LETTER TO THE EDITOR
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A Case of Relapsed/Refractory Primary Central Nervous System B-Cell Lymphoma with Renal Insufficiency Successfully Treated with Linperlisib

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To the editor,

Primary central nervous system lymphoma (PCNSL) is a rare malignant tumor(1). Standard treatments include methotrexate-based chemotherapy, whole-brain radiotherapy and drugs including temozolomide, rituximab, and BTK inhibitors are also used(1). Chimeric antigen receptor T-cell (CAR-T) therapy has also shown efficacy(2). For relapsed/refractory PCNSL (R/R PCNSL), salvage regimen including thiotepa, ifosfamide, etoposide, and rituximab, has achieved response rates up to 52%, but which requires strict organ function and is associated with significant toxicity(3). In addition, many clinical trials are conducted to evaluate the efficacy of other drugs in the treatment of R/R PCNSL, such as immunomodulator (lenalidomide and pomalidomide), PD-1 monoclonal antibody(2). Here, we present a case of R/R PCNSL with renal insufficiency successfully treated with linperlisib.

A 62-year-old male, presented to Peking union medical college hospital (PUMCH) in May 2019 with decreased vision for 3 months. The ophthalmological examination showed vitreous opacity and yellowish-white lesions in the inferior temporal retina. The interleukin-6 (IL-6) in the aqueous humor was 10.6 pg/ml, and interleukin-10 (IL-10) was 71.4 pg/ml. A diagnostic left vitrectomy was performed and pathological tests revealed numerous immature lymphocytes, some cells with degenerative changes, suggestive of lymphoma. Flow cytometry of the vitreous fluid demonstrated approximately 60.4% monoclonal B cells, with CD19 positive, positive for CD19 but negative for CD10, FC7, and CD23, with restricted Lambda light chain expression and approximately 79.9% of the cells expressing Ki-67. Gene rearrangement analysis showed positive arrangements for IgH FR1-JH, IgH FR2-JH, IgH

FR3-JH, consistent with high-grade non-Hodgkin B-cell lymphoma. Brian MRI revealed a patchy abnormal signal in the left precentral gyrus with abnormal enhancement. Whole-body PET/CT showed no evidence of extracranial disease. He was diagnosed as PCNSL and treated with seven cycles of R2-MTX (rituximab + lenalidomide + methotrexate) regimen based on previous PUMCH research(4), achieving complete remission. The main complications included hypertension, diabetes, left kidney stones. Surgical intervention was not performed due to ongoing lymphoma treatment. The patient's baseline serum creatinine was within the normal range. During the first cycle of methotrexate ($3.5g/m^2$), serum creatine increased from 98umol/L to 163 umol/L. Genetic testing revealed an MTHFR TT genotype, associated with slower methotrexate metabolism and increased risk of methotrexate-related nephrotoxicity. In subsequent cycles, the methotrexate dose was reduced to $2.5g/m^2$, with close monitoring. Serum creatinine stabilized at approximately 120 μmol/L, and estimated glomerular filtration rate (eGFR) fluctuated between 50–60 ml/min/1.73 m^2. Lenalidomide (25mg/day) was administered as maintenance therapy, in accordance with a PUMCH trial protocol(5). In November 2020, he developed unsteady gait and intermittent anomic aphasia. Brain MRI showed a patchy abnormal signal beside the posterior horn of the left lateral ventricle. Brian PET/CT showed a slightly high-density lesion in the same region with significantly increased metabolic activity. The IL-10 in cerebrospinal fluid was 176.0 pg/ml. Based on the findings, it was considered as R/R PCNSL without brain biopsy(6). Due to chronic renal insufficiency, a regimen of sintilimab (200mg once every 3 weeks) and zanubrutinib (160mg bid) was initiated based on the prior experience of PUMCH, and continued for 2 years, achieving a best efficacy of partial remission (PR). In March 2023, treatment was switched to zanubrutinib monotherapy. After eight months, he developed unsteady gait and decreased vision . Brain MRI revealed a slightly high signal in the splenium of the corpus callosum. Sintilimab was reintroduced; however, after two cycles, the lesion continued to enlarge. In January 2024, he was changed to linperlisib (80mg qd) monotherapy. Drug concentrations in cerebrospinal fluid and blood were determined 2 hours after medication, which were 369.141 ng/ml and 43.78 ng/ml, and the blood-brain barrier (BBB) crossing rate was 11.86%. After ten months of treatment, the patient's neurological symptoms improved, and brain MRI demonstrated lesion shrinkage and signal reduction, consistent with PR (Figure 1). There were no significant abnormalities monitoring blood routine, liver and kidney functions. At the latest follow-up in July 2025, the patient maintained PR without any ongoing therapy.

Linperlisib, a selective phosphatidylinositol 3-kinase-δ (PI3Kδ) inhibitor approved for relapsed/refractory follicular lymphoma(7). Given that PCNSL frequently harboring MYD88L265P and CD79B mutations, which may be critical for B-cell receptor (BCR) signaling, lymphocyte survival, and tumor proliferation(1, 8), linperlisib may also respond to this signal pathway. additionally, linperlisib may enhance the cytotoxicity of anti-CD20 therapies by targeting BCR-dependent survival pathways. Pharmacokinetic analysis in this case confirmed blood–brain barrier penetration, with CSF concentration exceeding the drug's IC50 (4.6 nM/2.7 ng/mL)(8). Linperlisib-related adverse events mainly included pneumonia and hematological toxicity.

In conclusion, treatment of R/R PCNSL remains challenging in patients with renal dysfunction. This case highlights the potential of mechanism-based agents scuh as linperlisib to achieve durable responses in unfit or organ-impaired populations. Further clinical studies are warranted to clarify its efficacy and safety.

Keywords: Linperlisib, Primary Central Nervous System Lymphoma, B-Cell Lymphoma, relapse

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Informed Consent: This research involves Human Participants, and consent for the publication of one`s personal details, images, videos, and/or other identifiable information in the manuscript had been collected and could be acquired upon necessary request from authors.

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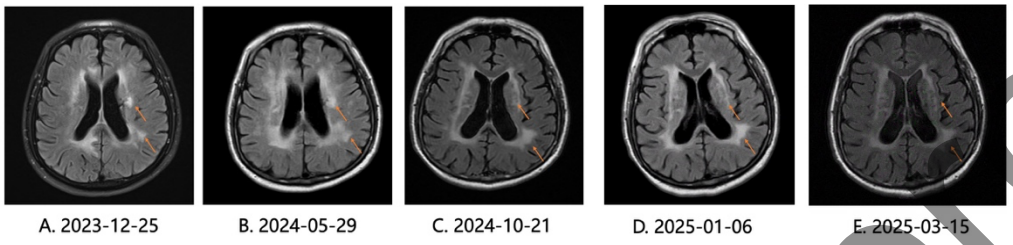

Figure 1: Sequential brain MRI findings during treatment with linperlisib. (A), brain MRI on 25th, Dec, 2023: yellow arrow showed tumor relapse. (B), brain MRI on 29th, May, 2024: decreased signal intensity of the relapsed tumor. (C), brain MRI on 21st, Oct, 2024: further reduction in size and signal intensity of the lesion. (D), brain MRI on 6th, Jan, 2025: decreased size and signal maintained. (E), brain MRI on 15th, Mar, 2025: lesion size and signal remained stable at the reduced level.