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Two New Observational Studies Suggest Future Directions in Lung Cancer Chemoprevention

Lung Cancer Frontiers is published by The Snowdrift Pulmonary Conference and supported by a generous grant from the Flight Attendant Medical Research Institute (FAMRI) of Miami, Florida. It is hoped that the next series of issues will help to disseminate knowledge based on our experiences in early lung cancer identification and treatment, based upon studies originally conducted in Grand Junction, Colorado.

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Two New Observational Studies Suggest Future Directions in Lung Cancer Chemoprevention

By: York E. Miller, M.D.

The concept of cancer chemoprevention is attributed to Sporn, who coined the term in a manuscript published 30 years ago (1). Chemopreventive agents are

either nutrients or drugs that delay or prevent the development of cancer. Hormonal manipulations have at least some efficacy for breast and prostate cancers and colorectal adenomas are decreased by cyclooxygenase inhibitors, although the effect of these drugs on colorectal cancer is not clear. There are no effective chemopreventive agents for lung cancer. Interestingly, Saccomanno, who pioneered sputum cytology, published the first lung cancer chemoprevention trial, using cytology as an intermediate endpoint, in 1982 (2). Observational and in vitro studies strongly suggested that retinoids would be effective for lung cancer chemoprevention, but when beta carotene and other retinoids were studied in randomized controlled trials, a harmful (20% increase in lung cancer) effect was surprisingly found (3, 4). These studies were an expensive, but valuable, lesson in that following what was the commonly held assumption that retinoids would be protective without a prospective trial would have certainly increased lung cancer deaths.

While observational studies have

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Emphasis Now on Lung Cancer Prevention

It is a fact that lung cancer is diagnosed more frequently in former than current smokers. While the final solution to lung cancer is primary prevention, or early cessation of smoking, we need new strategies to reduce the likelihood of lung cancer occurring in former smokers, long after they have quit. The latest clinical studies of inhaled corticosteroids are encouraging as summarized by York Miller and the controlled clinical study that follows.

There are other approaches under study which may also prove effective, i.e., iloprost, selenium, Cox 2 inhibitors. Comments on each are included.

Soon we will have the results of the randomized controlled trial of chest x-rays vs CT in CT screening. Already Claudia Henschcke has accumulated data that supports CT in heavy smokers.



obvious limitations, two recent reports suggest potentially valuable approaches to lung cancer chemoprevention. Both were conducted in patient populations getting care at Department of Veterans Affairs medical centers and used the computerized databases in the VA Health Care system to advantage. In the first, Parimon and colleagues examined the frequency of lung cancer diagnosis in veterans prescribed inhaled corticosteroids, a drug for which animal studies have shown chemoprevention(5, 6). An approximately 60% reduction in lung cancer was found in the group taking high dose inhaled corticosteroids with good compliance. The shortcoming of this study is that only a small percentage, (just 500 of 10,000!) of such patients were highly compliant with this medication. While a statistically significant difference was found, additional trials are needed. This would be a good area for the NHLBI and NCI to collaborate, as COPD patients have a greatly increased risk for lung cancer.

In the second study, the effect of thiazolidinediones (TZDs; rosiglitazone or pioglitazone) prescribed for diabetes mellitus on lung cancer diagnosis was studied(7). TZDs target a transcription factor, PPAR gamma, which has been supported as chemopreventive in animal models of lung cancer(8). 11,289 TZD users were compared to 76,389 TZD non-users, all diabetics. After adjusting for confounding variables such as race, age, other drug use, etc., the TZD users had a 33% lower relative risk for lung cancer. This study has a large population; the lack of standardized smoking histories is the major drawback. Other agents, including selenium and the prostacyclin analog iloprost (which likely acts through PPAR gamma as do the TZDs) are being evaluated in preliminary trials(9-12).

