Survival After Treatment of Small-Cell Lung Cancer: an Endless Uphill Battle

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The evidence linking tobacco exposure with cancer of the aerodigestive tract is incontrovertible and inarguable. The lethality of this potent carcinogen is best reflected in the death rates from lung cancer, which represent only a portion of tobacco-related cancer deaths. In the United States, the number of deaths from lung cancer in 1997 will exceed those from breast, prostate, and colon cancers combined, despite a much lower incidence of lung cancer overall (1). Tobacco’s highly addictive properties and intensive marketing are the major factors in sustaining substantial worldwide tobacco use despite the clear danger it represents.

Of all lung cancers, small-cell, undifferentiated cancer is the type most strongly associated with tobacco, with only 3% of patients with this cancer having no history of active exposure (2). Metastatic small-cell lung cancer (SCLC) is rapidly fatal if untreated, producing death within 6–12 weeks. However, combination chemotherapy can prolong patient survival by several months. For patients with disease limited to the chest (nonmetastatic disease), the prospects for long-term survival are brighter and appear to be even better for those who receive etoposide/cisplatin-based chemotherapy and concurrent thoracic radiation (3–6). Two-year survival in these patients has exceeded 40% in several phase II trials and a recent phase III trial, approximately double the survival rate seen with alkylator- or anthracycline-based therapies, older treatments that are inherently more difficult to combine with thoracic radiation therapy (7). This modicum of success in treating limited SCLC is, however, diminished in these survivors by the high rate of death due to second primary cancers and many other causes, as reported by Tucker et al. (8) in this issue of the Journal.

In contrast to other tobacco-related cancers, such as non-small-cell lung cancer or squamous cell cancer of the head and neck, where the high risk of a second tobacco-related cancer has been apparent for more than 20 years (9), recognition of a similar phenomenon in patients with SCLC is a consequence of relatively recent therapeutic success and has been well documented only in the past decade. Tucker et al. have derived their data by grouping together and analyzing multiple institutions’ previously reported experience with survivors of SCLC, yielding 611 long-term survivors and 103 total second cancers. Their results generally confirm findings from the individual studies and indicate that these patients have a sevenfold increased risk of second tobacco-related cancers. Non-small-cell lung cancer occurred most commonly, representing 50% of second cancers overall. Unlike patients with a first primary non-small-cell lung cancer, whose risk of a second lung cancer is stable over time, the risk of a second primary lung cancer increased over time for small-cell survivors, with a cumulative incidence of 44% at 14 years. The highest risk occurred in those who continued to smoke after diagnosis, an effect that had been noted previously, although variably (10). Most significant is the authors’ observation that the risk of a second cancer in persons who continue to smoke was increased in those who received either thoracic radiation therapy or treatment with alkylating drugs. This effect was not seen in former smokers or those who stopped smoking at diagnosis of SCLC. Although both radiation therapy and cytotoxic drugs have been implicated in second cancers that occur in patients with other index cancers, with the exception of treatment-related leukemias, Tucker et al. are the first to demonstrate this effect in survivors of SCLC, and the clear association with continued tobacco exposure is striking.

The message here is old and obvious—patients should stop smoking! This should eliminate the excess risk related to radiation therapy and alkylating agent exposure. The effectiveness of thoracic radiation therapy makes it unreasonable to suggest that it should be abandoned, and chemotherapy is already limited in most patients to four to six courses, with little if any exposure to alkylators. But, by the time patients are diagnosed with SCLC, most of the damage is already done. This is reflected by the 60% of the patients in the Tucker series who had stopped smoking prior to or at diagnosis and who still experienced a ninefold increased risk of a second lung cancer. In contrast to the gradual decrease in lung cancer risk observed in former smokers without an index cancer (11), survivors of SCLC who stopped smoking at diagnosis experienced an increasing risk over time, reflecting the mix of environmental and genetic factors in lung carcinogenesis. The authors suggest that, given their high risk and the associated high mortality of a second lung cancer, SCLC survivors are excellent candidates for secondary chemoprevention trials with retinoids.

