Future Directions in Non-Small-Cell Lung Cancer: A Continuing Perspective

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Non-small-cell lung cancer (NSCLC) will increasingly come under better control as the current approaches to therapy are more broadly employed and as new therapies are deployed against recently elucidated molecular.

Despite the absence of any highly visible breakthrough presentation, the 8th World Conference on Lung Cancer in Dublin, Ireland, was a true watershed event. Trends that have been developing over the last decade have now become clear, and the need for new approaches is compelling. In the context of a continuing perspective on these meetings,[1] enormous progress has been made in the treatment of non-small-cell lung cancer (NSCLC), in the understanding of the molecular events leading to lung cancer, and in the war against tobacco. Complacency based on these advances would, however, be folly. The continued lack of progress against small-cell lung cancer (SCLC), the absence of major progress in diagnostic imaging, and the continued slow pace of translating biologic understanding to clinical application are frustrating. Underlying all of this is our inability to complete pivotal randomized trials in a timely fashion.

**Trends That Have Become Established Patterns**

**NSCLC Is, Stage for Stage, More Successfully Treated Than SCLC**

Much of the past 2 decades has been absorbed with extolling the curability of SCLC and intensifying its treatment so as to increase the number of cures achieved.[2] The corollary to this was the ongoing denigration of any therapy other than surgery for NSCLC. Table 1 is a comparison, albeit an unconventional one, of outcomes for patients with SCLC and NSCLC. As a group, and for virtually any specific stage of disease, patients with NSCLC now clearly have an equal or superior outcome compared with patients with SCLC. The era during which we justified treating just about anyone with SCLC because [they do so well] and withheld treatment from patients with NSCLC because [they do so poorly] is now clearly at an end.

**Adenocarcinoma Is Now the Most Common Histologic Subtype of Lung Cancer**

Most investigators in lung cancer matured during the era when squamous cell carcinomas were the predominant form of non-small-cell lung cancer. With uncommon exceptions in certain nations, this trend has now been totally reversed.[3] Whether this represents a change in the spectrum of inhaled carcinogens due to increasing use of filtered products is speculative, albeit intriguing. The emergence of adenocarcinomas, with their tendency for earlier metastasis, means that clinical practices, endoscopic screening for asymptomatic brain metastases and more frequent use of mediastinoscopy in patients with negative computed tomography scans will have to be re-evaluated.

**Multimodal Therapy Has Replaced Unimodal Therapy in Many Clinical Settings**

With the exception of very early stage IA NSCLC and widespread NSCLC or SCLC, evidence suggests that combinations of treatment modalities are superior to single-modality treatment (Table 2). An adjunct to this is the emergence of the thoracic oncologist who may be trained in any of the modalities but is widely experienced in using all available modalities of treatment.

**Therapeutic Imperative** Has Triumphed Over Nihilism and Cost Cutting

Although highly variable across cultures, the concept that a patient wants to be treated, despite long odds against success (the therapeutic imperative) is now well established. Earlier objections to this approach, especially for patients with metastatic NSCLC, centered around the lack of a survival benefit and the worsening of quality of life due to treatment-related toxicity. It is now clear from randomized trials and meta-analyses that treatment for metastatic NSCLC improves survival, albeit modestly,[4-6] that patient symptoms are improved in most cases,[7-10] that the emetogenic side effects of therapy can be abrogated,[11,12] and that the cost-benefit ratio is clearly in favor of including chemotherapy for the treatment of locally advanced[13] and metastatic NSCLC.[14] One
hopes that the era of studies comparing treatment vs best supportive care is now truly over.

**Where Has Clear Progress Been Made?**

**Tobacco Control**

Although the accumulated damage from decades of tobacco abuse will continue to plague us well into the next century, the tide appears to have finally turned. As a result of extraordinarily brave political action by former commissioner David Kessler, md, the Food and Drug Administration in the United States has recognized and documented the addictive nature of nicotine and has moved to regulate its use as a drug.[15,16] It is expected that a similar action will ensue in Europe with the election of the Labour Party in England and a formal end to British opposition to an advertising ban in Europe.[17] Canada has passed legislation to restrict advertising and limit tar and nicotine content[17] and, most extraordinarily, the tobacco industry in the United States has been forced to its knees in court by several states, resulting in settlement agreements that reimburse tobacco-related health costs, end or restrict most advertising, and severely limit access to tobacco products for minors. As of this writing, at least one firm has admitted to covering up their knowledge of tobacco’s harmful effects, thus ending one of the longest scientific fantasies ever promulgated by an industry. For these efforts to have long-term success, the changes in consumer behaviors need to be sustained. The revelations of “doping” of cigarettes by manipulation of nicotine content[18] have had a clear impact on the glamour associated with smoking.

