S23. Key Issues in Lung Cancer Chemoprevention Trials of New Agents

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Lung cancer is the most common cause of cancer death worldwide. With the large reservoir of former and current smokers who are already at risk of the disease, chemoprevention is a potentially effective means of lung cancer control. Key issues that need to be addressed in Phase II trials of new agents include selection of high-risk subjects and choice of surrogate endpoint biomarkers (SEB).

The lifetime risk of lung cancer among smokers is less than 20%. A major factor that influences the cost per life-year saved with chemopreventive intervention is the specificity of the test to identify individuals harboring significant pre-malignant lesions. To assess the efficacy of chemopreventive agents, it is also important to be able to localize pre-malignant lesions to determine the effect of treatment using these lesions as SEB. Although diffuse molecular damage of the bronchial epithelium can be demonstrated in heavy current and former smokers, dysplastic lesions, especially high grade dysplasia, are found in only ~30% men and ~10% women. Instead of performing bronchoscopy on every high-risk smoker, we have developed a unique sputum induction method combining high frequency chest wall oscillation and hypertonic saline nebulization to reduce unsatisfactory sputum sample rates to <3%. Computer-assisted image analysis is then performed on the sputum cells. With this approach we can reduce the number of bronchoscopies by 50%, while detecting one or more sites of dysplasia in 75% of the subjects we bronchoscope using a sensitive quantitative autofluorescence bronchoscopy device that we have also developed. The same device can also be used to measure the size of the dysplastic lesions so that only subjects with dysplastic lesions larger than the size of a bronchial biopsy will be enrolled into the clinical trial to decrease the likelihood of regression of the lesions due to mechanical removal, unrelated to the effect of the chemopreventive agent. Non-biopsy methods, such as confocal micro-endoscopy and optical coherence tomography, are being developed to monitor the effect of the treatment.

At the present time, bronchial dysplasia is one of the best SEB for Phase II trials. One of the drawbacks is the interobserver variation in the diagnosis of dysplasia, especially for low-grade dysplasia. If only subjects with moderate/severe dysplasia were eligible, a large number of subjects would need to be screened and bronchoscoped. Retinoids have not been shown to be effective in chemoprevention of lung cancer. Our previous Phase II trials, including one that compared retinol with placebo, gave us the opportunity to evaluate the choice of SEB. We observed that if we performed quantitative nuclear morphometry on the bronchial biopsies and enrolled subjects with metaplasia/dysplasia plus an abnormal morphometry index, we could reduce the number of subjects required for the study by more than 50%, while maintaining the power of the study compared to using moderate/severe dysplasia alone as inclusion criteria. Other promising biomarkers, such as quantitative methylation markers, are currently under investigation. Further studies are required to develop SEBs that are specific for peripheral adenocarcinoma.