First Precision Medicine Trial in Cancer Prevention Identifies Molecular-based Chemoprevention Strategy

Study finds genetic predictor of oral cancer risk; proof of principle may apply to other cancers

November 06, 2015 | Scott LaFee

A team of scientists, led by researchers at University of California, San Diego Moores Cancer Center and The University of Texas MD Anderson Cancer Center, report that a genetic biomarker called loss of heterozygosity or LOH is able to predict which patients with premalignant mouth lesions are at highest risk of developing oral cancer.

The findings, published in the November 5, 2015 online issue of *Journal of the American Medical Association Oncology*, present a new tool that could be used to identify patients most likely to benefit from chemoprevention — and may be applicable to preventing other types of cancer.

More than 300,000 people are diagnosed with oral cancer worldwide each year, and 145,000 will die from this disease, which is the most common type of head and neck cancer.

"One of the greatest challenges in developing chemopreventive agents is to identify the population at highest cancer risk," said William N. William, Jr. MD, associate professor at MD Anderson, which led the enrollment and design of the study. "Not all patients with an oral premalignant lesion will develop oral cancer. By using a molecular test that can identify those at highest risk, we can focus preventive efforts on these specific individuals."

Erlotinib, marketed as Tarceva, is an inhibitor of the epidermal growth factor receptor (EGFR), a protein responsible for the development of many cancer types, including head and neck cancer. It is currently approved for the treatment of specific lung and pancreatic cancers and has shown promise in preventing oral cancer in animal models.

The Erlotinib Prevention of Oral Cancer (EPOC) trial involved 379 patients at five sites across the country. All had premalignant lesions in their mouths. Following study enrollment, participants were evaluated for LOH, a chromosomal abnormality characterized by the loss of chromosomal regions, which include tumor suppressor genes.

Patients who tested positive for LOH were considered to be at high risk for oral cancer and were randomized to receive either erlotinib or a placebo for one year. The study's primary endpoint was to determine if fewer patients treated with erlotinib would develop oral cancer, compared to those that received placebo.

"To the best of our knowledge, EPOC represents the first study of oral premalignant lesions to use cancer as the primary endpoint, and the first molecularly-based precision medicine trial design in cancer prevention," said Scott Lippman, MD, director of Moores Cancer Center at UC San Diego Health and senior author of the six-year study. The study began in 2006 when Lippman was chair of the Department of Thoracic/Head and Neck Medical Oncology at MD Anderson.

The EPOC study demonstrated that LOH predicted a higher oral cancer risk. LOH-negative patients had a three-year cancer-free survival rate of 87 percent compared to 74 percent for the LOH-positive group. However, patients who took erlotinib showed no statistical difference in terms of cancer-free survival rates after three years: 74 percent for participants given erlotinib compared to 70 percent for those taking placebo. Patients with both LOH and EGFR copy number gains had the highest incidence of cancer, but still did not benefit from erlotinib.

The lack of erlotinib benefit overall is disappointing, said Lippman, but still an important finding.

"It's vital to know what doesn't work as well as what does, and this research furthered progress in other ways," Lippman said. "For example, we demonstrated that erlotinib-treated patients who develop a skin rash, a common side effect of the drug, had the lowest incidence of oral cancer. Further investigations of this association could point to novel biomarkers, mechanisms and trial designs related to the effects of EGFR-targeted agents in patients with oral premalignant lesions or head and neck cancers."

Another key aspect of EPOC was the collection of blood and tissue samples throughout the study, which will now be used in follow-up research. William said further evaluation of the molecular underpinnings of these observations will hopefully lead to discovery of novel mechanisms of resistance and targets for personalized cancer prevention. MD Anderson was recently awarded a grant by the Cancer Prevention Research Institute of Texas to perform extensive molecular profiling of the EPOC specimens.

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Disclosures: Co-author Ignacio Wistuba has served on the advisory boards of Genentech/Roche, Ventana, GlaxoSmithKline, Celgene, Bristol-Myers Squibb, Synta, Clovis and AstraZeneca and participated in educational activities for Boehringer Ingelheim, Pfizer and Medscape. Edward Kim has served on the advisory boards of Celgene and Eli Lilly.

Funding for this research came, in part, from OSI Pharmaceuticals, the National Cancer Institute (grants PO1CA106451, P50CA097007 and P30CA016672), the Cancer Prevention and Research Institute of Texas and the Conquer Cancer Foundation.

Full study: http://doi.org/10.1001/JAMAONCOL.2015.4364

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