PCNSL (ML)

ML-3

A CASE OF PRIMARY CENTRAL NERVOUS SYSTEM ANAPLASTIC LYMPHOMA KINASE POSITIVE ANAPLASTIC LARGE CELL LYMPHOMA AT NEUROHYPOPHYSIS AND PINEAL GLAND.

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The majority of primary central nerve system (CNS) lymphomas (PCNSL) are diffuse large B-cell lymphomas. Anaplastic large cell lymphoma (ALCL) that is a type of T-cell tumor is very rare in the PCNSL. ALCLs are divided into two entities: anaplastic lymphoma kinase (ALK)-positive and ALK-negative. We report a case of a 26-year-old woman who presented with a one month historyof headache and nausea. Magnetic resonance imaging (MRI) of the brain revealed pituitary and pineal gland mass diagnosed as ALK-positive ALCL by endoscopic brain biopsy. She underwent chemotherapy following methotrexate (MTX) and cyclophosphamide + doxorubicin + vincristine + prednisolone (CHOP). The follow-up contrast-enhanced brain MRI showed no recurrent lesion after chemotherapy. In previous reports, most of the lesions were in cerebral hemisphere, dura mater and spinal cord. Many of these patients were given primary diagnoses of meningitis. To our knowledge, there is no case report of initial diagnosis of germinoma due to lesions in Neurohypophysis and pineal gland as in this case.

Key words: primary central nerve system lymphomas | naplastic large cell lymphoma | anaplastic lymphoma kinase | Neurohypophysis and pineal gland

ML-4

A CASE OF PRIMARY CNS LYMPHOMA DIAGNOSED 5 YEARS AFTER STEREOTACTIC RADIOSURGERY.

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Central nervous system primary malignant lymphoma (PCNSL) is rarely diagnosed as multiple metastatic brain tumors. Almost tumors recure early after receiving stereotactic radiosurgery (SRS). Regardless of the fact, the following case report displays PCNSL, diagnosed five years after the initial treatment with SRS as brain metastases of unknown primary origin. This extraordinal case suggests long-term follow-up regarding PCNCL. The case was a 55-year-old woman with a history of a total hysterectomy for cervical cancer. She developed left paralysis. Brain MRI confirmed a 27 mm contrast-enhanced lesion in the right frontal lobe and three other lesions. SRS was performed as a diagnosis of multiple brain metastases for urgent symptom relief. No extra-cranial cancerous lesions were found. Unknown primary cancer was a probable diagnosis at that time. Two years after SRS, local regrowth of tumor of the right frontal primary motor area was discovered. Re-irradiation was performed. Cerebral edema, contrast enhancement, and left paralysis progressed following five months, taking an oral corticosteroid. Craniotomy and debulk. The pathological diagnosis was brain radiation necrosis due to no viable tumor cells. New lesions in the left temporal lobe and basal ganglia appeared three years after surgery. Awake craniotomy was performed for the left temporal lobe lesion. Histopathology showed diffuse growth of tumor cells with a high nucleocytoplasmic ratio and irregular nuclear shape. Immunohistochemistry revealed positive CD10, CD20, CD45 (LCA), MUM1, and negative CD3, CD5. The Ki- 67 labeling rate was as high as almost 100% to diagnose diffuse large B-cell lymphoma, PCNSL. Multidrug chemotherapy consisting of rituximab, high-dose methotrexate, procarbazine, and vincristine were performed. Complete remission was obtained without any serious adverse events. Considering the residual radiation necrosis, whole-brain irradiation was avoided. Moreover, consolidation therapy was performed only with high-dose cytarabine therapy.

