Chemoprevention Strategies for Lung and Upper Aerodigestive Tract Cancer

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Abstract

The field cancerization hypothesis suggests that carcinogen exposure affects the entire epithelial lining of the lungs and upper aerodigestive tract. The concept that common exposures place the entire epithelium at risk for the development of invasive cancer is supported both by the occurrence of premalignant lesions such as leukoplakia and squamous metaplasia, and by the development of multiple primary tumors within the field. Chemoprevention trials in lung and upper aerodigestive tract cancer have included studies to reverse premalignant lesions and to prevent second primary tumors. Promising results have been reported in both settings using the retinoid 13-cis-retinoid acid. Several clinical trials are in progress which attempt both to reduce cancer incidence and to determine the mechanisms and biological markers of successful chemoprevention.

Introduction

The tremendous impact of lung and upper aerodigestive tract cancer on U.S. mortality is well known, with over 150,000 deaths predicted in 1991 (1). The difficulties in battling this public health threat are also unfortunately familiar, with incidence rates for lung cancer in women continuing to climb (2). The problem is increasing despite the knowledge that tobacco exposure is the dominant risk factor for both lung and upper aerodigestive tract cancer (3, 4). As the result of tobacco and other carcinogenic exposures, millions of Americans are at increased risk for these cancers. Even with successful smoking cessation an increased risk would persist for over a decade.

The presence of this large population at increased risk for lung and upper aerodigestive tract cancer and the significant morbidity and mortality associated with these diseases have prompted efforts to develop prevention strategies in addition to smoking cessation. Chemoprevention, the administration of drugs before the diagnosis of cancer, in order to block the carcinogenic process, may be an important contributor to future prevention efforts. Epidemiological studies have helped identify potential chemoprevention agents, such as β-carotene and retinol (5, 6). Recently, the retinoids, natural and synthetic analogues of vitamin A, have become widely studied as chemopreventive agents for aerodigestive tract cancer, due in part to their effects on epithelium (7).

Interest in systemic treatments for cancer prevention in the aerodigestive tract has resulted from the understanding that the entire epithelial lining of the tract shares both common carcinogenic exposures and an increased cancer risk. Identification of the entire epithelium as condemned mucosa was first described by Slaughter et al. (8). They chose the term "field cancerization" to describe the diffuse histological abnormalities and multifocal nature of squamous cell cancers of the head and neck. Evidence supporting the field cancerization model includes the identification of intermediate markers, such as micronuclei, which correlate with exposure to known risk factors and increased cancer risk, development of premalignant changes within the field, and the increased risk of SPTs for patients with lung or head and neck cancers.

Field cancerization provides a powerful model for aerodigestive tract carcinogenesis and a basis for chemoprevention studies. This concept explains the diffuse nature of molecular, biochemical, and histological changes which occur in individuals with significant carcinogen exposure. In addition, patients at high risk for cancer are identified, providing a population likely to benefit from chemoprevention studies.

Chemoprevention Trial End Points

Chemoprevention trials differ significantly from cancer therapy trials and require attention to a distinct set of issues. In therapy trials, study end points, such as survival and response rates, are often less controversial than the end points in chemoprevention studies. For chemoprevention trials, a variety of end points may be appropriate. Chemoprevention is designed to block carcinogenesis, so there is great interest in identifying the critical steps of carcinogenesis which may be effectively interrupted. It would be ideal to directly measure the impact of chemoprevention agents on carcinogenesis. This approach would allow chemoprevention trials to be much shorter in duration, since researchers would not have to wait for the development of invasive cancers, which may take decades, to assess the impact of the intervention (9). Since the impact of the chemoprevention agent on carcinogenesis could be assessed for all patients, not just the minority who develop cancer, trials could also rely on smaller sample sizes. The difficulty has been to identify reliable intermediate markers.

A variety of different biomarkers have been proposed as intermediate end points in aerodigestive tract carcinogenesis (10). Molecular markers have appeal, because they may represent the specific critical steps in the process. Such markers would include the presence of oncogene amplification. Elevated levels of H-ras, K-ras, and myc, for example, have been observed in head and neck tumor specimens (11). The protooncogene int-2 has also been reported to be increased in squamous cell carcinomas of the head and neck (12). Similarly, several oncogenes, including myc and ras, have been implicated in lung cancer pathogenesis (13, 14). While these abnormalities may represent essential stages in carcinogenesis, there is not yet sufficient information to use these changes to assess the outcome of chemoprevention trials.

