Lung Cancer — Time to Move on from Chemotherapy

In 2001 lung cancer caused more than 1 million deaths worldwide. Despite the well-recognized link between tobacco use and the development of lung cancer, the number of new cases continues to rise, especially among women. In girls and women 15 to 64 years of age, lung cancer is now the leading cause of death from cancer, and this disease remains the most common cause of death from cancer in men.[1]

During the past 20 years, numerous efforts have been made to reduce the death rate among patients with lung cancer. Treatment involves surgery, radiation therapy, combination chemotherapy, or a combined approach. Yet after 20 years, the improvement in long-term survival has been slight. Indeed, today a minority of patients survive more than one year after diagnosis, and less than 15 percent survive for five years. In this issue of the *Journal,* two groups of investigators report on new combination-chemotherapy regimens for treating small-cell lung cancer[2] and advanced, inoperable non–small-cell lung cancer.[3]

Small-cell lung cancer accounts for 20 to 25 percent of all new cases of lung cancer. At diagnosis, 40 percent of patients have limited disease, defined as disease confined to the thorax. With chemotherapy plus radiotherapy and the selective use of prophylactic cranial irradiation, the median survival of these patients is 18 to 24 months, and up to 20 percent of them may survive for more than 2 years. Without treatment, the median survival is only 6 to 12 weeks.

Patients with extensive disease (the remaining 60 percent of all new cases of small-cell lung cancer) have, at the time of diagnosis, metastases involving one or more sites such as the brain, liver, bone, or bone marrow. With combination chemotherapy, the median survival of these patients is seven to nine months, and few, if any, live more than two years. Twenty years of clinical trials involving such patients have yielded an improvement in survival of only two months.[4] The current standard chemotherapy regimen is etoposide plus cisplatin (or carboplatin). In this issue of the *Journal,* Noda et al.[2] report results with a new combination of irinotecan (a topoisomerase I inhibitor) and cisplatin for the treatment of extensive small-cell lung cancer. They found a 3-month prolongation of the median survival with this combination (12.8 months, vs. 9.4 months with etoposide plus cisplatin), as well as an impressive 2-year survival rate of 19.5 percent with this regimen (as compared with 5.2 percent with etoposide plus cisplatin). These results appear to indicate an advance in the treatment of extensive small-cell lung cancer, but confirmatory trials are required before the new combination becomes the standard of therapy for this disease.

The role of chemotherapy in the treatment of advanced, inoperable non–small-cell lung cancer continues to be a subject of debate. In the late 1990s, many phase 2, single-institution trials of new agents alone or in combination with cisplatin found high response rates (40 to 50 percent) with these agents, and substantial numbers of patients survived for one or two years. The study of more than 1200 patients reported by Schiller et al. in this issue of the *Journal*[3] and the recent study of more than 400 patients by Kelly et al.[5] compared several combinations of agents. The results continue to raise questions about the role and efficacy of combination chemotherapy in advanced non–small-cell lung cancer. In both studies, the response rates were lower than expected (16.6 to 27 percent), as compared with the results of single-institution trials; the median survival ranged from 7.4 to 8.1 months, and the 1-year rate of survival approached 31 to 39 percent. In the study by Schiller et al., most patients had an excellent performance status (Eastern Cooperative Oncology Group performance status, 0 or 1). In this trial, excess toxic effects, some fatal, were noted among patients with a poor performance status, and after the results in the initial 66 patients with poor performance status were analyzed, further such patients were excluded from the trial.

These two studies[3,5] confirm that the benefits of combination chemotherapy among the fittest patients with advanced non–small-cell lung cancer are marginal (with perhaps a gain in median survival of two to three months). In addition, in the study by Schiller et al., there was no superior combination regimen, and these authors conclude that chemotherapy is best offered only to patients with a good performance status. Whether these results are an improvement over the results of older trials[6,7] is questionable when one considers the effects of stage migration (resulting from the increasingly detailed workup of patients), as well as the fact that in the other large trials,[3,5] patients with excellent performance status accounted for the majority of the eligible subjects.

