Subdividing NSCLC: Reflections on the Past, Present, and Future of Lung Cancer Therapy

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More than 60 years ago, Karnofsky and colleagues reported promising results with the introduction of nitrogen mustard, the prototype of alkylating agents, for the treatment of lung cancer.[1] Subsequent milestones in the development of lung cancer chemotherapy included the use of platinum agents in the 1970s and 1980s, while the 1990s brought several active agents that could be combined with platinum, namely the taxanes, gemcitabine (Gemzar), and vinorelbine.

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Although chemotherapy was shown to have a significant impact in the first- and second-line treatment setting of non–small-cell lung cancer (NSCLC), the effect on survival was modest. The duration of first-line chemotherapy for advanced lung cancer was eventually curtailed to no more than four to six cycles, as a consequence of poor long-term tolerability of chemotherapy drugs and their marginal benefit. The slow pace of advances in lung cancer chemotherapy and the overwhelming majority of negative phase III trials have given rise to titles and commentary referring to “the snail’s pace” and “sobering results.”[2,3]

Indeed, therapeutic nihilism has been deep-rooted in the approach to lung cancer; but perhaps not any more. In the year 2009, recent developments in the field have brought forward an impressive number of positive phase III trials of novel agents in advanced NSCLC, the results of which have enriched and complicated therapeutic options, hopefully for the ultimate benefit of individuals affected by this illness. The armamentarium for the new millennium is characterized by the addition of pemetrexed (Alimta), erlotinib (Tarceva), bevacizumab (Avastin), and cetuximab (Erbitux), with multiple other promising molecularly targeted agents in the pipeline.

Three-drug regimens with the addition of a molecularly targeted agent (bevacizumab or cetuximab) to platinum doublets have become a reality in standard practice, and the duration of first-line therapy has been expanded in the form of maintenance therapy using pemetrexed or erlotinib.

Histologic Subtypes of NSCLC
In this issue of ONCOLOGY, Drs. Selvaggi and Scagliotti provide a thorough and timely review of the emerging importance of histologic subtype in NSCLC. They have reviewed the most relevant literature, made thoughtful comments and reached appropriate conclusions. There are several well described differences between histologic subtypes of NSCLC in terms of anatomic location (eg, adenocarcinomas tend to be peripheral and squamous cell carcinomas central) and epidemiology (eg, the proportion of adenocarcinoma cases is increasing). Although histology may carry a prognostic significance regardless of therapy, of foremost importance have been recent observations showing that histologic subtype is predictive of safety or efficacy after treatment with specific therapeutic agents.

First, histologic subtype—and specifically, squamous cell histology—has implications for the safety of antiangiogenesis agents. Bevacizumab, a monoclonal antibody against the vascular endothelial growth factor, improves the efficacy of first-line platinum-based chemotherapy for NSCLC and was granted regulatory approval in 2006. The drug is contraindicated in squamous cell NSCLC because of
an unacceptable rate of life-threatening or fatal tumor-related bleeding complications associated with its use. Other antiangiogenesis agents have been safely studied in squamous cell histology, but recently reported results suggest a potential detrimental effect of sorafenib (Nexavar) in patients with squamous cell NSCLC [4].

Second, the antitumor activity of new agents, like pemetrexed and the epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), such as erlotinib and gefitinib, varies between NSCLC subtypes. Subset analyses of three phase III trials with pemetrexed that enrolled almost 3,000 patients with advanced NSCLC offer conclusive evidence to support the notion that pemetrexed has inferior activity in squamous NSCLC in either first-line, second-line, or maintenance therapy, which led to a modification of pemetrexed US Food and Drug Administration (FDA) labeling that restricts its use to non-squamous cell NSCLC. Also, initial reports showed that adenocarcinoma histology is predictive of response to EGFR-TKIs, though subsequent phase III placebo-controlled randomized studies have demonstrated that survival benefit from erlotinib is not restricted by histology and includes patients with squamous cell NSCLC [5].

