Tirabrutinib

Tirabrutinib (brand name Velexbru) is a drug used for the treatment of autoimmune diseases and hematological malignancies.

Tirabrutinib was approved in March 2020 in Japan for the treatment of recurrent or refractory primary central nervous system lymphoma.

In addition, tirabrutinib is in clinical development by Ono Pharmaceutical and Gilead Sciences in the United States, Europe, and Japan for autoimmune disorders, chronic lymphocytic leukemia, B cell lymphoma, Sjogren's syndrome, pemphigus, and rheumatoid arthritis.

Tirabrutinib is an irreversible inhibitor of Bruton's tyrosine kinase.

Case series

The safety, tolerability, efficacy, and pharmacokinetics of tirabrutinib, a second-generation, highly selective oral Bruton's tyrosine kinase inhibitor, were evaluated for relapsed/refractory primary central nervous system lymphoma (PCNSL).

Methods: Patients with relapsed/refractory PCNSL, Karnofsky performance status ≥70, and normal end-organ function received tirabrutinib 320 and 480 mg once daily (q.d.) in phase I to evaluate dose-limiting toxicity (DLT) within 28 days using a 3 + 3 dose escalation design and with 480 mg q.d. under fasted conditions in phase II.

Results: Forty-four patients were enrolled; 20, 7, and 17 received tirabrutinib at 320, 480, and 480 mg under fasted conditions, respectively. No DLTs were observed, and the maximum tolerated dose was not reached at 480 mg. Common grade ≥3 adverse events (AEs) were neutropenia (9.1%), lymphopenia, leukopenia, and erythema multiforme (6.8% each). One patient with 480 mg q.d. had grade 5 AEs (pneumocystis jirovecii pneumonia and interstitial lung disease). Independent review committee assessed overall response rate (ORR) at 64%: 60% with 5 complete responses (CR)/unconfirmed complete responses (CRu) at 320 mg, 100% with 4 CR/CRu at 480 mg, and 53% with 6 CR/CRu at 480 mg under fasted conditions. Median progression-free survival was 2.9 months: 2.1, 11.1, and 5.8 months at 320, 480, and 480 mg under fasted conditions, respectively. Median overall survival was not reached. ORR was similar among patients harboring CARD11, MYD88, and CD79B mutations, and corresponding wild types.

Conclusion: These data indicate favorable efficacy of tirabrutinib in patients with relapsed/refractory PCNSL [1)].

Case reports

Yoshioka et al. reported that tirabrutinib was administered via nasogastric tubes to treat an elderly patient with primary central nervous system lymphoma (PCNSL). The patient was a 76-year-old woman who underwent endoscopic biopsy of multiple intracerebral masses, which resulted in the diagnosis of diffuse large B-cell lymphoma. The patient was diagnosed with PCNSL and was started on

an induction regimen of systemic chemotherapy with rituximab in combination with high-dose methotrexate. However, after the second cycle of chemotherapy, the tumor grew rapidly, and the patient went into a coma. As a result, the treatment was changed to nasogastric tube administration of tirabrutinib suspension. After 1 week of tirabrutinib administration, the patient's level of consciousness improved, and furthermore, after 2 weeks of tirabrutinib administration, the patient was able to take tirabrutinib orally. Although oral administration is the standard route of administration for tirabrutinib, this case study showed that the nasogastric tube administration of tirabrutinib suspension is a therapeutic option for patients with impaired consciousness or dysphagia [2)]

A 64-year-old patient with recurrent PCNSL enrolled in the phase I/II clinical trial of tirabrutinib, a second-generation BTK inhibitor designed for treating relapsed/refractory PCNSL. The left cerebellum lesions on magnetic resonance imaging disappeared one month after tirabrutinib treatment. The patient died because of suspected pneumocystis pneumonia and acute exacerbation of interstitial pneumonia 43 days after starting tirabrutinib. An autopsy confirmed no viable tumor cells in the entire brain, including the left cerebellum lesion, confirming complete obliteration of tumor cells by tirabrutinib. This letter pathologically confirms the effect of tirabrutinib on relapsed/refractory PCNSL for the first time in humans.Trial registration: JapicCTI-173646. Registered 14 July 2017, https://www.clinicaltrials.jp/cti-user/trial/ShowDirect.jsp?japicId=JapicCTI-173646 [3)].

Recovery from coma of a patient having acute progression of primary central nervous system lymphoma using tirabrutinib and methylprednisolone [4)].

1)
Narita Y, Nagane M, Mishima K, Terui Y, Arakawa Y, Yonezawa H, Asai K, Fukuhara N, Sugiyama K, Shinojima N, Kitagawa J, Aoi A, Nishikawa R. Phase I/II study of tirabrutinib, a second-generation Bruton's tyrosine kinase inhibitor, in relapsed/refractory primary central nervous system lymphoma. Neuro Oncol. 2021 Jan 30;23(1):122-133. doi: 10.1093/neuonc/noaa145. PMID: 32583848; PMCID: PMC7850159.
2)
Yoshioka H, Okuda T, Nakao T, Fujita M, Takahashi JC. Experience with nasogastric tube administration of tirabrutinib in the treatment of an elderly patient with primary central nervous system lymphoma. Int Cancer Conf J. 2021 Jun 5;10(4):290-293. doi: 10.1007/s13691-021-00491-1. PMID: 34567940; PMCID: PMC8421486.
3)
Okita Y, Kano-Fujiwara R, Nakatsuka SI, Honma K, Kinoshita M. Histological verification of the treatment effect of tirabrutinib for relapsed/refractory primary central nervous system lymphoma. Exp Hematol Oncol. 2021 Apr 26;10(1):29. doi: 10.1186/s40164-021-00222-5. PMID: 33902692; PMCID: PMC8077707.
4)
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