News Release

Title
Publication of the world’s first prospective clinical trial for intravascular large B-cell lymphoma ~Establishment of current safe and effective treatment leading to the improvement of outcomes in patients with intravascular large B-cell lymphoma~

Key Points
• Intravascular large B-cell lymphoma (IVLBCL) is a rare type of malignant lymphoma. The disease normally lacks lymphadenopathy, which makes accurate diagnosis difficult. Although the rituximab containing chemotherapies has improved clinical outcomes of IVLBCL, high risk of secondary central nervous system (CNS) involvement still remains an issue to be resolved.
• Phase 2 prospective trial aimed to determine the safety and efficacy of R-CHOP combined with high-dose methotrexate and intrathecal chemotherapy as CNS-oriented therapy in untreated IVLBCL was conducted. The result of the study displayed good outcomes.
• The result of this study provides the world’s first evidence of clinical outcomes in IVLBCL based on a prospective trial and a current safe and effective treatment which warrants future investigations.

Summary
Kazuyuki Shimada (Lecturer, Department of Hematology, Nagoya University Hospital), Professor Hitoshi Kiyoi (Professor, Department of Hematology and Oncology, Nagoya University Graduate School of Medicine), Motoko Yamaguchi (Lecturer, Department of Hematology, Mie University Hospital), and members of IVL study group in Japan (Representative, Tomohiro Kinoshita) conducted the world’s first prospective trial for untreated IVLBCL and have established current safe and effective treatment, which warrants future investigations.

Malignant lymphoma is one of hematological malignancy known to be quite heterogenous. IVLBCL is a rare type of malignant lymphoma characterized by the lack of lymphadenopathy; which makes accurate diagnosis difficult. Patients with IVLBCL have been treated with R-CHOP therapy, standard treatment for diffuse large B-cell lymphoma, however the high risk of secondary CNS involvement has been important clinical issue. Moreover, there has been no evidence based on prospective trials, and a standard treatment has not been established.

In the present study, phase 2 trial of R-CHOP combined with high-dose methotrexate and intrathecal chemotherapy as CNS-oriented therapy was conducted. Thirty-eight patients with untreated IVLBCL without apparent CNS involvement at diagnosis were enrolled. The primary endpoint of 2-year progression-free survival was 76%, and secondary endpoints were overall survival (OS) at 2 years of 92% and the cumulative incidence of secondary CNS involvement at 2 years of 3%, respectively. The adverse events were manageable. This trial is the world’s first prospective trial for IVLBCL, and a large-scale prospective trial would not be realistic due to its rarity. The result of the trial thus provides a current safe and effective treatment and warrants future investigations.

The treatment in this study could be immediately translatable to patients with IVLBCL as all the
drugs has been approved within the Japanese insurance system. This study is supported by the Practical Research for Innovative Cancer Control, the Japan Agency for Medical Research and Development (AMED) and has been published in the Lancet Oncology on March 11 2020 at 23:30 GMT.

**Research Background**

IVLBCL is a rare type of malignant lymphoma characterized by the selective growth of tumor cells in the lumina of small vessels. The disease normally lacks lymphadenopathy, whose diagnosis is known to be difficult. Patients with untreated IVLBCL has been treated with R-CHOP therapy, a standard regimen for DLBCL, however, the high incidence of secondary CNS involvement has been a clinical issue to be resolved. Moreover, no prospective trial for the disease has been conducted due to its rarity, and no standard regimen has been established.

**Research Results**

To determine the safety and efficacy of R-CHOP combined with CNS-oriented therapy including high-dose methotrexate and intrathecal chemotherapy in untreated IVLBCL patients without apparent CNS involvement at diagnosis, the multicenter phase 2 clinical trial was conducted. Thirty-eight patients, median age of 66 (range, 38-78), were enrolled. 2-year PFS as primary endpoint was 76% (figure 1), and OS at 2 years and the cumulative incidence of secondary CNS involvement at 2 years were 92% and 3%, respectively (figure 2). All the toxicities were manageable.
Research Summary and Future Perspective

This study provides the world’s first evidence based on a prospective trial for untreated IVLBCL patients. Considering the rarity of the disease, a large-scale prospective trial would not be realistic, and the treatment in this trial could be a current safe and effective treatment, which warrants future investigations. The treatment in this study can be immediately translatable to clinical practice in untreated IVLBCL patients without apparent CNS involvement at diagnosis between 20 to 79 years old. Further improvement of outcomes of IVLBCL would be expected.

Publication


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Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone combined with high-dose methotrexate plus intrathecal chemotherapy for newly diagnosed intravascular large B-cell lymphoma (PRIMEUR-IVL): a multicentre, single-arm, phase 2 trial

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