferate by changing CD44-directed signal pathways. Moderate hypoxia promoted HIF-2a/OPN/CD44 pathway, resulting in phenotypic transition to high proliferative tumors.