Current Status of Retinoid Chemoprevention of Lung Cancer

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Clinical trials have suggested that retinoid chemoprevention prevents the development of second primary tumors following head and neck or non-small-cell lung cancer. The findings of these initial studies are now being

Introduction

Chemoprevention is a strategy to prevent the development of cancer through the administration of drugs. This approach is now being widely studied in a variety of clinical settings [1]. The poor prognosis of lung cancer patients has led investigators to study chemoprevention as a means of decreasing lung cancer incidence. Tobacco cessation and public health efforts to prevent the next generation from becoming addicted to tobacco must be the mainstays of lung cancer prevention. Even with successful cessation, however, an increased risk of developing lung cancer persists in former smokers for more than a decade. Chemoprevention may be a means of decreasing the incidence of lung cancer among both current and former smokers.

The central idea guiding lung cancer chemoprevention efforts is the concept of the diffuse injury of respiratory epithelium resulting from chronic carcinogen exposure. Slaughter and his colleagues initially described this process as field cancerization [2]. The widespread injury to the respiratory epithelium led investigators to consider a systemic treatment. The concept of chemoprevention is also supported by the understanding of epithelial carcinogenesis as a multistep process. Among the potential agents for lung cancer chemoprevention, the use of retinoids, compounds with vitamin A-like activity, is supported by the results of both epidemiologic studies and animal experiments [3-6]. For clinical studies, the development of oral leukoplakia as a model of tobacco-associated carcinogenesis has also been useful in developing possible regimens for lung cancer chemoprevention [7]. The lesions of oral leukoplakia are premalignant and, over a period of years, may develop into invasive cancers [8]. Trials have demonstrated that retinoids, including isotretinoin (Accutane, 13-cis-retinoic acid), could reverse these lesions [9].

The concept of field cancerization is supported not only by the frequent occurrence of premalignant lesions, such as leukoplakia, in carcinogen-exposed individuals, but also by the development of multiple primary tumors. For patients who survive an initial head and neck or lung cancer, development of a second primary tumor within the respiratory epithelium represents a great threat to their health [10-12]. For patients who have been treated for a head and neck cancer, the lifetime risk of developing a second primary tumor exceeds 30%. Building on the results of oral leukoplakia studies, retinoid chemoprevention trials have recently focused on the prevention of second primary tumors in patients who have been treated for a head and neck or lung cancer.

Completed Retinoid Chemoprevention Studies

In a landmark study, Hong et al [13] described a reduction of second primary tumors in head and neck cancer patients treated with isotretinoin. Following surgery and/or radiation therapy for squamous cell cancer of the head and neck, patients were randomly assigned to either isotretinoin, 50 to 100 mg/m²/day, or placebo given for 1 year as an adjuvant treatment. In the initial report, with a median follow-up of 32 months, second primary tumors had developed in 12 (24%) of the placebo-treated patients, compared with only two (4%) of the isotretinoin-treated patients ($P = .005$). The retinoid treatment had no impact on the recurrence of the initial cancer. Isotretinoin apparently suppressed foci of damaged epithelium from progressing into invasive cancer, but was ineffective as therapy once the cancer had developed. The second primary tumors that occurred during the study were predominantly in the carcinogen-exposed field of the head and neck, lungs, and esophagus. Although the results of this small trial (103 patients) are impressive, the high-dose retinoid treatment was associated with considerable toxicity. Side effects included dry skin, cheilitis, elevated
triglycerides, and conjunctivitis. One third of the isotretinoin-treated patients were unable to complete the year of therapy as planned.

Recently, the data have been reanalyzed, with the median follow-up extended to 54.5 months (Table 1) [14]. With longer follow-up, the retinoid-treated patients have continued to have fewer second primary tumors; seven (14%) in the isotretinoin group, compared with 16 (31%) in the placebo group ($P = .042$). When only those second primary tumors that developed in the carcinogen-exposed field were considered, the results were more impressive, with second primary tumors developing in only three (7%) of the isotretinoin patients, compared with 13 (33%) in the placebo-treated group ($P = .008$). These results suggest that the beneficial chemopreventive effect of isotretinoin persisted after the year of treatment. The suppression of second primary tumors occurred despite the fact that the patients, as a group, took less of the retinoid than had initially been intended when the study was designed.

