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PURPOSE: In the present study, we performed a retrospective review of patients receiving carboplatin based chemotherapy followed by radiotherapy for newly diagnosed primary intracranial germ cell tumors. In order to identify an optimal germ cell tumor treatment strategy, we evaluated treatment outcomes and toxicity and compliance.

METHODOLOGY: This study included 110 consecutive patients with newly diagnosed primary intracranial germ cell tumors. The drug doses and administration schedule of carboplatin-etoposide (CARB-VP) were as follows: carboplatin (300 mg/m2 daily for 1 days), and etoposide (100 mg/m2 on days 1 to 3). Ifosfamide-carboplatin-etoposide (ICE) treatment comprised ifosfamide (1500 mg/m2 daily for 3 days), carboplatin (300 mg/m2 daily for 1 days), and etoposide (100 mg/m2 daily for 3 days). Patients with germinomatous germ cell tumors (pure germinoma or germinoma with STGC) basically receive three cycles of CARB-VP and a total dose of 30Gy whole ventricular radiotherapy. We delivered combination therapy consisting of combined ICE chemotherapy and craniospinal irradiation followed by the complete resection of the residual tumor for nongerminomatous malignant germ cell tumors.

RESULTS: The median follow-up time was 11.0 years (range, 0.5–37.8 years). The 5-year total survival rates of germinomatous and nongerminomatous germ cell tumors were 97.2% and 66.7%, respectively. The 10-year and 20-year total survival rates of germinomatous germ cell tumors were 95.7% and 90.0%, respectively. Adverse events related to carboplatin based chemotherapy are not detected. Furthermore, no treatment-related deaths were observed.

CONCLUSIONS: Our treatment with surgery, carboplatin based chemotherapy followed by radiotherapy is effective in treating primary intracranial germ cell tumors, especially in germinomatous group.

NQPC-08

SHORT-TIME INTENSIVE REHABILITATION FOR PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA

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PURPOSE: Many reports presented that patients with GBM had stable HRQoL during their remission time. However, there are few reports on the situation of ADL that is the basis of QOL. This prospective study was designed to evaluate the effectiveness of intensive rehabilitation for physically disabled patients with GBM after the initial treatment. PATIENTS and METHOD: Sixteen patients with newly-diagnosed glioblastoma presenting with severe physical disabilities were registered after the completion of postsurgical radiation therapy combined with TMZ. All patients were evaluated by means of a core set of clinical scales of Functional Independence Measure (FIM), Sitting Balance score, Standing Balance score, and Minimental State Examination (MMSE). Patients were evaluated before the beginning and at the end of rehabilitation treatment. The daily rehabilitation program consisted of individual 180-min. sessions of treatment, seven days a week, for four to six consecutive weeks. Speech therapy was included when aphasia was diagnosed. RESULTS: Fifteen of 16 patients presented with improved physical functioning score, and seven of 16 patients returned to their independent life at home, CONCLUSION: A short-time intensive rehabilitation (4 to 6seeks) is effective for GBM patients during TMZ withdrawal period after the postoperative radiation therapy. This effective program requires close teamwork with the medical cooperation teams in the medical and rehabilitation hospitals: explanation to patients of the significance of the short-term rehabilitation, which is different from stroke rehabilitation, adjustment of hospitalization date considering radiotherapy and chemotherapy schedule, and adjustment of MRI imaging or bevacizumab administration schedule during rehabilitation.

PCNSL (ML)

ML-01

PATHOLOGICAL CHARACTERISTICS OF PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA WITH ATYPICAL RADIOLOGICAL FINDING