The remaining clouds on this horizon are significant, however. Cigar smoking has regained its cachet and, though less dangerous than cigarette smoking, it threatens the societal pressures against smoking behaviors. Finally, the legislation and legal actions in Europe and North America have had little or no impact on sales or marketing in Central and South America, Eastern Europe, and Asia.

**Understanding the Molecular Changes Leading to Development and Progression of Lung Cancer**

Initial studies demonstrating the presence of autocrine and paracrine growth control in lung cancer[19-22] have been followed by the recognition that these receptors are generally tyrosine kinases, and that the growth signal is transferred to the nucleus by a complex signal transduction machinery that includes activation of vital proteins such as Ras, GTPase, Raf, and MAP kinase, which in turn translocate to the nucleus and activate transcription factors.[23] Receptor tyrosine kinases (RTKs) can also signal more directly to the nucleus by activating signal transducers and transcription activators (STATs) that dimerize, bind directly to DNA, and activate transcription.[24] Cell division is stimulated by RTKs through activation of cyclin-dependent kinases that allow cells to progress through the cell cycle.[25] Overexpression or inappropriate expression of several RTKs and constitutive overexpression of cyclin-dependent kinases and signal transducers and transcription activator proteins appear to be involved in sustaining the growth of malignant cells.[26] Although not yet fully characterized, the sequence of genetic changes leading to development of lung carcinogenesis also is being unraveled. Mutations in up to 10 to 20 recessive or dominant oncogenes appear common in each cancer and may be related to abnormalities of DNA repair.[27] Abnormal p53, myc, and Rb genes and gene products have been described as having a series of recessive oncogenes (FHIT homoygous deletion region FRA3B fragile site, BAP-1, ACL5 homozygous deletion region, and the VHL gene region) exposed during 3p allelic loss, a common finding in lung cancer.[28] What is less clear is how these aberrations directly affect cell-signaling mechanisms that lead to continued cell proliferation.

**Real Progress Has Been Made Against NSCLC**

Because of the enormous numbers of NSCLC patients, even small changes in long-term outcome affect thousands of individuals. Progress in the past several years, however, has been far more than incremental. In the management of metastatic NSCLC, the introduction of paclitaxel (Taxol),[29,30] docetaxel (Taxotere),[31,32] vinorelbine (Navelbine),[33,34] gemcitabine (Gemzar),[35,36] and the topoisomerase I inhibitors topotecan (Hycamtin)[37] and irinotecan (Camptosar)[38] led to a series of doublet studies incorporating cisplatin (Platinol) or carboplatin (Paraplatin), resulting in now-routine 1-year survival rates of 40% and better, with measurable 2-year survival rates.[39] Paclitaxel/cisplatin,[40] vinorelbine/cisplatin,[41,42] and gemcitabine/cisplatin[43] have all proven superior to older regimens, and comparisons between and among them are under way. The combination of paclitaxel/carboplatin has become a de-facto community standard in the United States. Despite the fact that only phase II trial results are available,[44] this combination has become the comparative arm in each of the cooperative group trials currently under way in the United States (Table 3). Combinations of these new agents with surgery and/or radiation are now
under active investigation and may represent our first real impact on systemic disease.[45,46] Previous expectations that patients with locally advanced NSCLC would have only a 5% 5-year survival rate with radiation alone have now been eclipsed by regular expectations of 20% to 30% 5-year survivals with various permutations of sequential and concurrent chemotherapy, radiation, and possibly surgery.[47,48]

**Where No Real Progress Has Been Made**

**Treatment of SCLC**

SCLC remains a true therapeutic enigma. Despite its exquisite sensitivity to most chemotherapeutic agents, we have seen little progress in treatment of SCLC over the past decade. No combination of new agents or addition of new agents have yet demonstrated superiority over standard etoposide (VePesid)/cisplatin.[49] Although the issue of consolidative chest radiotherapy in limited disease[]and its timing[]seem secure, the inability to reduce local recurrences significantly by alterations in dose or fractionation has continued to bedevil the field.[50] Dose escalation continues to offer little in the way of a therapeutic advance[51] and, despite all of the early work in neuroendocrine growth factors in SCLC, no anti-growth- factor therapy has been established.[52]

