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

on medication. Summary: According to the results we obtained, the response rate was the same as that in the phase I / II study, and the progression-free survival was slightly longer.

Key words: PCNSL | Tirabrutinib | DLBCL

ML-18

HIGH-DOSE CHEMOTHERAPY SUPPORTED BY AUTOLOGOUS STEM CELL TRANSPLANT IN RELAPSED AND REFRACTORY PRIMARY CNS LYMPHOMA

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While whole brain radiation therapy (WBRT) has been performed as consolidation therapy in primary central nervous system lymphoma (PCNSL), high-dose chemotherapy supported by autologous stem cell transplant (HDC/ASCT) is widely investigated today as an alternative treatment strategy, given the high risk for radiation-induced neurotoxicity in WBRT. Various conditioning regimens have been investigated in phase II trials, which report non-inferiority of HDC/ASCT in efficacy and preservation of neurocognitive function in comparison with WBRT. Besides its promising efficacy, treatment-related deaths are reported in 11% in patients treated by a conditioning regimen using thiotepa, busulfan and cyclophosphamide (TBC), which raises a concern for safety. Among several conditioning regimens, analysis using registry data of Japan Society for Hematopoietic Cell Transplantation has revealed that the use of conditioning regimens containing thiotepa was a positive factor for longer PFS. According to the result of a phase I trial in Japan which investigated HDC/ASCT using thiotepa and busulfan (BuTT), thiotepa was approved by the pharmaceuticals and medical devices agency (PMDA) on March 2020. In comparison with the TBC regimen, cyclophosphamide is omitted, and the dose of thiotepa is lower (250 mg/m^2, 3 days in TBC; 5 mg/kg, 2 days in BuTT) in BuTT, therefore BuTT could be less toxic in comparison with TBC, and no treatment-related deaths were observed in the phase I study in Japan. Further investigation on the efficacy and safety of BuTT in actual clinical practice is warranted. We have constituted a multidisciplinary team in our institution in order to perform HDC/ASCT using BuTT in relapsed/refractory PCNSL. Treatment indications are as follows; 65 years old or younger, previously treated by rituximab, methotrexate, procarbazine and vincristine (R-MPV), good organ function and neurological status. Future directions along with preliminary treatment results will be discussed at the meeting.

Key words: PCNSL | High-dose chemotherapy | BuTT

CNS METASTASIS (MET)

MET-3

A CASE OF INTRAPITUITARY ADENOMA METASTASIS FROM ADVANCED GASTRIC CANCER

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Metastasis from extracranial tumor into a pituitary adenoma is a rare case. We report a case of metastasis from gastric cancer to a giant pituitary tumor. A 65-year-old man had been drinking more water and had an increased frequency of urine in 10 years. From that time, the patient was gradually aware of the pain in his left eye. In 20XX the patient had a sudden severe headache and pain of his eyes and visited an ophthalmologist. The patient was referred to our institution with general malaise and nausea, vomiting. A cerebral MRI disclosed Extensive neoplastic lesions from the base of the skull to the nasal cavity. The left eye had esotropia and abduction disorder. Laboratory test demonstrated hyponatremia (Na 126mEq/L) and decreased in plasma osmolality (273mOsm/kg), D-dimer, fibrinogen and CA19-9 were high level. One week after admission, the patient's symptom was getting worse. The patient underwent FDG PET/CT, which showed FDG avid in the gastric wall and clivus tumor. The lesion was suspected gastric cancer and performed Esophagogastroduodenoscopy. The biopsy-based pathology was showed cubic and round cells with high NC ratio and signet-ring cells containing mucin. And clivus tumor was biopsied at an otolaryngologist because part of the tumor was exposed from the nasal cavity. The biopsy-based pathology was showed a small amount of adenocarcinoma cells which is surrounded by pituitary adenoma. The patient was diagnosed as intrapituitary adenoma metastasis from advanced gastric cancer and has been started radiation therapy. But the level of consciousness dropped sharply, so radiation therapy had become difficult to continue. The patient transferred to palliative care ward and died 3 months after his first visit. In this case, diagnosis and treatment were difficult due to the that the image was a finding a malignant tumor and the rapid progression of symptoms.