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BACKGROUND: If the brain tumor is suspected to be a primary central nervous system lymphoma (PCNSL) on radiological findings, it is general to perform biopsy to obtain the pathological diagnosis. Glioblastomas (GBs) must be distinguished from PCNSLs. In addition to commonly used contrast-enhanced T1-weighted imaging, diffusion-weighted image (DWI), and apparent diffusion coefficient (ADC) value, the following characteristics of PCNSLs were reported to be essential for this purpose: 1) no increase in blood flow on perfusion images obtained by the arterial spin labeling (ASL) method; 2) less microbleeding on T2*-weighted images (T2*). However, we experienced some exceptional cases. PURPOSE: To clarify the histopathological features of PCNSLs those had atypical radiological findings. METHOD: 62 consecutive PCNSL cases (40 males, 22 females, mean age 65.4 years, range 35–84) treated in our department from April 2013 to March 2020 were retrospectively analyzed. We compared the following features between 47 biopsy cases showing typical image findings as PCNSLs (Group A) and 15 surgically resected cases with atypical findings (Group B), 1) number of blood vessels per hyper 10 fields, 2) occupying area of blood vessels per unit area, 3) immunoreactivity of vascular endothelial growth factor (VEGF), and 4) germinal center B-cell (GCB) subtype. RESULTS: In Group A, the number of blood vessels in the tumor was 39.3 on average, and the area occupied by blood vessels was 3.8%. In Group B, the former was 133.2, and the latter was 9.9%. There was no significant difference in VEGF expression and GCB subtype. CONCLUSION: In PCNSLs showing with high blood flow and microbleeds, the blood vessels were rich and partial bleeding was confirmed histologically. We should analyze much more cases to set the threshold both of the ADC value and the absolute value of blood flow calculated by the ASL method to distinguish between PCNSLs and GBs.

ML-02

CHEMOTHERAPY FOR PATIENTS WITH RELAPSED OR REFRACTORY PRIMARY CNS LYMPHOMA

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BACKGROUNDS: Standard of care for patients with primary CNS lymphoma (PCNSL) has been high-dose methotrexate (HD-MTX)-based multiagent immunochemotherapy, particularly with R-MPV-A with or without whole-brain radiotherapy (WBRT), however, the optimal treatment for relapsed/refractory (r/r)PCNSL has not been established yet. Approval of a second-generation BTK inhibitor, tirabrutinib, for r/rPCNSL in Japan in March 2020, prompted us to evaluate retrospectively efficacy of R-MPV-A for r/rPCNSL to compare their activities. PATIENTS: Histologically proven PCNSL patients treated at relapse in our institution from April 2000 to November 2019 were analyzed. Outcomes were compared between those treated with RMPVA or other regimens. RESULTS: Among 148 PCNSL patients identified, 73 had at least one relapse, of whom 47 received salvage chemotherapy including 23 treated with RMPVA, 14 with HD-MTX monotherapy, and 11 with DeVIC (DEX, etoposide, ifosfamide, CDBCA). Median age/KPS were 69 yo (20–87)/ 80 (40–100), 27 patients had received prior WBRT. RMPVA was given at the first relapse in 11 patients, median number of RMPV cycles was 8 (1–4 cycles: 10; 8 cycles 13). CR/CRu were achieved in 19 (83%), response rate was 87%, while there were two PDs (9%). After median follow-up of 21.9 months, the median PFS after salvage RMPVA was 13.0 m (95%CI: 9.1–16.9), 1-year overall survival (OS) was 82%, median OS was 70.0 m (95%CI: 12.9–127.1), which were longer than those in 24 patients with salvage treatment other than RMPVA (mPFS 4.4 m, P=0.054; mOS 13.6 m, P=0.009). Median PFS and OS for HD-MTX monotherapy were 5.1m and 36.6 m, while those for DeVIC were 4.4 m and 9.1 m, respectively. Treatment was generally well-tolerated but there was one treatment-related death. CONCLUSIONS: Salvage RMPVA at relapses was active and associated with longer survival compared with other regimens, necessitating further development of salvage regimens incorporating tirabrutinib in the future studies.

ML-04

THE INFLUENCE OF SURGICAL INTERVENTION FOR HIGH-DOSE METHOTREXATE CHEMOTHERAPY IN THE PATIENTS WITH PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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OBJECT: Surgical resection is not the standard of treatment for primary central nervous system lymphoma (PCNSL). Some recent studies suggest that resection might be beneficial. The aim of this study was to examine the effect of surgical treatment in terms of the time from surgery to chemotherapy.

METHODS: We retrospectively analyzed all patients with PCNSL treated at Hokkaido University Hospital between 2001 and 2018 to assess the effect of selection for resection on the response of Methotrexate chemotherapy. We identified the days from surgery to chemotherapy, complications, the response of Methotrexate (CR/CRu rate) and prognostic factors including progression free survival (PFS) and overall survival (OS).