**Staging and Diagnostic Imaging**

Although immunoscintigraphy[53] and positron emission tomography[54] have shown promise in detecting asymptomatic lesions, it is totally unclear whether any of these techniques add to the standard well-performed history and physical examination and chest/upper abdominal computed tomography scan. As chest magnetic resonance imaging has found a niche in better ascertaining chest wall or mediastinal soft-tissue invasion, so too may positron emission tomography scanning be useful in distinguishing post-treatment scarring from residual tumor.[54] The recent changes to the staging system were hardly worth the effort.[55] Separating the T1N0 cases into a very favorable stage IA and redefining T3N0 lesions as stage II were needed, but the far more critical nuances of staging IIIA/B disease were ignored. Failure to distinguish single-station or limited N2 disease (III from our classification) (Table 4)[56] from bulky N2 disease means that we will suffer another decade of uninterpretable phase II studies of preoperative therapy.[56] It is hard enough to convince community (and many university) surgeons to do an adequate mediastinal evaluation, but then wasting those efforts on a staging system that does not recognize the findings is tragic. Worse yet is the continued inclusion of malignant pleural effusions in the definition of stage IIIB disease.

**Inability to Translate Increased Recognition of Molecular and Cell-Surface Markers Into Diagnostic or Therapeutic Utility**

With the possible exception of ras mutations, the myriad molecular and neuroendocrine markers identified have yet to have an impact on day-to-day diagnostic or prognostic practices.[57] Although numerous approaches to gene therapy have been under way for some time, little or no progress has been made toward demonstrating any systemic effect on patients[] cancers.[58] While this failure may represent our incomplete understanding of gene expression and will be remedied by further knowledge, it also may show that our concept of the distribution, uptake, and activity of large molecules is flawed by technical problems unrelated to biologic specificity.

**Inability to Complete Phase III Trials in a Timely Fashion**

Awaiting the outcome of critical phase III trials has become a process of frustration reflecting the potential clinical irrelevance of the findings. This holds true even in studies of metastatic NSCLC, where accrual is rapid and outcomes readily definable. For example, by the time it became clear that paclitaxel 135 mg/m² or 250 mg/m² given over 24 hours combined with cisplatin was superior to standard etoposide/cisplatin,[40] the regimen had been long since supplanted in practice by use of a 3-hour infusion of paclitaxel/carboplatin.[44] Similarly, the Intergroup neoadjuvant trial is grinding along at a pace that may allow its eventual completion, but whether anyone will rush to use the etoposide/cisplatin/radiation approach several years from now is highly questionable.

**What Does the Future Hold?**

In this highly personal view of what may be expected over the next several years, I would like to suggest several possible trends that may hold promise.

**Signal Transduction Pathways Will Become an Increasingly Important Venue for Therapeutic Management**

The process by which RTKs embedded in the cell surface signal to the nucleus is susceptible to pharmacologic manipulation by small molecules. Table 5[23,59-68] lists several suggested
approaches reported at the 8th World Conference. As activity is demonstrated for each of these compounds, the standard procedures of clinical pharmacology and clinical investigation may move these compounds to clinical trial relatively rapidly.

**New Clinical Trial Methodologies Will Be Forced to Emerge, Especially For Multimodal Studies**

The International Adjuvant Lung Cancer Trial presents an intriguing possibility for future study design.[69] In this trial, patients may receive any of several vinca/cisplatin combination therapies following a complete resection. The issue is not whether a specific adjuvant therapy improves survival, but whether the concept of adjuvant therapy is beneficial without regard to the specific regimen.

Let us apply this logic to the Intergroup trial currently under way in the United States. The study entails a compromise regimen of combination etoposide/cisplatin and radiation, followed by either surgery or more radiation. The fundamental issue is whether surgical resection adds any benefit to treatment by combined chemoradiation or whether the issue already has been decided by the completeness of the response. By forcing the use of a compromise regimen that may soon be irrelevant in clinical practice, the main purpose of the study suffers. In order to get the requisite number of randomized cases for analysis, a far larger patient cohort is needed to allow for the usual causes of dropout. It might make more sense to take all patients with a greater than 50% response to preoperative chemoradiation (any variation) and randomize to surgery or not. This is the pragmatic approach often applied in community settings, and resolutions reached via this approach seem far more important than purity of study design achieved by employing a single regimen in highly selected patients.

**Molecular and Cellular Markers of Early Detection and Prevention Will Emerge**

The recognition that multiple mutations accumulate in the fully malignant cell results in great difficulty in sorting out their individual impact on outcome. The likelihood that fewer mutations exist in metaplastic or dysplastic cells suggest a corresponding reduction in complexity. With the completion of the Human Genome Project and the emergence of fixed arrays, it will be possible to screen clinical specimens, including sputum or bronchial washings, for literally hundreds or thousands of genes or gene products. Although unlikely to emerge before the year 2000, meeting these technologic breakthroughs will revolutionize our potential for early detection of lung cancer.

**References:**


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