Key words: primary CNS lymphoma | stereotactic radiosurgery | delayed diagnosis

ML-7

LIQUID BIOPSY FOR MYD88 MUTATION IN CEREBROSPINAL FLUID IN PATIENTS WITH SUSPECTED PRIMARY CNS LYMPHOMA

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Background: Treatment intervention for central nervous system lymphoma (CNSL) requires pathological diagnosis by surgical biopsy. However, there are some cases in which the risk of surgery is high due to age, comorbidities, localization of lesions, etc. We are developing a CNSL diagnostic method based on the detection of MYD88 L265P mutation by digital PCR (dPCR) using CSF-DNA, and a high accuracy with a sensitivity of 92.9% and a specificity of 100% has been reported. Here, we report two cases with suspected brain stem CNSL, whose treatment strategy was determined by integrated clinico-laboratory information including neurological presentations, imaging, and the result of liquid biopsy. Result: Case 1. A 63-year-old woman visited our hospital with a complaint of right hemiplegia, which deteriorated in two months. MR images revealed a contrast-enhancing lesion in the left midbrain-ventral pons, suggesting CNSL. Biopsy was not considered because of its location, while dPCR using CSF-DNA showed a cluster of MYD88 mutation signals. Based on these work-ups, she was treated with high-dose methotrexate-based chemotherapy, resulting in a complete response with marked improvement of symptoms. Case 2. An 83-year-old man was referred for a history of diplopia and ataxic gait lasting for a month. MR images revealed an invasive lesion on his right midbrain-dorsal pons. Biopsy was declined due to the location, and liquid biopsy using CSF-DNA was performed to assist the diagnosis. In the first test, the CSF-DNA yield was too insufficient to determine the mutation signal by dPCR. The second dPCR using sufficient amount of CSF-DNA resulted in the Target/Total value of 0.049% which was lower than the threshold, suggesting the absence of MYD88 mutation. The patient underwent radiation therapy accordingly.Conclusions: CSF MYD88 mutation analysis by dPCR may have clinical utility and requires sufficient amount of CSF-DNA for exclusion of noise signals.

Key words: liquid biopsy | MYD88 | digital PCR

ML-10

TIRABRUTINIB, A SECOND-GENERATION BTK INHIBITOR IN RELAPSED AND REFRACTORY PRIMARY CNS LYMPHOMA: A SINGLE INSTITUTE STUDY

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BACKGROUND: The prognosis of relapsed and refractory (r/r) primary CNS lymphoma (PCNSL) is poor, and the development of new therapeutic agents is desirable. Comprehensive genetic analysis of PCNSL has shown that MYD88 and CD79B are frequently mutated and are oncogenic drivers, suggesting that Bruton's tyrosine kinase (BTK), which is located downstream of MYD88 and CD79B, may be a reasonable therapeutic target. Tirabrutinib is a second-generation oral BTK inhibitor recently approved in Japan for the treatment of r/r PCNSL. In this study, we evaluated the efficacy and safety of tiraburtinib treatment of r/r PCNSL at Saitama Medical University. MATERIAL AND METHODS: Eighteen patients with r/r PCNSL to HD-MTX-based regimens were treated with 480 mg tiraburtinib daily under fasting conditions until disease progression. RESULTS: The median age was 63.5 years, and the median KPS was 70. Nine patients (50%) achieved a CR, 2 (11%) had a partial response, 3 (17%) had stable disease, and 4 (22%) had progressive disease. After a median follow-up of 17.3 months, the median progression-free survival was 7.9 months, and the median overall survival was 23.6 months. There were four cases of long-term treatment lasting more than one year. Grade 3 or higher adverse events were observed in 1 case of maculopapular rash, 1 case of cardiac failure, 1 case of neutropenia, and 1 case of lymphopenia. CONCLUSION: Tiraburtinib can be administered relatively safely to patients with relapsed or refractory PCNSL, and a certain degree of efficacy can be expected. Which patients can be treated with tiraburtinib over the long term, when can stop tirabrutinib treatment for patients with long-term CR, and the mechanism of tiraburtinib resistance needs to be determined.

Key words: primary CNS lymphoma | Bruton's tyrosine kinase inhibitor | Tirabrutinib

ML-11

TIRABRUTINIB TREATMENT FOR RECURRENT OR REFRACTORY PCNSL

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Since 2020, tirabrutinib which is a Bruton's tyrosine kinase (BTK) inhibitor has been available for recurrent or refractory PCNSL cases. The number of studies reporting efficiency and adverse effect of tirabrutinib

treatment for recurrent or refractory PCNSL has been limited yet. In this study, we investigated clinical course of eight refractory or recurrent PCNSL cases treated with tirabrutinib in our institute.