Because the high-dose isotretinoin used in this adjuvant study was poorly tolerated, there was considerable interest in determining if the chemopreventive effect could be maintained using lower, less toxic doses. The findings of a recent randomized oral leukoplakia chemoprevention trial are encouraging [15]. Patients were initially given a 3-month induction course of high-dose isotretinoin, followed by a 9-month maintenance treatment with a low dose of isotretinoin, 0.5 mg/kg/day, or beta-carotene, 30 mg/day. The low-dose isotretinoin was effective in maintaining the benefits achieved during the induction phase; only two (8%) of the patients in the isotretinoin group had progression of the leukoplakia during the maintenance treatment, compared with 16 (55%) of the beta-carotene group ($P < .001$). The low-dose isotretinoin was also well tolerated; none of the isotretinoin patients discontinued therapy during the maintenance treatment due to toxicity (Table 2).

A group from France has recently reported the findings of a study that evaluated the efficacy of the synthetic retinoid etretinate (marketed as Tegison in the United States for the treatment of psoriasis) to prevent second primary tumors following squamous cell cancer of the oral cavity or oropharynx [16]. Patients were randomly assigned to treatment with etretinate, 50 mg/day for 1 month, followed by 25 mg/day for 24 months, or placebo. Among the 316 patients studied, there was no reduction in second primary tumors associated with the retinoid treatment. The two treatment groups were equivalent both for the occurrence of second primary tumors and relapse of the initial cancer. This prospective trial did, however, confirm the high rate of second primary tumors following head and neck cancer. With a median follow-up of 41 months, 24% of the patients had developed a second primary tumor. Consistent with the concept of field carcinogenesis, 79% of the second primary tumors occurred within the head and neck, lungs, or esophagus. Interpretation of this report was hampered by the lack of detail with regards to tobacco intake, alcohol history, compliance, and toxicity [17].

In a trial performed among 307 patients following resection of a stage I non-small-cell lung cancer, Pastorino et al. [18] observed a beneficial effect associated with retinyl palmitate treatment. Following surgery, patients were randomly assigned to treatment with retinyl palmitate, 300,000 IU per day for 1 year of observation. Compliance was estimated to be greater than 80%, and the retinyl palmitate was well tolerated. Only three patients dropped out of the treatment arm due to toxicity from the retinoid.

Retinyl palmitate treatment was associated with a reduction in second primary tumors. Eighteen patients in the retinyl palmitate group developed second primary tumors, compared with 29 patients in the control group. Reduction of tobacco-associated second primary tumors was more pronounced. With a median follow-up of 46 months, 13 retinyl palmitate-treated patients developed tobacco-associated second primary tumors, compared with 25 patients in the control group. The time to the development of a tobacco-associated second primary tumor also favored the retinyl palmitate-treated patients ($P = .045$). This study provided the rationale for the ongoing European study known as Euroscan (described below).

Another approach to retinoid chemoprevention of lung cancer has been to test the ability of these agents to reverse histologic or cytologic changes that may precede the development of invasive disease. Arnold et al. [19], for example, evaluated the ability of etretinate, 25 mg/day, to reverse sputum atypia in specimens collected from chronic smokers. Changes in sputum atypia were assessed at the completion of a 6-month treatment period. No difference between the etretinate and placebo groups in the degree of sputum atypia was noted.