A number of other intermediate markers are also being studied to assess their role as end points for chemoprevention studies. These potential end points include markers of squamous differentiation, such as transglutaminase, involucrin, and keratins (15). Other markers have been chosen in an effort to assess cellular proliferation, including proliferating cell nuclear antigen, Ki-67, and DNA polymerase α. Not enough is known about the expression of these markers to use them as the end points for a chemoprevention trial.

The most widely studied intermediate marker for the aerodigestive tract is the presence of micronuclei (16). Micronuclei

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3 The abbreviations used are: SPT, second primary tumor; CR, complete response; PR, partial response.

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Chemoprevention trials present a series of design problems which must be successfully addressed (19). Single-arm studies have been reported but are weakened by uncertainty about the correct end point. Marked sputum atypia, a potential end point for lung chemoprevention trials, for example, may regress without intervention or the alteration of risk factors (20). There has also been considerable variation in the reported success of single-arm studies using comparable interventions. Randomized trials remain the gold standard for chemoprevention studies, especially given the uncertainty about end points and comparability of study results. In some settings, the efficiency of the randomized trial may be improved using a factorial design or other modification (21, 22).

Large sample sizes and long follow-up periods are generally required for chemoprevention studies designed to demonstrate a reduction in diagnosed cancers. Even the calculation of necessary sample size for these trials is complicated by the long period during which dropout may occur (23). An approach to these sample size and compliance problems in chemoprevention trials has been to focus on patients with both a perceived and actual increased risk of cancer. Patients with significant smoking history, asbestos exposure, or a history of previous cancer, for example, may be more willing to comply with protocol requirements based on their personal concern about cancer. These populations are also more likely to benefit than the population as a whole from a successful chemoprevention approach. A recent feasibility study demonstrated that patients successfully treated for head and neck cancer could be recruited for a SPT chemoprevention trial (24). Chemoprevention trials studying high-risk populations and using the development of cancer as an end point often require randomization of over 1,000 patients to have sufficient statistical power.

Chemoprevention trials also require a reappraisal of the risks and benefits for participants. Primary tumor chemoprevention trials include many participants who would never develop cancer and so side effects must be almost nonexistent. In contrast, SPT chemoprevention trials may use regimens with greater toxicities, given the greater risk for each participant of developing cancer. The risks and side effects of the chemoprevention agent will also affect recruitment and compliance in the trial.

Another important consideration in the design of chemoprevention trials is the impact of confounding variables. Trials studying the effect of supplementation with dietary components such as β-carotene, for example, must consider the diets of the participants. An individual participant could drop in to the treatment arm through a change in diet. Since tobacco is a critical risk factor for aerodigestive tract cancers, changes in smoking status must be assessed. Imbalance in smoking status between treatment arms could bias the study results. Smoking cessation efforts for all participants must be a component of these trials, since the dangers of this exposure are well documented.

Chemoprevention Trials for Lung and Upper Aerodigestive Tract Cancer

Bronchial Metaplasia. Exposures which are associated with a marked increase in lung cancer incidence, such as tobacco use or uranium mining, are also clearly associated with abnormalities in the bronchial epithelium (25–27). Epithelial changes observed in exposed individuals have included the loss of cilia, basal cell hyperplasia, the presence of atypical nuclei, and squamous cell metaplasia (28, 29). Squamous cell metaplasia refers to replacement of the ciliated, columnar bronchial lining with cells resembling a squamous cell epithelium. Because of the strong association of these bronchial epithelial changes with the risk factors for lung cancer and because of the widespread presence of these changes in the lungs of lung cancer patients, squamous metaplasia has been considered a histological marker of carcinogenesis. Several chemoprevention studies have been performed in patients with bronchial metaplasia, in hopes that successful reversal of the metaplasia would correlate with a reduction in lung cancer risk.