Molecular Basis for Response and Resistance
The differential response to certain novel agents by histologic subtype of NSCLC may have a molecular basis. Higher levels of expression of thymidylate synthase in squamous cell carcinoma may be the basis of resistance to pemetrexed in these cancers.[6] Furthermore, a number of molecular abnormalities, such as EGFR and KRAS mutations and EML4-ALK fusion oncogene, are seen in higher frequency in adenocarcinomas, and can affect response to treatment with EGFR-TKIs. Recent randomized clinical trials showed that patients with EGFR mutation–positive NSCLC have longer progression-free survival when treated with first-line EGFR-TKIs vs chemotherapy, which has led to the widely accepted use of first-line EGFR-TKI monotherapy in patients with advanced NSCLC with a known EGFR-activating mutation. It is possible that the higher incidence of EGFR mutations in adenocarcinomas may have led to previous observations suggesting that EGFR-TKIs are particularly active in adenocarcinomas. Finally, tumors harboring the newly described EML4-ALK fusion gene are rare in unselected patients with lung cancer but are seen more frequently in patients who are never-smokers or light smokers, have adenocarcinoma histology or wild type EGFR and KRAS, and are sensitive to novel agents that target this abnormality.[7,8]

Modern Pathology
NSCLC used to be an appropriate diagnosis in pathology reports at a time when there was no clinical need to make a distinction between NSCLC histologic subtypes. Currently, pathologists should make every effort to precisely subclassify NSCLC according to World Health Organization (WHO) guidelines. Although a major distinction is now almost mandatory between squamous and non–squamous cell NSCLC, other less common subtypes, such as large cell neuroendocrine carcinoma or bronchoalveolar carcinoma, have unique features that may also be relevant to prognosis and/or therapy.

An accurate diagnosis is usually made on resection specimens and in cases of well differentiated tumors. However, difficulties are often encountered when a limited amount of diagnostic tissue, such as cytology or small surgical biopsy specimens, is available. This is not uncommon in patients with advanced NSCLC, as well as when the tumor has poor differentiation. Moreover, reproducibility between pathologists in the classification of lung cancer into histologic types is suboptimal. Pathologists’ experience can be a significant factor, with less intra- and interobserver variability seen among experts in lung pathology.

If distinction between different subtypes of NSCLC cannot be made on routine hematoxylin and eosin (H&E) sections with certainty, histochemical stains (mucicarmine, periodic acid Schiff diastase) and immunoperoxidase studies (thyroid transcription factor-1, surfactant apoprotein, p63, cytokeratins 5/6) should be performed. Molecular biomarkers, such as microRNA[9] and gene-expression profiling,[10] can potentially assist in distinguishing histologic subtypes of NSCLC, but such methods have not yet been incorporated into standard practice. Underlying molecular abnormalities will require more attention in the future. A number of prognostic gene-expression signatures have been reported for lung adenocarcinomas.[11,12]

Looking Ahead
It is expected that in the future we will not only rely on histologic classification of lung cancer but may define lung cancer tumor types based on specific molecular profiles. The first steps into the molecular era of lung cancer therapeutics are slowly being made. Cooperative groups have endorsed and incorporated biomarkers in the design of a number of phase III clinical trials in advanced NSCLC (eg, N0723; NCT00738881) and in the adjuvant chemotherapy setting for resected NSCLC (eg, CALGB-30506; NCT00863512). Lessons from approaches in the management of other solid tumors
are ripe to be studied and applied to lung cancer. For example, strategies in the adjuvant treatment of breast cancer that employ gene signatures have paved the way in this direction.

A better understanding and characterization of lung cancer at a molecular level is likely to be the basis for the leap in therapeutic outcomes we wish to achieve. Histologic subtype is a phenotype often driven by molecular alterations. Many institutions, including ours, have implemented routine testing of non-squamous cell NSCLC for the presence of EGFR- and KRAS-activating mutations, and, more recently, EML4-ALK rearrangements. Clinicians will be required to work closely with the pathologist and, possibly in the years to come, the molecular biologist to make the best decision possible. Customizing treatment to the individual patient’s tumor is anticipated to further improve patient outcomes in the future, even in lung cancer.

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