Lung Cancer 79 (2013) 254–261

Contents lists available at SciVerse ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Randomized phase II trial of sulindac for lung cancer chemoprevention

Paul J. Limburg[a,*], Sumithra J. Mandrekar[a], Marie Christine Aubry[a], Katie L. Allen Ziegler[a], Jun Zhang[a], Joanne E. Yi[a], Michael Henry[a], Henry D. Tazelaar[b], Stephen Lam[c], Annette McWilliams[c], David E. Midthun[a], Eric S. Edell[a], Otis B. Rickman[a], Peter Mazzone[d], Melvyn Tockman[e], John F. Beamis[f], Carla Lamb[f], Michael Simoff[g], Charles Loprinzi[a], Eva Szabo[h], James Jett[a], For the Cancer Prevention Network

[a] *Mayo Clinic, Rochester, MN, United States*
[b] *Mayo Clinic in Arizona, Scottsdale, AZ, United States*
[c] *British Columbia Cancer Agency, Vancouver, BC, United States*
[d] *Cleveland Clinic, Cleveland, OH, United States*
[e] *H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, United States*
[f] *Lahey Clinic Medical Center, Burlington, MA, United States*
[g] *Henry Ford Hospital, Detroit, MI, United States*
[h] *Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, United States*

ARTICLE INFO

Article history:
Received 22 June 2012
Received in revised form
13 November 2012
Accepted 14 November 2012

Keywords:
Lung cancer
Chemoprevention
Phase II clinical trial
Sulindac
NSAIDs

ABSTRACT

Introduction: Sulindac represents a promising candidate agent for lung cancer chemoprevention, but clinical trial data have not been previously reported. We conducted a randomized, phase II chemoprevention trial involving current or former cigarette smokers (≥30 pack-years) utilizing the multi-center, inter-disciplinary infrastructure of the Cancer Prevention Network (CPN).
Methods: At least 1 bronchial dysplastic lesion identified by fluorescence bronchoscopy was required for randomization. Intervention assignments were sulindac 150 mg bid or an identical placebo bid for 6 months. Trial endpoints included changes in histologic grade of dysplasia (per-participant as primary endpoint and per lesion as secondary endpoint), number of dysplastic lesions (per-participant), and Ki67 labeling index.
Results: Slower than anticipated recruitment led to trial closure after randomizing participants ($n = 31$ and $n = 30$ in the sulindac and placebo arms, respectively). Pre- and post-intervention fluorescence bronchoscopy data were available for 53/61 (87%) randomized, eligible participants. The median (range) of dysplastic lesions at baseline was 2 (1–12) in the sulindac arm and 2 (1–7) in the placebo arm. Change in dysplasia was categorized as regression:stable:progression for 15:3:8 (58%:12%:31%) subjects in the sulindac arm and 15:2:10 (56%:7%:37%) subjects in the placebo arm; these distributions were not statistically different ($p = 0.85$). Median Ki67 expression (% cells stained positive) was significantly reduced in both the placebo (30 versus 5; $p = 0.0005$) and sulindac (30 versus 10; $p = 0.0003$) arms, but the difference between arms was not statistically significant ($p = 0.92$).
Conclusions: Data from this multi-center, phase II squamous cell lung cancer chemoprevention trial do not demonstrate sufficient benefits from sulindac 150 mg bid for 6 months to warrant additional phase III testing. Investigation of pathway-focused agents is necessary for lung cancer chemoprevention.

1. Introduction

Lung cancer is the most common malignancy worldwide [1] with approximately one-half of all incident cases attributable to cigarette smoking [2]. Since an estimated 90 million smokers reside in the U.S. alone [3,4], there is an urgent need for novel lung cancer prevention strategies. Bronchial dysplasia can be readily identified by fluorescence bronchoscopy [5–7] and represents a plausible surrogate endpoint biomarker for early phase lung cancer chemoprevention trials [8,9]. Although change in bronchial dysplasia primarily informs the prevention of squamous cell carcinoma, this readily measurable endpoint plays a key role in chemoprevention agent development [10] and has been previously employed in several early phase clinical trials [11–14].

* Corresponding author at: 200 First Street SW, Rochester, MN 55905, United States. Tel.: +1 507 266 4338; fax: +1 507 266 0350.
E-mail address: limburg.paul@mayo.edu (P.J. Limburg).

0169-5002/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.lungcan.2012.11.011

Nonsteroidal anti-inflammatory drugs (NSAIDs) may provide lung cancer chemopreventive benefits through multiple mechanisms that are mediated, at least in part, by cyclooxygenase (COX)-2 inhibition [15–18]. Animal studies have shown that COX inhibitors can suppress lung tumorigenesis [19,20] and three small, short-term phase II clinical trials have reported beneficial effects from celecoxib (a selective COX-2 inhibitor) on bronchial Ki67 labeling index [21–23]. However, none of the trials reported to date were designed or powered to address changes in bronchial histopathology. Ongoing concerns regarding the cardiovascular toxicity of selective COX-2 inhibitors [24,25] have prompted renewed interest in non-selective COX inhibitors, such as sulindac, for chemopreventive applications [26]. In this context, we conducted a randomized, double-blind, phase II trial of sulindac versus placebo among current or former smokers with histologically confirmed bronchial dysplasia at baseline.

