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Lack of Apparent Neurotoxicity in Older Patients with Primary Central Nervous System Lymphoma Receiving Long-term Tirabrutinib: Report of 2 Cases

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Abstract

Older patients represent a unique and vulnerable subgroup, requiring careful consideration when determining treatment options. Treatment-related leukoencephalopathy is commonly observed in older patients months to years after receiving radiotherapy and/or methotrexate for primary central nervous system lymphoma (PCNSL). Tirabrutinib is an orally available, highly selective, and potent second-generation Bruton's tyrosine kinase inhibitor (BTKi) approved for treating recurrent/refractory PCNSL in Japan. However, limited studies evaluate the imaging findings in patients receiving tirabrutinib. In this study, we reported 2 cases of older patients with PCNSL who did not develop treatment-related neurotoxicity or leukoencephalopathy after long-term administration of tirabrutinib.

Keywords: older, leukoencephalopathy, primary central nervous system lymphoma, tirabrutinib

Introduction

Patients aged older than 60 years account for more than 50% of all primary central nervous system lymphoma (PCNSL) cases and are at a higher risk of treatment-related toxicities.[1)] Neurotoxicity is a common consequence of chemoradiotherapy, characterised by deterioration in cognitive function, mood alterations, and imaging findings that often correlate with leukoencephalopathy. Due to the significant association between whole-brain radiotherapy (WBRT) combined with high-dose methotrexate (HD-MTX) and the incidence of neurotoxicity, WBRT should be avoided. Unfortunately, approximately 26% of patients receiving HD-MTX treatment alone still experience neurotoxicity.[2)] Recently, tirabrutinib, an orally available and potent second-generation Bruton's tyrosine kinase inhibitor (BTKi), has been approved in Japan for treating refractory or recurrent PCNSL cases. This drug is generally well tolerated and has high kinase specificity. However, studies reporting the treatment-related imaging findings of tirabrutinib are limited. In this report, we describe 2 cases of long-term tirabrutinib treatment without neurotoxicity or leukoencephalopathy.

Case Report

Case 1

A 76-year-old woman was admitted to our hospital with a head injury following a month of headaches and worsening gait disturbance. Her Karnofsky Performance Score (KPS) was 50%, and her Mini-Mental State Examination (MMSE) score was 13 out of 30. Imaging studies revealed multiple deep-seated tumours (Fig. 1A-C). An endoscopic transventricular biopsy confirmed a diagnosis of diffuse large B-cell lymphoma (DLBCL). No other PCNSL lesions were found in ocular and spinal examinations. A whole-body computed tomography (CT) scan did not show systemic lymphoma, confirming the PCNSL diagnosis. She began treatment with rituximab, HD-MTX, procarbazine, and vincristine (R-MPV). After 5 courses, a partial response was observed (Fig. 1D-F). Due to moderate renal impairment and the patient's refusal of consolidation radiother-

