Precision Drug Discovery and Clinical Practice

Do-Hyun Nam

Department of Neurosurgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, South Korea

Email: nsnam@skku.edu

Despite advanced data sciences to identify targets and classifications of brain tumors, gliomas remain one of the most challenging medical conditions due to their tumor heterogeneity and unique microenvironment, including the blood-brain barrier and brain-specific immune responses.

Genome-based studies on the evolution of tumors after radiation-chemotherapy have shown that targeting founding alterations could provide benefits in these heterogeneous cancer cells. Among them, the FGFR3-TACC3 fusion (F3-T3) mutation is one of founding alterations that persists after radiation-chemotherapy. Most F3-T3-positive gliomas have high microvessel density (MVD) and co-overexpression of FGFR3, and occasionally exhibit extra-central nervous system metastasis.

F3-T3-positive gliomas have a sufficient vascular supply and a relatively low influence of the blood-brain barrier. Additionally, patient selection can be made by detecting only FGFR3 immunostaining, making it a potential target for successful clinical trials. To this end, antibody-drug conjugates targeting the F3-T3 fusion mutation, conjugated with a topoisomerase-1 inhibitor (Topo-1), have been developed. The preclinical results have shown the enhanced anti-tumor effects of this antibody-drug conjugate, both alone and in combination with temozolomide in a brain orthotopic F3-T3+ PDX model.

Based on these preclinical results, it is suggested that the analysis of the unmet medical needs and its genetic characteristics could be utilized for the development of precision drug discovery for gliomas, which remain a challenging medical condition.