In order to evaluate the effect of the chemopreventive agent directly in the bronchial epithelium, a group of French investigators performed a study using serial bronchoscopy, with endobronchial biopsies taken from chronic smokers [20-22]. In this uncontrolled phase II study, patients found to
have squamous metaplasia of the bronchial epithelium in specimens obtained during their initial bronchoscopy were treated with etretinate, 25 mg/day for 6 months. After the completion of the treatment course, the investigators noted a decline in the extent of squamous metaplasia. As the result of this study, a randomized trial was performed in the United States [23]. Asymptomatic chronic smokers were recruited to participate. Volunteers underwent bronchoscopy with endobronchial biopsies taken from six specific anatomic sites. Participants who were found to have a squamous metaplasia index greater than 15% and/or dysplasia were then randomized to 6 months of treatment with either isotretinoin, 1 mg/kg per day, or placebo. Of the 152 participants initially registered in the study, 93 had a metaplasia index greater than 15%. The results of the 6-month treatment course were recently published for 69 study participants [23]. For the group as a whole, the extent of metaplasia declined over time. There was no significant difference, however, between the isotretinoin and placebo groups in the reduction of metaplasia. The most important predictor of a decline in the extent of metaplasia was smoking cessation during the treatment period. While the results of this study were consistent with the findings in the French study with etretinate, the presence of a control group in the isotretinoin study completely altered the interpretation of the results.

Neither sputum atypia nor squamous metaplasia of the bronchial epithelium is likely to be useful as an intermediate marker of lung carcinogenesis, and both are too variable and nonspecific to guide chemoprevention trials. Sputum specimens, endobronchial biopsies, or bronchial washings may, however, be used to study other, potentially more powerful markers of lung carcinogenesis. There is now considerable interest in studying markers of proliferation, genetic injury, or oncogene expression, which may be critical in tobacco-associated carcinogenesis [24-28]. Understanding of the retinoic acid receptors may lead to the improved efficacy and decreased toxicity of retinoid chemoprevention [29,30]. No intermediate marker of lung carcinogenesis has yet been validated that could serve as a surrogate endpoint for lung cancer incidence in chemoprevention trials [31]. Such a marker would be extremely useful in aiding the clinical development of lung cancer chemoprevention.

Completed Carotenoid Chemoprevention Studies

Unlike the retinoid lung cancer chemoprevention trials, which have focused on prevention of second primary tumors and reversal of premalignancy, carotinoid trials have generally been designed as primary prevention trials that have large sample sizes and take many years to complete. Recently, the results of a beta-carotene and alpha-tocopherol study were published [32]. Investigators in Finland recruited 29,133 male smokers living in southwest Finland. Using a 2 × 2 factorial design, study participants received alpha-tocopherol (50 mg/day) alone, beta-carotene (20 mg/day) alone, both agents, or placebo. Participants continued the intervention for 5 to 8 years. During the course of the study, 876 new lung cancer cases were diagnosed. An 18% increase in lung cancer incidence was observed among the study participants given beta-carotene (\( P = .01 \)). Overall mortality was also higher, by 8%, in the beta-carotene group (\( P = .02 \)). Administration of alpha-tocopherol did not significantly alter either lung cancer incidence or overall mortality. The unexpectedly poor outcome associated with beta-carotene could not be explained by differences in smoking status. The results of this study highlight the need to perform careful trials before widely implementing a chemoprevention regimen derived from dietary epidemiologic studies.

Current Retinoid Studies

The promising results of the studies by Hong and Pastorino are currently being evaluated in large, multi-institution chemoprevention trials. The North American study uses a randomized, placebo-controlled design to evaluate the efficacy of low-dose isotretinoin in preventing second primary tumors. The European Euroscan study is using a 2 × 2 factorial design to study retinyl palmitate and \( N \)-acetylcysteine in second primary tumor prevention. Both studies will accrue more than 1,000 lung cancer patients.

North American Intergroup Study—An NCI-sponsored, randomized, placebo-controlled trial will determine if low-dose isotretinoin prevents the development of second primary tumors following resection of a stage I non-small-cell lung cancer. The study is being performed using the intergroup mechanism. Patients enrolled in the study initially participate in an 8-week run-in period, to establish a compliant patient population (Figure 1). Patients are then assigned by random allocation to treatment with either isotretinoin, 30 mg/day, or placebo. The treatment period continues for 3 years, with all participants then followed for an additional 4 years.
The eligibility criteria for the study are summarized in Table 3. All patients must have undergone successful resection of a stage I non-small-cell lung cancer, T1N0M0 or T2N0M0 by pathologic evaluation. An aspect of the eligibility criteria that is unique to chemoprevention trials is the long period of eligibility after surgery. Retinoid chemoprevention appears to prevent second primary tumors but not recurrence of the initial tumor. In addition, the risk of developing a second primary tumor persists at a stable rate for several years, so patients may be enrolled in the study up to 3 years after their lung cancer resection.

