

The Evolving Role of Histology In the Treatment of Non-Small Cell Lung Cancer

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Lung cancer is the second most common type of cancer (after prostate in men and breast in women) and a major cause of cancer-related mortality.^{1,2} An estimated 222,520 new cases of lung cancer are expected in 2010, accounting for about 15% of cancer diagnoses. The incidence rate is declining significantly in men, from 102.1 cases in 1984 to 71.3 cases per 100,000 in 2006. In women, the rate is approaching a plateau after a long period of increase.² Lung cancer accounts for more deaths than any other cancer in both men and women. An estimated 157,300 deaths, accounting for about 28% of all cancer deaths, are expected to occur in 2010.²

HISTOLOGY

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. These are subcategorized as adenocarcinoma (44%), squamous cell carcinoma (23%), large cell (4%), and not otherwise specified (28%).³ Adenocarcinomas mostly involve peripheral airways and are the most common subtype in never-smokers. They metastasize frequently, and are associated with mutations in the K-RAS gene and the **endothelial growth factor receptor (EGFR)**. Squamous cell carcinomas typically arise in more central airways, have stronger association with tobacco smoking and have high levels of **thymidylate synthetase (TS)** and increased expression of ERCC1.

For decades the differentiation of lung cancers for the purpose of treatment was made on the basis of NSCLC versus **small cell lung cancers (SCLC)**. The standard of care for unresectable, locally advanced and metastatic NSCLC is platinum-based duplet therapy combined with newer third-generation agents the standard of care. This was supported by multiple trials done during the 1980s and early 2000s. One such trial compared four platinum-based doublet regimens in 1100 patients;⁴ a modest overall survival benefit of approximately 8 months was seen among all groups. An older phase III study did not show a difference in survival com-

paring four different chemotherapeutic regimens.⁵ Another trial by Scagliotti et al⁶ compared **gemcitabine and cisplatin (GC)**, **carboplatin and paclitaxel (PCb)** with **vinorelbine and cisplatin (VC)** in locally advanced or recurrent/metastatic NSCLC and showed no significant differences in response rate or overall survival with either of the combinations. A retrospective subgroup analysis of this study failed to show that histology was predictive of outcomes in either of the PCb, GC or VC arms.⁷

This approach is starting to shift. Recently, histology is being used to guide therapy. Some chemotherapy drugs have shown to be more effective while others are associated with increased rates of adverse events in certain histological subgroups of NSCLC. For example, pemetrexed, an antifolate cytotoxic drug, is more effective in the non-squamous cell group both in chemo-naïve patients as well as second line and maintenance settings; and the newer anti-VEGF inhibitors (bevacizumab) and **epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs)** are associated with increased toxicity in patients with squamous cell histology.

NSCLC HISTOLOGY AND EFFICACY (TABLE 1)

Scagliotti et al⁸ conducted the largest phase III randomized non-inferiority study comparing GC versus **cisplatin plus pemetrexed (CP)** in 1725 patients with

untreated advanced NSCLC. Non-inferiority was documented because the median survival time was an identical 10.3 months in each arm. Progression-free survival and objective response rates were also comparable. Interestingly, for the first time histology demonstrated a role in predicting response to a cytotoxic chemotherapy combination as among the 847 patients with adenocarcinoma, CP had median overall survival of 12.6 compared to 10.9 months in the CP arm (p=0.03). In contrast, the opposite was seen for the 473 patients with squamous cell carcinoma, with survival favoring the CG arm compared with the CP arm (p>0.05). There was statistically significantly more grade 3 to 4 granulocytopenia, thrombocytopenia, and anemia and increased febrile neutropenia associated in the gemcitabine-containing arm.

