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Chemotherapy Outcomes by Histologic Subtypes of Non–Small-Cell Lung Cancer: Analysis of the Southwest Oncology Group Database for Antimicrotubule-Platinum Therapy

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Abstract

Histological subtyping has been advocated to select chemotherapy for patients with advanced stage non–small-cell lung cancer (NSCLC). Data from four randomized trials (S9308, S9509, S9806 and S0003) administering an antimicrotubular agent (a taxane or vinorelbine) plus platinum in patients receiving first line treatment for advanced stage NSCLC were analyzed. Of 1146 patients included in this analysis there was no difference in OS or PFS by histological subtype. Since the great majority of advanced NSCLC patients continue to receive chemotherapy, defining molecular-based predictive markers of responsiveness is warranted.

Objective: Histologic subtyping has been advocated to select chemotherapy for patients with advanced-stage non–small-cell lung cancer (NSCLC). To determine whether histologic subtype was associated with efficacy for the commonly used antimicrotubule (AMT) agents, paclitaxel, docetaxel, and vinorelbine plus a platinum compound, we examined the Southwest Oncology Group (SWOG) lung cancer database. **Methods:** Data from 4 randomized trials (S9308, S9509, S9806, and S0003) administering an AMT agent plus platinum in patients receiving first-line treatment for advanced-stage NSCLC were analyzed. Overall survival (OS) and progression-free survival (PFS) comparisons were performed using Cox proportional hazard regression, adjusting for sex. Median survival times were estimated by Kaplan–Meier. **Results:** Of 1146 patients included in this analysis, 640 had adenocarcinoma (56%), 220 had squamous cell carcinoma (19%), 121 had large cell carcinoma (11%), and 165 had NSCLC not otherwise specified (NOS) (14%). Median OS times by histologic subtypes were 8.5, 8.4, 8.2, and 9.6 months, respectively, and median PFS times were 4.2, 4.3, 4.3, and 4.6 months, respectively. No difference in OS or PFS was observed by histologic subtype and, specifically, between nonsquamous and squamous histologies. **Conclusions:** This pooled analysis from 4 SWOG trials using an AMT-platinum regimen did not show a difference in survival outcomes by histologic subtype. Because the majority of patients with advanced NSCLC continue to receive chemotherapy, defining molecular-based predictive markers of responsiveness is warranted.

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Introduction

Despite recent advances in targeted therapies for subsets of patients with oncogene-driven lung adenocarcinomas, chemotherapy remains the standard of care for the majority of patients with advanced-stage non–small-cell lung cancer (NSCLC). Over the last 2 decades, chemotherapy options for patients with lung cancer have increased: The taxanes paclitaxel, docetaxel, gemcitabine, vinorelbine, and pemetrexed are all acceptable platinum partners in the first-line setting. Because randomized trials suggest that these doublets are equally efficacious, choosing a regimen is predominantly based on toxicity profile and schedule of administration.[1] Predictive biomarkers for cytotoxic chemotherapy that could more reliably guide our decision-making are needed.

Preclinical and subsequent clinical data have suggested histology-specific efficacy of chemotherapy in NSCLC, particularly relevant to pemetrexed.[2-4] In a preplanned analysis of a large randomized phase III trial (JMDB) comparing combination pemetrexed and cisplatin with combination gemcitabine and cisplatin in the first-line therapy of patients with advanced-stage NSCLC, a statistically significant treatment-by-histology interaction was demonstrated wherein patients with nonsquamous cell cancers treated with pemetrexed and cisplatin achieved longer overall survival (OS) than those with squamous cell histology treated with the same regimen.[4] Likewise, the pemetrexed combination resulted in longer survival in nonsquamous cancers than the gemcitabine-based regimen. There were no significant differences by histology for response rates or progression-free survival (PFS). Histologic analyses of 2 additional randomized phase III trials confirmed differential efficacy of pemetrexed for OS by histologic subtype.[5] Thus, a new treatment paradigm emerged for histology-based therapy of NSCLC with pemetrexed. More recently, a randomized trial in advanced NSCLC of a newer taxane compound, Abraxane (Celgene Corp., Summit, NJ), has also suggested histology-related differences in efficacy, with increased response rates in patients with squamous cell cancers.[6]

The study of histology associations with chemotherapy outcomes is plausible inasmuch as histologic subclassifications represent tumor cells from different cellular origins known to have different genomic composition and biological behaviors. In this regard, recent studies using genomic sequencing methodologies have shown that although both adenocarcinomas and squamous cell cancers of the lung demonstrate high degrees of genomic derangement based on the number of mutations per DNA megabase, 10 to 15 times more than most childhood or hematologic malignancies, they are largely distinct from each other in terms of genomic abnormalities.[7,8]

To assess a potential role of histology in the efficacy of an antimicrotubule (AMT) agent, we conducted a retrospective analysis of randomized Southwest Oncology Group (SWOG) lung cancer trials investigating paclitaxel, docetaxel, or vinorelbine together with a platinum compound. Taxanes are among the most commonly used drugs for the treatment of NSCLC worldwide and have served as the backbone for a number of SWOG trials in advanced-stage NSCLC.

