

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: James L. Abbruzzese, MD

Chemoprevention of Head and Neck Cancer

James L. Mulshine, MD
Vice President and Associate Provost for Research
Rush University Medical Center

H&O What is the definition of chemoprevention?

JM The term “chemoprevention” was coined by Dr. Michael Sporn several decades ago and refers the phase of drug intervention in which the target is preclinical cancer—the preinvasive phase of cancer—usually administered to high-risk individuals. Whereas the management of clinically evident disease is treatment, chemoprevention refers to the use of drugs in individuals who are at high risk of developing cancer but in whom disease is not yet clinically evident.

H&O What might be the characteristics of a candidate for head and neck cancer chemoprevention?

JM Individuals with tobacco exposure who have undergone successful treatment for a stage I cancer at some site within the head and neck would be likely candidates. A study several decades ago by Slaughter and colleagues and other studies since then have demonstrated that when a first cancer occurs in connection with tobacco exposure, the likelihood that other cells have been mutagenized by tobacco exposure, leading to subsequent cancers, is very high. Clinical trials of chemoprevention in head and neck cancer (HNC) have reported second cancers occurring within 10 years of a first cancer in approximately 10–30% of patients.

H&O What types of regimens have been explored for chemoprevention of HNC?

JM Chemoprevention for HNC first garnered attention based on clinical trials by Drs. Ki Hong, Scott Lippman, and others at the University of Texas M. D. Anderson

Cancer Center, in which vitamin A analogs, typically 13-cis retinoic acid, were evaluated for the treatment of oral leukoplakia and for chemoprevention in individuals at risk for aerodigestive cancer. Initially, there was much enthusiasm surrounding this approach because early studies in leukoplakia showed favorable results. However, larger randomized controlled trials evaluating 13-cis retinoic acid against a definitive endpoint of mortality reduction and parallel studies of chemoprevention in HNC and lung cancer raised issues regarding the occurrence of second cancers in the treatment arms of the studies.

The issue of second cancers has been a theme of chemoprevention trials in lung cancer, raised in particular by a Finnish study of beta-carotene, a precursor of vitamin A. The rationale for using beta-carotene was based on solid epidemiologic data showing that vitamin A deficiencies were associated with higher rates of cancer. However, a subset analysis of this trial showed a significantly increased incidence of lung cancer in the interventional arm versus the control arm. This finding was somewhat controversial because a large study at Harvard showed no such association, nor did a study at M. D. Anderson Cancer Center, although the latter did report a shortened time to progression in the chemoprevention arm. Even though metastatic progression and carcinogenesis are very different dynamics, these reports became linked and slowed the investigation of chemoprevention.

Thus, the development of clinical trials for chemoprevention of HNC has been a challenging road so far. A number of chemoprevention trials are ongoing in high-risk cohorts.

H&O Could you explain why tobacco exposure is a likely reason to administer HNC chemoprevention?

JM Slaughter and coworkers developed the theory that, among people who smoke, a large quantity of tobacco is crossing the aerodigestive tract, leading to multifocal sites of initiation of carcinogenesis. The leading cause of death in individuals successfully treated for their first HNC in some series has been lung cancer and, conversely, individuals treated for lung cancer have been reported to develop second cancers in other aerodigestive sites,

with HNC being one of the most common sites. This notion is known as “field carcinogenesis” and is a proven clinical entity.

The hypothesis that a chemoprevention agent effective for HNC would likely be effective for lung cancer and vice versa is plausible, and underscored by the use of retinoids in these settings. However, neither the trials mentioned above nor other small pilot studies with analogs of retinoids, such as fenretinide, or the new more selective retinoids, which interact with just one of the nuclear proteins associated with a retinoid effect, have shown a clear benefit. Ongoing studies are asking important questions, such as: What dose is associated with a favorable chemoprevention effect? What biochemical and molecular events are related to adequate pharmacologic dosing? What are the surrogates of a favorable clinical effect? The identification of surrogates would be key to accelerating the development of chemopreventive agents and regimens for HNC.

H&O What surrogate markers of clinical effectiveness are being explored?

JM Much work has been done at the M. D. Anderson Cancer Center and other institutions examining various retinoid signaling downstream molecules, cyclin-D1 expression, and other biochemical and molecular pathways. Many of these potential surrogates are conceptually attractive, but none have yet been validated for routine use in the clinical setting.