Eight PCNSL cases treated with tirabrutinib included four recurrent cases and four refractory cases. Five cases obtained CR or PR after 26.8 days administration of tirabrutinib and other two cases also exhibited obvious improvement of clinical symptoms after 23.5 days administration of tirabrutinib. Among three cases exhibiting intraocular lesions, two cases revealed improvement of visual dysfunction and the other case obtained SD status of intraocular lesion. The most frequently found adverse effect was the skin rash. CTCAE grade 2 (n=2) or 3 (n=2) rash was found after mean 16 days or 94 days of tirabrutinib administration, respectively. Two cases with grade 3 rash could start taking the low-dose tirabrutinib after improvement of rash. Althouth one case experienced shingles, no other case experienced serious adverse effects.

Although adverse effect of rash was frequently found, we could obtain high response rate of tirabrutinib treatment for recurrent or refractory PCNSL cases. We need to establish quantitative assessment method for analysis of treatment response of tirabrutinib for intraocular lesions.

Key words: Tirabrutinib | PCNSL | Skin rash

ML-12

CLINICAL IMPACT AND MANAGEMENT OF SKIN-RELATED DISORDERS DURING TREATMENT OF RELAPSED PCNSL BY TIRABRUTINIB

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BACKGROUNDS: Tirabrutinib is a second-generation Bruton's tyrosine kinase (BTK) inhibitor, approved by the Japanese Pharmaceutical and Medical Devices Agency (PMDA) for relapsed and refractory PCNSL in March 2020. Skin-related disorder (SRD)s are the most prevalent adverse events in tirabrutinib, which accounted for 54.5% in a phase I/II trial. While the use of tirabrutinib is increasingly considered in clinical practice, the prevalence and clinical impact of tirabrutinib-related SRDs in real-world practice remains unclear. METHODS: Relapsed PCNSL patients treated with tirabrutinib at the author's institution were identified, and divided into those with SRDs (SRD group), and without SRDs (non-SRD group). Response rate and progression-free survival (PFS) were retrospectively analyzed and compared between the two groups. RESULTS: Eleven patients were identified (median age: 73 [range: 50–83], median KPS: 70 [range: 40–90]), which included six (54.5%) from the SRD group and five (45.5%) from the non-SRD group. Response rate was 100% in the SRD group and 60% in the non-SRD group. Median PFS was 2.8 months in the SRD group and 36.3 months in the non-SRD group, which yielded no significant difference (p=0.446). While antihistamine prophylaxis using fexofenadine was performed in seven patients, among them SRDs were observed in three (27.3%). SRDs lead to tirabrutinib interruption (for seven days or more) in two (18.2%), dose reduction in three (27.3%), and discontinuation in two (18.2%) patients. Four patients in whom tirabrutinib was interrupted or discontinued due to SRDs had shorter PFS, compared with the two patients from the SRD group in whom tirabrutinib was continued (median PFS: 2.3 and 29.6 months, respectively) (p=0.049). CONCLUSIONS: SRDs substantially lead to tirabrutinib interruption or discontinuation, which could result in early PD. Since fexofenadine prophylaxis seems ineffective for preventing SRDs, other antihistamines should be considered. Establishment of the optimal management of tirabrutinib-related SRDs is warranted.