Similar results were seen when single-agent pemetrexed was compared with docetaxel in a randomized phase III trial for second line treatment of advanced NSCLC. This non-inferiority trial established the role of pemetrexed in the second line setting. Overall response rates of 9.1% vs. 8.8% and median survival of 8.3 versus 7.9 months were seen with pemetrexed and docetaxel, respectively.⁹ A retrospective analysis using subset histology data showed better survival with pemetrexed for non-squamous group comparing with docetaxel, and once again the reverse was true for squamous cell histology.¹⁰

Table 1. Selected studies on the role of NSLC histology of chemotherapy efficacy

Study	Design	Regimen	Overall Survival (months)	
			Non-Squamous	Squamous
Scagliotti [8]	Phase III	Cisplatin/pemetrexed	11.8	9.4
	First line	Cisplatin/gemcitabine	10.4	10.8
Peterson [10]	Retrospective	Pemetrexed	9.3	6.2
	Second line	Docetaxel	8.0	7.4
Ciuleanu [11]	Phase III	Pemetrexed	15.5	9.9
	Maintenance	Best supportive care	10.3	10.8

RR: response rate, PFS: progression free survival OS: overall survival

Maintenance therapy with pemetrexed has also shown improved progression-free survival versus placebo for advanced lung cancer of non-squamous NSCLC patients that did not progress after 4 cycles of platinum-based duplet chemotherapy. In a phase III double blind study, 663 patients were randomly assigned to receive pemetrexed plus best supportive care versus placebo and best supportive care every 21 days until disease progression. Pemetrexed significantly improved PFS 4.3 versus 2.6 months ($p < 0.0001$) and overall survival 13.4 months versus 10.6 months ($p = 0.12$). Subgroup analysis again showed that when comparing with placebo, progression free survival (PFS) was superior in the non-squamous group (4.5 vs. 2.6 months, $p < 0.00001$) than squamous cell (2.8 vs. 2.6 months, $p = 0.039$) and objective response rate was also better for non-squamous than the squamous cell group.¹¹

The significant treatment-by-histology interaction indicates that patients with non-squamous histology treated with pemetrexed had higher survival compared to all others in the trials. One hypothesis is the higher expression of TS in squamous cell carcinomas compared to non-squamous histology. TS is one of the main target enzymes of pemetrexed and its higher expression in squamous cell cancers possibly makes them resistant to pemetrexed therapy which in turns leads to decreased efficacy as compared to non-squamous non-small cell histology. This hypothesis is based on *in vitro* studies showing over expression of TS correlates with reduced sensitivity to pemetrexed.

NSCLC HISTOLOGY AND SAFETY (TABLE 2)

Bevacizumab is a humanized anti-vascular endothelial growth factor (VEGF) antibody, which exert a direct antiangiogenic effect by binding to and clearing VEGF from the tumor microenvironment. Additional antitumor activity may be obtained via the effects of bevacizumab on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells. Bevacizumab has been studied in phase II and III trials in combination with standard platinum-based duplet therapy, and it has been approved by FDA as a first line agent for non-squamous NSCLC.

This approval is based on the higher incidence of pulmonary hemorrhages in patient with squamous NSCLC. In a phase II trial,¹² chemo-naïve patients with stage IIIB or IV NSCLC were treated with PCb versus PCb and bevacizumab. Six patients (9%) in the bevacizumab groups had pulmonary hemorrhage and four of them were fatal. Subset analysis showed that 31% of these episodes occurred in squamous cell group whereas only 4% occurred in non-squamous group. In a randomized phase III study (ECOG 4599),¹³ platinum-based duplet therapy with or without bevacizumab was evaluated; 878 patients with recurrent or advanced non-squamous NSCLC (stage IIIB or IV) were assigned to chemotherapy with PCb alone or PCb plus bevacizumab. Chemotherapy was administered every 3 weeks for six cycles, and bevacizumab was administered every 3 weeks until disease progression was evi-

dent or toxic effects were intolerable. Median OS was significantly improved (12.3 vs. 10.3 months, respectively) with significant improvement in response rates (35% vs. 15%) and PFS (6.2 vs. 4.5 months). Clinically significant bleeding was about 4.4% in bevacizumab group compared with 0.7% in controls. Another study (AVAiL)¹⁴ evaluated the combination of CG and bevacizumab versus CG and placebo as first line agent for advanced non-squamous NSCLC. Response rate and median PFS were better in the bevacizumab-containing group; however, the incidence of fatal pulmonary hemorrhage was approximately 1%.