Observational studies are useful for choosing agents for randomized controlled trials of lung cancer chemoprevention, but are not adequate for moving these agents to clinical practice, as the beta carotene story has taught us(3, 4). At least, we now have several promising new leads, both of which may yield significant reductions in lung cancer risk and are supported by both animal and in vitro studies as well. The area of lung cancer chemoprevention is not yet ready for clinical application, but is poised to move forward. Consider the implications if pulmonologists could practice lung cancer prevention as is now done for cardiovascular disease with lipid lowering agents and antihypertensives.

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Selected Peer-Reviewed Literature

1.
Eur J Cancer Prev 2007;16:184-191

Chemoprevention of lung cancers from CARET, the beta-carotene and retinol efficacy trials, and prospects for the future.

Omenn GS
University of Michigan, Ann Arbor,
Michigan, USA

The objective of this paper was to review the strategies for lung cancer chemoprevention.

The objective of this paper was to review the strategies for lung cancer chemoprevention. A retrospective assessment of the major findings from the most informative lung cancer chemoprevention clinical trials [alpha-tocopherol (vitamin E), beta-carotene trial and beta-carotene and retinol efficacy trial] was employed. Both trials and many others showed no benefit from what was once the prime candidate for lung cancer chemoprevention, beta-carotene. Furthermore, both trials found that beta-carotene, alone or in combination with vitamin E or retinyl palmitate, increased the incidence of lung cancers and the total and cardiovascular mortality rates. In conclusion, design, conduct, documentation, relationships with participants, and preparedness for unexpected findings are all important for chemoprevention research. Trials are necessary to test inferences from observational epidemiology and animal models. Multiple classes of promising agents are available for evaluation and for eventual randomized trials.

Editorial Comment (TLP): A retrospective assessment of the major findings in this astonishing trial

. . . increased the incidence of lung cancers and the total and cardiovascular mortality rates.

Trials are necessary to test inferences from observational epidemiology and animal models.

Our hypothesis was that among patients with surgically resected non-small cell lung cancer (NSCLC), incidentally detected cancers were common, were less likely to require pneumonectomy, and were associated with better stage-adjusted survival.

of beta-carotene believed to be promising as a chemoprevention agent in lung cancer came as a huge surprise. In fact, when beta-carotene was given with vitamin or retinyl palmitate, it actually increased the incidence of lung cancer and cardiovascular mortality rates. So there is caution that careful study design must be undertaken before trials in man.

2.

J Thorac Oncol 2007;2:125-130

Clinical Characteristics and Survival of Patients with Surgically Resected, Incidentally Detected Lung Cancer

Raz DJ, Glidden DV, Odisho AY, Jablons

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Francisco CA

BACKGROUND:: There is little information on the clinical characteristics and outcomes of patients with surgically resected, incidentally detected lung cancers. Our hypothesis was that among patients with surgically resected non-small cell lung cancer (NSCLC), incidentally detected cancers were common, were less likely to require pneumonectomy, and were associated with better stage-adjusted survival. METHODS:: Two hundred seventy-four patients with NSCLC who underwent surgical resection between 1999 and 2004 were studied. The clinical

Patients with incidentally detected NSCLC had smaller and earlier-stage cancers, were less likely to undergo pneumonectomy (3% versus 13%, $p = 0.005$), and were more likely to have bronchioloalveolar carcinoma (15% versus 5%, $p = 0.003$).

Despite aggressive multimodality treatment, 5-year survival of stage III non-small cell lung cancer (NSCLC) remains <30%.

Patients with cancers detected incidentally by CT scan may have better stage-adjusted survival. .

