The Role of Histology with Common First-line Regimens for Advanced Non-small Cell Lung Cancer

A Brief Report of the Retrospective Analysis of a Three-arm Randomized Trial

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Introduction: Although histology has not consistently been associated with treatment outcome in advanced non-small cell lung cancer, a recent phase III trial comparing pemetrexed plus cisplatin and gemcitabine plus cisplatin (GC) demonstrated better efficacy for pemetrexed plus cisplatin in nonsquamous (adenocarcinoma and large cell carcinoma) carcinoma than in squamous cell carcinoma. Herein, retrospective analysis is used to explore the potential predictive and prognostic role of non-small cell lung cancer histology in patients treated with three first-line, platinum-based regimens.

Methods: Survival and time to progression (TTP) data from a phase III trial comparing paclitaxel plus carboplatin (PCb), GC, and vinorelbine plus cisplatin (VC) were analyzed. Using Cox multiple regression, factors for one model included treatment (PCb, GC, and VC), histology (squamous, adenocarcinoma, large cell, and other), gender, Eastern Cooperative Oncology Group performance status (0/1 and 2), stage (IIIB and IV), number of metastatic sites ($\leq$1 and $>$1), and smoking history (yes or no). In another model, histology was simply considered as squamous versus nonsquamous. An interaction value of $p < 0.10$ was considered significant.

Results: Baseline patient and disease characteristics for the 607 treated patients were balanced among the arms. No significant treatment-by-histology interaction was seen in either model for either end point. Nevertheless, histology was a significant prognostic factor for survival in the first model ($p = 0.0183$) and marginally significant for TTP ($p = 0.0783$). Subsequent pairwise comparisons of histology groups demonstrated a survival advantage for squamous cell carcinoma over adenocarcinoma ($p = 0.0021$).

Conclusions: Histology was not predictive of PCb, GC, or VC treatment effect for either survival or TTP. Histology was prognostic for survival, with better outcomes associated with squamous cell carcinoma.

Key Words: Predictive factor, Prognostic factor, Histology, Non-small cell lung cancer.

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Tumor histology has not consistently been identified as a prognostic factor in patients with advanced non-small cell lung cancer (NSCLC).[1–3] Nevertheless, a preplanned subset analysis by histology in a recent, large, phase III study showed longer survival for pemetrexed plus cisplatin than gemcitabine plus cisplatin (GC) in patients with nonsquamous NSCLC histology, whereas patients with squamous cell carcinoma had shorter survival with pemetrexed/cisplatin compared with GC.[4] Similarly, phase II and III studies showed that patients with nonsquamous NSCLC experience better efficacy with pemetrexed-containing regimens.[5–8] These findings indicate that histology is a predictive factor for efficacy outcomes of pemetrexed-containing regimens in patients with advanced NSCLC.

Because histology has been associated with efficacy for pemetrexed-containing regimens, the question remains whether histology is predictive of outcomes for other cytotoxic regimens. This retrospective analysis explored the potential predictive and prognostic role of histology in a phase III study comparing three first-line, platinum-based regimens

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for advanced NSCLC: GC, paclitaxel plus carboplatin (PCb), and vinorelbine plus cisplatin (VC).[9]

METHODS

Patients

This retrospective analysis was conducted using the patient database of a previously published study[9] in which patients were considered eligible according to the following criteria: chemonaive, histologically or cytologically confirmed stage IIIB (wet or dry) or stage IV NSCLC, ≥1 measurable lesion (World Health Organization criteria), an Eastern Cooperative Oncology Group performance status (PS) of 0 to 2, and adequate organ function. Study design and treatment schema were previously published. Patients received up to six cycles of gemcitabine 1250 mg/m^2 on days 1 and 8 plus cisplatin 75 mg/m^2 on day 2 of a 21-day cycle (GC); paclitaxel 225 mg/m^2 plus carboplatin AUC 6 mg/ml/min, both on day 1 every 21 days (PCb); or vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 plus cisplatin 100 mg/m^2 on day 1 every 28 days (VC).

Statistical Methods

This retrospective analysis incorporated all randomized patients who received treatment. Cox-adjusted analyses of overall survival (OS) (measured from randomization to death) and time to progression (TTP) (measured from randomization to disease progression or death) were used to determine the effects of the following factors: treatment (PCb, GC, and VC), gender, Eastern Cooperative Oncology Group PS (0/1 and 2), disease stage (IIIB and IV), number of metastatic sites (≤1 and >1), smoking history (yes or no), and histology (model 1: squamous carcinoma, adenocarcinoma, large cell carcinoma, or other; model 2: squamous or nonsquamous). Median survival was estimated using the Kaplan-Meier method.[10] Predictive associations were concluded if there was a significant ($p < 0.10$) treatment-by-characteristic interaction within the regression models. Prognostic associations were determined if there was a significant ($p < 0.05$) characteristic main effect within the regression models. Pairwise comparisons were performed using Cox-adjusted analysis.