Patients and Methods

We analyzed data from 4 randomized SWOG trials (ClinicalTrials.gov Identifier: NCT00003587; NCT00049335) that administered platinum plus an AMT in one or both arms of the study. All studies were conducted in chemo-naive patients with American Joint Committee on Cancer 6th edition stage IIIB (pleural effusion only) and stage IV NSCLC (without brain metastasis) and performance status of 0-1. Study S9308 was a randomized phase III trial comparing cisplatin with cisplatin and vinorelbine. A statistically significant survival advantage was demonstrated for patients receiving the combination, with a median survival of 8 months compared with 6 months for cisplatin monotherapy ($P = .0018$).[9] S9509 built on the previous study in evaluating whether a carboplatin and paclitaxel doublet was superior to the established regimen of cisplatin combined with vinorelbine. Efficacy was identical between the 2 randomized arms, with a median survival of 8 months.[10] S9806 explored the sequential administration of chemotherapy using a randomized phase II design. Patients received a platinum doublet, gemcitabine plus carboplatin or cisplatin plus vinorelbine, for 3 cycles followed by 3 cycles of single-agent paclitaxel or docetaxel, respectively. The efficacy results were comparable to doublet regimens.[11] S0003 addressed the role of a triplet combination as a strategy to increased antitumor activity. Patients were randomized to receive carboplatin and paclitaxel with or without the hypoxic cytotoxin tirapazamine. The triplet did not increase survival over the standard 2-drug regimen.[12] Both arms of the study were included in this analysis.

Statistical Analysis

OS and PFS were estimated by the Kaplan–Meier method.[13] Formal comparisons for OS and PFS between histologic groups were done by Cox proportional hazards regression, with adjustment for sex. The possibility of a histology-by-sex interaction for OS or PFS was explored and ruled out. All analyses were performed using SAS systems 9.1 and 9.2 (SAS Institute Inc., Chicago, IL).

Results

From 1993 to 2002, 1146 protocol-eligible patients received an AMT agent plus platinum for the first-line treatment of advanced NSCLC. Cases that were eligible and reported on for the original protocol but were missing information with regard to histology were not included in the analysis. The patient characteristics and histologic distribution of each trial are presented in Table 1. There were no significant differences between protocols with respect to the proportions of different histologic subtypes. The baseline characteristics, including age, PS, and stage, were well balanced between the histologic subtypes. A significantly higher number of male patients had squamous cell histology (21% of male vs. 15% of female patients, $P = .0006$). Sixty-two percent of female patients had adenocarcinoma vs. 53% of male patients.

Efficacy by Histology

No difference in OS or PFS by histologic subtype was observed in this analysis. As shown in Table 2, the hazard ratios (HRs) for OS were 0.94 (95% confidence interval [CI], 0.81-1.10) for squamous cell carcinoma, 0.97 (95% CI, 0.80-1.18) for large cell carcinoma, and 0.95 (95% CI, 0.80-1.13) for NSCLC not otherwise specified (NOS) with adenocarcinoma as the reference. Figure 1A displays the OS curve showing similar median survivals of 8 to 9 months, irrespective of histology. Likewise, no difference in PFS was observed by histology, as depicted in Table 2 and Figure 1B. Patients with squamous cell carcinoma had an HR of 0.97 (95% CI,

Table 1 Patient Characteristics of Study Sample (N = 1146)