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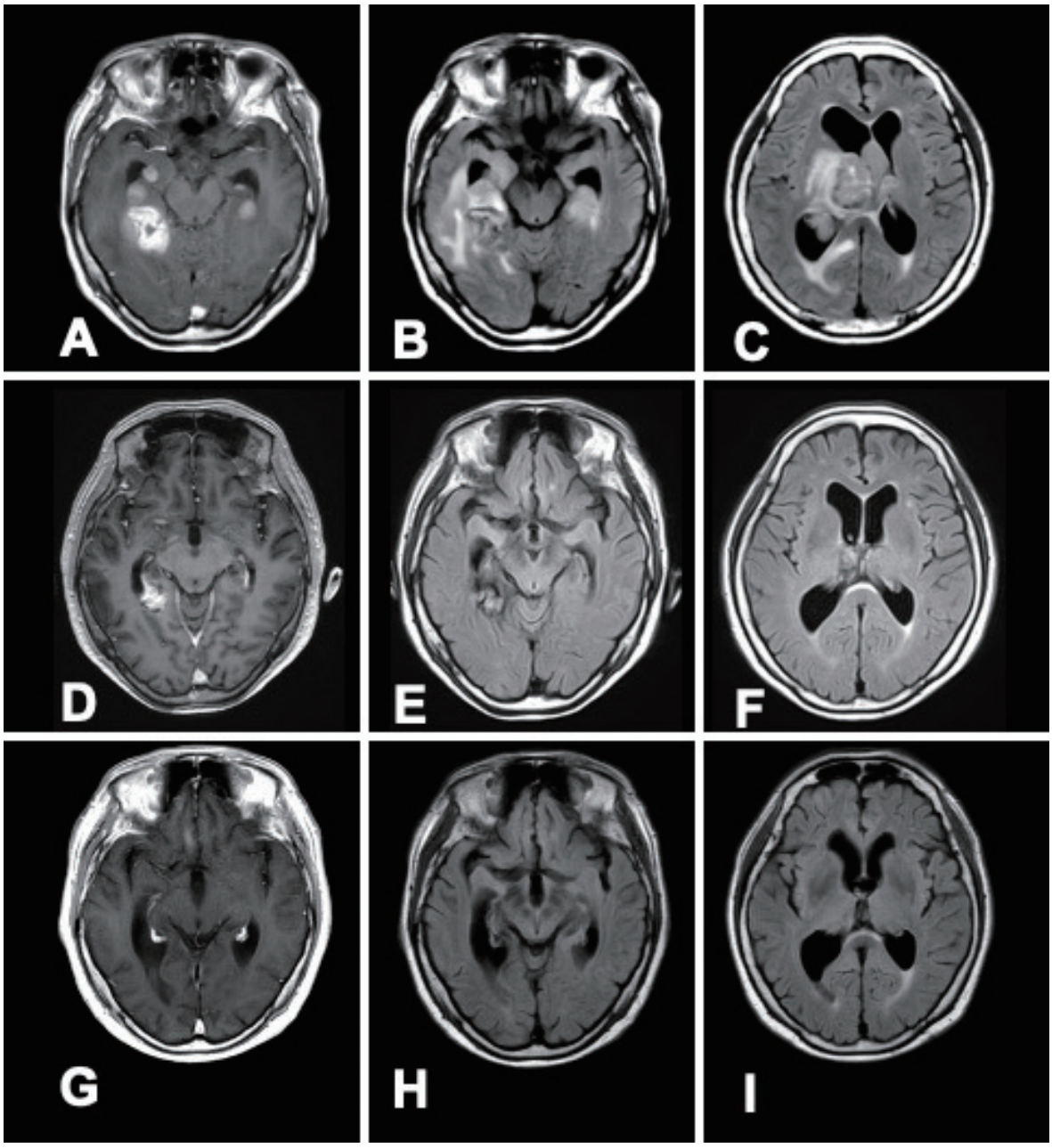

Fig. 1 Case 1. (A) Axial Gd-T1, (B) axial FLAIR, and (C) axial FLAIR images prior to treatment initiation. Multiple lesions were identified in the right thalamus and bilateral temporal lobes. Following 5 cycles of R-MPV, residual tumours were still detected in (D) axial Gd-T1, (E) axial FLAIR, and (F) axial FLAIR images. No evidence of tumour development or progressive white matter changes, including leukoencephalopathy, was found in (G) axial Gd-T1, (H) axial FLAIR, and (I) axial FLAIR images taken after 32 months of tirabrutinib treatment. FLAIR: fluid-attenuated inversion recovery; Gd-T1: gadolinium-enhanced T1-weighted imaging; R-MPV: rituximab, high-dose methotrexate, procarbazine, and vincristine

apy, treatment was changed to 480 mg of tirabrutinib daily under fasting conditions for the residual tumour. Her KPS was 70% at the start of tirabrutinib administration. During treatment, she developed transient leukopenia and neutropenia, and a skin rash appeared within a week but was promptly treated with betamethasone. Complete remission was achieved, with no cognitive deterioration observed after 32 months of tirabrutinib administration. Her MMSE score was 22, and her KPS was 80%. Imaging studies showed no tumour progression, white matter changes, or brain atrophy (Fig. 1G-I).

