ML-02
THE ROLE OF MAINTENANCE HIGH-DOSE METHOTREXATE CHEMOTHERAPY IN ELDERLY PRIMARY CNS LYMPHOMA PATIENTS
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BACKGROUND: The addition of high-dose methotrexate (HD-MTX)-based brain irradiation to whole brain irradiation (WBRT) has improved the prognosis of primary central nervous system lymphoma (PCNSL). However, the high neurotoxicity rates observed, especially in the elderly, raised interest in chemotherapy-only treatments. Withholding radiotherapy substantially decreases the risk of neurotoxicity, however, disease control may be compromised. In the elderly who cannot tolerate WBRT as a consolidation, maintenance treatment may serve as a feasible approach after an initial response. We treated ePCNSL with induction immunochemotherapy, maintenance chemotherapy with HD-MTX and deferred WBRT. Here, we retrospectively investigated the prognosis for ePCNSL that became CR after the induction chemotherapy. MATERIAL AND METHODS: Newly diagnosed ePCNSL (median age: 74 years) received biweekly rituximab(HD-MTX) for cycles (induction) followed by monthly rituximab(HD-MTX) for 2 cycles (consolidation) and then were treated differently according to the radiological response. With CR patients, HD-MTX was continued with every 3 months (maintenance) for 2 years. Patients who did not obtain consent for maintenance therapy were followed up. For PD patients, immunochemotherapy was interrupted and WBRT initiated immediately. Patients with PR and SD were treated with alternative chemotherapy with temozolomide and/or stereotactic radiotherapy or WBRT. RESULTS: The median PFS was 24.6 months and median OS was 27 months for the entire cohort. Of the 42 ePCNSL, 26 had CR after induction and consolidation, of which 18 cases were carried out maintenance (M+) and 8 cases were followed up (M-). Median PFS was 73 months in the M+ group and 24.5 months in the M- group. Median OS is 102.2 months versus 27.6 months, respectively. Both mPFS (P=0.016) and mOS (P<0.001) were significantly prolonged in the M+ group, compared to the M- group. CONCLUSION: It was suggested that maintenance treatment with HD-MTX may improve the prognosis for ePCNSL that reached complete response after induction therapy.

ML-03
DIAGNOSIS AND TREATMENT OF PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA IN HIV POSITIVE PATIENTS
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INTRODUCTION: HIV infection is known to cause a variety of central nervous system complications, such as malignant lymphoma (ML), toxoplasmosis, cryptococcal encephalopathy, progressive multifocal leukoencephalopathy (PML), brain tuberculosis and HIV encephalopathy. In our hospital, we performed brain biopsy for HIV-positive patients with primary central nervous system lymphomas suspected malignant lymphoma, or cases difficult to diagnose with blood, cerebrospinal fluid, and imaging alone. In this study, we retrospectively examined HIV-positive patients who underwent brain biopsy at our hospital, and analyzed diagnosis and treatment of patients with ML. Methods HIV-positive patients who underwent brain biopsy in our hospital from January 2010 to April 2019 were examined in this study. We analyzed background factors, preoperative examination results, pathological diagnosis, treatment and prognosis. RESULTS: There were 1,894 HIV-positive patients who were treated at our hospital during the...
period, of which 16 cases underwent a total of 18 brain biopsies. The final diagnosis was 7 ML (6 PCNSL, 1 brain metastasis), 3 toxoplasma encephalitis, 2 herpes simplex, 1 human immunodeficiency virus encephalitis, 1 Legionnaires' disease, 1 cerebral sarcoidosis, 1 lymphomatous meningitis, 2 intracranial abscesses, 2 non-Hodgkin's lymphoma, 1 autoimmune meningoencephalitis, 1 Castleman's disease, 1 metastatic breast carcinoma, 1 metastatic ovarian carcinoma, 1 metastatic sarcoma, 1 metastatic melanoma, 1 metastatic prostate carcinoma, and 1 metastatic renal cell carcinoma. In 16 cases, the diagnosis was confirmed by histologic examination, 1 case by magnetic resonance imaging, 1 case by cerebrospinal fluid examination, and 1 case by positron emission tomography. CONCLUSIONS: The delayed neuronal toxicity due to RT is a serious problem especially for elderly patients. Further careful assessment is needed.