	S9308	S9509	S9806	S0003	All
Age, years					
Median	63	62	61	62	62
Minimum	33	32	25	28	25
Maximum	83	83	83	80	83
Sex					
Male	140 (68%)	275 (68%)	112 (63%)	232 (64%)	759 (66%)
Female	66 (32%)	127 (32%)	65 (37%)	129 (36%)	387 (34%)
Performance Status[a]					
0	73 (35%)	144 (36%)	70 (40%)	115 (32%)	402 (35%)
1	131 (64%)	251 (62%)	104 (58%)	226 (63%)	710 (62%)
Missing	2 (1%)	7 (2%)	3 (2%)	19 (5%)	31 (3%)
Histology					
Adenocarcinoma	111 (54%)	213 (53%)	97 (55%)	219 (61%)	640 (56%)
Squamous cell	41 (20%)	92 (23%)	32 (18%)	55 (15%)	220 (19%)
Large cell	28 (14%)	39 (10%)	19 (11%)	35 (10%)	121 (11%)
NSCLC NOS	26 (13%)	58 (14%)	29 (16%)	52 (14%)	165 (14%)
Stage (AJCC 6th ed.)					
IIIB	16 (8%)	44 (11%)	32 (18%)	54 (15%)	146 (13%)
IV	190 (92%)	358 (89%)	133 (75%)	307 (85%)	988 (87%)
Missing	0	0	12 (7%)	0	12 (1%)
Total N	206	402	177	361	1146

Abbreviations: AJCC = American Joint Committee on Cancer; NOS = not otherwise specified; NSCLC = non–small-cell lung cancer.
[a]Zubrod scale.

Table 2 Progression-Free and Overall Survivals by Cell Type, Adjusted for Sex

Variable	HR	95% CI		*P* Value
PFS				
Adenocarcinoma	Referent			
Squamous[a]	0.97	0.83	1.13	.71
Large cell[a]	0.99	0.81	1.20	.89
NSCLC NOS[a]	0.88	0.74	1.05	.15
SCC vs. non-SCC (reference)	1.00	0.86	1.16	.96
OS				
Adenocarcinoma	Referent			
Squamous[a]	0.94	0.81	1.10	.43
Large cell[a]	0.97	0.80	1.18	.76
NSCLC NOS[a]	0.95	0.80	1.13	.55
SCC vs. non-SCC (ref)	0.95	0.82	1.11	.52

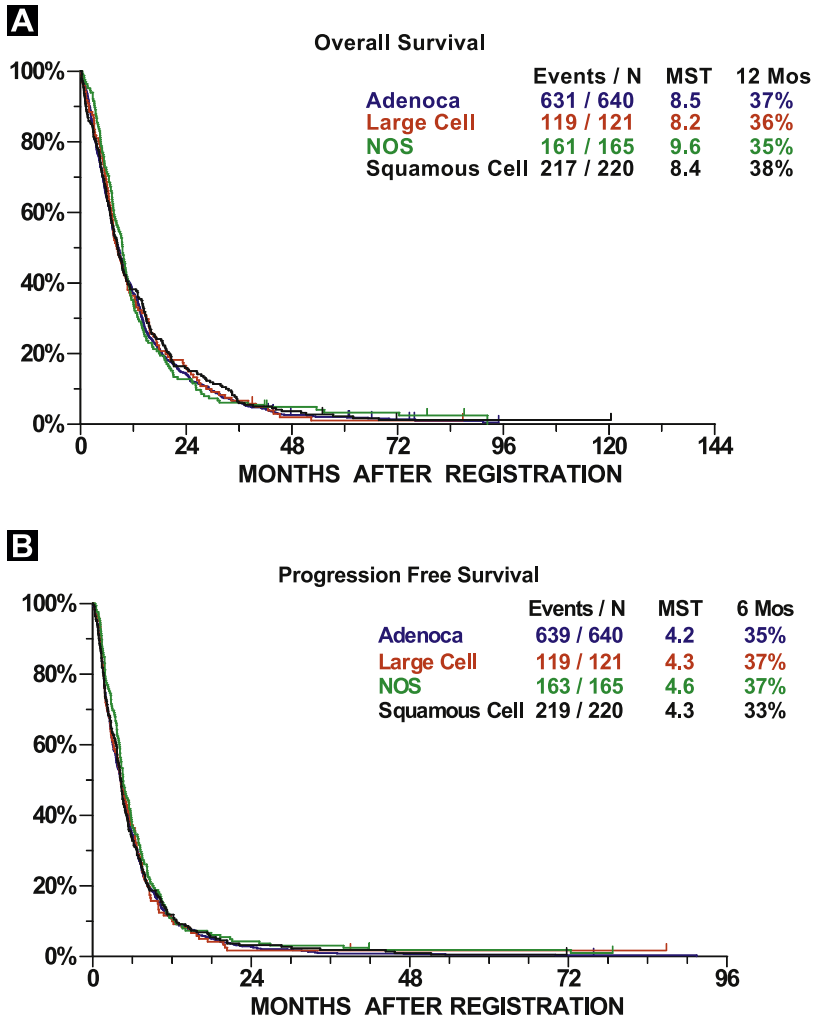
Abbreviations: CI = confidence interval; HR = hazard ratio; NOS = not otherwise specified; NSCLC = non–small-cell lung cancer; OS = overall survival; PFS = progression-free survival; SCC = squamous cell carcinoma.
[a]Adenocarcinoma as referent for comparisons.