Case 2

An 80-year-old man with a history of heart failure and

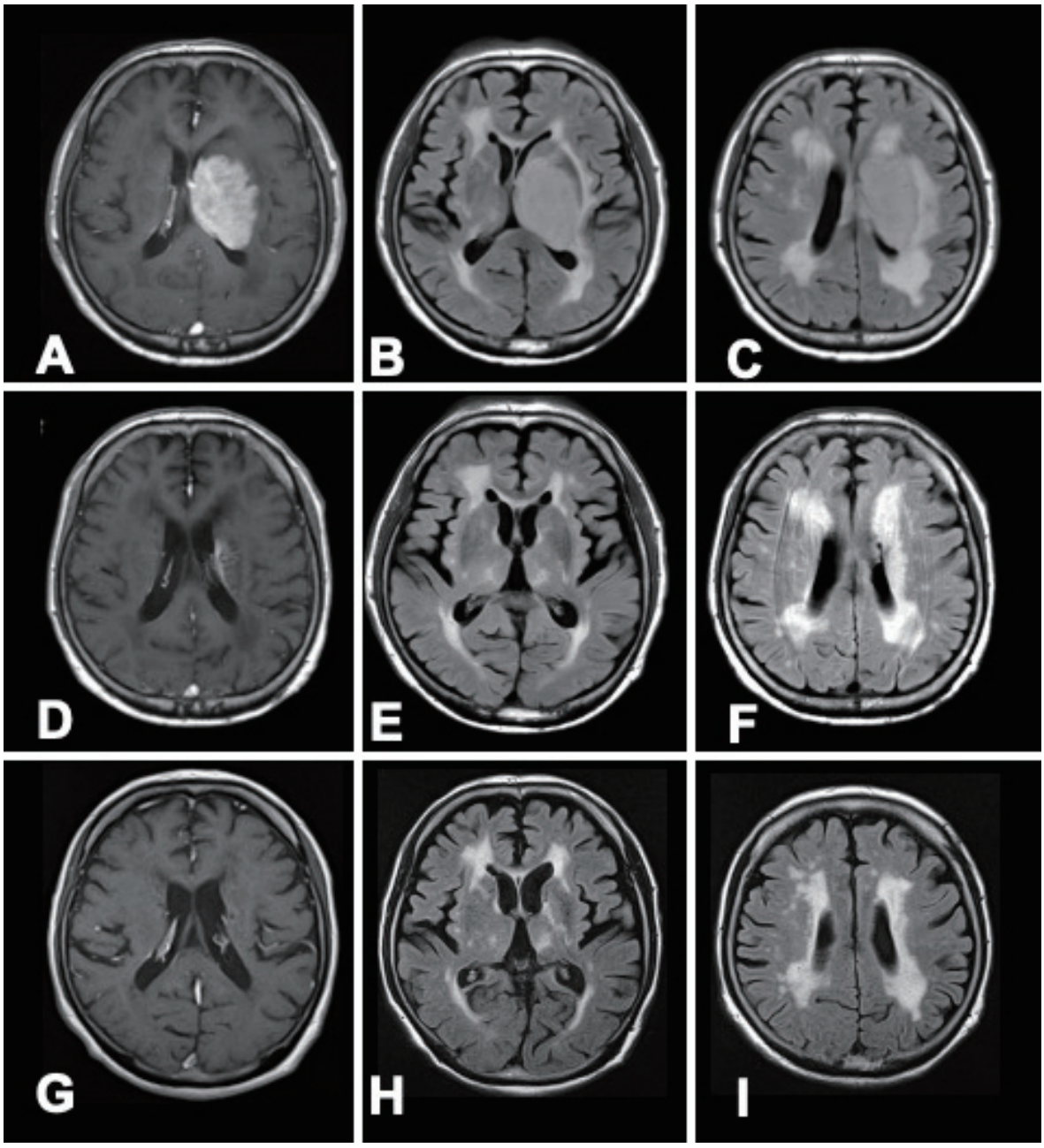

Fig. 2 Case 2. (A) Axial Gd-T1, (B) axial FLAIR, and (C) axial FLAIR images prior to treatment initiation. The tumour was located in the left thalamus with diffuse white matter changes. (D) Axial Gd-T1, (E) axial FLAIR, and (F) axial FLAIR images following 2 cycles of platinum-based multi-drug chemotherapy with rituximab, carboplatin, and etoposide. (G) Axial Gd-T1, (H) axial FLAIR, and (I) axial FLAIR images after 20 months of tirabrutinib treatment showed no tumour progression and no progressive white matter changes, including leukoencephalopathy. FLAIR: fluid-attenuated inversion recovery; Gd-T1: gadolinium-enhanced T1-weighted imaging

atrial fibrillation was admitted to our hospital with right hemiparesis and cognitive impairment. His MMSE score was 14, and his KPS was 50%. Imaging revealed a left paraventricular deep white matter tumour invading the thalamus and basal ganglia (Fig. 2A-C). A stereotactic biopsy confirmed DLBCL. No other PCNSL lesions were detected in ocular and spinal examinations. A whole-body CT scan ruled out systemic lymphoma, confirming the PCNSL diagnosis. Due to heart failure, HD-MTX treatment was avoided. The patient received 2 cycles of platinum-based chemotherapy with rituximab, carboplatin, and etoposide before developing severe thrombocytopenia, after which tirabrutinib was initiated (Fig. 2D-F). He began 480 mg of tirabrutinib daily under fasting conditions for the

residual tumour. At the start of tirabrutinib treatment, his MMSE score was 22, and his KPS was 70%. During treatment, he experienced transient neutropenia but tolerated tirabrutinib well. Complete remission was achieved. After 20 months of continuous tirabrutinib administration, his KPS improved to 90%, and his MMSE score to 29. Imaging studies showed no tumour progression, white matter changes, or brain atrophy (Fig. 2G-I).

