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 [30–100] and 70 [40–100]. There was no 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 neurosurgical symptoms: bleeding, 1 worsening of headaches in biopsy patients, 1 epidural abscess, 1 epilepsy, 1 chronic subdural hematoma, 2 temporal 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/CrRu 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/I 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 tyro sine kinase inhibitor, was approved for the indication of relapsed or refractory PCNSL (r/rPCNSL) based on the results of a phase II/I 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 5.6 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 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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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 hematologic 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 digital PCR. The mutational status obtained by liquid biopsy was compared with that of the matched biopsy specimen examined by pyrosequencing. RESULTS: 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 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 cranialtomies 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 pathologically diagnosed with PCNSL. Immunochemistry for CD20, CD20, CD68, and CD8 was carried out on all cases, and the expression of PD-L1 and PD-L2 was evaluated. 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 (Rb=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 LDL 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=30–14 months, 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 primary central nervous system lymphoma (PCNSL), the role of consolidation therapy 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 were subsequently treated either by WBRT of 24 Gy 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: 40–80]), 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
toxicities was high (92%), but mostly manageable without major complications. Fourteen patients received 3 g/m², 4 patients received 2 g/m², 7 patients received 1 g/m² of cytarabine, and the rate of grade 4 leukopenia/thrombocytopenia was 64% (7%), 25% (60%), and 28% (29%), respectively. **DISCUSSION:** HD-cytarabine consolidation therapy with dose modification according to age groups for PCNSL was feasible and well-tolerated in patients 80 years of age or younger. The efficacy of HD-cytarabine was undetermined and further investigation is warranted.

**ML-09**

**THE REAL-WORLD OF ELDERLY PCNSL THERAPY IN TOHOKU AND NIIGATA AREA ACCORDING TO RETROSPECTIVE ANALYSIS:** AND CALLING FOR INVESTIGATION OF THE TOHOKU BRAIN TUMOR STUDY GROUP

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**INTRODUCTION:** Recently, the number of cases of primary central nervous system lymphoma in elderly patients(EL-PCNSL) has been increasing. However, the treatment options may be insufficient because of poor performance status and pre- and post-treatment complications. Therefore, we analyzed the risk factors for EL-PCNSL in the Tohoku and Niigata areas of Japan and clarified the REAL-WORLD of EL-PCNSL therapy.

**MATERIALS & METHODS:** We performed a retrospective study of 46 cases of primary CNS lymphoma patients aged 71 years or older from eight facilities during the last 8 years. We analyzed patient information, radiotherapy/chemotherapy or not, PFS, OS, RRs, second-line therapy, pre- and post-treatment complications, outcomes, and risk factors for poor prognosis. The log-rank test was used for univariate analysis, and Cox regression analysis was used for a multivariate analysis of risk factors.

**RESULTS:** Of the 142 cases registered, five differed from PCNSL pathologically, three receiving BSC were excluded, 31 were treated without biopsy, three were treated based on CSF-findings, and 100 were treated with biopsy. Total 134 cases were followed. The median age was 76 years, pretreatment KPS was 50%, and 118 cases (88%) had 21 pretreatment complications. The treatment contents consisted of various combinations depending on the attending physician.

The retrospective overall PFS was 16 months and OS was 24 months. In the early treatment phase, out of 16 cases with dropout, four had tumor and four had complication deaths occurred. There were 77 deaths (58'), 19 internal medical deaths (14%), and 33 complication deaths (24%). Poor prognostic risk factors were <60% posttreatment KPS, complications involving pretreatment cardio-vascular and central nervous system disease, posttreatment pneumonia or severe infection, and absence of radiation or chemotherapy. **CONCLUSIONS:** Pretreatment KPS did not affect poor outcomes, but posttreatment KPS <60% and pre- and post-treatment complications did. Radiotherapy and chemotherapy are reportedly effective, but additional research to clarify the details of these modalities is needed.