0.83-1.13), patients with large cell carcinoma had an HR of 0.99 (95% CI, 0.81-1.20), and patients with NSCLC NOS had an HR of 0.88 (95% CI, 0.74-1.05). Median PFS was approximately 4 months for all histologic subtypes. Male sex was associated with a worse OS HR of 1.17 (95% CI, 1.03-1.32; $P = .01$), but not with PFS. Evaluation by nonsquamous vs. squamous histology (with nonsquamous as the reference group) revealed an HR for OS of 0.95 (95% CI, 0.82-1.11) with median survival times of 8.8 months and 8.4 months, respectively, and an HR for PFS of 1.00 (95% CI, 0.86-1.16) with median survival time for each of 4.3 months (Table 2 and Fig. 2). Objective response rates were not evaluated in this study.

Efficacy by Histology, AMT Agent, and Trial

Because of the variability in trial design among the 4 studies, we reanalyzed the data with the 2 standard of care regimens, paclitaxel plus carboplatin (S9509, S0003) and vinorelbine plus cisplatin (S9308). Data from 792 patients were analyzed. There was no

Figure 1 (A) OS by Histology. (B) PFS by Histology



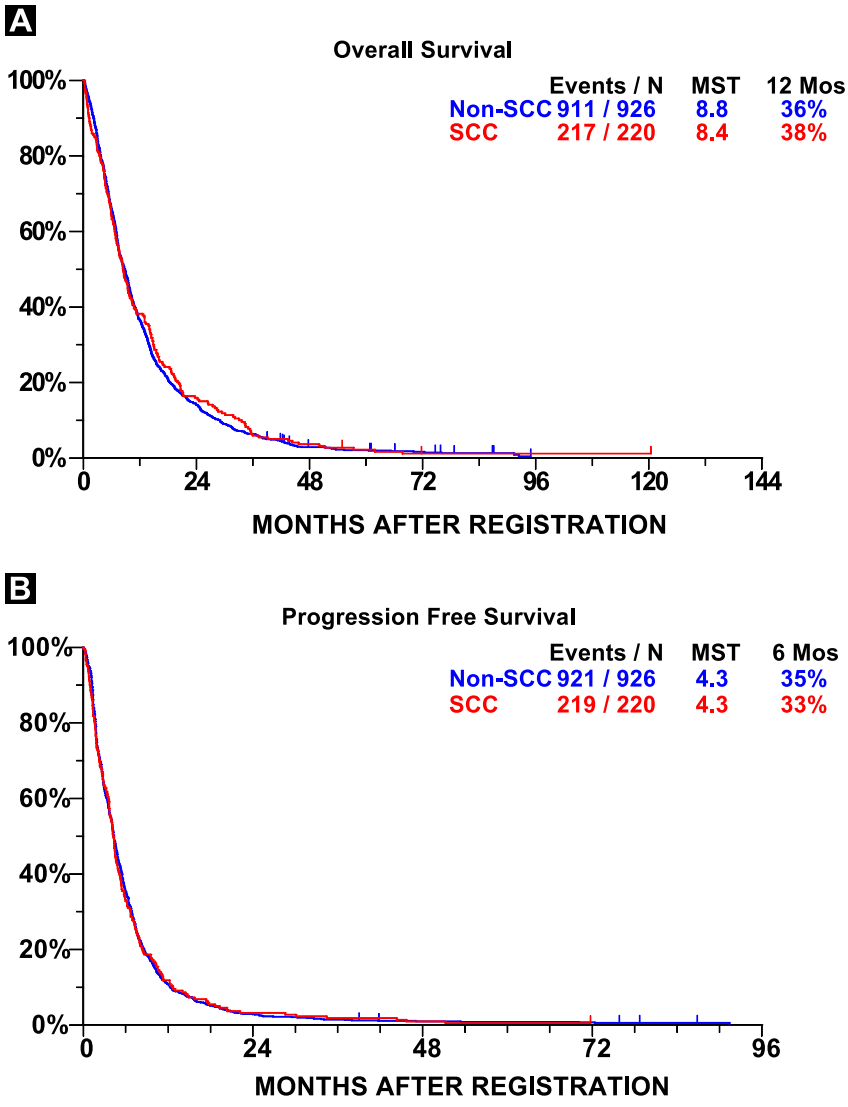
Abbreviations: MST = mean survival time; NOS = not otherwise specified.

significant difference in treatment outcome by histology with either AMT regimen. Because the mechanism of action of these 2 AMT agents differ, we also reexamined the data for vinorelbine plus cisplatin (N = 407) and for paclitaxel plus carboplatin (N = 385) separately. The median number of cycles of vinorelbine plus cisplatin in both studies was 3, and the median number of cycles of paclitaxel and carboplatin in both studies was 4. Histology did not influence PFS or OS in patients treated with vinorelbine (Fig. 3). There was a significantly poorer PFS for patients with adenocarcinoma vs. all other histology who received paclitaxel (HR, 1.32; 95% CI, 1.08-1.62; $P = .006$) (Fig. 4). However, there was no difference by histology in OS.