Key words: pituitary adenoma | gastric cancer | tumor-to-tumor metastasis

MET-4

CLINICAL INVESTIGATION OF THE CASES RECURRED AS DISSEMINATION AFTER POSTOPERATIVE LOCAL IRRADIATION FOR METASTATIC BRAIN TUMORS

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Last year, the authors examined the outcome of the patients with metastatic brain tumor (MBT)treated by whole-brain irradiation (WBRT)or local irradiation (LRT)after surgery. As a result, it was shown that the overall survival (OS) was same but the recurrence pattern was different. Furthermore, it was shown that there were some cases with disseminated recurrence in the LRT group. One year has passed, cases showing disseminated recurrence after LRT were examined. The subjects were 28 patients for whom LRT was selected as postsurgical irradiation since December 2017, with an average age of 66.2 years and a male-female ratio of 19: 9. Non-small cell lung cancer was the most in 17 cases. During the observation period, recurrence was observed in 12 cases, new outbreaks at other sites in 8 cases, disseminated recurrence in 4 cases, and no local recurrence. There was no clear difference in kinds of carcinoma and removal fashion between disseminated recurrence cases and other cases. Disseminated recurrence occurred between 3–10 months after surgery, 2 presented with headache, 1 with convulsions, 1 confirmed during follow-up of images, and all underwent WBRT. The lesions shrank after irradiation, but they were easy to re-grow, and the prognosis was poor. On the other hand, 10 cases died in 24 cases other than disseminated recurrence, but all cases died of primary cancer. Although LRT after surgery is non-inferior to WBRT in terms of OS and has the advantage of maintaining cognitive function, this study shows that there is a considerable risk of disseminated recurrence regardless of the removal fashion or kinds of carcinoma. It was also shown that prognosis after disseminated recurrence was poor. It is desirable to select postoperative irradiation after explaining the recurrence pattern, and when LRT is adopted, it is necessary to consider setting a short observation interval immediately after irradiation.

Key words: metastatic brain tumor | recurrence | dissemination

MET-5

SALVAGE SURGICAL RESECTION AFTER LINAC-BASED STEREOTACTIC RADIOSURGERY AND RADIOTHERAPY FOR BRAIN METASTASIS

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Methods: Between November 2009 and December 2018, 335 consecutive patients with 1085 brain metastases were treated with SRS/fSRT for newly diagnosed brain metastasis at our hospital. Nineteen of 335 patients (5.6%) and 19 of 1044 brain metastases (1.8%) went on to receive SSR after SRS/fSRT during this study period. Two patients underwent multiple surgical resections. Nineteen consecutive patients underwent 21 SSRs. Results: The median time from initial SRS/fSRT to SSR was 14 months (range: 2–96 months). The median follow-up after SSR was 15 months (range: 2–76 months). The range of tumor volume at initial SRS/fSRT was 0.12–21.46 cm3 (median: 2.19 cm3). Histopathological diagnosis after SSR was recurrence, radiation necrosis (RN) and cyst formation in 13 and 6 cases, respectively. The time from SRS/fSRT to SSR were shorter in the recurrence than in the RNs and cyst formation, but these differences did not reach statistical significance ($p = 0.07$). The median survival time from SSR and from initial SRS/fSRT was 17 months and 74 months, respectively. The cases with recurrence had a significantly shorter survival time from initial SRS/fSRT than those without recurrence ($p=0.045$).Conclusion: The patients treated with SRS/fSRT for brain metastasis need long-term follow-up. SSR is a safe and effective treatment for the recurrence, RN, and cyst formation after SRS/fSRT for brain metastasis.

Key words: brain metastasis | stereotactic radiosurgery | radiation necrosis