Abstract 9997

Oral Iloprost for the Chemoprevention of Lung Cancer

Type: Late Breaker Scientific Abstract

Category: I) LUNG DISEASES / 09.24 - Lung Cancer: Clinical Aspects (CP)

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Abstract Body

Rationale: Prostacyclin supplementation (genetic overexpression and the oral prostacyclin analogue iloprost) prevents development of lung cancer in a variety of murine models, including cigarette smoke exposure. Based on these promising results, a multi-center, double-blind, placebo controlled, phase II trial of iloprost in subjects at increased risk for lung cancer was designed and recently completed.

Methods: Subjects were selected for the trial if they met the following criteria: current or former smoker (> 20 pack years); at least mild cytologic atypia on sputum cytology; no previous history of cancer. Autofluorescence and white light bronchoscopy was performed with 6 standard endobronchial sites biopsied, along with all other abnormally appearing areas. Subjects were then randomized to oral iloprost (in escalating doses) or placebo for 6 months and then a second fluorescent bronchoscopy with repeat biopsy of all the central airway areas sampled during the first bronchoscopy. The predetermined primary endpoint for the study is bronchial histology in all subjects, as well as in current and ex-smokers separately.

Results: The enrollment goal of 152 subjects was met, of which 125 completed two bronchoscopies. Subjects were well matched in terms of age and tobacco exposure. The endobronchial biopsies were scored on a 1-8 scale based on WHO criteria. Endobronchial histology was summarized within patients using three separate measures: worst biopsy score (Max), dysplasia index (DI - defined as the percentage of biopsies with a score of at least 4 (mild dysplasia) or worse), and average of all biopsy scores (Avg). Avg for current smokers was 3.0 (SD = 1.1) and Avg for former smokers was 2.1 (SD = 1.0), a statistically significant difference ($p< 0.001$). There were no statistically significant differences between treatment groups in any of the baseline histologic measures. The follow-up bronchoscopy was performed on 60 subjects in the iloprost group and 65 subjects in the placebo group. In former smokers, those receiving oral iloprost exhibited a significant improvement in all three histologic measures. The observed change was 0.41 better in *Avg* (p=0.010), 1.1 points in *Max* (p=0.002), and a decrease in *DI* of 11.6% (p=0.006). Analysis of matched abnormal biopsies showed the most marked improvement in *Max* of 1.37 (p=0.022). Similar histologic improvements were not observed in subjects receiving iloprost who continued to smoke during the trial.

Conclusions: Oral iloprost significantly improves endobronchial dysplasia in former smokers and deserves further study to determine if it can prevent the development of lung cancer.

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