Discussion

This large retrospective analysis of 4 SWOG randomized trials did not show an association between histology and treatment outcome with an AMT-platinum combination in patients with advanced NSCLC. Both PFS and OS were similar among the histologic subclassifications. If histology was categorized more broadly into nonsquamous vs. squamous, again no differences in PFS or OS were observed. These results are consistent with the retrospective analysis of the Eastern Cooperative Oncology Group 1594. Three of the four treatment arms in this study administered an AMT, either paclitaxel or docetaxel plus a platinum compound. No treatment effect by histology was observed regardless of the platinum doublet administered or within histologic subsets receiving the same therapy.[14] An analysis of a large European phase III trial comparing paclitaxel/carboplatin, gemcitabine/cisplatin, and vinorelbine/cisplatin also did not find a treatment-by-histology interaction for time to progression or OS.[15] In the practice setting, an analysis of the SEER-Medicare database from 1997 to 2002 was conducted to determine the survival impact of histology on elderly patients treated with chemotherapy.[16] Once again, no treatment—histology interaction was observed.

Figure 2 (A) OS Nonsquamous Cell vs. Squamous Cell Histology. (B) PFS Nonsquamous Cell vs. Squamous Cell Histology

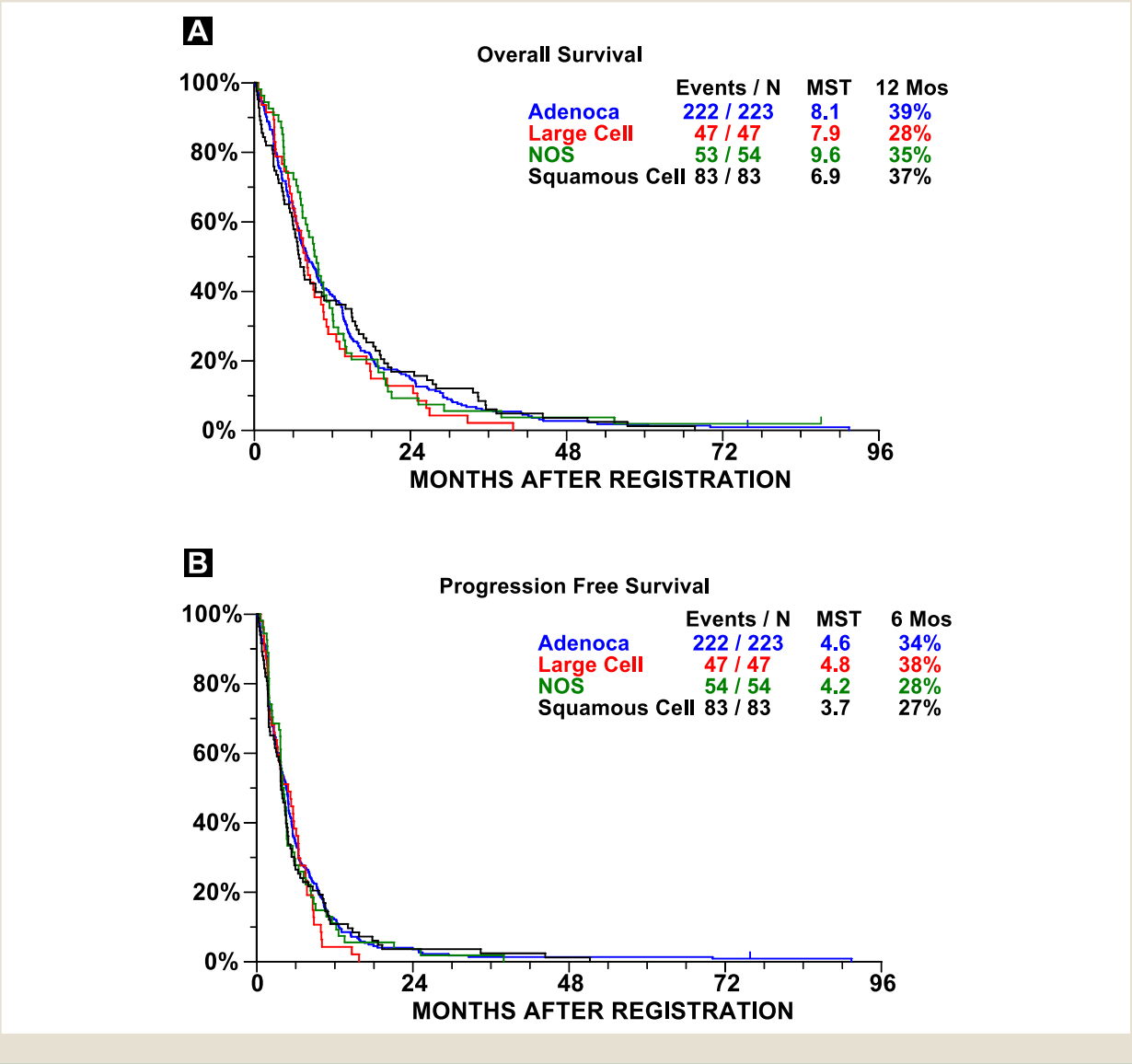


Abbreviations: MST = mean survival time; SCC = squamous cell carcinoma.

Data from older studies suggest a potential relationship between histology and outcome. A meta-analysis of individual patient data from 9 randomized clinical trials published between 1990 and 2007 compared treatment outcomes between regimens that differed only by the platinum agent administered, cisplatin vs. carboplatin, reported a statistically significant treatment interaction by histology.