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Editorial

Histology Matters: Individualizing Treatment in Non-Small Cell Lung Cancer

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A critical advance in the treatment of advanced non-small cell lung cancer (NSCLC) over the last 20 years has been the development of tolerable platinum-based chemotherapy doublets [1]. Despite this, the estimated survival time of patients is still only slightly >12 months in the best large, randomized clinical trials [2, 3], and only 6 months for the general population with newly diagnosed advanced NSCLC [4]. Interestingly, a recent analysis of the Surveillance, Epidemiology, and End Results data from 1990–2005 does demonstrate a significant but modest improvement in the treatment of stage IV lung cancer over the last 15 years, with 1-year survival rates improving by 6% and 2-year survival rates improving by 3%. Within this recent analysis, it is clear that different histologic subtypes of NSCLC have had differential improvements. Patients with adenocarcinoma histology have seen an 8% improvement in their 1-year survival rate, from 15% to 23%, even in an era before the clinical significance of histology was recognized. Much of this benefit was achieved during the 2002–2005 period, in which erlotinib, gefitinib, and pemetrexed were approved, and during that period the observed survival duration for patients with the adenocarcinoma and squamous cell histologic subtypes diverged for the first time in history. With multiple new treatments that appear safer and more effective in patients with adenocarcinoma, this difference is likely to widen in the coming years. It is clear that histology is critical in choosing the appropriate therapy for NSCLC patients. In this editorial, specific treatment implications for each histological subtype are addressed. Going forward, it is likely that improved molecular testing will augment and even replace histologic classification alone.

For patients with adenocarcinoma, treatment options have grown dramatically over the last few years. First-line treatment consists of four to six cycles of a platinum-containing chemotherapy doublet, plus bevacizumab for eligible patients. The incorporation of pemetrexed into bevacizumab-containing first-line regimens appears to be safe and effective [5], and a randomized phase III comparison of the benchmark regimen of carboplatin, paclitaxel, and bevacizumab with carboplatin, pemetrexed, and bevacizumab is ongoing. For patients with adenocarcinoma known to have an epidermal growth factor receptor (*EGFR*) mutation, first-line tyrosine kinase inhibitor therapy should be considered based on the recent Iressa® Pan-Asia Study (IPASS), which demonstrated better progression-free survival and quality of life in patients with an *EGFR* mutation treated with gefitinib as compared with chemotherapy [6].

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Table 1. Table of NSCLC therapies associated with effectiveness in particular histologies

Therapy	Histologic subtype	Notes
Erlotinib, gefitinib	Adenocarcinoma; nonmucinous bronchioloalveolar carcinoma	Higher response rates in tumors with *EGFR* mutations; negligible response rate in tumors with *KRAS* mutations; intermediate effects in some patients with other histologic types.
Pemetrexed	Nonsquamous NSCLC	Adenocarcinoma may be more susceptible because of lower thymidylate synthase levels.
Bevacizumab	Predominantly nonsquamous NSCLC	Higher risk for fatal pulmonary hemorrhage with squamous cell histology; risk may be lower with small peripheral squamous tumors.
Cetuximab	All	Higher relative benefit observed in patients with squamous histology.
Figitumumab (CP-751,871)	Squamous NSCLC	Phase III trial in combination with carboplatin and paclitaxel was terminated in December 2009 due to unanticipated toxicity and deaths.

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

However, identification of a *KRAS* mutation in the tumor strongly predicts resistance to this therapy, and it should be avoided in patients with known *KRAS* mutations [7, 8]. In the second-line setting, an overall survival benefit favoring both pemetrexed and erlotinib has been observed from the strategy of "switch maintenance": giving a noncrossresistant therapy before symptomatic or radiographic progression [3, 9]. Based on these data, the U.S. Food and Drug Administration (FDA) recently approved pemetrexed as maintenance therapy for patients with locally advanced or metastatic nonsquamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. This strategy is likely to be most beneficial for individuals in whom symptomatic progression of disease may preclude later treatment, but does have the theoretical downside of depriving patients of a treatment-free interval following first-line therapy.

Unfortunately, patients with squamous cell histology have relatively fewer options outside the scope of a clinical trial. For these patients, platinum-based doublet chemotherapy is still the mainstay of treatment. Although gemcitabine plus cisplatin was compared directly with pemetrexed plus cisplatin and appeared to have a more favorable response rate in patients with squamous cell histology [10], all nonpemetrexed containing chemotherapy doublets are probably similarly effective in squamous cell tumors. Regarding the role of targeted therapy, the monoclonal EGFR antibody cetuximab has a survival benefit in combination with cisplatin and vinorelbine, but not with carboplatin and paclitaxel [11, 12]. In the First-Line Trial for Patients with EGFR-Expressing Advanced NSCLC (FLEX), this improvement in survival appeared to be driven in part by a trend toward benefit in the 33% of enrolled patients with squamous tumors (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.64–1.00), as compared with adenocarcinoma patients, who have a smaller degree of benefit (HR, 0.95; 95% CI, 0.77–1.15). Therefore, a first-line regimen with cetuximab may be considered for patients with squamous cell histology. Following first-line treatment, the strategy of switch maintenance to erlotinib also appears to retain a progression-free survival benefit even in patients with squamous histology, but whether this is also true of overall survival has not yet been reported [9]. For second-line treatment and beyond, many other chemotherapy agents, except for pemetrexed, appear to have modest and equivalent activity in NSCLC patients regardless of histology. Of these, both erlotinib and docetaxel are FDA approved.

The diagnosis of bronchioloalveolar carcinoma (BAC), a less invasive subtype of NSCLC adenocarcinoma characterized by well-differentiated cells growing along pulmonary septae, may also imply a particular treatment strategy. This type of NSCLC may be enriched for mutations in the EGFR tyrosine kinase domain, which are strongly associated with response to EGFR tyrosine kinase inhibitor (TKI) treatment. However, there is variability in histology and molecular status even within this NSCLC subtype. In a series of 111 adenocarcinoma patients from our institution, *EGFR* mutations were observed in 47% of patients with nonmucinous BACs, but patients with the mucinous form of BAC never had an *EGFR* mutation, and six of seven actually had a *KRAS* mutation [13]. These data suggest that patients with nonmucinous BAC have a reasonable chance of responding to "empiric" EGFR TKI therapy, but that TKI treatment should probably be avoided in patients with mucinous BAC unless the molecular status is known.

In summary, an increasing array of therapeutic options

is becoming available for patients with advanced NSCLC (Table 1). As part of the growing effort to individualize therapy, histologic subtype must now be incorporated into treatment decisions. It is essential to obtain an adequate sample of tissue at the time of initial diagnosis for both histologic confirmation and molecular testing, preferably via surgical specimens, core biopsies, or serial fine-needle aspiration samples. Adequate tissue availability may be the key to identifying the most appropriate treatment for each patient, improving the chances of finding an effective therapy as early as possible in a patient's treatment. It is likely that the differential histological response to newer therapies actually reflects underlying differences in the molecular characteristics of the tumor. In fact, the lack of highly reproducible inter-pathologist agreement in the identification of squamous cell histology by H+E slides alone [14] may be improved by H + immunohistochemical staining for molecular markers such as TTF1, TP63, and others to classify tumors that otherwise do not appear histologically distinct [15]. Eventually, specific molecular testing for perturbations in genes like *EGFR*, *KRAS*, *ALK*, thymidylate synthase, and others will augment, and may even supplant, the role of histology in predicting responses to particular therapies.

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