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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 day), and etoposide (100 mg/m² on days 1 to 3). Ifosfamide-carboplatin-etoposide (ICE) treatment comprised ifosfamide (1300 mg/m² daily for 3 days), carboplatin (300 mg/m² daily for 1 day), and etoposide (100 mg/m² daily for 3 days). Patients with germinomatous germ cell tumors received etoposide or gemcitabine over 1 day, with STG (9%), immediately, and delivered three cycles of CARB-VP and a total dose of 30 Gy whole ventricular radiotherapy. We delivered combination therapy consisting of combined ICE chemotherapy and craniopelvic 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 3-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-TERM INTENSIVE REHABILITATION FOR PATIENTS WITH NEWLY DIAGNOSED GLOBLASTOMA

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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 Mini-mental 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 aphasias 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 imaging (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*; and 3) hyperintense signal on DWI.

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).

ML-02

CHEMOTHERAPY FOR PATIENTS WITH RELAPSED OR REFRACTORY PRIMARY CNS LYMPHOMA

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BACKGROUND: Standard of care for patients with primary CNS lymphoma (PCNSL) has been high-dose methotrexate (HD-MTX)-based multiagent immun chemotherapy, particularly with R-MPV-A 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. Eight patients were those treated with R-MPV-A 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, docetaxel, and CBZCA). Median age was 65.4y (20–87y) 80 (40–100), 27 patients had received prior WBRT. RMPVA was given at the first relapse in 11 patients, median number of RMPVA cycles was 8 (1–4 cycles; 10; 8 cycles; 13); CR/Cru were achieved in 19 (83%), response rate was 91%, while there were two PDs (9%). Median follow-up of 21.9 months, the median PFS after salvage RMPVA was 13.0m (95%CI: 9.1–16.9), 1-year overall survival (OS) was 82%, median OS was 70.0m (95%CI: 12.9–127.1), which were longer than those in 24 patients with salvage treatment other than RMPVA (16.8m, P=0.054; mOS was 40.9m, median PFS and OS for HD-MTX monotherapy were 5.1m and 36.6m, while those for DeVic were 4.4m and 9.1m, respectively. Treatment was generally well-tolerated but there was one treatment-related death. CONCLUSIONS: 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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BACKGROUND: Primary CNS lymphoma (PCNSL) may be treated with chemotherapy without whole-brain radiotherapy (WBRT). However, the role of surgical intervention for high-dose methotrexate (HD-MTX)-based chemotherapy in PCNSL may not be fully understood. The aim of this study was to clarify the influence of surgical intervention for high-dose methotrexate (HD-MTX)-based chemotherapy in PCNSL patients and its relationship with overall survival (OS). METHODS: We retrospectively reviewed the medical records of 57 consecutive patients with PCNSL who were treated at our hospital from April 2000 to November 2019. The patients were divided into two groups: Group A, who received surgical intervention; and Group B, who did not receive surgical intervention. The outcomes were compared between the two groups. RESULTS: The median age of patients in Group A and Group B was 67 years (range 35–84) and 65 years (range 35–84), respectively. The overall response rate was 92% (9/10 patients) in Group A and 86% (26/30 patients) in Group B. The median OS was 27.9 months (95% CI: 14.8–not reached) and 25.1 months (95% CI: 9.9–40.3), respectively. However, there was no statistically significant difference in OS between the two groups (P=0.72). CONCLUSIONS: Surgical intervention for high-dose methotrexate (HD-MTX)-based chemotherapy in PCNSL patients may be not associated with better overall survival compared with patients who did not receive surgical intervention.
RESULTS: A total 105 patients were identified. 84 patients underwent biopsy and 21 patients underwent surgical resection. Their median age was 63 [31–78] and 68 [44–77], respectively. Their Karnofsky Performance Status (KPS) were 70 [70–100] and 70 [40–100]. There were no significant differences. Patients undergoing biopsy and those undergoing resection had comparable rates of complications for all complication type. Overall, 4 biopsy patients and 3 resection patients experienced at least one complication. They were composed of 2 symptomatological bleeding, 1 worsened ascites, 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 undergoing biopsy than in those undergoing resection (P=0.0015), PFS was significantly shorter in patients undergoing resection than in those undergoing 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 undergoing 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 II/III 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 II/III study in Japan. In this study, 44 Japanese patients with r/rPCNSL were treated with TIR 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 5.6 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 AE s were neutropenia (9.1%), lymphopenia, leukopenia, and erythema multiforme (6.8%) each. One patient with 480 mg QD had grade 5 AEs (pneumocystis jiroveci 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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BACKGROUND & 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 feasibility. 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 MYD88 deletion or 6265P 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 [30-100] and 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 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 who were 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 sub-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 than intratumoral 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 (R^2=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=30–126.6; low PD-L1=24 months, 95%CI=11–48; p=0.032; for peritumoral macrophages: high PD-L1=60 months, 95%CI=37.0–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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BACKGROUND: While consolidation therapies which incorporate whole brain radiotherapy (WBRT) and/or chemotherapy such as high dose (HD)-cytarabine are commonly applied following induction chemotherapies in 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 HD-cytarabine 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 or older who had obtained a complete response (CR) after HD-cytarabine. Both groups received consolidation treatment with data cutoff in June 2019 (Narita et al. Neuro Oncol. 2020). In the study, 42 patients were identified: median age (range: 38–82), 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