RESULTS

A total of 612 patients entered the study between August 1998 and May 2000 and were randomized; 607 were treated (205 GC, 201 PCb, and 201 VC). Baseline characteristics were well balanced among treatment arms (Table 1). When the baseline characteristics were examined by histology, independent of treatment received, each characteristic varied slightly with the exception of disease stage. For example, patients with squamous cell carcinoma were more likely (approximately 10%) to be male, have PS of 0/1, not to have multiple metastatic sites, and have a history of smoking (data not shown). Analyses of efficacy endpoints (adjusted and unadjusted) showed no significant differences between treatment arms.[9]

Using Cox multiple regression analysis of OS and TTP, the potential predictive and prognostic role of histology was examined using two histology models (Table 2). No significant treatment-by-histology interaction was seen in either model for either end point (Table 2, column 4, all values $p > 0.10$), confirming that histology was not predictive of efficacy outcomes for any of the three regimens. Considering the treatment effect (Table 2, column 2), neither model showed any significant differences between treatments. In model 1, histology was a significant prognostic factor for OS ($p = 0.0183$) and was marginally significant for TTP ($p = 0.0783$) (Table 2, column 3). Nevertheless, model 2 did not identify histology as a prognostic factor. Additional Cox regression analyses identified gender, PS, number of metastatic sites, and smoking history as significant prognostic factors for OS ($p < 0.05$) in both models; the same factors, except gender, were also significant for TTP ($p < 0.05$).

After histology was identified as a significant prognostic factor using model 1 ($p = 0.018$), pairwise comparisons of histologic groups for survival were performed (Table 3). The comparisons revealed a statistically significant survival ad-

TABLE 1. Baseline Patient and Disease Characteristics

Characteristics	Percentage of Patients GC ($N = 205$)	PCb ($N = 201$)	VC ($N = 201$)
Male	81	76	78
ECOG performance status 0 or 1	95	92	92
Stage IV disease	81	82	81
Histology			
Adenocarcinoma	50	48	55
Squamous cell carcinoma	33	32	27
Large cell carcinoma	6	10	6
NSCLC not otherwise specified (NOS)/other	11	10	11
>1 Metastatic site[a]	26	28	33
Smoking history	80	77	82

[a] $N = 167$ for GC, 164 for PCb, and 163 for VC.

ECOG, Eastern Cooperative Oncology Group; GC, gemcitabine/cisplatin; NSCLC, non-small cell lung cancer; PCb, paclitaxel/carboplatin; VC, vinorelbine/cisplatin.

TABLE 2. Cox Regression Results (p)[a]

	Treatment	Histology	Treatment-by-Histology Interaction
Model 1 (four histologic groups[b])			
Survival	0.6302	**0.0183**	0.2326
TTP	0.2629	0.0783	0.3397
Model 2 (nonsquamous vs. squamous)			
Survival	0.6089	0.1005	0.5235
TTP	0.2590	0.7196	0.1674

[a] Bold p is significant.

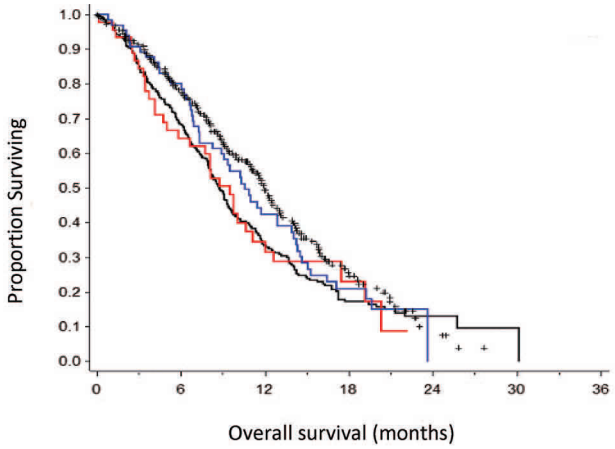
[b] The four histologic groups in model 1 were squamous cell carcinoma, adenocarcinoma, large cell carcinoma, or other.

Nonsquamous, all non-small cell lung cancer histologic types except squamous cell carcinoma; squamous, squamous cell carcinoma; TTP, time to progression.

