Chemoprevention Strategies in Lung Carcinogenesis*
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Chemoprevention entails using specific agents to suppress carcinogenesis and thereby prevent the development of primary or second primary cancers. Because the concept of chemoprevention in patients with or at risk of lung cancer is new, ongoing clinical trials are based on data from epidemiologic and preclinical research, as well as on results of chemoprevention studies in head and neck cancer. The latter studies have provided a model for such studies in lung cancer, considering the two diseases have a similar etiology and biology of field carcinogenesis. Beta-carotene, natural vitamin A, and the retinoids may be effective chemopreventive agents. However, chronic administration of such agents may be required to prevent the development of cancer. Results of chemoprevention trials in head and neck cancer have demonstrated effective inhibition of the development of second primary tumors with the synthetic retinoid 13-cis-retinoic acid; investigators are hopeful this will be repeated in patients with lung cancer. Results of ongoing phase III trials and continued advances in the epidemiologic and biologic study of lung carcinogenesis should contribute to future research in this area.

*Chest* 1993; 103:155-195

Lung, head and neck, and esophageal cancers are the most devastating aerodigestive tract cancers. Lung cancer is the major cancer-related cause of death among both men and women in the United States. Three principal modalities are currently used to control this disease: (1) smoking-cessation programs as primary prevention; (2) local therapy for early and locally advanced disease; and (3) chemotherapy for advanced disease.

Smoking-cessation programs have begun to reduce the incidence of smoking in developed countries; however, the rate of reduction has been gradual and is irrelevant to the millions of cases of lung cancer that will occur in the coming decades. Although patients with early stage lung cancer can be treated successfully with local therapy, they face an approximately 4 percent per year risk of developing second primary tumors (SPTs), the leading cause of death in early stage disease. The low survival rate in late-stage disease has been improved only negligibly by primary chemotherapy. The few long-term survivors of late-stage disease are also subject to development of SPTs. Clearly, new strategies are needed to control lung neoplasms.

One new approach is chemoprevention, the intervention with specific agents to suppress carcinogenesis and thereby prevent the development of primary or second primary cancers. Chemoprevention is not only an important new approach to lung cancer, it is also being investigated extensively in other epithelial tumors, including head and neck, colon, and breast cancers, which remain major public health hazards despite advances in cancer control and therapy.

Chemoprevention trials differ from standard chemotherapy trials in many respects, including actual and perceived risks, adherence, recruitment, and diet. There are two pivotal differences, however, one of which is toxicity. Patients at risk of SPT are generally willing to accept toxicities that would not be acceptable to the general population. The other pivotal difference is the choice of study end points, which directly affects both sample size and study duration (Table 1). Standard primary lung cancer chemoprevention studies require follow-up of many thousands of subjects for at least 5 and up to 10 years. The use of intermediate end points (eg, cytologic atypia, bronchial metaplasia, and molecular markers) would greatly enhance statistical power by reducing sample size and study duration, but no such end points have been validated prospectively to correlate with cancer incidence in the context of a chemoprevention trial.

**Biology**

The primary biologic rationale for chemoprevention in the aerodigestive tract comprises the concepts of multistep epithelial cancer development and field carcinogenesis.

The development of squamous cell carcinoma in the lung is histologically characterized by the multistep progression from hyperplasia through metaplasia, dysplasia, and carcinoma in situ to invasive cancer.

The histologic sequence of the development of lung cancer is not clear. Alterations in specific oncogenes (eg, ras, myc, and erb-B gene families), tumor suppressor genes (eg, retinoblastoma, p53), and cytogenetic structures (involving chromosomes 1p, 3p, 6q, 7, 9p, 11p, 15p, 17p) have been reported in lung cancer.

Studies of nonmalignant high-risk tissue, premalignant tissue, and tissue adjacent to lung cancer have identified genotypic and phenotypic changes that support the concept of multistep field carcinogenesis. Phenotypic alterations associated with lung carcinogenesis include altered cell differentiation markers (eg, cytokeratins and surface glycoproteins) and proliferative patterns (eg, as measured by proliferating cell nuclear antigen). Although the precise sequence of genotypic and phenotypic alterations in early- and late-stage carcinogenesis is currently unclear, this multistep process of carcinogenesis provides an opportunity to intervene pharmacologically to prevent the development of invasive cancer.

