The Epidermal Growth Factor Receptor Axis: Support for a New Target for Oral Premalignancy

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Abstract

This perspective on the report by Benchekroun et al. in this issue of the journal (beginning on page 800) examines new studies of factors in the epidermal growth factor receptor (EGFR) axis (including copy number alterations at the EGFR locus) that potentially predict the development of oral cancer; this work was conducted in a chemoprevention trial cohort of patients with oral premalignant lesions. The new data raise the possibility that a subset of oral premalignant lesions may benefit from specific therapeutic targeting of the EGFR axis. Cancer Prev Res; 3(7); 797–9. ©2010 AACR.

The surge of pathway-specific discovery in cancer biology in recent years has accelerated the pace of trials using therapeutic agents tailored to specific molecular alterations in individual patient tumors characterized by rearrangements in a particular molecular pathway. This tailoring, or personalizing, concept is currently being applied in clinical practice and clinical trials for a variety of solid and liquid tumors, including breast and lung cancers and chronic myelogenous leukemia. Many of these pathway-directed agents exhibit a more favorable toxicity profile in comparison with traditional cytotoxic chemotherapy, and an intriguing question is whether or not this concept can be applied to chemoprevention studies of premalignant disease.

In this issue of the journal, Benchekroun et al. present the first report on epidermal growth factor receptor (EGFR) expression and gene copy number in oral premalignant lesions (OPL), which were analyzed in a series of longitudinal and prospectively collected samples (1). This novel report places the question of EGFR-directed therapy front and center of the search for effective therapy for oral premalignant disease. Progression to oral squamous cell carcinoma (OSCC) increased significantly among EGFR-overexpressing lesions that also had an increased EGFR gene copy number, as measured by fluorescence in situ hybridization (FISH). These data suggest that increased EGFR copy number may be a marker for a higher-risk group that also has a potentially higher likelihood of benefit from EGFR inhibitors. This suggestion is supported by data in non–small-cell lung cancer (2, 3). These data raise the exciting possibility that increased EGFR copy number may be a good candidate marker (of high risk and EGFR inhibitor sensitivity) for testing the concept of personalized medicine in the context of oral premalignant disease.

A complex and dynamic process of mutation and expansion of altered cells within mucosal surfaces underlies the clinical and histologic changes in OPLs (4). OPL patients often develop multiple cancers over the course of years within a broad field of altered epithelium. The outgrowth of molecularly altered cells leads to abnormal clonal patches of cells that can be discrete and multifocal and can extend over large areas of affected epithelium. Such clonal patches are often clinically and histologically apparent but may have a benign clinical and histologic appearance (5). Clinically, histologically, and molecularly apparent fields of change alter with time, and these changes can extend over decades. The Benchekroun et al. article draws attention to the importance of this phenomenon; of 11 OPLs where OSCC developed at the same site, 10 were FISH positive and only one was FISH negative. In contrast, OSCCs that developed at sites other than those of a baseline OPL were equally associated with FISH-positive and FISH-negative OPLs. This indicates that patients with OPLs that developed into cancer likely developed OSCCs at sites involved with broader areas of premalignant clonal patches with the potential to develop into OSCC.

OPLs comprise a wide spectrum of clinical lesions with variable outcomes (6). Leukoplakia is the most common clinical type of OPL, and the rate of transformation of dysplastic leukoplakia to malignancy can vary from 15% to 35%, with times to progression ranging from months to decades. The presence of dysplastic areas in OPLs provides some indication of risk, and increased risk has generally been associated with a higher grade of dysplasia. Even OPLs with no evidence of dysplasia, however, may have a significant risk of progression, and the search for additional predictors of malignant progression spans several decades. Of the many factors proposed to
indicate the oral cancer risk of an OPL, only loss of heterozygosity (LOH) in key chromosomal loci has been consistently identified as an independent predictor of progression to malignancy (7, 8). The strong association of LOH with risk in this setting is undergoing validation testing in independent prospectively collected sets of OPLs, including from those the ongoing Oral Cancer Prediction Longitudinal study in British Columbia. LOH analysis is already being used to select high-risk oral leukoplakia patients in at least two multi-institutional trials in the United States, including the longer-term Erlotinib Prevention of Oral Cancer study and the short-term phase II Cetuximab for Treatment of High-Risk Pre-malignant Upper Aerodigestive Lesions trial.

The search for effective chemoprevention agents in the setting of OPLs has been challenging, to say the least. For the past few decades, retinoids have been the most fully explored molecules for modulation of OPL progression to malignancy, with significant limitations in terms of efficacy and side effects. The 162 patients from the study reported by Benchekroun et al. (1) were originally enrolled in a trial of the retinoid retinyl palmitate alone or combined with β-carotene versus low dose of the retinoid 13-cis-retinoic acid for reducing the risk of oral cancer; none of the interventions was effective (9). This trial and its predecessor retinoid trials have highlighted the challenges of clinical trials in this area, including (a) the potential need for long-term therapy with agents that may have low-grade but persistent toxicity; (b) difficult accrual and retention to studies with an end point (OSCC) that can take up to 5 or more years to develop; and (c) the inability to precisely define high-risk study populations based on histologic criteria alone.