The study will enroll 1,260 patients. The accrual period for the study is intended to be 3 years. Currently, 712 patients have been enrolled from 148 institutions. Over the past year, an average of 36 patients have been enrolled in the study each month.

The study end point is the development of a second primary tumor. All cases of second primary tumors and recurrent disease are reviewed by a central committee, to insure consistent application of the study definition of a second primary tumor. Results of the study will be masked until the completion of the follow-up period.

A study with a comparable design is being performed to determine if the same dose of isotretinoin, 30 mg/day, will prevent the development of second primary tumors following treatment of a stage I or II squamous cell cancer of the head and neck. This study was initiated through the M.D. Anderson Cancer Center and its affiliates, and the Radiation Therapy Oncology Group. The study will soon become an intergroup trial. The study was initiated before the lung cancer second primary tumor prevention trial, and so more long-term data are available regarding toxicity [33]. In this study, isotretinoin, 30 mg/day, has been well tolerated in these previously treated cancer patients. Only a few grade 3 toxicities, dry skin, cheilitis, conjunctivitis, and glossitis, have been observed. In the treatment arm with the most toxicity, 27% of the patients have required dose modifications due to side effects.

Another head and neck cancer second primary prevention trial was initiated in the Northern California Oncology Group and is now being performed through the Eastern Cooperative Oncology Group. This study will compare a very-low-dose isotretinoin regimen with placebo. **Euroscan Study**—European investigators are evaluating the efficacy of retinyl palmitate, 300,000 IU/day, and the antioxidant N-acetylcysteine, 600 mg/day, in the prevention of second primary tumors [34]. The study uses a 2 × 2 factorial design in which participants receive retinyl palmitate alone, N-acetyl-cysteine alone, both drugs, or placebo. Patients will continue the treatment for 2 years. Euroscan includes patients who have been treated for an early-stage squamous cell cancer of the head and neck and patients who have had resection of a non-small-cell lung cancer. The lung cancer study includes patients who have been treated for T1N0-1, T2N0-1, or T3N0 cancer. The agents have been well tolerated. Accrual for this study continues, with more than 2,450 patients enrolled. A sample size of 2,600 is planned [35].

**Ongoing Carotenoid Trials**

The role of beta-carotene in preventing the development of an initial lung cancer will be further assessed in the ongoing Carotene and Retinol Efficacy Trial (CARET) [36,37]. The trial is a multi-institution study comparing the combination of beta-carotene, 30 mg/day, and retinyl palmitate, 25,000 IU/day, with placebo. The trial will recruit 13,700 high-risk smokers and 4,000 participants with occupational asbestos exposure. The CARET study is based on carefully conducted pilot studies.

The Physicians Health Study will evaluate the effect of beta-carotene, 50 mg every other day, on the incidence of cancer at all sites [38]. This placebo-controlled trial will also evaluate the impact of alternate-day aspirin on cardiovascular mortality. It is not yet known if the incidence of lung cancer in the study population will be high enough to determine the effect of the carotenoid.

**Future Studies**

Long-term survivors of small-cell lung cancer are another patient population that may benefit from retinoid chemoprevention. Although most patients die from their initial cancer, survivors remain at very high risk for the development of second primary tumors [39-41]. An intergroup trial has been proposed to determine if isotretinoin could prevent the development of second primary tumors in these patients.

The addition of chemoprevention trials to smoking cessation efforts is also an area of interest for future studies. Individuals motivated to attempt to quit smoking may also be interested in chemoprevention studies. Retinoid chemoprevention may decrease the risk of an initial cancer in
these individuals and is currently being considered as a research strategy. If retinoids are to be used in primary prevention studies, then efforts to decrease toxicity through the choice of agents will be extremely important.

At present, lung cancer chemoprevention remains an experimental approach. It is hoped that successful completion of ongoing phase III studies will establish a role for retinoid chemoprevention in decreasing the incidence of lung cancer. The availability of intermediate markers would greatly aid in the development of lung cancer chemoprevention.

References:


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