**ML-13**

**THE PRIMARY TREATMENT OUTCOMES AND FUTURE PROBLEMS OF ELDERLY PATIENTS IN OUR INSTITUTE**

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**BACKGROUND AND PURPOSE:** Since the introduction of HD-MTX, effectiveness after irradiation has become a problem mainly in elderly patients. In this study, we evaluated the treatment outcomes of over 70 years old PCNSL patients after HD-MTX introduction. Subjects and METHODS: From April 2009 to December 2019, there were 46 cases of PCNSL patients who had been treated in our institute. The HD-MTX treatment group had 42 cases and the R-MPV-A treatment group had 4 cases. In the HD-MTX treatment group, 30–40 Gy of whole brain irradiation was performed (n=32), and the R-MPV-A treatment group had 4 cases. In the HD-MTX treatment group, the first relapse was 116 days, the median OS after relapse was 590 days. The median post-relapse progression-free survival (PFS) of the 10 patients undergoing M-re at the first relapse was 116 days, the median OS after relapse was 590 days. The median time of radiation free period and delayed neuropsychological toxicity was 19.5 months (95% CI: 1–55), respectively. CR might be promising but the problems of some serious AEs and low CR rate with HD-MTX alone should be resolved.

**ML-14**

**RE-CHALLENGE AND MAINTENANCE THERAPY OF METHOTREXATE FOR ELDERLY PCNSL PATIENTS WITH LOW SCORED KPS**

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**PURPOSE:** The delayed neurological toxicity after high dose methotrexate (HD-MTX) followed by radiotherapy (RT) is a serious problem for elderly primary CNS lymphoma patients. We started maintenance therapy (MT) with MTX after achieving complete remission (CR) to defer RT for elderly patients. No irradiation (n=10) was 12.4 months. The R-MPV-A treatment group (n=4) had a remission rate of 100% after chemotherapy. Of the 26 cases whose cause of death could be identified in the HD-MTX treatment group, 38% (15/26) had tumor-related death and 30% (8/26) had pneumonia or suffocation.

**CONCLUSION:** R-MPV-A has a high remission rate even in elderly patients, and if the irradiation dose can be reduced or avoided with R-MPV-A, ADL maintenance will be expected in elderly patients.

**ML-15**

**THE FUTURE DIRECTION OF TREATMENT DEVELOPMENT FOR PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL)**

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**PURPOSE:** We found that the combination of high-dose Methotrexate (HD-MTX)-based therapy and histone deacetylase inhibitor (HDACI) had a therapeutic effect on PCNSL. In addition, this trial, tirabrutinib, a Bruton’s tyrosine kinase inhibitor, was approved for marketing as a single agent for relapsed/refractory PCNSL, and new therapeutic development is expected. We will examine the treatment results of PCNSL in our department retrospectively and discuss the future direction of treatment development. METHODS: From 2001 to 2014, 82 newly diagnosed PCNSL patients treated with HD-MTX/Procarbazine (MP) as initial remission induction chemotherapy were retrospectively analyzed. **RESULTS:** Complete response (CR) was obtained in 38 patients (46.3%) after initial chemotherapy, and the median overall survival (OS) in the CR and non-CR groups was 2636 days and 748 days, respectively, and significantly shorter in the non-CR group (p<0.01). In the CR group, 27 cases (71.1%) recurred and 12 cases received HD-MTX re-challenge (M-re), 14 cases received treatment other than M-re (1 case did not receive treatment), the median OS after relapse was 590 days. The median post-relapse progression-free survival (PFS) of the 10 patients undergoing M-re at the first relapse was 116 days, the median OS after relapse was 590 days. The median post-relapse PFS of 16 patients receiving other treatments was 38 days, the median OS after relapse was 532 days. There was no difference in PFS and OS after recurrence in treatment at the first recurrence (p>0.15, p=0.55). **CONCLUSION:** The OS of non-CR patients in the initial chemotherapy and the OS after recurrence after CR were short. The possible directions of PCNSL treatment development include 1) increasing the CR rate with initial chemotherapy and maintaining CR for a long time for newly diagnosed PCNSL, and 2) finding an effective treatment for recurrence. New drugs such as tirabrutinib and HDACIs may be breakthroughs.