Nevertheless, long-term chemoprevention trials and longitudinal observational studies such as those that are ongoing in Canada may have unexpected benefits. The ability to define high-risk patients and potential concurrent alterations in molecular pathways associated with the high risk of these patients may pave the way for pathway-directed therapeutic interventions. The effort of Benchekroun et al. in defining EGFR as a likely independent prognostic factor based on data from a completed chemoprevention trial does have precedents in the general literature of head and neck squamous cell carcinoma (HNSCC). Elevated EGFR expression predicted a worse disease-free and cause-specific survival in HNSCC (10). Increased EGFR copy number or EGFR expression also has been shown to be associated with prognosis in HNSCC (11–14). A landmark trial showed that the EGFR-targeting monoclonal antibody cetuximab plus radiotherapy improved survival and local-regional control of HNSCC (versus radiotherapy alone; ref. 15). Cetuximab plus platinum-fluorouracil chemotherapy improved overall survival, when compared with platinum-fluorouracil-based chemotherapy alone, in patients with recurrent or metastatic HNSCC (16). These trials (15, 16) have established EGFR as the only therapeutic molecular target in head and neck cancer that has been validated in phase III studies.

In the context of these positive trials of agents that target the EGFR axis in treating head and neck cancer in general, the current report of an association of increased EGFR copy number with OPL progression is cause for real excitement. The identification of a molecular alteration in the EGFR axis that is associated with OPL progression and the ready availability of well-characterized drugs that target this axis immediately suggest treatment of EGFR-high-copy-number OPLs with these agents. As noted above, at least two ongoing trials are using EGFR-directed agents in somewhat different designs. The Erlotinib Prevention of Oral Cancer study (http://clinicaltrials.gov/ct2/show/NCT00524017) examines histologic response in patients with high-grade oral dysplasia and/or LOH-positive lesions treated with weekly cetuximab (versus placebo). The Cetuximab for Treatment of High-Risk Pre-malignant Upper Aerodigestive Lesions trial (http://clinicaltrials.gov/ct2/show/NCT00402779) examines oral-cancer–free survival in LOH-positive OPL patients treated with daily erlotinib (versus placebo). The Cetuximab for Treatment of High-Risk Pre-malignant Upper Aerodigestive Lesions trial examines histologic response in patients with high-grade oral dysplasia and/or LOH-positive lesions treated with weekly cetuximab (versus placebo) for 8 weeks. These trials will accrue many patients with EGFR alterations and will conduct some examination of response and/or cancer development in relationship to EGFR status.

It must be admitted that some issues with the report by Benchekroun et al. highlight both the difficulty of studying OPLs and certain drawbacks of retrospective analyses of clinical trial cohorts. The central finding of the study—EGFR copy number is strongly and independently correlated with progression to oral cancer—has some limitations. Although 162 patients were enrolled in the trial, only 49 OPLs were examined with FISH for EGFR copy number, opening the possibility of selection bias and issues associated with generalizing from findings in small subsets. Because clinical trial cohorts tend to be fairly highly selected, it would be very interesting to validate the present findings in less selected cohorts, including large population cohorts, such as those assembled in comprehensive national registries of countries including Canada.

The Benchekroun et al. study also highlights basic challenges in studying the EGFR axis, including the definition of an increased EGFR copy number. An OPL with an increased EGFR copy number was simply defined as being FISH positive for chromosome 7 copy increase (EGFR is located on chromosome 7), and it is unclear whether modest copy number increases defined as “FISH positive” in the Benchekroun study rise to the level or biological significance of gene amplification that is associated with significant EGFR overexpression. In other words, is there evidence that the copy number increases defined in this study would necessarily result in biologically significant increases in EGFR protein or the activation of targets downstream of EGFR? It is particularly interesting that a blinded observer-based assessment of the larger cohort did not show a significant association of EGFR expression status with oral cancer development. An automated assessment of EGFR, however, found a significant association of EGFR expression status with oral cancer development, but the hazard ratio was modest compared with
that of dysplasia determined by standard histology. It could be argued that copy number increase at chromosome 7 is a marker for numerical chromosomal alterations/genetic instability in general and that the high-risk OPLs marked by a FISH-positive status within this cohort have other, non-EGFR-axis alterations that contribute to their high-risk status. That said, it would be of great interest to determine if previously published LOH prognostic markers for OPL progression also predicted progression within this cohort (7, 8).

Despite these issues, the association of results of an automated and thus presumably unbiased assessment of EGFR expression status with oral cancer development in a large cohort of OPLs is reassuring and provides support and impetus for determining whether EGFR pathway blockade can prevent oral cancer in patients with high-risk OPLs. Of interest, a correlation between response to EGFR-blocking agents and EGFR status has yet to be established in HNSCC. It is possible that EGFR-directed therapies in OPLs, as in HNSCC, may have a significant therapeutic effect that does not necessarily relate to EGFR amplification. Current investigations into the factors that correlate with HNSCC response to an EGFR inhibitor may find that response involves tumor dependence on the functional presence, rather than activation or upregulation, of the EGFR pathway (17).

Last, the study by Benchekroun et al. with 162 patients is the largest prospective trial in OPL patients to date, highlighting the significant challenges associated with conducting large chemoprevention trials in such patients. This study further highlights the potential of well-designed randomized controlled chemoprevention trials, whether modest or large scale, for producing important, albeit unintended, advances such as defining prognostic markers for OPL progression to malignancy. The substantial time and effort involved in conducting such trials in the setting of OPLs allows for the longitudinal evaluation of OPL progression and the determination of molecular pathway alterations that contribute to oral cancer development, even when the pathways are not specifically incorporated into the original trial design. This work also underscores the need to develop longitudinal cohorts that complement the trial studies by allowing OPL progression to be followed in large populations.

Disclosure of Potential Conflicts of Interest

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