.....

characteristics of patients with incidentally detected and symptomatic NSCLC were compared. A proportional hazards model was used to compare the stage-adjusted mortality rate of patients with incidentally detected and symptomatic NSCLC. RESULTS:: One hundred patients (36%) had incidentally detected NSCLC. Patients with incidentally detected NSCLC had smaller and earlier-stage cancers, were less likely to undergo pneumonectomy (3% versus 13%, $p = 0.005$), and were more likely to have bronchioloalveolar carcinoma (15% versus 5%, $p = 0.003$). Patients with incidentally detected cancers had a stage-adjusted hazards ratio (HR) of mortality of 0.9 compared with symptomatic patients (0.6-1.4, $p = 0.64$). Patients with cancers detected incidentally on computed tomography (CT) had a stage-adjusted HR of 0.5 (0.2-1.5, $p = 0.15$). CONCLUSIONS:: Early-stage NSCLC is commonly detected incidentally. Patients with incidentally detected lung cancers are more likely to have bronchioloalveolar carcinoma histology, less likely to undergo pneumonectomy, and overall have similar stage-adjusted survival compared with symptomatic patients. Patients with cancers detected incidentally by CT scan may have better stage-adjusted survival, but our study was not sufficiently powered to detect this effect.

Editorial Comment (TLP): The relatively good survival rate of incidentally detected lung cancer is well known. Now with CT becoming increasingly utilized and

soon to become the standard of care lung cancer will be diagnosed in early stages much more readily than when reliance upon standard radiology was done. We look forward to great progress in the area of early identification and intervention, particularly when we begin to target high risk groups for CT and perhaps training techniques.

3.

J Thorac Oncol 2007;2:273-281

Does Intensive Follow-Up Alter Outcome in Patients with Advanced Lung Cancer?

Benamore R, Shepherd FA, Leighi N, Pintilie M, Patel M, Feld R, Herman S

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BACKGROUND: Despite aggressive multimodality treatment, 5-year survival of stage III non-small cell lung cancer (NSCLC) remains <30%. To detect relapse, progression, or development of a second primary cancer early, many clinicians perform follow-up scans. To assess the impact of routine scanning, we compared clinical trial patients who had study-mandated scans with those treated off-study who had less intensive radiologic follow-up. METHODS:: The hospital cancer registry and trials databases were searched for patients with locally advanced NSCLC who had undergone multimodality treatment

with curative intent. Baseline demographics were collected as well as frequency and results of clinical and radiologic follow-up. RESULTS:: Forty trial patients and 35 nontrial control patients were identified. Trial patients underwent significantly more imaging, particularly in the first 2 years (2.9 versus 2.0 body scans per year, $p = 0.0016$; 1.1 versus 0.4 brain scans per year, $p < 0.001$) but did not have more frequent follow-up visits. Forty-five cancers were detected (41 relapses, four metachronous primary tumors) in 44 (59%) patients. Of these, 28 (64%) sought medical attention that led to detection before a scheduled appointment or procedure. There was no significant difference in time to relapse or second primary in trial and nontrial patients ($p = 0.80$). Twenty-three patients had localized relapse, but only 15 could be treated with curative intent. Despite the trial group demonstrating a higher number of asymptomatic cancers and being offered potentially curative therapy more frequently, there was no significant difference in survival between trial and nontrial patients. CONCLUSION:: In patients with locally advanced NSCLC, frequent cross-sectional imaging does not alter survival after combined modality therapy.

Editorial Comment (TLP): This study shows that more frequently imaging during the first two years following aggressive multi modality treatment for Stage III non small cell lung cancer does not identify patients at higher rates of relapse.

Of these, 28 (64%) sought medical attention that led to detection before a scheduled appointment or procedure.

Eligible patients were required to have NSCLC unsuitable for curative therapy and baseline hemoglobin (Hgb) levels less than 121 g/L.

4.

