Old weapon, new target: Dasatinib against angioimmunoblastic T-cell lymphoma

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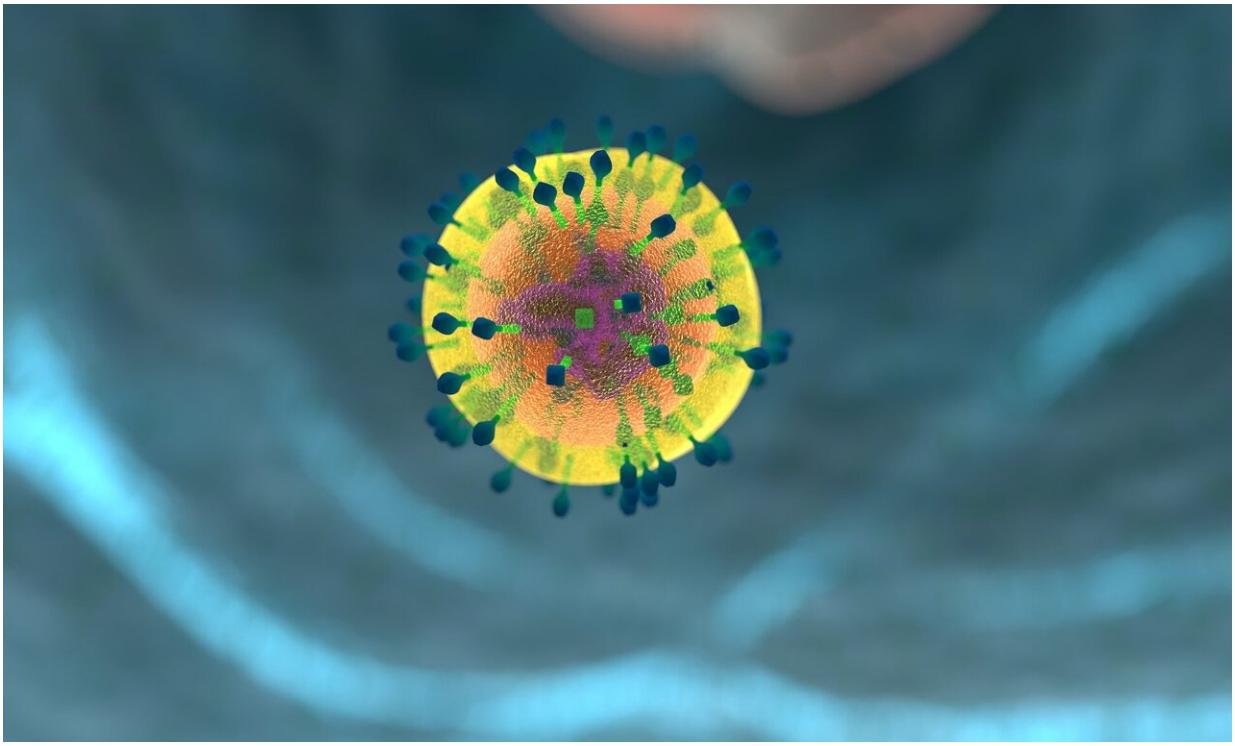

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Researchers from the University of Tsukuba have shown by in vivo experimentation on a mouse model that angioimmunoblastic T-cell lymphoma is highly dependent on T-cell receptor signaling. Further trials also suggest that dasatinib, by targeting the TCR pathway, improved outcomes in both the mouse model and in a clinical trial of five patients

who relapsed or were refractory to conventional therapy and therefore showed promise as a candidate drug for AITL treatment.

Angioimmunoblastic T-cell lymphoma (AITL) is an intractable form of non-Hodgkin lymphoma with a bleak prognosis. In a recent study, researchers from the University of Tsukuba, Japan, have demonstrated that T-cell receptor (TCR) signaling activated by specific gene mutations led to development of AITL-like lymphoma in experimental mice. Further results from a linked clinical trial suggest that the multi-kinase inhibitor dasatinib, used to treat specific leukemias, shows potential as an effective drug for this disease for relapsed or refractory AITL.

Lymphomas form a group of related cancers that affect the lymphatic system. They are classified according to the type of white blood cells (lymphocytes) affected as B-cell lymphomas or T-cell lymphomas. AITL is a rare and often aggressive T-cell lymphoma with a five-year survival of below 30%. Patients with AITL present with high fever, skin rash and symptoms suggestive of immune activation. Many patients have specific altered genes including the DNMT3A, TET2, IDH2, and RhoA genes, though the exact role these gene mutations play in the development of the disease is not fully understood.

Researchers at the University of Tsukuba first showed that TET2 loss paired with expression of the G17V RHoA mutant in mice led to development of AITL-like lymphoma. By targeting the TCR pathway, dasatinib successfully suppressed disease progression in AITL model mice and prolonged survival. "Our findings suggest that AITL is highly dependent on TCR signaling and that dasatinib could be a promising candidate drug for AITL treatment," says Dr. Mamiko Sakata-Yanagimoto, Associate Professor at the department of Hematology, Faculty of Medicine, and a senior author of the study.

The researchers followed this with a phase 1 clinical trial involving

patients with relapsed/refractory AITL following prior chemotherapy and/or autologous stem cell transplantation. Dasatinib, administered as a single drug, achieved partial responses in all evaluable patients; moreover, there were no previously undocumented safety concerns.

"Recently, many new drugs have been introduced as promising therapeutics for primary T-cell lymphomas including AITL," says Professor Shigeru Chiba, main author of the study. "However, currently there are no monotherapies that satisfactorily improve overall survival in relapsed or refractory cases. Our work suggests that targeting the TCR pathway should be considered in developing AITL treatment strategies."

Dasatinib, an oral drug long used to treat specific Philadelphia chromosome-positive leukemias, is on the WHO Model List of Essential Medicines. Given the encouraging outcomes of this study, further research is needed to firmly establish its place amongst therapeutics for AITL, especially regarding efficacy against specific mutations as well as clinical applicability and safety profile.

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