新薬は肺がん治療薬として有望である（Abstract: 8009）

新たなEGFR阻害薬は難治性非小細胞肺がんにおいて有望な作用を示す

New EGFR inhibitor shows promising activity in treatment-resistant non-small cell lung cancer

新規変異型選択的EGFRチロシンキナーゼ阻害薬（TKI）、AZD9291の第1相試験の結果は、EGFR変異を有する進行非小細胞肺がん（NSCLC）を有し標準的なEGFR阻害薬に対して不応の患者に対して新たな治療選択肢として有望であることを示した、との研究結果が第50回American Society of Clinical Oncology学会で発表された。このスタディにおいて、EGFR変異を有し1回以上の標準的なEGFR療法後に疾患が悪化した進行NSCLC患者199人が異なる用量のAZD9291を投与された。全ての用量および全てのサブグループ（脳転移患者を含む）において奏効が認められた。全体で、51%の患者に腫瘍の縮小を認めた。T790M変異が確認されている患者89人のうち64%においてAZD9291が奏効したのに対し、T790M陰性患者では23%であった。データカットオフの時点で、ほぼ全ての患者において奏効は持続して認められ、最長で8か月間以上持続した。この治療法が全生存期間を延長するかを究明するためには、さらに長期の経過観察が必要である。重要なことに、AZD9291は腫瘍内EGFRを選択的に標的とし、承認済みのEGFR TKIsよりも皮膚毒性が少ないようである。

Full Text

Findings from a phase I study of a new mutant selective EGFR tyrosine kinase inhibitor (TKI), AZD9291, point to a promising new treatment option for patients with advanced, EGFR mutant, non-small cell lung cancer (NSCLC) that is resistant to standard EGFR inhibitors according to researcher presented at the American Society of Clinical Oncology's 50th Annual Meeting. Roughly 50 percent of patients experienced tumor shrinkage, and the drug worked particularly well in patients with the T790M mutation (detected in 60 percent of patients), which causes the most common form of EGFR therapy resistance.

"There is currently no standard treatment for patients with lung cancer who experience disease progression after initial therapy with an EGFR kinase inhibitor," said lead study author Pasi A. Jänne, M.D., Ph.D., a professor of medicine at Dana-Farber Cancer Institute and Harvard Medical School in Boston, MA. "Although it is still a bit early, our study suggests that AZD9291 may offer an effective new therapy option for these patients, without the skin side effects we typically see with existing EGFR inhibitors."

EGFR mutations are found in 10-15 percent of Caucasian patients and about 40 percent of Asian patients with NSCLC. Many of these patients initially respond well to approved EGFR inhibitors erlotinib and afatinib, but all ultimately become resistant to this therapy – generally within 10 to 14 months. Many patients become resistant to EGFR inhibitors through the development of another mutation, the T790M mutation. The only therapy that is somewhat effective in patients with the T790M mutation is a combination of two EGFR inhibitors (afatinib and cetuximab), but it is very toxic.

In this study, 199 patients with advanced NSCLC harboring EGFR mutations, whose disease progressed after one or more standard EGFR therapies, received different doses of AZD9291. Responses were observed at all dose levels and in all subgroups of patients, including those with brain metastasis.

Overall, 51 percent of patients experienced tumor shrinkage. Among the 89 patients with a confirmed T790M mutation, 64 percent responded to AZD9291, vs. 23 percent of T790M-negative patients. The responses were still ongoing in nearly all patients at data cut-off, with the longest response lasting more than eight months.

Longer follow up is needed to determine if this therapy prolongs overall survival. Given that these data show that AZD9291 is working more effectively for patients with the T790M mutation, future studies of this drug will be limited to this subgroup of patients, according to the researchers.

Importantly, AZD9291 selectively targets EGFR in tumors and appears to cause fewer skin toxicities than approved EGFR TKIs. While existing drugs block both the mutant EGFR in the tumor and the normal EGFR in the skin (and other organs), which often leads to debilitating skin rash or acne, AZD9291 acts mostly on the mutant EGFR in a tumor.

"The reduced skin toxicity seen with AZD9291 heralds greater precision in targeting cancer mutations and sparing healthy tissues which retain normal germ line EGFR status," said Peter P. Yu, M.D., FASCO, ASCO President-Elect.

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