Molecular Targeting: the New Challenge in Lung Cancer Prevention

Ugo Pastorino

Negative results from large-scale clinical trials (1–3) have resulted in a general skepticism toward lung cancer chemoprevention in humans. One has to consider, however, the enormous difficulties that clinicians encountered in their early attempts to counteract lung carcinogenesis, including attempts at intervention in individuals with decades of intense smoking exposure, or even during active smoking, using single chemopreventive agents that had limited proven efficacy and substantial side effects.

From this first generation of clinical trials, we have learned that retinoids may be active only at relatively high doses, where toxicity becomes a limiting factor, and their biologic effect, when clinically detectable, is not permanent (4). For example, neither the reversal of oral premalignancy nor the reduction in the incidence second primary cancers was sustained after retinoid treatment was discontinued (5,6). This phenomenon is indicative of phenotypic growth suppression without the concomitant eradication of neoplastic clones. Moreover, the number of individuals who had to be treated and tested for a long period of time was large given the relatively low underlying cancer incidence, which was only 0.5% per year in heavy smokers (1,2) and up to 2% per year in prior lung cancer patients (7). Nonetheless, the fundamental achievements of such chemoprevention trials were their contributions to our understanding of the preclinical phases of lung cancer and the identification of biomarkers relevant to field carcinogenesis (8). Knowledge of the molecular targets of chemopreventive agents represents the most valuable byproduct of otherwise “negative” studies and provides a basis for future research extending from early detection to pharmacologic intervention and gene therapy.

In this issue of the Journal, Soria et al. (9) report on the ability of N-(4-hydroxyphenyl)retinamide (4-HPR) to reduce the expression of human telomerase reverse transcriptase catalytic subunit (hTERT) in bronchial biopsy specimens obtained from heavy smokers enrolled in a double-blind chemoprevention trial (10). The authors reported that the reduction in hTERT messenger RNA (mRNA) expression after 6 months of 4-HPR treatment compared with baseline values in the 4-HPR arm or post-treatment values in the placebo arm was statistically significant when the analysis was based on biopsy sites (P = .01) but not when the analysis was based on individual participants (P = .37). Of interest, there was no relationship between the modulation of hTERT expression and other histopathologic features, such as the presence of squamous metaplasia or Ki-67 expression. Moreover, it appears from the first report of the same chemoprevention trial (10) that 4-HPR did not alter the levels of retinoic acid receptor (RAR)-β mRNA in the bronchial epithelium as was observed after 13-cis-retinoic acid administration with a similar trial design (11). These results highlight a new and possibly RAR-independent molecular mechanism of action of 4-HPR against telomerase. In the chemoprevention trial (10), 4-HPR was unable to reverse metaplasia or dysplasia.

In conclusion, the study by Soria et al. (9) represents an outstanding contribution to translational research in the field of chemoprevention. The value of hTERT expression and modulations
tion should be further explored in future chemoprevention trials, possibly in combination with other molecular markers, such as those encoded by tumor suppressor genes.

REFERENCES


