News Release

Title

***CD79B* Y196 Mutation is a Potent Predictive Marker for Favorable Response to R-MPV in Primary Central Nervous System Lymphoma**

Key Points

- R-MPV achieved an excellent tumor control rate (61.6% and 69.9% of 5-year progression-free and overall survival rates, respectively)
- Patients with *CD79B* Y196 mutations exhibited prolonged survival in the R-MPV cohort. However, the association of *CD79B* Y196 mutation with a better prognosis was not observed in the HD-MTX cohort, which indicated that *CD79B* Y196 mutation was a predictive marker for a favorable response to R-MPV.
- We established an all-in-one rapid genotyping system for *MYD88* L265P and *CD79B* Y196 mutation. The rapid identification of *MYD88* L265P and *CD79B* Y196 mutations can be helpful not only for the accurate molecular diagnosis of PCNSL but also for the prediction of response to R-MPV.

Summary

A research group led by Dr. Junya Yamaguchi, Dr. Fumiharu Ooka, and Dr. Ryuta Saito of the Department of Neurosurgery, Nagoya University Graduate School of Medicine, performed an integrated analysis of genetic abnormalities and prognosis in 85 cases of primary central nervous system lymphoma (PCNSL) and found that the *CD79B* Y196 mutation was a predictive marker for favorable response to R-MPV therapy for PCNSL. In addition, using the *MYD88* L265P mutation as a diagnostic marker, which is specific and frequently observed in PCNSL, we developed a system to rapidly analyze the *MYD88* L265P and *CD79B* Y196 mutations, enabling molecular diagnosis of PCNSL and prediction of response to R-MPV therapy in approximately 90 minutes.

PCNSL is one of the rare malignant brain tumors that predominantly affects the elderly, but its incidence is increasing with the aging of the population in recent years. Although the prognosis of PCNSL has improved with the development of chemotherapy, data on long-term prognosis and prognostic factors in a large number of patients have been insufficient due to the rarity of the disease. We analyzed the genetic abnormalities and prognosis of PCNSL in 85 patients treated with R-MPV or HD-MTX therapy and found that R-MPV therapy has a better long-term prognosis than conventional HD-MTX therapy and that patients harboring *CD79B* Y196 mutation are more sensitive to R-MPV therapy and have a better prognosis. This prognostic benefit of the *CD79B* Y196 mutation was not observed in patients who treated with HD-MTX therapy, indicating that the *CD79B* Y196 mutation is a predictor of good response to R-MPV therapy. Furthermore, using the *MYD88* L265P mutation as a diagnostic marker, we developed a rapid analysis system for the *MYD88* L265P and *CD79B* Y196 mutations, making it possible to determine the molecular diagnosis of PCNSL and predict response to therapy within 90 minutes. The results obtained from this study are expected to enable rapid and accurate molecular

diagnosis of PCNSL and stratification of treatment based on the presence or absence of the *CD79B* Y196 mutation.

Research Background

Primary central nervous system lymphoma (PCNSL) is a rare brain tumor, but it is more common in the elderly people, and its incidence is increasing with the aging of the population in recent years. Unlike most malignant brain tumors, PCNSL is highly sensitive to chemotherapy and radiation therapy, so surgery is limited to biopsy for diagnosis, and chemoradiotherapy is the standard treatment strategy. Although the prognosis has improved with the development of chemotherapy, the current treatment strategy is to increase the intensity of chemotherapy and decrease or omit the intensity of radiotherapy, because late effects after radiotherapy, such as cognitive impairment, are problematic for long-term survivors. Currently, R-MPV therapy combined with reduced dose radiotherapy is widely administered. However, due to the rarity of the disease, the long-term prognosis and response predictive factors of R-MPV therapy have not been investigated in a large number of patients. In addition, recent comprehensive genetic analyses have reported that point mutations in the MYD88 and CD79B genes are frequently found in PCNSL, but the relationship between these gene mutations and prognosis has not been sufficiently investigated. Therefore, our research group investigated the long-term prognosis of R-MPV therapy compared to HD-MTX therapy, which has been the standard of care, and the relationship between the mutations and prognosis.

Research Results

We investigated the relationship between genetic abnormalities and prognosis in 85 patients with newly diagnosed PCNSL. 21 of the 85 patients were treated with HD-MTX regimen and 64 with R-MPV. R-MPV had a significantly better prognosis than HD-MTX (R-MPV cohort: 5-year Progression-free survival/overall survival = 82.5%/61.6% vs. HD-MTX cohort: 5-year progression-free survival/overall survival = 47.7%/23.8%, log-rank test: progression-free survival/overall survival = $P < 0.001$ / $P = 0.021$). (Figure 1) Long-term survivors tended to have a better quality of life in the R-MPV cohort. Genetic analysis identified the *MYD88* L265P mutation in 70.2% of patients and the *CD79B* Y196 mutation in 40.4% of patients. We found that patients harboring the *CD79B* Y196 mutation had significantly better progression-free survival and overall survival (*CD79B* Y196 positive: 5-year progression-free survival/overall survival = 88.8%/88.8% vs *CD79B* Y196 negative: 5-year progression-free survival/overall survival = 50.0%/58.1%, log-rank test: progression-free survival/overall survival: $P = 0.028$ / $P = 0.040$). This result was not observed in patients treated with HD-MTX therapy, indicating that the *CD79B* Y196 mutation is a predictive marker for favorable response to R-MPV therapy.

The *MYD88* L265P mutation is highly specific for PCNSL among malignant brain tumors and can be applied as a diagnostic marker, and we developed a system to determine the molecular diagnosis of PCNSL and response to R-MPV therapy by determining the *MYD88* L265P and *CD79B* Y196 mutation. In four consecutive patients scheduled for biopsy surgery, the gene was extracted from the collected tumor tissue and analyzed by this system, and an accurate determination was obtained within 90 minutes.

Research Summary and Future Perspective

By analyzing a large number of PCNSL cases, our research group has identified the excellent long-term results of R-MPV therapy, the role of the *CD79B* Y196 mutation as a predictive marker for favorable sesponse to R-MPV therapy, and developed a rapid analysis system for the *MYD88* L265P and *CD79B* Y 196 mutations. The system will enable rapid induction of chemotherapy by providing a molecular diagnosis of PCNSL rapidly after biopsy, which has previously required about a week after biopsy, and will be applicable to stratification of treatment intensity, such as omitting radiotherapy, based on the presence or absence of *CD79B* Y196 mutation.

Publication

CD79B Y196 Mutation is a Potent Predictive Marker for Favorable Response to R-MPV in Primary Central Nervous System Lymphoma

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