Saccomano et al. (30) reported the results of a study to reverse abnormal sputum cytology with the retinoid 13-cis-retinoic acid. In this study, patients were treated with doses ranging from 0.5 to 2.5 mg/kg/day. Duration of treatment also varied, from as short a period as 1 day to 40 weeks. All of the 26 patients studied had abnormal sputum cytology, and in some patients this was the only apparent pathology, whereas 5 of the patients were known to have invasive tumor. Smoking status was not reported. The study did not observe an improvement in sputum cytology with retinoid treatment. Subsequent studies have benefited from the use of bronchoscopy specimens, taken from standardized sites, for assessing treatment effects and administration of a uniform regimen during the study. A study of heavy smokers (>15 pack-years) reported by Gouveia et al. (31) described the effects of treatment with 25 mg etretinate/day for 6 months in patients with an initial index of metaplasia >15%. The index of metaplasia was calculated by dividing the number of histological sections with metaplasia by the total number of sections examined, which was then multiplied by 100 and expressed as a percentage. Thirty-four of the 70 smokers initially screened were eligible for treatment. The report described an improvement in the metaplasia index for 10 of 11 patients who had completed the protocol (P < 0.01). The study demonstrated the ability to use bronchoscopy specimens and a quantitative assessment of metaplasia, but the results were weakened by the small sample size and single-arm design. A subsequent paper by the same researchers described the results for a larger series of patients treated with the same protocol. In this report, 144 smokers underwent initial bronchoscopy, and 61 were found to have an index of metaplasia >15 (32). Among the 34 evaluable patients who completed the protocol, the metaplasia index improved with retinoid therapy from 34.57% to 26.96% (P < 0.001). For the 4 patients who stopped smoking...
A clinical trial is under way at M. D. Anderson to study the effects of retinoids, using bronchial metaplasia as a lung cancer chemoprevention model. Bronchoscopy specimens obtained from heavy smokers are assessed for the index of metaplasia. Patients with a metaplasia index >15 or the presence of dysplasia are randomized to receive placebo or 1.0 mg 13-cis-retinoic acid/kg/day for 6 months. In this double-blind trial, bronchoscopy is repeated at 6 months. For patients who do not demonstrate an improvement on follow-up bronchoscopy, the treatment code is broken, and patients initially treated with placebo cross over to receive a 6-month course of 13-cis-retinoic acid followed by bronchoscopy. Over 100 patients have undergone initial bronchoscopy, with 58 patients randomized. Results of the drug intervention are not yet available. This trial will also establish the association between retinoid reversal of bronchial metaplasia/dysplasia and intermediate markers of genetic alteration, dysregulated proliferation, and differentiation.

Oral Leukoplakia. Another histological marker of premalignancy is oral leukoplakia. Oral leukoplakia has been defined as “a white patch or plaque that cannot be characterized clinically or pathologically as any other disease, and again it must be emphasized that this use of the term is unrelated to the absence or presence of dysplasia” (33). Obviously, the term describes a heterogeneous group of conditions, rather than a single entity. Within this category there presumably may exist a variable risk for development of a subsequent oral cancer. These lesions are frequently associated with prolonged oral carcinogen exposure, such as chewing tobacco, betel nut chewing, or the use of snuff (34–36). The association between the presence of these lesions and oral cancer is supported by the finding of adjacent leukoplakia lesions in 36% of oral cavity cancers (37). The association of oral leukoplakia and oral cancer has also been demonstrated by studies following these patients over time. Silverman et al. (38) followed 257 oral leukoplakia patients for 7.2 years and observed the development of 45 (17.5%) squamous carcinomas (38). Invasive cancers developed both in patients with benign hyperkeratosis and in those with dysplasia, although dysplastic lesions were more than twice as likely to progress to cancer. Other studies have also reported an increased cancer risk for oral leukoplakia patients (39).

Chemoprevention studies have demonstrated the ability of β-carotene, retinol, and retinoids to produce clinical improvement in oral leukoplakia (35–37, 40–49). The characteristics of these trials are summarized in Table 1. Response rates have varied considerably in these trials, especially for β-carotene. Toxicity has also varied between trials and has generally been a much more significant problem for retinoid trials. A problem for all of the trials has been the high rates of recurrence when the chemoprevention agent has been stopped.

Several important aspects of oral leukoplakia chemoprevention were demonstrated in the randomized, double-blind trial comparing a placebo to 13-cis-retinoic acid (48). Both clinical and histological responses were significantly higher among the 13-cis-retinoic acid–treated patients (P = 0.0002 and P < 0.01, respectively). Although only 2 patients dropped out due to toxicity of the retinoid, 47% of the 17 patients treated with 2 mg/kg required a dose reduction. The observed toxicities were self-limited and included dry skin, cheilitis, conjunctivitis, and hypertriglyceridemia. Unfortunately, when the retinoid was stopped, 9 of 16 patients who had responded to therapy relapsed within 2 to 3 months.

