Larotrectinibは多様な腫瘍タイプに効果的である (Abstract LBA2501)

新薬は小児および成人のがん種を問わず、持続的な有効性を示す

New drug shows durable efficacy across diverse pediatric and adult cancers

分子標的、経口、がんの発生部位に関係なく変異の型に基づく、初めての療法ー患者の年齢やがんの種類にかかわらず有効な薬剤ーが開発されたようである。Larotrectinibは、がん細胞内のTRK遺伝子が他の遺伝子と融合する際の遺伝子異常による産物であるトロポミオシン受容体キナーゼ(TRK)融合蛋白質の、選択的阻害薬である。17の異なる型の進行がんを有する成人および小児を対象とした臨床試験において、larotrectinibによる治療は76%の患者で奏効を認めた。Larotrectinibに対する奏効は持続的であり、79%が治療開始後12か月の時点で持続していた。このスタディ結果は2017年American Society of Clinical Oncology年次集会で取り上げられた。

Full Text

Scientists may have developed the first targeted, oral, tumor-type agnostic therapy – a cancer medicine that works comparably well across many kinds of cancer, regardless of patient age. In clinical trials of adults and children with 17 different types of advanced cancer, larotrectinib treatment resulted in responses in 76% of patients. Response to larotrectinib has been durable, with 79% of responses ongoing 12 months after starting treatment.

The study was featured at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting.

Larotrectinib is a selective inhibitor of tropomyosin receptor kinase (TRK) fusion proteins, which are a product of a genetic abnormality when a *TRK* gene in a cancer cell fuses with one of many other genes. It is estimated that this abnormality occurs in about 0.5% – 1% of many common cancers, but in greater than 90% of certain rare cancers, such as salivary gland cancer, a form of juvenile breast cancer, and infantile fibrosarcoma.

"*TRK* usions are rare, but occur in many different cancer types. In fact, at this point it is hard to find a cancer type where *TRK* fusions have not been reported," said lead study author David Hyman, MD, Chief of Early Drug Development at Memorial Sloan Kettering Cancer Center in New York. "These findings embody the original promise of precision oncology: treating a patient based on the type of mutation, regardless of where the cancer originated. We believe that the dramatic response of tumors with *TRK* fusions to larotrectinib supports widespread genetic testing in patients with advanced cancer to see if they have this abnormality."

Researchers analyzed data from 55 patients with *TRK* fusions enrolled in three ongoing phase I and phase II clinical trials. All patients (12 children and 43 adults) had locally advanced or metastatic cancer, including colon, lung, pancreatic, thyroid, salivary, and gastrointestinal cancers, as well as melanoma and sarcoma.

"This dataset, subject to independent central radiology review, will be submitted to FDA for larotrectinib's regulatory approval. If approved, larotrectinib could become the first therapy of any kind to be developed and approved simultaneously in adults and children, and the first targeted therapy to be indicated for a molecular definition of cancer that spans all traditionally-defined types of tumors," said Dr. Hyman.

In the first 50 patients with 17 different cancer types who have been on the study long enough to have at least two scans, 38 (76%) of these patients had a response. Of those, three patients with pediatric sarcomas previously not amenable to surgery went on to receive potentially curable surgery after larotrectinib shrank the tumors.

The median duration of treatment response has not yet been reached, as the majority of patients are still responding to treatment. At 12 months into treatment, 79% of responding patients remain progression free. To date, the longest duration of treatment response has been 25 months and is ongoing.

The most common side effects were fatigue and mild dizziness, which was expected as the normal TRK protein has a role in controlling balance. No patients needed to stop treatment due to side effects.

"Because larotrectinib was designed to target only TRK, it has been very well tolerated and does not cause many of the side effects associated with chemotherapy and multi-targeted therapy," said Dr. Hyman.

"Though the study is small and early, it demonstrates compelling evidence that may pave the way for a new class of drugs for rare tumors that could inform the future of precision medicine," said Sumanta Kumar Pal, MD, ASCO Expert.

TRK fusions were first discovered in colon cancer in 1982, but only recent technological advances, particularly next-generation sequencing (NGS), have enabled systematic detection of this abnormality. To date, scientists have found more than 50 different partner genes that fuse with one of three *TRK* genes (NTRK 1, 2, and 3).

TRK fusions arise early in cancer development and remain present as tumors grow and spread. The abnormal TRK fusion proteins are constantly "turned on," sending cancer cells signals to keep growing and dividing. "*TRK* fusions are like an ignition switch for cancer," said Dr. Hyman.

Although there are other experimental treatments that block TRK along with other proteins, larotrectinib is the first to selectively block TRK. This characteristic improves potency of the drug, while lowering side effects.

The researchers have identified what they believe to be the primary means by which tumors may grow resistant to larotrectinib, and they are studying another TRK-targeted therapy, LOXO-195, for the treatment of patients with cancer that regrows after initially responding to larotrectinib.

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