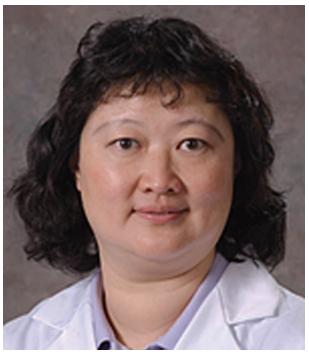
Editorial

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

Tianhong Li

Division of Hematology & Oncology, University of California Davis Cancer Center, Sacramento, CA, USA

J Thorac Dis 2010; 2: 189-191. DOI: 10.3978/j.issn.2072-1439.2010.11.9



Tianhong Li

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-

No potential conflict of interest.

Correspondence to: Tianhong Li, MD, PhD. Division of Hematology & Oncology, University of California Davis Cancer Center, 4501 X Street, Suite 3016, Sacramento, CA 95817, USA. Tel: 916-734-3772, Fax: 916-734-7946. Email: tianhong.li@ucdmc.ucdavis.edu.

Submitted Nov 16, 2010. Accepted for publication Nov 18, 2010.
Available at www.jthoracdis.com

ISSN: 2072-1439

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 section 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 been 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, polled 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 IIII 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.

References

1. Brambilla E, Travis WD, Colby TV, Corrin B, Shimosato Y. The new World Health Organization classification of lung tumours. Eur Respir J 2001;18:1059-68.
2. Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2004;22:2184-91.
3. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542-50.
4. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol 2009;27:1227-34.
5. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol 2010;21:1804-9.
6. Scagliotti G, Novello S, von Pawel J, Reck M, Pereira JR, Thomas M, et al. Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non-small-cell lung cancer. J Clin Oncol 2010;28:1835-42.

7. Jänne PA, Gurubhagavatula S, Yeap BY, Lucca J, Ostler P, Skarin AT, et al. Outcomes of patients with advanced non-small cell lung cancer treated with gefitinib (ZD1839, "Iressa") on an expanded access study. Lung Cancer 2004;44:221-30.
8. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Gefinitb in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-32.
9. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39.
10. Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-500.
11. Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and gefinitb. Proc Natl Acad Sci U S A 2004;101:13306-11.
12. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
13. Rudin CM, Avila-Tang E, Harris CC, Herman JG, Hirsch FR, Pao W, et al. Lung cancer in never smokers: molecular profiles and therapeutic implications. Clin Cancer Res 2009;15:5646-61.
14. Gandara DR, Mack PC, Li T, Lara PN Jr, Herbst RS. Evolving treatment algorithms for advanced non-small-cell lung cancer: 2009 looking toward 2012. Clin Lung Cancer 2009;10:392-4.
15. Motoi N, Szoke J, Riely GJ, Seshan VE, Kris MG, Rusch VW, et al. Lung adenocarcinoma: modification of the 2004 WHO mixed subtype to include the major histologic subtype suggests correlations between papillary and micropapillary adenocarcinoma subtypes, EGFR mutations and gene expression analysis. Am J Surg Pathol 2008;32:810-27.
16. Rodig SJ, Mino-Kenudson M, Dacic S, Yeap BY, Shaw A, Barletta JA, et al. Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population. Clin Cancer Res 2009;15:5216-23.
17. Shaw AT, Yeap BY, Mino-Kenudson M, Digumarthy SR, Costa DB, Heist RS, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 2009;27:4247-53.
18. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543-51.
19. Syrigos KN, Vansteenkiste J, Parikh P, von Pawel J, Manegold C, Martins RG, et al. Prognostic and predictive factors in a randomized phase III trial comparing cisplatin-pemetrexed versus cisplatin-gemcitabine in advanced non-small-cell lung cancer. Ann Oncol 2010;21:556-61.
20. Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009;374:1432-40.
21. Righi L, Papotti MG, Ceppi P, Billè A, Bacillo E, Molinaro L, et al. Thymidylate synthase but not excision repair cross-complementation group 1 tumor expression predicts outcome in patients with malignant pleural mesothelioma treated with pemetrexed-based chemotherapy. J Clin Oncol 2010;28:1534-9.
22. Gandara DR, Grimminger PP, Mack PC, Danenberg PV, Lara P Jr, Danenberg KD. Histology- and gender-related associations of ERCC1, RRM1, and TS biomarkers in 1,802 patients with NSCLC: Implications for therapy. J Clin Oncol 2010;28:S7513.
23. Baguley BC, McKeage MJ. ASA404: a tumor vascular-disrupting agent with broad potential for cancer therapy. Future Oncol 2010;6:1537-43.
24. McKeage MJ, Jameson MB, AS1404-201 Study Group Investigators. Comparative outcomes of squamous and non-squamous non-small cell lung cancer (NSCLC) patients in phase II studies of ASA404 (DMXAA)–retrospective analysis of pooled data. J Thorac Dis 2010;2:199-204.
25. McKeage MJ, Reck M, Jameson MB, Rosenthal MA, Gibbs D, Mainwaring PN, et al. Phase II study of ASA404 (vadimezan, 5,6-dimethylxanthenone-4-acetic acid/DMXAA) 1800mg/m(2) combined with carboplatin and paclitaxel in previously untreated advanced non-small cell lung cancer. Lung Cancer 2009;65:192-7.
26. McKeage MJ, Von Pawel J, Reck M, Jameson MB, Rosenthal MA, Sullivan R, et al. Randomised phase II study of ASA404 combined with carboplatin and paclitaxel in previously untreated advanced non-small cell lung cancer. Br J Cancer 2008;99:2006-12.