The Dawn of a Revolution in Personalized Lung Cancer Prevention

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Abstract

Lung cancer prevention and early detection, which have fallen on hard times for more than the past 20 years, seem to have turned a corner toward better times ahead. Exciting new results of randomized controlled trials that targeted the arachidonic acid pathway, including a celecoxib trial reported by Mao and colleagues in this issue of the journal (beginning on page 984) and a trial of the prostacyclin analog iloprost, complement recently reported 20%–30% lung cancer mortality reductions, either with aspirin in targeting the arachidonic acid pathway or with computed tomography screening. The new results show encouraging activity personalized to former smokers and/or people expressing predictive biomarkers. These trials and technological advances in molecular profiling and imaging herald substantial clinical advances on the horizon of this field. Cancer Prev Res; 4(7); 949–53. ©2011 AACR.

*It was the best of times, it was the worst of times...it was the spring of hope, it was the winter of despair*

—Charles Dickens (A Tale of Two Cities)

The well-known litany of disappointments in clinical lung-cancer prevention includes the Alpha-Tocopherol, Beta-Carotene (ATBC) trial, Carotene and Retinol Efficacy Trial (CARET), Lung Intergroup Trial (LIT), and the finding that, important as smoking cessation is, half of all new lung cancers arise in former smokers (1–5). Furthermore, a very recent randomized controlled trial (RCT) of selenium to prevent new cancer in resected early-stage lung-cancer patients reported negative outcomes (6). The worst of times. For people living with an increased risk of lung cancer, however, the glass is starting to look somewhat fuller. Reversing decades of disappointing results of lung cancer early detection research with chest–X-ray screening (7), the definitive randomized controlled National Lung Screening Trial (NLST) showed that screening high-risk current or former smokers with computed tomography (CT) scans reduced lung-cancer mortality by 20%, a remarkable but far from bloodless success (8). CT scanning became the most contentious debate of the lung cancer field—one side asserting that it should be implemented only after a definitive RCT has confirmed benefit (8). Success has many “fathers,” and both camps claimed affirmation, even vindication, by the NLST results. Meanwhile, and more subtly, analyses of RCTs of daily aspirin to reduce the risk of vascular disease found a 30% reduction in lung-cancer mortality in people taking daily aspirin for five or more years (10). The early-2011 report of this clinical targeting of the arachidonic acid pathway is prelude to three trials reported in the past year showing that targeting the same pathway with different agents is effective in reversing proliferation or histologic changes in the lungs of former smokers (11–13).

These three trials effectively targeted arachidonic acid metabolic pathways with the cyclooxygenase-2 (COX-2)–specific inhibitor celecoxib or the prostacyclin analog iloprost in former and/or current smokers. Celecoxib reduced the proliferation marker Ki-67 in former smokers but had no significant effects on histology, and iloprost reversed histologic abnormalities in the lungs of former smokers, all of which not only reinforces the importance of smoking cessation for risk reduction (14) but also introduces the potential of personalizing prevention to former smokers. Indeed, as will be discussed later, one of the celecoxib trials took personalization a step further with the identification of potential molecular predictive markers for this agent. These markers and the activity involving former smokers are the first important personalizing steps of lung cancer chemoprevention, and together with the NLST, represent important strides toward reducing the national and worldwide burden of lung cancer, which has largely eluded the grasp of cancer therapy and prevention to date (15, 16).

A number of explanations have been given for several decades of clinical failure to translate epidemiologic clues into successful chemoprevention approaches for lung cancer. Although each of these numerous explanations is valid in its own right, none of them alone is adequate to completely explain the litany of defeats suffered by clinical investigators in this domain (17). They include inadequate mouse models of respiratory premalignancy,
imprecise interpretation of epidemiologic data, marginally active compounds being given at physiologically tolerable but pharmacologically ineffectual doses, the formidable obstacle of reversing premalignancy in the setting of continued tobacco exposure (17), and the absence of a personalized approach to lung-cancer prevention akin to that being undertaken in the therapeutic realm (17, 18). All of the negative trials yielded useful data, however, as did the few encouraging early lung-cancer chemoprevention studies. Perhaps the most valuable of these earlier efforts was a retinoid trial conducted by Lee and colleagues in active smokers; these investigators showed that, although ineffective in reversing metaplasia index overall, smoking cessation (during trial) reduced the metaplasia index (regardless of arm), and even more so in the retinoid arm (19). Suggesting that lung-cancer prevention may be more effective in former smokers, this trial was followed by the first lung cancer RCT exclusively in former smokers (20) which supported this personalizing approach.