Discussion

Neurotoxicity is a chemoradiotherapy-related toxicity observed in patients receiving chemotherapy, radiotherapy, or both. Clinical symptoms of neurotoxicity include deterioration in cognitive function, behavioural problems, and mood alterations, which radiologically correlate with the presence of leukoencephalopathy. Leukoencephalopathy is defined as the presence of white matter hyperintense lesions on fluid-attenuated inversion recovery and T2-weighted images appearing after treatment.[3] Among patients receiving HD-MTX-based chemotherapy, 46% showed radiological neurotoxicity and 26% exhibited clinical neurotoxicity.[2] In another study, approximately half of the patients developed leukoencephalopathy within 2.8 to 10.7 months after initiating HD-MTX-rituximab and HD-MTX, respectively.[4] In some cases, the condition can severely progress, leading to permanent neurological deficits and even death.[5] Platinum-based chemotherapy is also associated with neurotoxicity. Ryan et al.[6] reported the incidence of reversible posterior leukoencephalopathy with impaired consciousness and seizures in an older patient who received a combination of carboplatin and etoposide. Therefore, the condition warrants careful consideration.

Considering the risk of delayed neurotoxicity, we decided to avoid irradiation and instead administer a second-generation BTKi, tirabrutinib, which is widely used for relapsed or refractory PCNSL in Japan. Tirabrutinib shows excellent selectivity, inhibitory activity, a broader safety window, and lower toxicity than first-generation BTKi. Yonezawa et al.[7] revealed that daily administration of tirabrutinib resulted in an overall response rate of 63.6%. With a median follow-up of 37.1 months, daily 480 mg tirabrutinib under fasting conditions was associated with improved progression free survival of 5.8 months and not reached overall survival in patients with relapsed/refractory PCNSL.

Tirabrutinib is generally well tolerated and safe, with frequently reported mild to moderate side effects, including skin-related disorders, diarrhoea, and haematologic adverse events such as lymphopenia, neutropenia, thrombocytopenia, anaemia, and leukopenia.[7-9] The reported fatal side effects were *Pneumocystis jirovecii* pneumonia and interstitial lung disease.[7] Approximately 70.5% of patients discontinued tirabrutinib treatment, mostly due to disease progression rather than adverse drug events, and 18.1% and 16.3% of patients received continuous tirabrutinib for 2 and 3 years, respectively.[7] In our study, both patients experienced transient cytopenia and recovered without medical intervention. The first patient experienced a skin rash during tirabrutinib administration, effectively alleviated by betamethasone. These patients were able to receive tirabrutinib continuously for over 20 months, and all treatment-related side effects resolved without complications.

The KPS scores were generally well-preserved. Both patients presented with a baseline KPS score of 70%, and throughout treatment, the KPS score was maintained above 70%. This finding is consistent with a previous study by Arakawa et al.,[10] which showed that KPS and quality of life scores were relatively well-preserved during tirabrutinib treatment. The MMSE is an important tool for evaluating neurocognitive function and serves as an independent prognostic factor for survival in patients with PCNSL.[11] However, studies reporting MMSE scores in patients receiving tirabrutinib are scarce. We report the MMSE score of the second patient, which improved from 22 to 29 during tirabrutinib treatment. A similar finding was documented by Okamura et al.,[12] who reported an improvement of over 10 points in the MMSE score after 150 days of continuous tirabrutinib administration in a patient ineligible for methotrexate. In addition to the well-preserved KPS and MMSE scores, our study highlighted the absence of leukoencephalopathy in both patients. To the best of our knowledge, no study has reported the neurotoxic effects of tirabrutinib, suggesting that this drug may have lower neurotoxicity in older patients than other chemotherapies. Nevertheless, further studies with adequate sample sizes and imaging are essential to confirm these findings.

Our cohort exhibited a favourable safety profile, good tolerability, and reduced neurotoxic effects with tirabrutinib, making it an ideal treatment option for older patients who are particularly susceptible to the adverse effects of chemoradiotherapy.

Acknowledgments

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Consent to Participate

Informed consent was obtained from all participants.

Conflicts of Interest Disclosure

All authors have no conflict of interest.

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