[17] Patients with squamous histology had longer survival times and higher response rates when treated with cisplatin compared with carboplatin (interaction test $P = .098$ and $= .046$, respectively). Hirsch et al[18] conducted a literature review of therapeutic trials evaluating histology as a marker of outcome. Seven studies reported a significant association between OS or response rate to a specific cytotoxic regimen and histology. The authors acknowledged that differences in the study design, treatment regimens administered, failure to adjust for sex, and lack of formal treatment by histology interaction tests in several of the studies made it difficult to draw any meaningful conclusions about the association of histology with therapeutic outcome in advanced NSCLC.

Possible limitations of our study also include the different treatment regimens administered and study designs used, but additional analyses to address these differences did not alter our findings. In particular, the inclusion of S9806 may be questioned because it differed from the other 3 trials in that it was a randomized phase II study and the only trial that used a sequential treatment design. When this study was removed from the data set, no difference in survival by histology was observed. Finally, our results may have been influenced by the additional chemotherapy partners administered with the AMT agent. The unexpected finding of a poorer PFS outcome in the adenocarcinoma group treated with paclitaxel and carboplatin is puzzling and was not seen in the other

Figure 3 (A) OS by Histology for the Cisplatin/Vinorelbine Subgroup. (B) PFS by Histology for the Cisplatin/Vinorelbine Subgroup