It is clear that new approaches are required. These should include prevention, screening and early detection, and novel treatments based on our understanding of the biology and molecular biology of this disease. Tobacco products kill more than 450,000 Americans each year, and another 50,000 die of the effects of secondhand smoke. A tobacco-free environment would greatly improve the health of our society and would reduce the rates of death from coronary artery disease, lung cancer, and chronic lung disease.[8]

Will the early detection of lung cancer decrease mortality from the disease? In early studies, screening with radiography of the chest or cytologic examination of sputum samples did not improve survival, and thus screening for lung cancer fell out of favor.

However, several new approaches are noteworthy. One is the use of spiral computed tomography (CT) at low doses of radiation.[9,10] This procedure can detect nodules highly suggestive of lung cancer in asymptomatic persons who are at high risk. In one study of 1000 such persons, 23 of 27 cancers (85 percent) detected with the use of spiral CT were stage I cancers.[9] Chest radiography alone detected only seven cancers in this group (26 percent). Since most of the cancers that were detected with spiral CT were early-stage tumors curable by surgery, this technique may reduce mortality from lung cancer. However, because there still are no data on mortality from lung cancer after screening with spiral CT, this technique cannot currently be advocated for mass screening.

Studies of the molecular biology of lung cancer and lung-cancer cell lines have increased our understanding of the multistep pathway for the pathogenesis of lung cancer. Genetic alterations such as mutant K-*ras* and *TP53* genes are detectable on cytologic examination of sputum and bronchial-lavage samples.[11,12] The use of such molecular markers, combined with advances in bronchoscopy (e.g., laser-induced fluorescence endoscopic bronchoscopy), may make possible the detection of preinvasive and invasive lung cancer and the identification of the site of the lesions in persons at high risk.[13] The detection of very early lesions in persons at risk would also identify candidates for studies of chemoprevention. Prospective trials are required to determine whether the use of these invasive approaches in asymptomatic persons will reduce mortality from lung cancer.

Another approach is chemoprevention in persons who are at risk.[14] To date, several large, randomized trials of beta carotene, retinol, and isotretinoin for the prevention of lung cancer have not produced positive results. Indeed, in one trial of the combination of beta carotene and retinol (the Carotene and Retinol Efficacy Trial), there was a 28 percent increase in the incidence of lung cancer in the subjects who received the supplements, along with a 17 percent increase in overall mortality in this group.[15] These results are disappointing, but as we learn more about the molecular carcinogenesis of lung cancer, more specific sites for chemoprevention can be identified and targeted.

Chemotherapy in advanced lung cancer has reached a plateau; there are few differences among various combinations of drugs. However, there are now several reports of the use of biologic agents with unique mechanisms of action in this disease. Epidermal growth factor receptor is overexpressed in most cases of non–small-cell lung cancer.[16] Of the many strategies that have been developed to target this receptor, the two most extensively evaluated are monoclonal antibodies against the extracellular domain of the receptor (e.g., trastuzumab [Herceptin]) and inhibition of the tyrosine kinase region of the receptor. Two tyrosine kinase inhibitors, ZD1839 and OSI-774, have antitumor activity in advanced non–small-cell lung cancer, even in patients in whom previous chemotherapy has failed.[17,18] These and other novel biologic agents entering phase 1 and phase 2 trials offer the best hope for the future therapy of lung cancer. Confirmation of the activity of such agents in advanced disease would open the possibility of using them in early-stage disease, either as adjuvant therapy or in combination therapy. All physicians caring for patients with lung cancer should, in the absence of contraindications, consider inviting their patients to participate in these ongoing, pivotal trials.

The current treatment of advanced small-cell and non–small-cell lung cancer with combination chemotherapy is nonspecific, nonselective, and toxic. New combinations of chemotherapy are not likely to make substantial improvements in survival. However, prevention, early detection, and the use of specific biologic targets offer optimism and hope that mortality from this disease may be reduced.