2. Materials and methods

The study protocol was approved by appropriate Institutional Review Boards at each participating site (ClinicalTrials.gov, NCT00368927). Participants provided written informed consent prior to any study-related procedures. The Mayo Clinic Cancer Center Data and Safety Monitoring Board reviewed safety data every 6 months.

2.1. Subject recruitment

Subjects were enrolled at six institutions from 2006 to 2009. The target population was defined as current or former smokers, age 40–79 years, with either no history of lung cancer or stage I NSCLC resected ≥1 year prior to the baseline evaluation. General inclusion criteria were: normal organ function; no evidence of malignancy on chest X-ray; no current NSAID use (except aspirin ≤81 mg qd), or other potentially interfering compounds; and ECOG performance status ≤1. Women of childbearing potential were required to document a negative pregnancy test prior to enrollment. Exclusion criteria were: history of malignancy within the preceding 3 years (other than resected stage I NSCLC); currently breastfeeding; use of other investigational agents; or uncontrolled intercurrent illness.

2.2. Baseline evaluation

Eligible subjects were required to have at least one site of biopsy-confirmed bronchial dysplasia on bronchoscopy exam, performed <45 days prior to randomization by experienced endoscopists under white light and fluorescence settings, using an Olympus BF40D (or comparable) bronchoscope and Onco-LIFE device. At least one biopsy sample was taken from each area suspicious for intraepithelial or invasive neoplasia, with the location carefully recorded. Additional biopsies were taken from 6 pre-defined areas of visually normal epithelium: main carina, right upper lobe carina, right middle lobe carina, right lower lobe-superior segment carina, left upper lobe carina, and left lower lobe superior segment carina.

2.3. Intervention assignments and on-study assessments

Subjects were randomly assigned to receive sulindac 150 mg bid or identical placebo bid for 6 months (1:1 ratio) using a dynamic allocation procedure to balance marginal distributions of the specified stratification factors: smoking status (former versus current); history of lung cancer (yes versus no), and number of dysplastic lesions at baseline (1–3 versus >3). A telephone interview was conducted at Month 1, and a physical exam and safety assessment were performed at Month 3.

2.4. Post-intervention evaluation

Physical exam, blood work, and bronchoscopy were repeated at Month 6 using the same standardized protocol employed at baseline. Biopsies were obtained from all sites sampled at baseline, as well as from any newly identified suspicious areas.

2.5. Tissue processing and histologic interpretation

Bronchial mucosa biopsy samples were fixed in 10% neutral buffered formalin and paraffin-embedded. Two pulmonary pathologists, blinded to the intervention assignments, independently classified the histologic findings according to WHO/IASLC criteria [27]: normal, basal cell hyperplasia, or metaplasia; mild dysplasia; moderate dysplasia; severe dysplasia; carcinoma in situ; or invasive cancer. Discrepancies in biopsy interpretation were adjudicated in collaboration with a third pathologist to achieve consensus.

2.6. Mucosal proliferation

Mucosal proliferation was assessed by Ki67 immunostaining (MIB-1 clone; 1/100, Dako Antibody diluent, Dako, Carpenteria, CA). Ki67 analyses were limited to subjects with paired biopsy samples adequate for immunostaining and were assessed throughout the thickness of the bronchial epithelium. Immunoreactivity was scored as the percentage of positively staining cells (i.e., Ki67 labeling index) in 5% increments (range = 0–100%) by a pulmonary pathologist.

2.7. Compliance and adverse event monitoring

Intervention compliance was monitored using a standardized agent diary, which was reviewed during each telephone call or study visit. Adverse events were classified and graded using NCI Common Terminology Criteria, version 3.0 (www.ctep.cancer.gov), with maximum grade per subject and event type recorded across the duration of intervention.

2.8. Statistical considerations

The primary endpoint was defined as change in histologic grade of bronchial dysplasia, based on a per-participant analysis. Secondary endpoints included change in the number of bronchial dysplastic lesions, modulation of Ki67 expression, and observed adverse event profiles. Lesion-specific change in bronchial dysplasia was also analyzed as a secondary endpoint, with categories of complete response (CR), partial response (PR), progressive disease (PD), or stable disease (SD) defined as: CR = regression of a dysplastic lesion to normal, hyperplasia, or metaplasia; PR = improvement of a dysplastic lesion by at least two histologic grades (except to normal, hyperplasia or metaplasia in which case CR was recorded); PD = worsening of a dysplastic lesion by at least two histologic grades and/or the appearance of any new dysplastic lesion; and SD = any response that did not meet the lesion-specific change state criteria outlined above. Participant-specific changes in bronchial dysplasia were categorized and defined as: CR = regression of all dysplastic lesions to normal, hyperplasia or metaplasia (with no new or progressing dysplastic lesions identified); PR = regression of one or more, but not all, dysplastic lesions (with no new or progressing dysplastic lesions identified); PD = worsening of one or more dysplastic lesions by at least 2 histologic grades and/or the appearance of any new dysplastic lesion; and SD = any response that did not meet the participant-specific change state criteria outlined above.