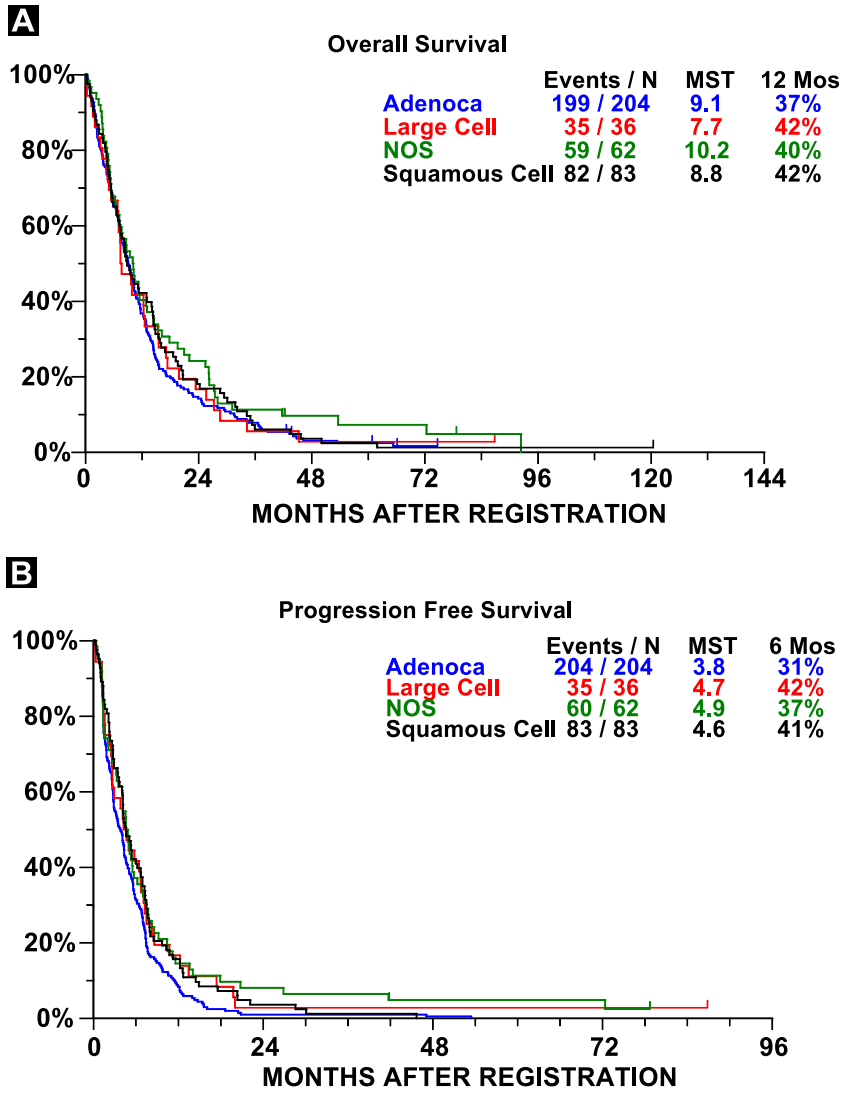


Abbreviations: MST = mean survival time; NOS = not otherwise specified.

studies. In fact, this group had favorable prognostic characteristics with a slightly higher percentage of performance status 0 and female patients compared with the other histologic subgroups. Unidentified factors must be influencing these results.

The most likely explanation for the lack of a treatment effect by histology is that histology is an insensitive marker of chemotherapy responsiveness. More promising mechanistic-based biomarkers have emerged for many chemotherapy agents, including AMT and platinum. For example, although multiple studies have shown that low expression of the nucleotide excision repair gene excision repair cross-complementation group 1 (ERCC1), measured as mRNA expression by reverse-transcriptase polymerase chain reaction or protein expression by immunohistochemistry, correlates with sensitivity to platinum compounds, findings have been mixed, and validation studies are in progress. Nevertheless, preliminary studies do suggest a histology relationship for ERCC1, with generally lower levels in adenocarcinomas.[19] With regard to AMT, class III β-tubulin (TUBB3), a building block for microtubules, has been extensively evaluated as a potential predictive biomarker. Studies investigating TUBB3 expression and AMT efficacy have shown conflicting results across tumor types. In NSCLC, a meta-analysis of 552 patients from 10 single-arm studies that evaluated tumor expression of TUBB3 in patients who received paclitaxel or vinorelbine-based regimens was conducted.[20] Eight of the studies used immunohistochemistry to detect TUBB3 expression. The objective response rate and OS time were significantly longer in the group of patients with low/negative TUBB3 expression (odds ratio, 0.28; 95% CI, 0.20-0.41; $P < .00001$; median ratio, 1.40; 95% CI, 0.89-0.90; $P < .00001$, respectively). A subgroup analysis by histology was not performed. A study by Dutch investigators examined

Figure 4 (A) OS by Histology for the Carboplatin/Paclitaxel Subgroup. (B) PFS by Histology for the Carboplatin/Paclitaxel Subgroup



Abbreviations: MST = mean survival time; NOS = not otherwise specified.

the relationship between the histology and the predictive role of TUBB3 on AMT efficacy outcomes.[21] They analyzed 261 specimens from a phase III trial of paclitaxel, gemcitabine, and cisplatin vs. vinorelbine and cisplatin for TUBB3 expression by immunohistochemistry. Patients with TUBB3-negative adenocarcinomas had significantly prolonged PFS (7.87 vs. 6.83 months, $P = .035$) and OS times (14.17 vs. 11.17 months, $P = .018$), suggesting that TUBB3 may be predictive of AMT activity. In contrast, an analysis of 4 randomized trials conducted in the adjuvant setting failed to show a predictive benefit of TUBB3, but it did not consider histology-specific effects.[22] An emerging taxane biomarker is the nuclear expression of mitotic checkpoint gene CHFR (checkpoint with forkhead and ring finger domains). CHFR is a key regulator of cell entry into mitosis. Immunohistochemical analysis of tumors from 41 patients treated with paclitaxel and carboplatin with or without bevacizumab revealed an association between expression level and treatment response and OS.[23] Thirty-two patients (78%) had tumors with nonsquamous histology. Reduced nuclear expression of CHFR was observed in 37% of tumors examined and was associated with a lower rate of tumor progression at first restaging (19% vs. 52%, $P = .033$) and prolonged survival (9.9 vs. 6.2 months, $P = .002$). A prospective study to further explore CHFR expression as a biomarker of taxane responsiveness is planned. Thus, the search for robust biomarkers of AMT efficacy continues.