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The Genetic Basis of Progressive Osseous Heteroplasia

IMPORTANT insights into the regulation of mineral-ion homeostasis, cartilage development, and thus bone growth have been obtained through the molecular definition of various genetic disorders. Several of these disorders, most of which are rare, are now known to be caused by mutations in a single gene, *GNAS1*, which gives rise to several different messenger RNA transcripts that are derived from the paternal allele, the maternal allele, or both and are either coding or noncoding. Because of this unusual complexity, *GNAS1* mutations can lead to a variety of different phenotypic changes.

In 1942, Fuller Albright and his colleagues described a syndrome, now known as pseudohypoparathyroidism type 1a, characterized by short stature, obesity, skeletal abnormalities, mental retardation, and often subcutaneous ossification.[1] These developmental defects, collectively called Albright's hereditary osteodystrophy (AHO), are associated with resistance to parathyroid hormone and often other hormones whose actions are mediated through G protein–coupled receptors.[2,3] Ten years later, Albright et al. described patients with AHO in whom there was no evidence of hormonal resistance and named this constellation pseudopseudohypoparathyroidism.[4] Subsequent molecular studies of patients with either pseudohypoparathyroidism type 1a or pseudopseudohypoparathyroidism revealed heterozygous inactivating mutations located in exons of *GNAS1* that encode the alpha subunit of the stimulatory G protein ($G_s\alpha$).[2,3,5] Retrospective analyses later revealed that a given *GNAS1* mutation leads to AHO irrespective of which parent transmits the defective gene, but hormone resistance occurs only if the genetic defect is inherited from a mother affected by either pseudohypoparathyroidism type 1a or pseudopseudohypoparathyroidism.[6]

During the past few years, it has become apparent that *GNAS1* encodes not only $G_s\alpha$ but also several splice variants, including XLαs, NESP55, and A/B (also referred to as 1A or 1′), and an antisense transcript.[2,3,7] Furthermore, it was determined that these alternative exons and their promoter regions are methylated on one parental allele, giving rise to transcripts derived only from the nonmethylated allele. To complicate the scenario even further, in most tissues the transcripts encoding $G_s\alpha$ are derived from both alleles; in addition, in a few tissues, including proximal renal tubular cells, adipocytes, and pituitary cells, $G_s\alpha$ appears to be expressed solely from the maternal allele.[8,9]

Recently, it was discovered that heterozygous inactivating mutations affecting one of the $G_s\alpha$-specific exons are the cause not only of pseudohypoparathyroidism type 1a and pseudopseudohypoparathyroidism, but also of progressive osseous heteroplasia (POH) and its variant, platelike osteoma cutis.[10,11] Other disorders caused by $G_s\alpha$-specific *GNAS1* mutations include the McCune–Albright syndrome (activating postzygotic mutations), acromegaly (activating somatic mutations), and pseudohypoparathyroidism type 1a combined with testotoxicosis (temperature-sensitive mutations).[2,3,9] In addition, pseudohypoparathyroidism type 1b, a disorder characterized by resistance to parathyroid hormone in the absence of additional developmental defects, was mapped to chromosome 20q13.3 and was shown to be paternally imprinted.[12] Since the linked region includes portions of *GNAS1*, it appears likely that pseudohypoparathyroidism type 1b is also caused by mutations in this complex gene. Evidence supporting this conclusion includes the finding that there is a loss of methylation of the maternal A/B exon and its promoter region in patients with pseudohypoparathyroidism type 1b; this loss presumably leads to the generation of A/B transcripts from the maternal allele and thus to impaired expression of $G_s\alpha$ in the renal cortex and possibly a few other tissues.[3,13] The importance of these epigenetic changes in *GNAS1* for the development of hormone resistance is underscored by findings in a patient with paternal uniparental isodisomy of chromosome 20q (i.e., both long arms of chromosome 20 are of paternal origin), in whom resistance to parathyroid hormone and other hormones (but not AHO) developed solely because of the lack of a maternal-specific pattern of methylation of *GNAS1*.[14]

In this issue of the *Journal*, Shore et al.[15] provide