EMERGENCE OF TYROSINE KINASE INHIBITORS AND THEIR RELATION TO HISTOLOGY

The EGFR family is part of a complex signal transduction network that is central to several critical cellular processes. About 10% of NSCLC respond to EGFR-targeted TKIs. More than 75% of “responders” have activating mutations in EGFR and EGFR sequence analysis is a useful method for predicting response and PFS following TKI therapy in NSCLC.¹⁵ The Food and Drug Administration (FDA) has approved the EGFR TKIs gefitinib and erlotinib for the treatment of advanced NSCLC.

A phase III open-label study (IPASS) randomly assigned previously untreated patients from East Asia with advanced NSCLC to receive gefitinib or PCb; 1217 patients with stage IIIB/IV lung cancer of adenocarcinoma etiology, non-smokers or former light smokers were included in the study. The primary end point was PFS. EGFR mutation data for 437 patients (36%) could be evaluated, 261 (60%) were positive for a mutation. The median PFS was 5.7 months in the gefitinib group and 5.8 months in the PCb group and 12-month PFS were 24.9% and 6.7%, respectively. In the EGFR mutation-positive subgroup, PFS was significantly longer among patients receiving gefitinib than among those receiving PCb ($p < 0.001$).¹⁶

Erlotinib has also been evaluated in the second and third line settings and lead to its inclusion as therapeutic armamentarium against NSCLC. Over 700 patients received erlotinib or placebo in a randomized trial and showed a response rate of 8.9% with a 2-month improved

Table 2. Selected studies on the incidence of bleeding complications with bevacizumab

Study	Regimens	Hemoptysis	Life-threatening pulmonary hemorrhage
Sandler [13]	Carboplatin/pemetrexed	0.5%	0.2%
	Carboplatin/pemetrexed + Bevacizumab 7.5 mg/kg	2.1%	1.6%
Manegold [14]	Cisplatin/gemcitabine	4.9%	0.3%
	Cisplatin/gemcitabine + bevacizumab 7.5 mg/kg	7%	1.2%
	Cisplatin/gemcitabine + bevacizumab 15 mg/kg	9.7%	0.9%

overall survival as compared to placebo. Bronchioalveolar carcinoma had the best response rate of 25% and, interestingly, severity of skin rash, a common side effect of EGFR TKIs, was strongly associated with higher survival rates.¹⁷

Sunitinib is a tyrosine kinase inhibitor and has shown some activity in a phase II trial of previously treated stage IIIB/IV NSCLC patients; ORR was 11% with overall survival of 23 weeks. Toxicities included life-threatening hemorrhage in 3 patients (2/23 squamous and 1/40 adenocarcinoma).¹⁸

CONCLUSION

The term NSCLC is no longer sufficient with regard to treatment selection, and according to the data abovementioned, we have few perspectives. First, we believe that for non-squamous NSCLC, the combination of cisplatin and pemetrexed with or without bevacizumab is emerging as a preferable chemotherapeutic regimen. However, this combination has not been investigated formally against many of the most commonly used combinations. Second, in a much selected group of patients with EGFR mutation-positive adenocarcinomas, gefitinib or erlotinib can be considered as a first line agent. Data show that it is inappropriate and potentially harmful to give TKI to a patient whose EGFR mutation status is unknown.¹⁹ Patients receiving erlotinib upfront who are EGFR mutation-negative have worse survival and cannot be rescued with chemotherapy. Third, patients with squamous cell lung cancers are not suitable for treatment with cisplatin and pemetrexed due to lower efficacy or for treatment with bevacizumab-containing regimens due to safety issues. Finally, many other molecular targets (HER-2, EML4-ALK) are being evaluated for targeted therapy, which have shown some promise in phase II trials. The treatment of advanced metastatic NSCLC is evolving, and researchers are testing different, novel drugs and personalizing chemotherapeutic combinations.

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The authors and/or significant others have no financial interests to disclose.

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