J Clin Oncol 2007;25:1027-1032

Comment in J Clin Oncol 2007;25:1021-1023

Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia

Wright JR, Ung YC, Julian JA, Pritchard KI, Whelan TJ, Smith C, Szechtman B, Roa W, Mulroy L, Rudinkas L, Gagnon B, Okaware GS, Levine MN

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PURPOSE: Previous trials have suggested a quality-of-life (QOL) improvement for anemic cancer patients treated with erythropoietin, but few used QOL as the primary outcome. We designed a trial to investigate the effects of epoetin alfa therapy on the QOL of anemic patients with advanced non-small-cell carcinoma of the lung (NSCLC). PATIENTS AND METHODS: A multicenter, randomized, double-blind, placebo-controlled trial was conducted. The proposed sample size was 300 patients. Eligible patients were required to have NSCLC unsuitable for curative therapy and baseline hemoglobin (Hgb) levels less than 121 g/L. Patients were assigned to 12 weekly injections of subcutaneous epoetin alpha or placebo, targeting Hgb levels between 120 and 140 g/L. The primary outcome was the difference in the change in Functional Assessment of Cancer

. . . a significant difference in the median survival in favor of the patients on the placebo arm of the trial (63 v 129 days; hazard ratio, 1.84; P = .04). The Steering Committee closed the trial.

Therapy-Anemia scores between baseline and 12 weeks. RESULTS: Reports of thrombotic events in other epoetin trials prompted an unplanned safety analysis after 70 patients had been randomly assigned (33 to the active arm and 37 to the placebo arm). This revealed a significant difference in the median survival in favor of the patients on the placebo arm of the trial (63 v 129 days; hazard ratio, 1.84; P = .04). The Steering Committee closed the trial. Patient numbers compromised the interpretation of the QOL analysis, but a positive Hgb response was noted with epoetin alfa treatment. CONCLUSION: An unplanned safety analysis suggested decreased overall survival in patients with advanced NSCLC treated with epoetin alfa. Although infrequent, other similar reports highlight the need for ongoing trials evaluating erythropoietin receptor agonists to ensure that overall survival is monitored closely.

The overall radiographic response rate was 38%, and the median survival was 8.6 months.

Editorial Comment (TLP): This recent report shows decreased overall survival in patients with advanced non small cell carcinoma of the lung (NSCLC) treated with erythropoietin alpha is unknown. Further studies are needed for confirmation as well as inquiry into possible mechanisms.

5.

J Thorac Oncol 2007;2:197-202

A Pharmacogenomic Study of Docetaxel and Gemcitabine for the Initial Treatment of Advanced Non-Small Cell Lung Cancer

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BACKGROUND::

Pharmacogenomic profiling is an attractive strategy for individualizing chemotherapy. Several genetic polymorphisms predict the survival of patients with non-small cell lung cancer treated with platinum-based chemotherapy. This phase II clinical trial was performed using a non-platinum-based chemotherapy doublet. The impact of previously identified polymorphisms on clinical outcomes was assessed.

METHODS:: Patients with advanced non-small cell lung cancer who had not received previous chemotherapy were treated with docetaxel 40 mg/m on days 1 and 8 and gemcitabine 800 mg/m days 1 and 8 every 21 days until disease progression or unacceptable toxicity. A pretreatment blood sample was obtained, and genomic DNA was analyzed for polymorphisms in DNA repair and metabolic genes. **RESULTS::** Forty-nine patients were enrolled and evaluated for response and survival. The overall radiographic response rate was 38%, and the median survival was 8.6 months. Nonhematologic toxicity was generally mild. Two treatment related deaths occurred: one due to neutropenic sepsis during the first cycle and one due to pulmonary edema after 12 cycles of treatment.

The wild-type XPD genotype was associated with prolonged survival and a significantly higher risk of grade 4 neutropenia ($p = 0.02$).

Five eligible trials were identified for a total of 865 patients: 433 patients had been assigned to 3wD, and 432 patients had been assigned to wD. Median age was 62 years (range, 26 to 80 years).

Polymorphisms in XPD, XRCC1, and XRCC3 did not significantly predict survival, but trends similar to those reported for platinum-based chemotherapy were observed. The wild-type XPD genotype was associated with prolonged survival and a significantly higher risk of grade 4 neutropenia ($p = 0.02$). CONCLUSION:: This regimen of docetaxel and gemcitabine is well tolerated and active for the treatment of advanced non-small cell lung cancer. The impact of XPD polymorphisms on hematologic toxicity is similar to what has been reported for platinum-based chemotherapy.