An abundance of preclinical data suggests that the COX-2/prostaglandin E2 (PGE2) signaling pathway plays a major role in lung carcinogenesis (21–23). COXs act on free arachidonic acid liberated from membrane phospholipids to overproduce PGE2 when COX-2 is upregulated, and PGE2 likely is a major driver of lung carcinogenesis (21). Our group was among the first to show that COX-2 expression was an indicator of poor prognosis in nonsmall cell lung cancer (24). These data plus animal data showing that inhibition of PGE2 suppresses lung tumorigenesis led to the development of COX-2 inhibitors for lung-cancer chemoprevention (21–24).

COX-2-targeting approaches have started to yield intriguing evidence. The trial by Kim and colleagues (11) randomized 204 current and former smokers to celecoxib or placebo for three months, with Ki-67 as the primary endpoint. The original celecoxib dose of 200 mg/bid was modified halfway through the trial to 400 mg/bid. Although negative overall, high-dose celecoxib produced a reduction of Ki-67 overall, which was provocatively more reduced in former smokers, and a nonsignificant reduction in metaplasia index in former smokers. The trial population included only 21% former smokers, however, and the subgroup of former smokers who received high-dose celecoxib was only 7 patients strong.

Based on their data showing that celecoxib downregulated PGE2 and interleukin 10 (IL-10) production in alveolar macrophages from active smokers (25), Mao and colleagues conducted a phase IIa single-arm trial of celecoxib for lung cancer prevention in active smokers (26, 27). They showed that six months of celecoxib treatment significantly downregulated Ki-67 in bronchial epithelial tissue obtained from 20 heavy smokers (25). Celecoxib also inhibited the production of PGE2 and IL-10 in the lung microenvironment. These promising results and certain considerations of smoking status, including poor results of active smokers and favorable trends of former smokers in large-scale prior chemoprevention trials, led these investigators to conduct a randomized, double-blind, placebo-controlled trial of celecoxib for lung-cancer prevention in former smokers, which is reported elsewhere in this issue of the journal (12).

This trial randomly assigned 137 former smokers to celecoxib (400 mg/bid) or placebo (12) for six months, at which time, patients crossed over for another six months of celecoxib or placebo. Patients were ≥ 45 years old, had at least 30 pack-years smoking history, and most important had ceased smoking for at least one year. Baseline and six-month bronchoscopies were available for 101 patients, who were evaluated for Ki-67, the primary endpoint. A mixed-effects analysis found that celecoxib was dramatically more active than placebo (P = 0.0006). The average change in Ki-67 labeling index was a 34% reduction with celecoxib versus a 3.8% increase with placebo (P = 0.04, T-test). Celecoxib had no significant effect on any of three measures of histopathology outcome [average and maximum World Health Organization (WHO) score and dysplasia index], although there was a trend favoring celecoxib in maximum histopathology score. Although Ki-67 is nonspecific and can be reduced in low-risk people without regard to carcinogenesis (28), its believability in this study stems from findings of substantial, significant reductions in Ki-67 versus placebo and, more important, of supportive changes in several specific molecular markers of inflammation and carcinogenesis. For example, celecoxib also reduced IL-6 gene (in BAL cells) or protein (in BAL fluid) expression, which is a key inflammatory mediator of lung carcinogenesis (29). Most impressive, the decrease in Ki-67 by celecoxib was associated with the clinical, radiographic response of lung nodules, including a complete resolution in some cases.

A provocative subset finding of this trial is that a high ratio of COX-2 to 15-hydroxyprostaglandin dehydrogenase (15-PGDH) mRNA in bronchoalveolar lavages (BAL) was a significant predictive (drug-sensitivity) marker of Ki-67 response to celecoxib (P = 0.002). This ratio is a surrogate for PGE2 level, which is diluted in BAL fluid and thus difficult to measure. Severe inflammation induces COX-2 and suppresses 15-PGDH in the lungs (30). A high ratio denotes a high level of PGE2 in lung tissue because 15-PGDH degrades PGE2, implying that PGE2 is the main driver of carcinogenesis in the group of individuals with this predictive marker. Another important finding is that people with a high baseline Ki-67 labeling index (theoretically at a higher lung cancer risk) benefitted from celecoxib (versus a low baseline index). Therefore, although Ki-67 is not apparently tied directly to the target(s) of COX-2 inhibition, it also may be a predictive marker for personalizing lung-cancer prevention with celecoxib.

