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Chemoprevention in SCCHN: the Persistent Need for Better Translation

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Description

Chemoprevention, in which the use of a systemic agent is intended to slow or reverse the process of carcinogenesis, has been a topic of extensive research for different malignancies including squamous cell carcinoma of the head and neck (SCCHN). Yet, despite significant efforts over the past decades and the substantial gain in knowledge of the biology of SCCHN premalignancy, there is limited evidence favoring this approach in subjects with premalignant lesions of the head and neck over the standard surgical and radiation options. Because of the discouraging initial results from the retinoid trials, more recent efforts have focused on targeting the epithelial growth factor receptor (EGFR) or its tyrosine kinases (TKs). After all, EGFR is highly expressed in SCCHN [1-3] and inhibition of EGFR or EGFR-TKs has been extensively studied in this disease [4,5]. This effort has culminated in a recent randomized, double blinded, placebo-controlled phase III trial of chemoprevention of oral cancer with EGFR-TKI, erlotinib, versus placebo (the EPOC trial). In an attempt to enrich for high-risk disease, this trial focused on examining the value of erlotinib in subjects with documented loss of heterozygosity (LOH) at either or both loci of chromosomes 9p21 and 3p14, serving as biomarkers for increased SCCHN risk [6]. Of a total of 398 subjects registered, 254 had high risk LOH-positive lesions, and 150 were randomized to erlotinib at 75 mg/day versus placebo for 12 months of intervention and a median follow up time of 35 months. Disappointingly, erlotinib did not improve the primary study endpoint, oral cancer-free survival in the LOH-positive patients, and the overall cancer-free survival in placebo- and erlotinib-treated patients was equivalent at 74% and 70%, respectively (hazard ratio [HR], 1.27; 95% CI, 0.68-2.38; P=0.45) [7]. One possible reason underlying the lack of clinical benefit may be the fact that only 29% of subjects on the erlotinib arm received 75% or more of the intended dose of erlotinib as a result of toxicities. Although the results were discouraging, this trial validated LOH as an important marker of oral cancer risk.

One major limitation to the success of chemoprevention in SCCHN is the challenge in accrual of healthy subjects onto relatively challenging trials with toxic therapeutic interventions. In addition, the lack of a reproducible method for assessing response of premalignant lesions has been a significant obstacle to chemoprevention studies in SCCHN. The compelling preclinical rationale for using the combination of EGFR-TKI and COX-2 inhibition in SCCHN prompted our interest in examining this combination in a phase I clinical trial of chemoprevention in SCCHN [8-10]. Even though the maximum tolerated dose of (MTD) of erlotinib in this combination was reached at 50 mg/day, skin rash was the main observed toxicity, hindering further dose escalation and halting the progress to a phase II and III design [11]. Despite these challenges, the reversal of dysplasia (pathologic CR or PR) observed in 63% of participants and the correlation of clinical responses with downregulation of biomarkers such as phosphorylated extracellular signal-regulated kinase (p-ERK) in serial biopsies, was all encouraging signs and suggested the possible utility of these markers as surrogate endpoints for response [11]. Of further interest are the findings of an association in gene expression between biopsy and cytobrush samples using NanoString technology [12]; our group was actually among the earliest to use formalin-fixed paraffin-embedded specimens for determining effective therapeutic targets in SCCHN [13]. We hope that these interesting findings may serve as proof-of-principle for the use of such surrogate markers in future chemoprevention trials.

In summary, the field of SCCHN chemoprevention is still in need of better translation of clinical responses into effective surrogate endpoints. The noted toxicities as well as poor accrual to studies remain major obstacles in promoting the clinical applications of cancer chemoprevention. Despite the good responses observed and the intriguing biomarker modulations in our phase I trial, the majority of subjects ultimately progressed to higher grade dysplasia or carcinoma. The current surge of interest in better tolerated natural dietary compounds as chemopreventive agents could result in longer administration periods with improved safety profile which may hopefully result in longer lasting clinical benefits.

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