Field carcinogenesis describes the diffuse, fieldwide mucosal carcinogenic effects of tobacco and alcohol. This hypothesis is supported by recent studies in humans that document the existence of clinical, histologic, biochemical, and molecular signs of premalignancy within the epithelium at risk, and by the higher risk of synchronous and metachronous SPT within the aerodigestive tract. In high-
risk patients, various stages of multifocal premalignant foci can be found throughout the lung and other sites of the aerodigestive tract.

**Clinical Trials**

Chemoprevention research in the lung is very new, and the vast majority of randomized trials have yet to be completed (Tables 1 and 2). Current ongoing randomized trials are based on data from epidemiologic and preclinical research, and on the results of chemoprevention research in the head and neck. Preclinical results suggest that long-term administration of chemopreventive agents may be necessary to prevent the development of cancer. Epidemiologic and head and neck cancer chemoprevention studies suggest that beta-carotene and natural vitamin A may be effective in chemoprevention; combinations of these agents are being tested in three primary lung cancer chemoprevention trials. Recent work in head and neck carcinogenesis has led to the study of synthetic retinoids in lung cancer chemoprevention.

This paper will focus on chemoprevention studies in the head and neck region, which provide an excellent model for the design of chemoprevention strategies in the lung. This relationship derives from the similar etiology and biology of field carcinogenesis in the two regions. Chemoprevention trials in the head and neck have indicated that retinoids have significant activity against oral premalignancy and the development of SPT. Retinoids are the natural derivatives and synthetic analogues of vitamin A and are potent regulators of normal and malignant cell growth and differentiation.

**Premalignancy Studies**

Oral leukoplakia, a white patch in the oral cavity that cannot be scraped off or classified clinically as any other disorder is a premalignant precursor of squamous cell carcinoma, tobacco-related, easily monitored, and has preclinical (in vitro and in vivo) models. It is, therefore, an ideal human model for aerodigestive tract carcinogenesis and the study of chemoprevention. Because of field carcinogenesis, results of trials in oral leukoplakia have important implications for cancers in other aerodigestive tract sites, including the lung.

Short-term oral leukoplakia chemoprevention trials have been conducted for over 30 years. Early trials were not controlled; nonetheless, they made important observations about the activity of supplemental vitamin A (topical or systemic) in reversing oral lesions. Clinical work with synthetic retinoids began over 20 years ago and includes 10 trials (>250 patients). The response rate to retinoid therapy has been >50 percent in every study, and the median response rate for all these studies is >75 percent. The best-studied retinoid is 13-cis-retinoic acid (13-cRA), which has been tested rigorously in two randomized trials.

Reported by Hong et al in 1986, the first placebo-controlled phase III chemoprevention trial in oral leukoplakia...
kia attracted worldwide attention. This study established the activity of high-dose 13-cRA compared with placebo. The trial was short-term, lasting only 3 months, but it revealed two major problems with the retinoid: (1) the relapse rate exceeded 50 percent within 2 to 3 months after stopping therapy, and (2) toxicity was unacceptably high for general chemoprevention study or use. The retinoid response must be maintained, but high-dose toxicity limits the duration of therapy.

These problems led to a 12-month randomized trial comparing the ability of low-dose 13-cRA and beta-carotene to maintain remission or nonprogression of oral carcinogenesis after high-dose 13-cRA induction. This trial was conducted in two phases: a 3-month induction phase employing high-dose 13-cRA in all patients and a 9-month maintenance phase in which patients were randomized to receive either low-dose 13-cRA or beta-carotene. Patients whose disease progressed at any time were removed from the study. Prior to randomization in the second phase, patients were stratified into four groups with different histologic and response-to-induction characteristics. This study's use of the retinoid 13-cRA was based on extensive preclinical data demonstrating the retinoid's significant anti-carcinogenic activity in many systems, on high-dose 13-cRA's significant activity in our 1986 trial, and on this agent's dose-related toxicity. The choice of beta-carotene for the maintenance comparison arm was based on several factors, including positive epidemiologic data on its effect on squamous cell malignancy of the aerodigestive tract. Beta-carotene and other natural, nontoxic, and relatively inexpensive agents would be ideal for long-term chemoprevention if their effectiveness, either alone or in combination, could be established.