The exciting current results with the COX-2:15-PGDH ratio provide the first substantial predictive molecular biomarkers of lung cancer chemoprevention. The predictive potential of the ratio is supported by the finding that intratumoral COX-2 predicted benefit from celecoxib plus chemotherapy (31). This biomarker work complements recent findings on cyclin D1 in the setting of lung cancer therapy but with prevention implications. Cyclin D1
marked the sensitivity of lung cancer patients to bexarotene plus erlotinib (18), a molecular-targeted combination with cancer preventive potential (32).

Because of its cross-over design, all patients of the present Mao and colleagues trial who completed 12 months of the study had received both placebo and celecoxib by the time of a planned follow-up CT scan at 12 months; 75 patients had both a baseline and 12-month scan. Forty-seven of these patients had at least one noncalcified nodule at baseline; nodule response and/or status at 12 months was a reduction or resolution in 12 of the 47 patients (25%), stable nodules in 34 patients, and a new nodule in 1 patient. These data suggest that celecoxib was reasonably effective in preventing the progression of premalignancy or reversing it (in 25%). These secondary CT data must be interpreted with caution, however. First and foremost, the six-month cross-over design prevented comparison of 12-month CT results in celecoxib versus placebo patients. (This design may have aided accrual, e.g., assuring potentially interested patients that they would receive drug and avoid consignment to placebo alone.) Furthermore, similar secondary CT endpoints in a positive trial of budesonide led to a RCT of budesonide with a primary endpoint assessed by CT. Patients with CT-detected high-risk lung nodules were invited to participate in the randomized budesonide chemoprevention trial, in which treatment-arm CT results did not improve (33). The present Mao and colleagues study (12) differs from the earlier budesonide trial (33), however, in that it found a strong correlation between its primary Ki-67 and secondary CT endpoints, whereas the budesonide trial did not report any such correlative results. Another interesting aspect of the Ki-67–CT association is its implication that celecoxib was active in central and peripheral lesions because Ki-67 in bronchoscopies reflects central-lung, squamous carcinogenesis, whereas CT data reflect peripheral-lung carcinogenesis leading to adenocarcinoma.

The third very recent targeted lung cancer prevention trial was conducted by Keith and colleagues. They tested an alternative approach for targeting the arachidonic acid pathway (13). Rather than inhibit COX-2, they increased a beneficial COX-2–related compound by administering oral iloprost, an analog of the arachidonic acid metabolite prostacyclin, which has antimitastatic and antiproliferative properties. After showing that genetic overexpression of prostacyclin synthase or iloprost prevented lung cancer in a variety of murine models, these investigators launched a randomized multicenter trial of iloprost versus placebo for reversing histologic premalignancy in 125 current or former smokers who had baseline and post-treatment bronchoscopies (75 to iloprost, 77 to placebo; the trial was conducted via an inter–SPORE (Specialized Programs of Research Excellence) mechanism). These patients were required to have cytologic atypia and thus were at a higher risk than were patients of the celecoxib trials, who were not so required. Premalignant changes were measured in three ways—average histologic score of all bronchoscopic biopsies (the primary endpoint), worst histologic biopsy score, and dysplasia index. Oral iloprost was ineffective in current smokers but reversed premalignant lesions in former smokers. Former smokers in the iloprost arm had a significantly reduced average histology score (by 0.41 units; \( P = 0.010 \)), maximal histology score (by 1.1 units; \( P = 0.0002 \)), and dysplasia index (12.45%; \( P = 0.006 \)) compared with former smokers in the placebo arm. Ki-67 was a secondary endpoint of this trial (whereas primary in the celecoxib trials) and was slightly, nonsignificantly reduced in the airways of former smokers of the iloprost arm. The drug was well-tolerated. This evidence of the efficacy of iloprost in former but not current smokers reinforces the importance of personalizing lung cancer prevention by smoking status.

