Everolimus prolongs progression-free survival for patients with neuroendocrine tumors

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Combination treatment with everolimus, an inhibitor of the mammalian target rapamycin (mTOR), and octreotide has shown to improve progression-free survival for patients with advanced neuroendocrine tumors and a history of carcinoid syndrome, according to researchers at The University of Texas MD Anderson Cancer Center.

Results of the international, randomized, placebo-controlled Phase III study were published today in the journal *Lancet*.

The treatment combination of everolimus and octreotide long-acting repeatable (LAR), a somatostatin analogue that has shown antitumor activity, led to a clinically meaningful five-month delay in tumor growth, compared to octreotide alone.

Neuroendocrine tumors, also known as carcinoids, are uncommon tumors arising from various primary sites. Frequently, carcinoids spread to the liver, causing a variety of symptoms termed carcinoid syndrome.

"There are currently no Food and Drug Administration (FDA) approved drugs for oncologic control of most neuroendocrine tumors," said James C. Yao, M.D., associate professor in MD Anderson's Department of Gastrointestinal Medical Oncology. "This research offers a promising option where there were limited options previously."

Dangerous and rare tumors

According to Yao, the number of people diagnosed with neuroendocrine tumors has increased more than five-fold over the past 30 years, from one in 100,000 people per year to 5.25 in 100,000 people per year. Nearly half of patients have regional or distant metastatic disease and 65 percent of those with advanced disease die within five years of diagnosis.

Everolimus, an immunosupressant agent used to prevent rejection of organ transplants, inhibits the mTOR protein, a central regulator of tumor cell division and blood vessel growth in cancer cells. Overaction of mTOR has been implicated in the pathogenesis of neuroendocrine tumors.

Preclinical studies have shown that mTOR inhibition may control growth of neuroendocrine tumors, and an earlier Phase II study at MD Anderson showed promising anti-cancer activity for everolimus in neuroendocrine tumors.

In May of this year, an international randomized Phase III study showed everolimus improved progression-free survival in pancreatic neuroendocrine tumors, a related disease, leading to its FDA approval for treatment of those rare tumors.

Somatostatin analogues, such as octreotide, improve hormone-related symptoms associated with neuroendocrine tumors. Octreotide LAR has also shown antitumor activity, prolonging time to disease progression in patients with certain types of neuroendocrine tumors.

Increase in progression-free survival

The study, named RADIANT-2, enrolled 429 participants with low-grade or intermediate-grade advanced (unresectable locally advanced or distant metastatic) neuroendocrine tumors and a history of carcinoid syndrome. Disease progression had been established by radiological assessment within the past 12 months.

Patients were given either 10 mg per day oral everolimus or placebo, both in conjunction with 30 mg intramuscular octreotide LAR, every 28 days. Treatment was continued until disease progression, withdrawal from treatment because of adverse effects or withdrawal of consent.

Median progression-free survival by was 16.4 months in the everolimus plus octreotide LAR group and 11.2 months in the placebo plus octreotide LAR group.

Side effects were higher but manageable in the combination arm. They included stomatitis (62 percent vs. 14 percent), fatigue (31 percent vs. 23 percent) and diarrhea (27 percent vs. 16 percent).

Next steps

Yao said additional exploratory analyses to adjust for the effect of randomization imbalances will be presented at American Society of Clinical Oncology (ASCO) gastrointestinal annual meeting in 2012.

"We are working with industry sponsor [Novartis] to develop a confirmatory study in neuroendocrine tumors," he said.

Provided by University of Texas M. D. Anderson Cancer Center

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