RESULTS: A total 105 patients were identified. 84 patients underwent biopsy and 21 patients underwent surgical resection. Their median age were 63 [31–78] and 68 [44–77], respectively. Their Karnofsky Performance Status (KPS) were 70 [30–100] and 70 [40–100]. There were any significant difference. Patients undergoing biopsy and those undergoing resection had comparable rates of complications for all complication type. Overall, 4 biopsy patients and 5 resection patients experienced at least one complication. They were composed of 2 asymptomatic bleeding, 1 wound abscess, 1 hydrocephalus in biopsy patients, 1 epidural abscess, 1 epilepsy, 1 chronic subdural hematoma, 2 temporary hemiparesis. Although the days from surgery to chemotherapy were significantly shorter in patients underwent biopsy than in those underwent resection (P=0.0015), PFS was significantly longer in patients underwent resection than in those underwent biopsy (P=0.0403), whereas there was no difference in OS.

DISCUSSION: Resection could delay the postoperative treatment. In this study, there was a significant delay of postoperative treatment in resection patients, however, CR/CRu rate after MTX was significantly better in those underwent resection than biopsy. We can see that resection for PCNSL might not necessarily worsen the prognosis.

ML-05

ONE-YEAR FOLLOW-UP DATA OF PHASE I/II STUDY OF TIRABRUTINIB IN PATIENTS WITH RELAPSED OR REFRACTORY PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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In March 2020, Tirabrutinib (TIR), a second-generation oral Bruton's tyrosine kinase inhibitor, was approved for the indication of relapsed or refractory PCNSL (r/rPCNSL) based on the results of a phase I/II study in Japan. In this study, 44 Japanese patients with r/rPCNSL were treated with TIR QD at 320 mg, 480 mg, or 480 mg in the fasted condition (480 mg fasted QD). The primary endpoint was overall response rate (ORR) assessed by an independent review committee according to International PCNSL Collaborative Group criteria. We previously reported the results of this study with data cutoff in June 2019 (Narita et al. Neuro Oncol. 2020). In the report, 17 of 44 patients were treated with TIR at 480 mg fasted QD which is an approved dose, and had ORR of 52.9%, median progression-free survival of 5.8 months, and median overall survival of not reached (median follow-up: 3.8 months). In 44 patients, ORR was similar among patients harboring either of the oncogenic mutants *CARD11*, *MYD88*, *CD79B*, or wild type. Throughout the whole patients, most common adverse events (AEs) at any grade were rash (31.8%), neutropenia (22.7%), leukopenia (18.2%), and lymphopenia (15.9%), and grade ≥3 AEs were neutropenia (9.1%), lymphopenia, leukopenia, and erythema multiforme (6.8% each). One patient with 480 mg QD had grade 5 AEs (pneumocystis jirovecii pneumonia and interstitial lung disease). We will present one-year follow-up data of this study at the meeting. As of data cutoff (February 2020), 11 of 44 patients continued to receive TIR, including 6 patients with 480 mg fasted QD. Updated data for overall survival, duration of response, and time to onset of AEs will also be presented. TIR is a promising new treatment for r/rPCNSL.

ML-06

DIAGNOSTIC VALUE OF LIQUID BIOPSY FOR CNS LYMPHOMA BY DETECTION OF SPECIFIC GENE MUTATIONS IN THE CEREBROSPINAL FLUID

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BACKGROUNDS & PURPOSE: Central nervous system lymphoma (CNSL) is the second most common primary malignant brain tumor. Brain biopsy is indispensable to confirm the diagnosis of CNSL, but has a potential risk of inducing hemorrhagic complications in the brain. Therefore, liquid biopsy using the cerebrospinal fluid (CSF) has attracted an attention as a less invasive diagnostic method. In this study, we established a digital PCR-based method to detect *MYD88* mutations in CSF and evaluated its efficacy. METHODS: Matched CSF and biopsy samples from CNSL patients collected before the start of chemotherapy were used. Cellular DNA and cell free DNA (cfDNA) of CSF were separately extracted from the pellet and the supernatant fraction of CSF, respectively. Presence of the *MYD88* L265P mutation was examined in each fraction by the digital PCR. The mutational status obtained by liquid biopsy was compared with that of the matched biopsy specimen examined by pyrosequencing. RESULT: A total of 36 paired samples were used. When the cutoff value of Target/Total ratio was 0.25%, sensitivity, specificity, and area under the curve (AUC) of the digital PCR detection using cellular DNA were 92.9%, 100%, and 0.95, respectively, while they were 100%, 100%, and 1.00 using cfDNA. CONCLUSION: We showed that the digital PCR method was highly sensitive and specific in detecting *MYD88* mutations in the CSF. We propose that CSF liquid biopsy may serve a clinically applicable surrogate to make a diagnosis of CNSL.

