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Precision medicine brings new hope to those with advanced urothelial cancer

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Five of six patients with advanced metastatic urothelial cancer and at least one of two specific genetic abnormalities, responded to treatment with afatinib, which was approved in 2013 by the Food and Drug Administration for patients with lung cancer, researchers report online in the *Journal of Clinical Oncology*.

One patient, who had both mutations, had stable disease for 16 months after taking afatinib. None of the other 17 patients in the trial, who lacked those specific abnormalities, had a significant response to the drug.

The trial was designed to see if daily 40 milligram doses of afatinib could prevent tumor progression for at least three months in patients who had developed resistance to the only first-line treatment for metastatic bladder cancer. Those who had one of the two mutations averaged 6.6 months without progression of their cancers. That was more than four times longer than patients without the mutations, who averaged only 1.4 months.

"Seven out of 23, or nearly 30 percent of these patients, had one of these potentially treatable mutations," said study director Peter O'Donnell, MD, an assistant professor of medicine at the University of Chicago. "The connections linking afatinib with a better response to treatment for this group of patients are encouraging. Our next step is to organize a follow-up trial focused entirely on patients with at least one of these mutations."

"Compared to other drugs which have been tried for refractory metastatic bladder cancer, including immune therapies which will likely be approved, the time to disease progression is significantly longer with afatinib in patients carrying the genetic abnormalities," he added. "There have been no other drugs approved in the U.S. in decades in this disease setting, and only one drug approved in Europe. Its progression-free time was half of what we are seeing with afatinib in this same population of patients."

Urothelial carcinoma (UC) is the fourth most common cancer among males and, at 16,000 deaths a year, the eighth leading cause of cancer death in the United States. It affects the kidney, urinary bladder and accessory organs. These cells come into contact with waste products in the urine, such as chemicals from cigarette smoke, which can cause cancer.

There has been limited progress in developing effective new treatments for UC in the last 25 years, the study authors note. "Platinum-based therapy remains the only standard of care, with no approved second-line therapies."

Afatinib (marketed as Gilotrif®) inhibits the activity of multiple forms of two proteins—human epidermal growth factor receptor 2 (Her2) and epidermal growth factor receptor (EGFR)—that stimulate rapid cellular growth and division. Both are commonly involved in the development and progression of UC.

The researchers enrolled 23 patients with advanced UC into a phase 2 clinical trial. The median age was 67 years old. All of them had progressive disease despite platinum-based combination therapy. They all received 40mgs of oral afatinib per day. They were carefully monitored for drug-related complications and evaluated with CT and MRI scans every six weeks. The most common side effects were

diarrhea (83 percent), followed by rash (78 percent) and fatigue (57 percent). The dose was reduced for three patients, but there were no treatment-related deaths.

Two patients had a partial response (some shrinkage of tumor). Seven had stable disease, and 14 had ongoing progression of the disease.

The key finding, however, was that five out of the six patients with molecular alterations in at least one of two specific genes—multiple copies of Her2, or mutations and multiple copies of ERBB3, abnormalities associated with a worse prognosis in previous studies—responded to the treatment.

The second patient to enter the study had alterations in both HER2 and ERBB3. This patient never progressed while on therapy. After 10.3 months, the patient developed a cardiac problem and was taken off the drug. After a short break, however, patient two resumed taking afatinib, outside of the trial. Her disease did not progress for another 5.7 months.

This study, the authors note, has several limitations, particularly its small sample size. But the ability to detect such significant differences in outcomes "raises the possibility that these molecular alterations are indeed highly correlated with afatinib responsiveness." It is also important, they add, to understand the mechanisms that enabled the disease to develop resistance to afatinib.

"In the era of personalized medicine," they add, "a nuanced understanding of molecular studies is vital for identifying patients most likely to benefit form selected therapies."

More information: *Journal of Clinical Oncology*, dx.doi.org/10.1200/JCO.2015.66.3047

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