Years of Research Come to Fruition With Launch of Oral Cancer Prevention Trial

Although news headlines and research dollars have focused largely on advances made in cancer treatments, prevention researchers are hard at work developing methods to stop cancer early—before it can even be called cancer.

At the October American Association of Cancer Research’s Fourth Annual Frontiers in Cancer Prevention Research conference in Baltimore, Scott Lippman, M.D., was honored with the Excellence in Cancer Prevention Research award. Lippman, professor of medicine and cancer prevention and chair of the Department of Clinical Cancer Prevention at the University of Texas M. D. Anderson Cancer Center in Houston, and his colleagues have been working for many years on strategies to delay oral cancers and, as a culmination of those efforts, will launch a chemoprevention trial early this year.

Like others in the prevention field, Lippman is capitalizing on advances in tumor biology to redesign prevention trials, which traditionally have been known for their many participants, long duration, and high costs. He and his colleagues are figuring out ways to lower these numbers as well as the risk to the participants.

One strategy is to better define the high-risk populations who participate in the trials and to use more targeted therapies that may increase anticancer effects with fewer side effects. Since most interventions are likely to have some side effects, it is critical to treat people at greatest risk who stand to gain the most from the intervention and to avoid treating those unlikely to develop the disease.

But finding factors that predict who is at high risk for oral cancer has not been easy. Tobacco and alcohol use are the major risk factors for oral squamous cell carcinoma, the most common head and neck cancer, which accounts for more than 300,000 new cancer cases annually worldwide. But even tobacco and alcohol use are not specific enough risk factors to identify a truly high-risk population.

Molecular markers for oral cancer have also been investigated. During oral carcinogenesis, the normal mucosa in the mouth develops into intraepithelial neoplasia (IEN); these may progress to red patches (erythroplakia) and finally to squamous cell carcinoma or invasive cancer. During this process, alterations of several tumor suppressor genes (FHIT, p16, and p53) occur, and cyclin D1, cyclooxygenase 2 (COX-2), and phospho-epidermal growth factor receptor (EGFR) are overexpressed. However, most people with IEN do not develop oral squamous cell carcinoma. Although these events are essential to the understanding of the process and will help guide the choice of drug targets, so far none of these molecular markers has been shown to be a reliable predictor of oral cancer.

However, in 2001, researchers from the Norwegian Radium Hospital and the University of Oslo discovered that an abnormal number of chromosomes, or aneuploidy, in oral IEN is associated with a high risk of oral cancer. They monitored 150 patients with oral white patches called leukoplakia that was classified as epithelial dysplasia—a known risk factor for oral cancer—for 9 years and found that cancer developed in 3% of patients (three of 105) with a normal number of chromosomes compared with 85% of patients (21 of 25) with aneuploid lesions. They also found a lower disease-free survival rate among patients with aneuploid lesions than those with diploid lesions (16% versus 97%). A few years later, the Norwegian investigators teamed up with Lippman and others at M. D. Anderson and found that aneuploid oral IEN is associated with a 72% risk of oral cancer mortality in 5 years despite surgical removal of the lesions.

With the ability to test for people who are at high risk for oral cancer, Lippman and colleagues then needed agents to treat the aneuploid lesions. Treatments such as radiotherapy and surgery have not proven effective. A derivative of vitamin A, 13-cis-retinoic acid, was shown to reverse oral IEN and to reduce the rate of head and neck secondary primary tumors, but the toxicity was not acceptable for long-term prevention, and lower doses were not effective. With no current standard of care, they turned to two promising molecular-targeted agents, inhibitors of COX-2 and EGFR.

There is tumor biology to support use of these inhibitors. Both COX-2 and EGFR are overexpressed in many premalignant and malignant tissues, including those of the mouth, and both are involved in processes linked to carcinogenesis such as cell proliferation and motility, immune surveillance, apoptosis, angiogenesis, and tumor invasion.

Data are emerging to suggest interactive signaling or crosstalk between COX-2 and EGFR. Activation of EGFR signaling leads to higher expression of the COX-2 enzyme, which in turn increases the level of prostaglandin E2, which can activate EGFR signaling.

Preclinical studies testing inhibitors to both EGFR and COX-2 in mice are also encouraging. Using mouse xenografts, Xin Zhang, Ph.D., at the Emory University School of Medicine in Atlanta, showed that the combination of EGFR and COX-2 inhibitors inhibited tumor growth of a human head and neck squamous cell carcinoma compared with either drug alone. Similarly, Giampaolo Tortora, M.D., Ph.D., of the University of Pisa in Italy found that human colon tumors grafted onto nude
mice were more successfully inhibited by the combination than by either drug alone.

Inhibitors of EGFR or COX-2 are now being tested in phase II studies for head and neck cancer or advanced non–small-cell lung cancer. “There is abundant preclinical data to support the hypothesis that dual targeting of the EGFR and COX-2 pathways will improve upon the effects of inhibiting either pathway alone,” said Lori J. Wirth, M.D., from the Dana-Farber Cancer Institute in Boston, who is involved in phase I head and neck cancer trials. “With our phase I study of combined EGFR and COX-2 inhibition with gefitinib plus celecoxib in recurrent/metastatic head and neck cancer complete, we now have preliminary data that suggest this may really be true in humans.”

So, with the ability to use chromosome number to identify a high-risk group of patients and a drug combination that shows promise in early trials, Lippman and his colleagues from Norway, M. D. Anderson, and Cornell University have designed an oral cancer prevention trial scheduled to start early this year. One of the first phase III prevention trials to use two targeted agents, the trial will be led by Jon Sudbø, M.D., D.D.S., from the Norwegian Radium Hospital in Oslo, Norway. The trial will be conducted in Norway, Denmark, Sweden, and Finland. Three hundred patients with aneuploid dysplastic oral lesions will be randomly assigned to 1 year of treatment with one of four treatments: the COX-2 inhibitor celecoxib (Celebrex) alone, the EGFR inhibitor erlotinib (Tarceva) alone, celecoxib plus erlotinib, or placebo. Researchers will monitor patients for 2–4 years looking for the number of cases of oral cancer that develop in each group.

The ability to identify a high-risk group (those with IEN and aneuploidy) means that the trial investigators will need to enroll only 300 patients for 5 years. If their trial included patients with oral leukoplakia (a group of patients at a much lower risk of developing oral cancer), they would have needed more than 3,000 patients who would have been monitored for 10 years.

“By focusing on a cohort at very high risk of development of cancer, this study can definitively answer in a relatively short period of time, using a fairly small number of participants, whether oral cancer can be prevented,” said Eva Szabo, M.D., of the National Cancer Institute’s Division of Cancer Prevention. “Based on a strong biologic rationale, this is one of the first studies to bring targeted agents already in use for cancer treatment to the prevention area. Finally, this study addresses whether a combination of treatments is more effective than individual agents, which has been an area of that is of much interest to the prevention research community.”

—Nancy J. Nelson

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