ML-07

HIGH EXPRESSION OF PD-L1 ON TUMOR-ASSOCIATED MACROPHAGE IS A PREDICTIVE FACTOR FOR FAVORABLE PROGNOSIS IN PCNSL

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PD-L1 and PD-L2 expression on tumor cells and tumor-infiltrating immune cells in primary central nervous system lymphoma (PCNSL) remains unclear. In the present study, we investigated the expressions of PD-L1 and PD-L2 in surgical specimens from needle biopsies and craniotomies to compare tumor tissue with surrounding tumor tissue (peritumoral tissue) and analyzed the correlation between expression of PD-L1/PD-L2 and survival in patients with PCNSL. We retrospectively analyzed the cases of 70 patients histologically diagnosed with PCNSL (diffuse large B-cell lymphoma). Immunohistochemistry for CD20, CD68, PD-L1, and PD-L2 was performed. In cases with specimens taken by craniotomy, the percentages of PD-L1- and PD-L2-positive macrophages were evaluated in both tumor and peritumoral tissue. The Kaplan-Meier method with log-rank test and Cox proportional hazard model were used for survival analysis. The tumor cells did not express very much PD-L1 and PD-L2, but macrophages expressed PD-L1 and PD-L2 in most of the patients. The median percentage of PD-L2-positive cells was significantly higher among peritumoral macrophages (32.5%; 95%CI: 0–94.6) than intratumoral macrophages (27.5%; 95%CI: 0–81.1, p=0.0014). There was a significant correlation between the percentages of PD-L2-positive intratumoral macrophages and PD-L2-positive peritumoral macrophages (p=0.0429), with very low coefficient correlation (ρ=0.098535). PD-L1 expression on macrophages was significantly associated with biological factors (intratumoral macrophages: better KPS, p=0.0008; better MSKCC score, p=0.0103; peritumoral macrophages: low proportion of LDH elevation, p=0.0064) and longer OS (for intratumoral macrophages: high PD-L1=60 months, 95%CI=30–132.6; low PD-L1=24 months, 95%CI=11–48; p=0.032; for peritumoral macrophages: high PD-L1=60 months, 95%CI=30.7-NR; low PD-L1=14 months, 95%CI=3–26). PD-L1 expression on peritumoral macrophages was strongly predictive of a favorable outcome (HR=0.30, 95%CI=0.12–0.77, p=0.0129). Macrophages in intratumoral and peritumoral tissue expressed PD-L1 and PD-L2 at a higher rate than tumor cells. PD-L1 expression, especially on peritumoral macrophages, seems to be an important prognostic factor in PCNSL.

ML-08

SAFETY AND EFFICACY OF CONSOLIDATION CYTARABINE FOR NEWLY-DIAGNOSED PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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BACKGROUNDS: While consolidation therapies which incorporate whole brain radiotherapy (WBRT) and/ or chemotherapies such as high dose (HD)-cytarabine are commonly applied following induction chemotherapies in primary central nervous system lymphoma (PCNSL), the optimal treatment for consolidation therapy has not been established. We aimed to investigate the safety and efficacy of consolidation cytarabine with a dose modification policy in PCNSL. Patients and METHODS: PCNSL patients initially treated by R-MPV (rituximab, methotrexate, procarbazine and vincristine) and subsequently treated either by WBRT of 24Gy followed by cytarabine (WBRT-AraC group), or cytarabine alone (AraC group) were identified. WBRT was deferred in patients 71 years old or younger who had obtained a complete response (CR) after R-MPV. Cytarabine was dose-modified according to age groups (3 g/m2 in patients 70 years old or younger, 2 g/m2 in patients aged 71–75 years, 1 g/m2 in patients aged 76–80 years). Toxicity profiles, progression-free survival (PFS), overall survival (OS) were analyzed. RESULTS: Twenty-five patients were identified (median age: 69 [range: 34–80], median KPS:70 [range: 40–90]), including 11 patients from the WBRT-AraC group, and 14 patients from the AraC group. Median PFS was unreached in the WBRT-AraC group, and 41.8 months in the AraC group. Median OS was unreached in both groups. The overall rate of grade 3/4 hematologic