TABLE 3. Pairwise Comparisons of NSCLC Histologic Groups for Survival: Hazard Ratios[a] and p[b]

	Squamous (n = 187)	Adenocarcinoma (n = 310)	Large cell (n = 54)	Other (n = 65)
Squamous	—	**0.0021**	0.1607	0.9724
Adenocarcinoma	1.42 (1.14–1.78)	—	0.6953	**0.0239**
Large cell	1.32 (0.89–1.96)	0.93 (0.64–1.34)	—	0.2090
Other	0.99 (0.71–1.39)	0.70 (0.51–0.95)	0.75 (0.48–1.17)	—

[a] Hazard ratios with 95% confidence intervals (in parentheses) are provided in the lower left data grouping. Reference histologic group in column heading; hazard ratios >1 indicate lower risk of death in histologic group in the column heading.
[b] Comparison p are provided in the upper right data grouping. Bold p are significant.
Large cell, large cell carcinoma; NSCLC, non-small cell lung cancer; squamous, squamous cell carcinoma.



		Median overall survival (months)	1-year overall survival rate (%)
Adenocarcinoma	—	8.8	33
Large cell carcinoma	—	9.5	34
Other	—	10.6	42
Squamous cell carcinoma	+ + +	11.9	49

FIGURE 1. Kaplan-Meier plot of overall survival by histology for combined treatment arms.

vantage for squamous cell carcinoma over adenocarcinoma (p = 0.0021). To a lesser extent, "other" histology was associated with longer survival than adenocarcinoma. Other pairwise comparisons were not significant. Survival by histology was plotted for the combined treatment arms to illustrate these findings (Figure 1).

DISCUSSION

This retrospective analysis of the phase III trial[9] did not identify any significant difference in the efficacy of three cytotoxic chemotherapy regimens according to histology. Among common cytotoxic therapies for advanced NSCLC, histology may only be a predictive factor of efficacy for pemetrexed-containing regimens. Although a mechanistic understanding of this phenomenon is not entirely clear, the differential expression of thymidylate synthase in adenocarcinoma and squamous cell carcinoma[11] might contribute to the differential efficacy of pemetrexed by histology. As an agent that inhibits thymidylate synthase and other enzymes involved in purine and pyrimidine synthesis,[12] pemetrexed would be less efficacious when these targeted, folate-dependent enzymes are highly expressed,[13] as they are in squamous cell carcinoma.

This analysis also investigated a potential prognostic role for histology in advanced NSCLC. Histology was found to be prognostic for survival, with better outcomes associated with squamous cell carcinoma and poorer outcomes with adenocarcinoma. Although previous studies have also suggested a prognostic role for histology, this has not been consistently reported.[3] As summarized by other authors,[3] among studies which tested chemotherapy in advanced NSCLC and identified a possible prognostic role for histology, approximately half concluded that squamous cell carcinoma (or nonadenocarcinoma) was associated with better outcomes, and half concluded that adenocarcinoma or nonsquamous histology was associated with better outcomes.[3] These different outcomes may well have to do with differences in subsequent lines of therapy, including the use of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors that have been shown to improve the survival of patients with EGFR mutations, which are usually seen in patients with adenocarcinoma.[14] Nevertheless, EGFR-inhibitors would not have impacted the study results presented here as they were not in general use during the years these data were collected (1998–2000).

In this analysis, histology was identified as a prognostic factor only when analyzed as four separate groups (model 1) but not when analyzed as two groups (model 2). This underscores the need to use multiple models when investigating these associations. Differential outcomes were confined to the two most distinct histologic groups, with squamous cell carcinoma performing significantly better than adenocarcinoma. When adenocarcinoma was analyzed in combination with large cell carcinoma and other histologic groups (collectively referred to as nonsquamous), the separation of adenocarcinoma and squamous was less pronounced. Although combining histologic groups is often necessary and appropriate, initial analysis using separate histologic groups may yield additional insight.

Interpretation of the presented results must acknowledge the limitations of this analysis, including the limited sample size, especially in the large cell and "other" histologic groups; a study population derived from a single country (all Italian study sites); and data derived from a study that

enrolled patients a decade ago. Regarding the latter point, evidence suggests that advanced NSCLC presentation and responsiveness have been affected over time by multiple factors. For example, changes in cigarette composition and design over the last few decades are thought to have influenced NSCLC histologic distribution.[15] Additionally, the definitions of NSCLC histologic categories have been refined in the last several years, potentially altering the composition of some categories of NSCLC histologic types.[3]

In conclusion, this retrospective analysis identified a prognostic role for histology in advanced NSCLC, with better outcomes associated with squamous cell carcinoma; however, histology did not predict differential efficacy for PCb, GC, or VC. Evidence presented here and in other recent reports[5–8] suggests that studies should continue to investigate histology and its possible association with efficacy outcomes in patients with advanced NSCLC.

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