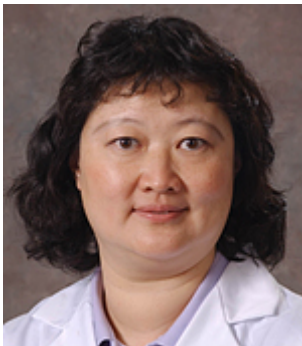


Patient selection in non-small cell lung cancer: Histologic versus molecular subtypes?

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Until recently, the selection of systemic therapy has not varied according to histologic subtypes of non-small cell lung cancer (NSCLC) and is largely empirical. Thus, the diagnosis of “non-small-cell lung cancer not otherwise specified” (NSCLC-NOS) has been a frequently-used, acceptable term for clinical decision-making, despite the fact that it is not recognized by the World Health Organization Classification of Lung Tumors (1). This paradigm has been challenged by new generation of rational cancer therapeutics.

The first emphasis on histology in treatment decision in NSCLC came from safety concerns about the first-in-class angiogenesis inhibitor bevacizumab. A randomized Phase II trial of carboplatin and paclitaxel alone or with low- or high-dose bevacizumab revealed a severe (and even fatal) occurrence of pulmonary hemorrhage in NSCLC patients with squamous histology receiving bevacizumab (2). Thus, patients with squamous histology were subsequently excluded from Phase III trials of bevacizumab and most of anti-angiogenesis inhibitors in advanced NSCLC (3-6). The identification of molecularly-defined cohorts of NSCLC patients who demonstrate dramatic clinical response to targeted agents has changed the landscape of lung cancer therapy. An epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI), gefinitb or gefitinib, was the first targeted therapy used for the treatment of NSCLC patients (7,8). Initial clinical experiences suggested that high tumor responses were observed among patients with adenocarcinoma and a light or never smoking history (9-11). These clinical observations led to the development of a Phase III trial of gefinitb compared with first-line chemotherapy doublets in this clinically selected patient population (12). Surprisingly, correlative molecular analyses in this Phase III study reveals that the key driver of response to EGFR TKIs is the presence of TK-activating EGFR mutations rather than histology, Asian ethnicity or clinical characteristics (13). The higher clinical responses observed in never or light smokers and NSCLC patients with adenocarcinoma rather than squamous histology are due to the higher prevalence of TK-activating EGFR mutations present in these patients. These results led to world-wide clinical testing for EGFR mutations for selecting those NSCLC patients for first-line therapy of an EGFR TKI in 2009 (14). Of note, papillary and micropapillary adenocarcinoma subtypes have been correlated with lung adenocarcinomas with EGFR mutations (15). However, the clinical value of subtyping histologic-genetic correlations in NSCLC remains to be determined as the genetic features for the majority of NSCLC have yet to be characterized and the histologic diagnosis of lung adenocarcinoma or squamous carcinoma could vary significantly between pathologists. Nevertheless, the cancer armentarium that might be selected by molecular biomarker status is quickly increasing. The echinoderm microtubule-

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associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) fusion oncogene represents the newest molecular target in NSCLC. Higher prevalence of EML4-ALK fusion oncogene has been found in adenocarcinoma rather than squamous histology of the lung (16,17).

Histology has also been correlated with clinical response to the new generation cytotoxic chemotherapy agent pemetrexed. Data from Phase III trials indicate that the efficacy of pemetrexed is limited to patients with nonsquamous histology (18,19). Most recently, a maintenance study with pemetrexed after first-line chemotherapy found almost all benefit confined to non-squamous NSCLC (20). However, central histology review of 93 patients (14%) enrolled in this Phase III study revealed 11% disagreement rate between local pathologists and central review pathologists in the histologic diagnosis of non-squamous versus squamous NSCLC (20). Further study suggests that histology may be a surrogate for Thymidylate Synthase (TS) expression and a much less sensitive discriminator for treatment choice (21). Gandara et al recently reported that the level of TS expression is likely the primary reason that squamous cell NSCLC responds poorly to pemetrexed (22). They found that median TS RNA expression level was almost twice as high in squamous cell carcinomas as in adenocarcinomas in a large database, but there was tremendous overlap of expression ranges in individual patient tumors. Not all squamous cell NSCLCs have high TS levels and not all non-squamous cell NSCLCs have low TS levels. Thus, evaluation of TS levels might allow clinicians to individualize pemetrexed treatment irrespective of histology. Increasingly, molecular biomarkers are being used to guide the selection of chemotherapy. For example, low ERCC1 expression predicts greater response to platinum chemotherapy and low RRM1 expression with greater response to gemcitabine. These promising molecular biomarkers are being prospectively validated in several ongoing clinical trials.

ASA404 (5,6-dimethylxanthenone-4-acetic acid or DMXAA) is a small-molecule tumor-vascular disrupting agent (Tumour-VDA) that was developed as an analogue of flavone acetic acid. ASA404 simultaneously targets at least two cell types, vascular endothelial cells and macrophages, within the tumor microenvironment. ASA404 induces decreases in tumor blood flow, increases in vascular permeability and increases in vascular endothelial apoptosis, all occurring within 1 h of administration in mouse tumors. Over a slightly longer time scale, ASA404 induces an increase in tumor concentrations of TNF and a number of other cytokines (23). In this issue of *Journal of Thoracic Disease*, McKeage et al (24) report the results of a retrospective, pooled analysis of the safety and activity of ASA404, in combination with standard carboplatin and paclitaxel chemotherapy from two Phase II trials of carboplatin and paclitaxel alone or with ASA404 (25,26). As the authors have appropriately acknowledged the limitations of the study,

they suggest that there are no significant differences of ASA404 in combination with carboplatin and paclitaxel chemotherapy between patients with squamous and non-squamous histologies. These and other studies support that squamous histology alone should not be a contraindication for an angiogenesis inhibitor. This observation and promising Phase II studies led to launching of two Phase III studies of ASA404 as a first-line or second-line treatment for NSCLC in combination with chemotherapy (ATTRACT-1, and ATTRACT-2). Although ATTRACT-1 has been terminated following interim data analysis showing futility, there were no safety concerns identified. Hopefully, correlative studies will shed the light of molecular biomarkers predictive of response to ASA404 from these trials in the near future. More mechanistic studies are also implicated to determine the clinical use of this agent in NSCLC.

In summary, although clinical and radiographic characteristics associated with different histology subtypes of NSCLC have been long noted, histology alone is unlikely to remain as the primary determinant in the selection of appropriate treatment. The identification of molecularly defined subtypes of NSCLC patients who demonstrate different clinical responses to specific cancer drugs has changed the landscape of lung cancer therapy and potentially of histology-based diagnoses. Future treatment decisions for lung cancer are likely to be based on molecular subtypes reflecting tumor biology rather than clinical features or histologic subtypes.

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