The negative recent randomized trial of selenium in over 1,700 patients with surgically resected stage I lung cancer (6) helps illustrate the motivation of the National Cancer Institute for commissioning a report on cancer clinical trials from the Institute of Medicine (34). This report has led to the development of synergistic programmatic approaches by a number of cooperative trials groups designed to improve the next generation of clinical approaches to various malignancies. Emerging alliances along these lines between the Eastern Cooperative Oncology Group (ECOG) and American College of Radiology Imaging Network (ACRIN) promise to lead to feasible lung cancer prevention approaches incorporating novel imaging, including both CT and positron emission tomography (PET) imaging, extending the use of CT imaging by Mao and colleagues (12) and others. ACRIN investigators conducted the aforementioned NLST (8). The combination of imaging expertise and a long history of cancer prevention research will allow these new cooperative-group alliances to develop early guidelines for the next series of lung-cancer screening and prevention trials. Undoubtedly, higher-quality anatomic and metabolic imaging will play a role. A major limitation of CT scanning for lung-cancer prevention research is its restriction to the peripheral lung, where tissue is unobtainable for assessing molecular biomarkers against the CT results. A way to overcome this limitation may be molecular imaging of the peripheral lung.

Molecular imaging, as well as appropriate intermediate biomarkers, will help streamline the development of chemopreventive agents. We recently found that the mammalian target of rapamycin (mTOR) inhibitor everolimus (10 mg) given for three weeks prior to surgery was highly effective in reducing metabolic uptake assessed by fludeoxyglucose positron emission tomography (FDG-PET) in patients with early-stage nonsmall-cell lung cancer; molecular pathway analyses are ongoing (35). This result is consistent with preclinical lung data from West and colleagues, which suggest that blockade of the AKT/mTOR signaling axis leads to abrogation of oncogene-addicted signaling pathways (36). The importance these data have for clinical prevention increases with consideration of recent data of Gustafson and others implicating activation of the phosphoinositide-3 kinase (PI3K)/mTOR axis in proximal airway epithelial cells of current and former smokers with dysplastic lesions and showing that PI3K activation could be
reversed with a PI3K inhibitor (myoinositol; ref. 37). Our preoperative mTOR-inhibitor study illustrates the potential of correlating clinical/biologic effects of targeted agents with imaging, and such window-of-opportunity trial designs likely will become increasingly important for developing targeted drugs and novel imaging techniques (38). An example of this promise with close reliance to the Mao and colleagues study is the current development of COX-2–targeting imaging using PET or single photon emission computed tomography (SPECT) tracers, which should allow the detection of COX-2–expressing lesions (in the peripheral airways, for example, where biopsy is difficult) and provide potential predictive information for COX-2 inhibitors in prevention and therapy (12, 31).

The four studies (either RCTs or RCT-based) of arachidonic acid-pathway targeting discussed here firmly show this approach’s potential for lung-cancer prevention (10–13). Given the increasing national focus on developing effective multimodality screening and prevention approaches for lung cancer, it is incumbent upon us to extend the recent successes of Keith and colleagues and Mao and colleagues with further personalized clinical testing that combines these chemopreventive approaches with CT screening (established now for identifying earlier-stage malignancies) and that is aimed ultimately at complementing CT screening for reducing the burden of lung cancer. An important, underappreciated component of approaches with molecular-targeted agents is smoking cessation, which must be emphasized, particularly in light of the growing evidence that targeted prevention is ineffective in active smokers (19, 25, 27, 33). Last, combining anatomic or CT-guided imaging with metabolic or PET-guided imaging in the highest-risk patient population may help in detecting premalignant lesions anatomically and in assessing their full metabolic potential.

Discourse, optimism, and commitment of lung-cancer prevention researchers have resulted in the generation of important data over the last few decades. Although successes have been minimal until recently, the biomarker-driven revolution, facilitated in substantial measure by RNA sequencing and other next-generation sequencing platforms (39, 40), is finally coming to fruition in the field of lung-cancer prevention. Having lived through the worst of times, we seem to be entering the best of times, with personalized (former smokers, predictive biomarkers), molecular-targeted prevention bringing meaningful population-wide reductions in the incidence and mortality of lung cancer perhaps just around the corner.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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