Seventy patients were registered in this induction/maintenance study. High-dose 13-cRA induction produced a complete plus partial remission rate of 55 percent. Beta-carotene was significantly less effective than low-dose 13-cRA: after the maintenance phase, the progression rate was 8 percent in the low-dose 13-cRA group vs 55 percent in the beta-carotene group. Furthermore, low-dose 13-cRA was well tolerated: toxic effects of grade 3 or greater severity were experienced by 34 percent of those who received high-dose 13-cRA compared with only 12 percent of those receiving the lower dose.

These two randomized trials established that high-dose 13-cRA and low-dose 13-cRA have significant activity in leukoplakia. Only one third of the established high dose, the maintenance 13-cRA dose (0.5 mg/kg/day) is the lowest dose ever studied in leukoplakia. Low-dose 13-cRA is currently undergoing further chemoprevention study in the aerodigestive tract, including adjuvant trials designed to prevent SPT associated with head and neck and lung cancers, which are discussed later.

Retinoids are unquestionably the most studied chemopreventive agents; the next best studied agent in oral leukoplakia is beta-carotene, but no phase III placebo-controlled study data exist for this agent. The only randomized study data addressing beta-carotene use are those from the phase III maintenance trial discussed previously. Stich and colleagues reported the first trials of beta-carotene, each of whom tested 180 mg/wk in unique high-risk populations (eg, Asian betel nut users). Their first trial (10 weeks of therapy) produced no clinical responses in Inuits with visible snuff-related white oral lesions. In a more recent trial from these investigators, conducted in Asian betel nut users and lasting 6 months, beta-carotene produced a 15 percent clinical complete response rate, which was not significantly different from that obtained with placebo. Four other single-arm trials employing beta-carotene doses of 30, 60, 90, and 120 mg/day produced respective overall response rates of 71, 61, 27, and 24 percent. This inverse relationship between increasing doses and decreasing response rates is unexplained. Phase III placebo-controlled trials are required to clarify this phenomenon.

Bronchial metaplasia is related to lung cancer as oral leukoplakia is related to oral cancer. The promising results obtained with 13-cRA in oral premalignancy and with another synthetic retinoid in a European nonrandomized study of bronchial metaplasia led to a 4-year placebo-controlled National Cancer Institute phase III trial of 13-cRA in bronchial metaplasia, which will be completed in 1992. Two other randomized studies, one using the retinoid etretinate and the other retinol plus beta-carotene, are attempting to reverse cytologic atypia in sputum.

Second Primary Tumor Prevention

A randomized adjuvant trial of high-dose 13-cRA has been conducted in "cured" head and neck cancer patients. Eligible patients included those with biopsy-proven stages I through IV (MO) disease who were rendered disease-free following surgery or radiation therapy or both. Patients were stratified by tumor site (oral cavity, oropharynx, hypopharynx, or larynx) and previous treatment (radiation, surgery, or both) to receive 13-cRA (50 to 100 mg/m2/day) or placebo for 12 months. Treatment was initiated no later than 10 weeks after surgery or 16 weeks after radiation. The study end point was recurrence of primary disease and development of SPT.