Conducting studies designed to search for surrogate markers can be quite difficult. In fact, any oncology clinical trial involving routine tissue acquisition can be very challenging. These studies are expensive and complicated, requiring coordination of a large number of professionals, and few institutions have been able to sustain such efforts. The group at M. D. Anderson Cancer Center and some others, including the SPORE (Specialized Projects of Research Excellence) sites, have conducted excellent research in this regard.

Several interesting pilot studies for a wide range of markers have been conducted, but none have yet emerged as robust tools in this setting. A growing body of evidence suggests that cyclooxygenase (COX)-2 activity and products of the COX enzyme are involved in the pathogenesis of HNC, oral cancers, and lung cancer, and so there has been increasing interest in studying COX-2 inhibitors in this setting. Recent reports of COX-2 inhibitor–associated toxicity have somewhat tempered these efforts, but studies are still ongoing.

H&O What is the association between COX-2 and these cancers?

JM The explanation of this association is controversial. There are data supporting the notion that prostaglandins themselves have a role. Other data suggest that agents that inhibit prostaglandins may also inhibit other critical pathways that may be more central to the cancer progression pathway.

The dose of a COX-2 inhibitor required to block enzymatic activity to an extent that would arrest tumor progression has yet to be identified. Studies have been conducted in animal models, but the investigations have not yet proceeded to clinical trials.

Our group completed a trial in oral leukoplakia, which arises from the same tissues as HNC. A study reported by Hong et al found that COX activity was involved in oropharyngeal carcinogenesis, and that COX-2 inhibitors could arrest progression of this cancer in animal models. Phase I/II studies of COX-2 inhibitors for the treatment of oral leukoplakia had identified a dosing schedule that appeared to be associated with a reduction of oral production of prostaglandins. Using an oral COX inhibitor delivered topically to the oral cavity in a randomized phase IIB trial with a vehicle control, we observed a reduction in the leukoplakia in approximately 25% of patients. This reduction occurred in both the treatment and vehicle arms, but was nonetheless intriguing because it was 2.5 times higher than what was expected based on previously published series. There is some speculation that the high alcohol content in the topical rinse was affecting nuclear factor κ B levels and carcinogenesis. More importantly, these findings correlated with a study of another COX inhibitor evaluated in skin cancer chemoprevention. Initially, the agent, diclofenac sodium (Solaraze, SkyePharma), did not penetrate through the areas of injured skin. However, the agent was reformulated and was found to be efficacious in a randomized controlled study. These findings have served as the rationale to continue evaluating local delivery of COX-2 inhibitors for chemoprevention of oropharyngeal cancer with an agent that is optimized for penetration of the keratin layer of the oral cavity, which is proliferated and disorganized in leukoplakia.

H&O How does one determine the benefit of chemopreventive therapy?

JM If a surrogate exists that reflects the success of the agent, a pilot study can be conducted in order to determine whether modulation occurs with the dose and schedule

being used. The most efficient way to obtain definitive proof is to define a very high-risk population with a measurable risk of developing new cancers (typically second cancers), randomize this population to experimental chemoprevention versus control, and follow these patients to see whether there is a difference in the incidence of HNC or lung cancer. A significant reduction in cancer incidence associated with the experimental arm would suggest that the regimen is an effective chemoprevention strategy.

Such studies require fairly large numbers of patients. In the original retinoid trials the complications were not lethal but the side effects were such that it was difficult for patients to undergo treatment for a long period of time. The initial trials were positive for the very-high dose, but when the dose was lowered in order to improve drug tolerability the positive effect was not observed. This issue presents a difficult situation for clinical trials. Decreasing a dose by 50% would likely decrease the potential ben-

efit of a chemopreventive strategy; however, in order to improve compliance, doses have been lowered. Indeed, the agents being studied at lower doses are not showing positive findings, but these outcomes do not reflect the potential benefit. Alternative local drug delivery strategies are being developed.

Suggested Reading

Smith W, Saba N. Retinoids as chemoprevention for head and neck cancer: where do we go from here? *Crit Rev Oncol Hematol*. 2005;55:143-152.

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