The importance of finding predictive markers of chemotherapy activity was recently illustrated by the POINTBREAK study.[24] A total of 939 patients with advanced disease and nonsquamous cell histology were randomized to receive paclitaxel and carboplatin plus bevacizumab followed by bevacizumab or pemetrexed and

carboplatin plus bevacizumab followed by pemetrexed and bevacizumab. There was no statistical difference in the primary end point of OS with an HR of 1.0 ($P = .947$). The median OS was numerically higher for the paclitaxel arm at 13.4 months compared with 12.6 months for the pemetrexed arm. In this first head-to-head comparison of pemetrexed and paclitaxel regimens, histology did not predict clinical efficacy, even though the trial was restricted to nonsquamous histology. A Norwegian Phase III trial comparing gemcitabine and carboplatin to pemetrexed and carboplatin also failed to show an association between histology and survival.[25] These trials illustrate the complexities underlying treatment responsiveness that remain insufficiently characterized by histology. Although a variety of potential biomarkers exist for this multi-targeted antifolate compound, a preclinical study suggested that thymidylate synthase (TS) is most prominently associated with pemetrexed cytotoxicity.[26] In clinical specimens, an association between TS levels and histologic subtype is present, as demonstrated by a large retrospective analysis of 1802 NSCLC specimens. When assessed by reverse-transcriptase polymerase chain reaction methodology, nonsquamous cell cancers had lower TS levels and high TS levels were found in squamous cell cancers ($P < .001$).[19] To determine whether there is a correlation between TS protein expression by H score and survival after pemetrexed-based chemotherapy, Christoph and colleagues[27] examined 207 pretreatment tumor specimens from patients receiving pemetrexed. By using the median H score as the cutoff point, patients whose cancers showed low TS expression had a prolonged PFS of 5.8 months compared with 3.7 months for those patients with high TS-expressing tumors (HR, 0.679; 95% CI, 0.484-0.953; $P = .025$). This translated into an OS benefit for the low expressors of 22.5 months vs. 14.9 months for high expressors (HR, 0.611; 95% CI, 0.399-0.938; $P = .024$). Although both studies showed TS levels grouped by histology, there was great interpatient heterogeneity in TS expression, with some squamous cell carcinomas demonstrating low TS expression and nonsquamous cell carcinomas demonstrating high TS expression. These data suggest that whether grouped by histology or biomarker, predicting individual patient outcomes from pemetrexed therapy remains complex.

Histology remains a key factor in selecting appropriate therapy; therefore, accurate subtyping is required. Our analysis confirms the changing histologic landscape of NSCLC observed in large epidemiologic studies that have shown a decline in the rate of squamous cell histology in the North American population relative to adenocarcinoma. Of concern is the static rate of NOS histology, which remained at 14% throughout the study period. This is no longer an acceptable diagnosis because treatment decisions for all patients with NSCLC are based on histologic subclassification. Furthermore, the emergence of highly effective targeted therapies that are histology-dependent requires pathologists to accurately subclassify the NOS subtype into the appropriate NSCLC histologic subset for subsequent molecular testing.[28]

Conclusion

Our study results are consistent with reported data showing no predictive effect of histology on AMT outcomes. The identification of molecular predictors of chemotherapy efficacy is a more promising path toward personalized therapy, and several molecular markers are presently undergoing prospective validation.

Clinical Practice Points

- Pemetrexed was the first chemotherapy agent to show histology dependent efficacy.
- To determine if therapeutic efficacy to the commonly used antimicrotubular agents, paclitaxel, docetaxel and vinorebline also correlates with histology we conducted this large retrospective analysis of four SWOG randomized studies.
- No correlation between histology and survival with was demonstrated with an antimicrotubular regimen.
- All patients with non-small cell lung cancer have an opportunity to benefit from an antimicrotublar-based treatment.
- Identifying response predictors will require a molecular approach.

Disclosure

K.K.: past consultant (compensated) for Bristol-Myers Squibb. F.R.H.: current consultant (compensated) to Lilly, Genentech/Roche, Boehringer Ingelheim, and Celgene; current grant support (to institution) from Celgene, Genentech, Amgen, and Morphotek. A.J.W.: past consultant (compensated) for Boehringer Ingelheim; past grant support (to institution) from Lilly Oncology. The other authors have no disclosures.

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