The findings of this trial led to the design of a subsequent trial which used 1.5 mg 13-cis-retinoic acid/kg/day for 3 months followed by a low dose of 13-cis-retinoic acid (0.5 mg/kg/day) or β-carotene (30 mg/day) for 9 months (49). This study confirmed the conclusion that 13-cis-retinoic acid caused the regression of the leukoplakia lesions by 62%. Unfortunately,

<table>
<thead>
<tr>
<th>Author</th>
<th>Ref.</th>
<th>Agent</th>
<th>Dose</th>
<th>Evaluable patients</th>
<th>Response (%) (CR + PR)</th>
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<tr>
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<td>40</td>
<td>β-Carotene</td>
<td>30 mg/day × 3 mos</td>
<td>17</td>
<td>71</td>
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<td>90 mg/day × 3 mos</td>
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<td>0.1% (topical)</td>
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<td>70 mg/d × 8 wks</td>
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<td>56</td>
<td>62</td>
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*13cRA, 13-cis-retinoic acid.
the less toxic \( \beta \)-carotene maintenance therapy did not effectively prevent relapse. The improvement of 13-cis-retinoic acid-treated patients was also observed by reduction of micronuclei.

The current M. D. Anderson oral leukoplakia trial will compare the combination of \( \beta \)-carotene and retinol versus 13-cis-retinoic acid. Treatment allocation is randomized, and the study will use 3 years of treatment followed by 2 years of follow-up. The combination of 30 mg \( \beta \)-carotene/day and 25,000 IU retinol/day was chosen based on studies suggesting that these agents may be synergistic in chemoprevention while having minimal toxicity (42, 50). The 13-cis-retinoic acid will be given at a dose of 0.5 mg/kg/day for year 1, then at 0.25 mg/kg/day for years 2 and 3. This lower dose is intended to preserve the efficacy demonstrated in earlier trials, while producing less toxicity. An important component of the trial will be the incorporation of a number of intermediate marker studies, including micronuclei.

Primary Lung and Upper Aerodigestive Tract Chemoprevention

Primary chemoprevention trials generally require extremely large sample sizes and long follow-up periods in order to demonstrate an effect. Sample size may be decreased somewhat by studying patients at high risk for developing cancer, an approach which has been adopted by most researchers. The chemoprevention regimen must have little if any associated toxicity. These problems have prompted some authors to question the feasibility of these trials (51). Despite this concern, however, several primary chemoprevention trials are currently under way for these cancers (Table 2). The trials have generally used naturally occurring nutrients as the chemoprevention agents. Results from these primary tumor chemoprevention trials are not yet available.

SPTs: A Model for Chemoprevention

Patients successfully treated for lung or head and neck cancer remain at significant risk for the development of a SPT. The distribution of SPTs supports the field cancerization hypothesis. This group of patients is ideally suited for chemoprevention studies. The patients are at increased risk for development of a SPT and would greatly benefit from successful chemoprevention. Compliance and acceptable toxicity may be somewhat greater, given the extent of the threat of cancer which these patients must face.

Head and Neck SPTs. The study of head and neck SPTs depends on the careful diagnosis of these tumors. Studies in this area have benefited from rigorous application of diagnostic criteria, modified from a report by Warren and Gates (59): (a) a distinct lesion separated from the primary tumor by >2 cm of normal epithelium; (b) a new cancer with a different histologic pattern of SPTs is consistent with field cancerization, with roughly one-half found in the head and neck, one-third in the lung, and one-fifth in the esophagus (66). Patients who develop SPTs have a poor prognosis; among laryngeal cancer patients, for example, 5-year survival for patients developing SPTs was 16.8%, compared with 43.5% for patients with a single primary tumor (67).

Lung SPTs. Following potentially curative surgical resection of primary lung cancer, patients remain at risk for the development of a SPT in the lung. Lung SPTs have been defined on the basis of (a) a different histological type; (b) a location in a different lobe; (c) a location in the contralateral lung; and (d) occurrence >3 years after initial diagnosis. For early-stage non-small cell lung cancer patients treated by surgical resection and observed for long periods of time, 10–25% of the patients have developed SPTs (68–70). In lung cancer patients, SPTs frequently occur in the lung and head and neck (71). Unfortunately, as with SPTs arising among head and neck cancer patients, the prognosis is poor for lung cancer patients who develop SPTs.