Editorial Comment (TLP): This is one of a growing number of studies showing new chemotherapeutic regimens useful in advanced small cell lung cancer. Thus, we are chipping away at the problem of advanced lung cell cancer with advances in chemotherapy.

6.

J Thorac Oncol 2007;2:125-130

Individual patient data meta-analysis of docetaxel administered once every 3 weeks compared with once every week second-line treatment of advanced non-small cell lung cancer

Di Maio M, Perrone F, Chiodini P, Gallo C, Camps C, Schuette W, Quoix E, Tsai CM, Gridelli C

Clinical Trials Unit, National Cancer Institute, Naples, Italy

PURPOSE: Although several randomized trials have been performed comparing weekly docetaxel (wD) with standard docetaxel once every 3 weeks (3wD) as second-line treatment of advanced non-small-cell lung cancer (NSCLC), no single trial had sufficient power to detect clinically relevant differences in survival.

METHODS: We performed a meta-analysis based on individual patient data from all identified randomized trials comparing wD with 3wD as second-line treatment of advanced NSCLC. Baseline characteristics, treatment assigned, and outcome data were collected for each patient. The primary end point was overall survival. All statistical analyses were stratified by trial.

RESULTS: Five eligible trials were identified for a total of 865 patients: 433 patients had been assigned to 3wD, and 432 patients had been assigned to wD. Median age was 62 years (range, 26 to 80 years). Performance status was 0 in 23%, 1 in 58%, and 2 in 16% of patients; 91% of the patients had received previous platinum, and 14% had received previous paclitaxel. With 733 deaths recorded (85%), median survival was 27.4 weeks for patients treated with 3wD, and 26.1 weeks for patients treated with wD ($P = .24$, log-rank test). There was no significant heterogeneity among the five trials. No relevant differential effect was detected in subgroup analyses. Significantly less severe and febrile neutropenia was reported with wD ($P < .00001$ for both), whereas no significant differences were observed for anemia, thrombocytopenia, and

nonhematologic toxicity.
CONCLUSION: wD shows similar efficacy compared with 3wD, and represents an alternative for second-line treatment of advanced NSCLC.

chronic disease and the development of innovative drug therapies offer new hope for the treatment of tobacco-dependent patients. The diagnosis of lung cancer provides a teachable moment to motivate patients to attempt tobacco abstinence on which clinicians should capitalize. We review the currently available pharmacologic approaches to the treatment of tobacco dependence.

Editorial Comment (TLP): This important article reviews the current available pharmacological approaches to the treatment of tobacco dependence. Accordingly we must put out efforts at prevention, as well as early identification and intervention.

The diagnosis of lung cancer provides a teachable moment to motivate patients to attempt tobacco abstinence on which clinicians should capitalize.

Editorial Comment (TLP): This simple study shows that less frequent docetaxel administration, i.e., once weekly, is equally effective. This is a significant advancement in the convenience of patients being treated for non small cell lung cancer.

7.

J Thorac Oncol 2007;2:249-256

Treating tobacco dependence: a review of the best and latest treatment options

Ebbert JO, Sood A, Hays JT, Dale LC, Hurt RD

Mayo Clinic College of Medicine, Rochester, Minnesota.

Globally, an estimated 85% of lung cancer in men and 47% of lung cancer in women is attributable to tobacco smoking. Tobacco dependence treatment remains the most cost-effective way to prevent morbidity and mortality from lung cancer. Several effective pharmacotherapies are available to treat tobacco dependence. However, the long-term effectiveness of these treatments has been limited because the majority of smokers who attempt to stop smoking eventually relapse. Approaching the treatment of tobacco use and dependence as a

Several effective pharmacotherapies are available to treat tobacco dependence. However, the long-term effectiveness of these treatments has been limited