S22. Chemoprevention of Lung Cancer: New Directions

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Despite major advances in our understanding of the molecular pathogenesis of lung cancer, survival after the diagnosis of lung cancer has not improved significantly over the past several decades. The refractoriness of advanced disease to current treatment modalities mandates the development of alternate strategies to reduce the public health burden from this disease. Targeting early phases of lung carcinogenesis that may be more amenable to treatment, thereby preventing the development of invasive and metastatic disease, offers one such attractive option. However, progress in prevention science depends on simultaneous advances in the identification of targeted non-toxic agents and in the development of methodologies to efficiently and appropriately evaluate promising new agents. Definitive phase III cancer prevention trials with cancer incidence endpoints require thousands of patients, substantial resources, and many years for completion. Previous phase III trials using beta-carotene, vitamin E, retinyl palmitate, N-acetylcysteine, and 13-cis retinoic acid failed to show any efficacy. Furthermore, harmful effects were demonstrated with some agents in current smokers. Therefore, phase II studies examining the effect of interventional agents on molecular, imaging, and histologic endpoints are needed to demonstrate preliminary safety and efficacy prior to embarking on large scale trials.

The identification of molecular pathways critical to lung carcinogenesis offers the opportunity to develop targeted therapies for prevention. Preclinical data show that anti-inflammatory agents such as corticosteroids are highly effective in preventing lung adenoma formation in carcinogen exposed A/J mice, although systemic toxicity precludes such trials in humans. In an attempt to optimize the risk/benefit ratio associated with corticosteroid use, regional drug delivery via aerosolization to minimize systemic toxicity is currently being employed in one ongoing phase II study. Similary, accumulating data implicate several arachidonic acid metabolites in lung carcinogenesis. Ongoing trials are currently evaluating specific inhibitors of the relevant pathways (COX-2 and 5-lipoxygenase inhibitors) for their lung cancer preventive potential. New trials of molecularly targeted agents are scheduled to begin in the near future. These trials also offer a unique opportunity to identify and evaluate novel surrogate endpoint biomarkers that may facilitate the future conduct of early phase clinical chemoprevention trials.