SPT Chemoprevention Trials

Head and Neck SPT Chemoprevention Trials. Based on the activity of retinoids in reversing oral premalignant lesions and the risks of both recurrent disease and SPTs among head and neck cancer patients, an adjuvant retinoid trial was performed as a randomized, double-blind study (72). Following therapy for squamous cell cancer of the head and neck, patients were treated for 1 year with 50–100 mg/m²/day 13-cis-retinoic acid or placebo. The initial report described a striking reduction in the number of SPTs among the patients receiving 13-cis-retinoic acid (2 or 4%) compared with placebo (12 or 24%) (\( P = 0.005 \)). With the extension of the median follow-up from 32 to 48 months, the difference has persisted, with one additional SPT among the retinoid-treated patients and two SPTs in the placebo group. Four patients, all in the placebo group, developed SPTs at multiple sites. In the placebo group, 12 of 14 SPTs occurred in the head and neck, lung, or esophagus,
consistent with the field cancerization hypothesis.

A difficulty for the study was the toxicity associated with high-dose retinoid therapy. The planned dose of 100 mg/m² had to be decreased to 50 mg/m², because of the number of patients requiring dose reductions. While mild side effects were experienced equally in the two treatment groups, more significant side effects were seen predominantly in the 13-cis-retinoic acid-treated patients. Sixteen of 49 retinoid-treated patients, compared with 3 of 51 placebo patients, did not complete the year of therapy due to toxicity. The toxicity observed in the study was self-limited and consistent with previous reports.

The design of this study, as an adjuvant trial, may have led to an underestimate of the impact of 13-cis-retinoic acid. Over one-half of the study participants presented with locally advanced disease and had the competing risks of local failure and distant metastases. The trial enrolled patients during a short interval (<16 weeks) following therapy for their primary tumor. Following initial therapy, the risk of local relapse declines, whereas SPTs continue to develop at an apparently constant rate for at least 8 years.

The findings of this study led to the design of a head and neck SPT chemoprevention trial. This randomized, double-blind, placebo-controlled trial will study the efficacy of 30 mg 13-cis-retinoic acid/day for 3 years to prevent SPTs. The study will enroll not only recently treated early-stage squamous cell cancer patients but also patients who have been free of their disease for up to 3 years. The study will be completed through the Radiation Therapy Oncology Group, the M. D. Anderson Cancer Center, and its affiliated Community Clinical Oncology Program centers. An important aspect of this clinical trial is the incorporation of basic science investigations into the study. Companion studies will examine the cyogenetic and molecular abnormalities associated with field cancerization, as well as investigate retinoid-responsive genes and receptors.

Lung SPT Chemoprevention Trials. Chemoprevention trials to prevent SPTs following resection of non-small cell lung cancer are currently under way. Pastorino et al. (73) have presented the interim results of an adjuvant trial using 300,000 IU vitamin A/day for 12 months (73). The outcome for 150 vitamin A-treated patients was compared with that of 157 control patients. Only 4 of the vitamin A-treated patients had to be decreased to 50 mg/m², because of the number of patients requiring dose reductions. While mild side effects were experienced equally in the two treatment groups, more significant side effects were seen predominantly in the 13-cis-retinoic acid-treated patients. Sixteen of 49 retinoid-treated patients, compared with 3 of 51 placebo patients, did not complete the year of therapy due to toxicity. The toxicity observed in the study was self-limited and consistent with previous reports.

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In the United States another trial is being developed which would evaluate the efficacy of 13-cis-retinoic acid in preventing lung SPTs. The study will evaluate this intervention in patients successfully treated for Stage I non-small cell lung cancer.

Summary

There is tremendous excitement over the prospects for the effective chemoprevention of lung and upper aerodigestive tract cancer. Recently completed trials have demonstrated the potential for the retinoid 13-cis-retinoic acid to interrupt field cancerization by reversing premalignant lesions and decreasing the incidence of SPTs. These interesting initial results must be verified in large chemoprevention trials. These trials must not simply address the effect of the intervention on tumor incidence, but must also investigate the molecular and biochemical changes which accompany multistep carcinogenesis. Understanding of the carcinogenic process should improve our ability to develop effective chemoprevention strategies.

References

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