ML-11
DETECTION OF MYD88 MUTATIONS FROM CELL FREE DNA AIDS IN THE DIAGNOSIS OF CENTRAL NERVOUS SYSTEM LYMPHOMAS
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BACKGROUND: Diagnosis of primary central nervous system lymphomas (PCNSL) can be challenging. We have shown that the detection of MYD88 mutation in cell free DNA (cfDNA) taken from cerebrospinal fluid (CSF) is reliable (JCO Precision Oncology, 2019; Leukemia and Lymphoma, 2019). We report four cases in which detection of MYD88 mutation in CSF is reliable (JCO Precision Oncology, 2019; Leukemia and Lymphoma, 2019). METHODS: Four most frequent mutations of MYD88 in PCNSL; 577N, K115N, P216S, L275F; were chosen from our previous study, and each mutant was generated by site directed mutagenesis in PIM1 cDNA cloned in an expression vector. Results of K115N mutant were transiently transfected into human cancer cell lines. Functional studies were carried out using various biochemical methods. RESULTS: Among the four mutants, increased phosphorylation of BCL-2 associated death promoter (BAD) at Ser112, which is a phosphorylation target of P115, was observed by expression of K115N mutant compared with wild type PIM1 in Hela and Nagai cells expressing endogenous BAD. Decreased cell death under camptothecin treatment was also observed in K115N mutant expressing Nagai cells compared with wild type PIM1-expressed cells. We also observed a significant shift in subcellular localization of P115 mutant; from the nucleus to the cytosol determined by immunochemistry and immunoblotting of nuclear and cytosolic fraction of the cells. Augmented cytosolic localization of P115 mutant was suppressed by inhibition of glycosylation. DISCUSSION: It is suggested that P115 K115N mutant may drive chemoresistance through increased BAD phosphorylation that suppresses cell death compared with wild-type P115 through modification of its subcellular localization, which might be regulated by its glycosylation status.

ML-12
MECHANISMS OF CELL DEATH INHIBITION THROUGH CHANGE IN SUBCELLULAR LOCALIZATION OF PIM-1 BY PIM1 GENE MUTATION RECURRENTLY FOUND IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMAS
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PURPOSE: High dose methotrexate (HD-MTX) followed by radiotherapy (RT) is a standard therapy for primary CNS malignant lymphoma. However, the delayed neuronal toxicity due to RT is a serious problem especially for elderly patients. To avoid RT toxicity, we performed re-challenge of HD-MTX until complete remission (CR). Furthermore, we started maintenance therapy of MTX for elderly and poor Karnofsky Performance Scale (KPS) patients who had received the interim results. METHODS: We performed HD-MTX (3.5g/m^2) therapy until achieving CR for patients whose ages were older than 70 years old and KPS was less than or equal to 60%. After achieving CR, 3 courses of MTX (3g/m^2) for 3 weeks were introduced every 3–4 months for 2 years. In cases of recurrence, HD-MTX was repeated. But when CR was not achieved by HD-MTX, RT was introduced. RESULTS: Number of patients was 8. Median age, median KPS, and median follow up periods were 73.y.o. (71–78), 40% (30–60), and 4.5mo. (1–42), respectively. CR rate was 75% but 2 patients did not achieve CR. One patient had a complication of acute tubular necrosis just after first use of HD-MTX and another died due to pneumocystis pneumonia after 4th HD-MTX. Two patients without RT maintained CR and good KPS over 2 years. Four patients with RT maintained CR but their KPS gradually deteriorated. DISCUSSION: Rechallenge of HD-MTX exhibits better results and comparable safety with standard treatment, but RT was unavoidable. In order to avoid RT, we started MTX maintenance therapy for elderly and poor KPS patients before recurrence. Our maintenance therapy is easy and good disease control for patients who had not received RT, however there were two serious adverse events. CONCLUSION: Rechallenge of HD-MTX and maintenance therapy of MTX might be promising but dangerous for elderly patients. Further careful assessment is needed.