Key words: PCNSL | tirabrutinib | Bruton's tyrosine kinase

ML-13

PRIMARY CENTRAL NERVOUS SYSTEM MALIGNANT LYMPHOMA IN A PATIENT WITH RHEUMATOID ARTHRITIS RECEIVING TOCILIZUMAB

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Background: Although the risk of developing malignant lymphoma is higher in patients with rheumatoid arthritis (RA) than in the general population, the occurrence of primary central nervous system lymphoma (PCNSL) in patients with RA is extremely rare. In recent years, there has been concern that biological disease-modifying antirheumatic drugs (DMRADs), which are widely administered to patients with RA, may increase the risk of developing cancer. We report the first case of PCNSL in a patient with RA who was treated with the biological DMRADs, tocilizumab. Case description: A 70-year-old man, who was diagnosed with RA in 2010 was treated with low-dose methotrexate from 2010 to 2015. He was started on tocilizumab in 2012. In 2018, he suffered from gait disturbance and was diagnosed with lumbar spinal stenosis. He underwent L2/3 posterior fusion surgery, but his paraplegia gradually deteriorated. Two months after the surgery, a head Gd-MRI showed multiple contrast-enhanced lesions in the basal ganglia and brain stem. A stereotactic brain biopsy was performed and DLBCL was diagnosed, and finally PCNSL was diagnosed because of no neoplastic lesions in other organs. He was treated with 5 courses of MTX 3.5g/m2 with rituximab and has been in remission for 23 months. He has maintained an independent life with residual paraplegia, but his ADLs gradually worsened. He was restarted on tocilizumab with a diagnosis of worsening RA. Conclusion: Low-dose methotrexate and biological DMRADs including tocilizumab, have been concerned to increase the risk of cancer in patients with RA, but there is no solid evidence. Since it has been a short time since the use of biological DMRADs, further accumulation of cases and careful follow-up are necessary.

Key words: Primary central nervous system lymphoma | Methotrexate | Tocilizumab

ML-16

FIRST CLINICAL EXPERIENCE OF ADMINISTRATION OF TIRABRUTINIB FOR THE PATIENTS WITH NEWLY DIAGNOSED PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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Tirabrutinib (TIR), a Burton's tyrosine kinase inhibitory drug, has been approved in Japan for treating relapsed/refractory primary central nervous system lymphoma (PCNSL). The authors recently encountered three patients with newly diagnosed refractory PCNSL using TIR.

Three patients, 48, 78 and 88 years-old males, diagnosed with PCNSL by histologically verification were firstly treated with high dose Methotrexate based chemotherapy (HD-MTX) and/or radiotherapy, however these cases were refractory for these standard treatments, demonstrated early cerebrospinal fluid dissemination or accompanied with severe adverse event. The authors decided to administrate TIR to these patients with a full informed consent. TIR demonstrated dramatic reduction of the volume of tumor on MRI within one month after administration of TIR, and improved the patient's performance status. However, one case demonstrated liver dysfunction and multiple brain abscess due to aspergillus infection, and one case demonstrated early progression of the tumor 49 days after starting TIR.

Administration of TIR for the patients with newly diagnosed refractory PCNSL demonstrated a rapid and dramatic clinical response, and presented with several clinical implications for this complicated condition.

Key words: Tirabrutinib | refractory primary central nervous system lymphoma | adverse event

ML-17

CLINICAL USEFULNESS OF TIRABRUTINIB IN RECURRENT PCNSL: SINGLE INSTITUTE EXPERIENCE.

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Background: Primary central nervous system lymphoma (PCNSL) is a lymphoma whose primary lesion is localized in the brain and spinal cord. Treatment is a combination of high-dose methotrexate-based chemotherapy and whole-brain irradiation, often leading to recurrence. Pathologically, non-GCB type diffuse large B-cell lymphoma (DLBCL) predominates. In DLBCL, constitutive activation of B cell receptor signal (BCR) is the tumor mechanism of tumor development and growth. Tirabrutinib is an inhibitor of Bruton's tyrosine kinase (BTK) located downstream of BCR. In a phase I / II study, an overall response rate was 64%. Currently, Tirabrutinib is used to treat relapsed or refractory PCNSL. Purpose: Tirabrutinib is a drug that has just been approved, and there are few reports of its use in clinical practice. We report on our experience with Tirabrutinib with a review of the literature. Methods: We retrospectively examined the clinical course of 11 recurrent PCNSL patients treated with Tirabrutinib at our institution. Results: The average age of the subjects was 68.7 years, and 7 cases were male. Tirabrutinib 480 mg was administered in all cases. The response rate was 60% (6/10 cases). The median progression-free survival was 4.3 months. The adverse events were Grade 3 neutropenia in 1 patient and Grade 2 skin disorder in 4 patients. Treatment was discontinued in 5 of the 11 patients due to the progression of the disease. Due to the eruption, Tirabrutinib was reduced to 320 mg in 1 patient and discontinued in 1 patient. Treatment was discontinued at the request of the patient in 1 case, and four patients are still