Initially reported in detail in 1990, this study found, after a median follow-up of 2.5 years, a significant reduction in SPT rates in the high-dose 13-cRA group compared to the placebo group, although primary disease recurrence was not inhibited significantly by the drug. After two years of additional follow-up, primary disease progression rates are now 33 percent in both groups, but SPT rates remain significantly different—8 percent in the 13-cRA group vs 29 percent in the placebo group (p = 0.007). The apparent persistent anticarcinogenic effect of 13-cRA suggests a several-year increase in the tumor latency period. This differs from the findings of preclinical and short-term oral leukoplakia studies, in which the retinoid chemopreventive effect wore off within months of stopping therapy. The optimal duration of chemopreventive retinoid administration is unclear. Besides the significant reduction in SPT overall, no SPT developed in the retinoid arm within the 12-month therapy period, no lung SPT developed in the retinoid arm both during and following surgery, and multiple SPTs developed only in the placebo group. In a subset analysis excluding non-tobacco-related SPT, the difference between SPT rates in the 13-cRA and placebo arms remained highly significant.

The clinical data from this adjuvant trial and other studies
monitoring patterns of treatment failures in head and neck cancer patients support the concept of field carcinogenesis. In the adjuvant study,\textsuperscript{16} 16 of 19 patients (total from both arms) developed SPT of squamous cell carcinoma type within the “field” of the upper aerodigestive tract (head and neck, lung, upper two thirds of the esophagus) and in the bladder. Survival was not prolonged in the group that received 13-cRA, probably because (1) the rates of primary disease recurrence were identical, or (2) high-dose 13-cRA’s significant toxicity kept many patients from completing the full 12 months of therapy. Furthermore, prospective follow-up with early SPT detection and therapy minimized the impact of SPT on the survival of patients in the placebo arm.

As stated above, SPTs are the major cause of death in early stage head and neck cancer and lung cancer patients.\textsuperscript{13} The SPTs develop from premalignant foci, either visible or invisible, that remain after local therapy. The adjuvant activity of high-dose 13-cRA against SPT led to implementation of two multicenter trials of low-dose 13-cRA designed specifically to prevent SPT in early stage disease: one, involving the University of Texas M.D. Anderson Cancer Center, Radiation Therapy Oncology Group, and Community Clinical Oncology Program, is treating patients with stage I or II head and neck cancer and began multicenter patient accrual in February 1992; the other, a recently activated intergroup trial, will treat patients with stage I non-small-cell lung carcinoma (NSCLC) (Table 2). The choices of dose and administration schedule were based on the randomized maintenance trial of 13-cRA in oral leukoplakia.\textsuperscript{18} To eliminate the diagnostic and survival problems and statistical issues associated with high competing rates of primary disease failure, both studies are including only patients with early stage disease. The primary end point of these large-scale trials will be SPT development.

Mechanistic Studies

Retinoids are the best studied chemopreventive agents. Major recent advances have been made toward understanding the retinoids’ mechanism(s) of action. It is now apparent that the nuclear receptors for the retinoids belong to a common superfamily that also includes familiar steroids, such as the glucocorticoids. The two major classes of retinoic acid receptors, the RAR and RXR series, have alpha, beta, and gamma subtypes and multiple isoforms.\textsuperscript{21} These receptors are involved in the selective regulation of gene transcription, which in turn regulates cell differentiation and proliferation.

Conclusion

Despite local and systemic therapy and smoking cessation programs, lung cancer remains the major cause of cancer-related death in the United States. Chemoprevention is an exciting and promising investigational modality for the control of lung carcinogenesis. Future directions for this research will hinge on forthcoming clinical results of ongoing phase III trials and continued advances in the epidemiologic and biologic study of lung carcinogenesis.

Current and planned lung cancer chemoprevention studies owe their designs in large part to extensive work already completed in the related system of head and neck carcino-

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Because of encouraging results in the control of SPT associated with head and neck cancers, hopes are high for controlling SPT in the lung in recently designed phase III trials. Second primary tumors are now a major problem in early stage disease\textsuperscript{13} and will become an even greater concern as primary therapy advances improve long-term survival rates in patients with later stage disease.\textsuperscript{3} Conducted on a multicenter and intergroup basis, these trials are available to early stage NSCLC patients throughout the United States and Europe (Table 2).

The results of the current series of SPT lung chemoprevention trials will determine future multimodality strategies in lung cancer, which may include primary and adjuvant therapy followed by long-term chemoprevention. Such an integrated approach may ultimately lead to major improvements in the survival of patients with lung cancer.

References