On the basis of molecular genetic analyses of lung cancers during the past 10–15 years, we are beginning to understand the events that typify this multistep process. Although SCLCs have a unique set of genetic alterations compared with non-small-cell cancers, there is clear overlap between the two, reflecting similar carcinogen exposure and etiology. While mutations or amplifications in proto-oncogenes have been identified in both major types of lung cancer, the most common genetic abnormality in lung cancer is gene inactivation (mutation and/or deletion of known or putative tumor suppressor genes) (12). This inactivation is generally detected as allele loss (loss of heterozygosity [LOH]), and involved loci and pertinent genes (in proximity)

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include 3p (putatively, FHIT), 9p (CDKN2 in non-small-cell lung cancer only, unknown in SCLC), 13q (RB, in SCLC only), and 17p (TP53) (13,14). Although first identified in established cancer, these genetic abnormalities can also be found in preneoplastic lesions of the bronchial epithelium of patients with non-small-cell lung cancer and in normal or slightly abnormal bronchial epithelium of smokers and former smokers (15–18). It is notable that particular changes, such as LOH at 9p and 17p, appear to persist despite smoking cessation, perhaps reflecting permanent damage. These findings, if validated, bear obvious implications for cancer prevention and detection strategies.

However, the validation of these genetic alterations as reliable biomarkers of progressive carcinogenesis awaits further study. From this standpoint, survivors of SCLC may serve as a wellspring of information on genetic changes during carcinogenesis. Because of the soaring risk of second lung cancers in these patients, systematic study of their “condemned” mucosa over time should be a powerful tool to determine the significance of the accumulated molecular alterations.

On a broader scale, an intervention approach for these patients is clearly needed. On the basis of epidemiologic data linking vitamin A deficiency with an increased risk of lung cancer, and a diet high in β-carotene-rich foods with a reduced risk of lung cancer, there is substantial rationale to test retinoids for cancer prevention in SCLC survivors (19). This is buttressed by the ability of retinoids to reverse premalignancy of the oral cavity and to prevent second cancers in patients with an index squamous cancer of the head and neck (20,21). Retinoids appear to regulate cell growth and differentiation through their effects on gene expression, mediated through interaction with nuclear receptors termed retinoic acid receptors (RARs) and retinoid X receptors (RXRs) (22). Recent investigations in premalignant lesions and squamous cell cancer of the upper aerodigestive tract and in non-small-cell lung cancer indicate that the expression of one of these receptors, RAR-β, is frequently suppressed or absent as compared with normal tissue (23,24). This implies that defects in a retinoid signaling pathway may contribute to carcinogenesis. More important, in premalignant oral lesions, the histologic response to retinoid therapy was associated with increased RAR-β expression (25). Researchers have demonstrated that RAR-β has tumor suppressor activity in transgenic mice expressing antisense RAR-β2 and in nude mice implanted with xenografts of a human lung cancer cell line that was transfected with an RAR-β expression vector (26,27). It is apparent that serial evaluation of RAR-β expression may be critical in interpreting the results of future chemoprevention trials with retinoids.

Ideally, intervention studies in these high-risk patients should begin immediately, encompassing the points raised above. There are, however, challenges in the conduct of such chemoprevention studies: One such challenge is controlling the undesirable side effects induced by many of the retinoids. For example, 13-cis-retinoic acid has a high incidence of mucocutaneous toxic effects while 9-cis-retinoic acid often induces severe headaches. This presents a particular difficulty because patients in chemoprevention studies must take these drugs for months or years, with these side effects leading to difficulties in compliance for even the most motivated patient. For this reason, there is a tremendous interest in developing less toxic agents or combinations of agents for use in chemoprevention trials. One such approach is that of combining 13-cis-retinoic acid and α-tocopherol, which has been shown to ameliorate some of the toxic effects of the retinoid. Currently, a phase III trial of 13-cis-retinoic acid versus placebo in SCLC survivors is on hold while methods are evaluated to circumvent toxicity without reducing efficacy. When this trial does begin, we should take every opportunity to learn from these subjects.

References

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