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Original article

p53-associated differential response to platinum-gemcitabine and platinum-paclitaxel in advanced non-small cell lung cancer

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Background: Platinum-paclitaxel and platinum-gemcitabine are commonly used first-line chemotherapies for advanced non-small-cell lung cancer (NSCLC). Currently, there is no established biomarker predicting the treatment outcomes of these two regimens. Previous studies have suggested that p53 expression might determine the response to platinum compounds and gemcitabine, but not paclitaxel. We hypothesized that p53 overexpression would predict a worse response to platinum-gemcitabine than to platinum-paclitaxel in patients with advanced NCSLC.

Objective: To investigate whether tumor p53 expression would be able to predict the treatment outcome of these two chemotherapy regimens in advanced NSCLC patients.

Methods: We identified patients with advanced NSCLC who had been treated with either platinum-gemcitabine or platinum-paclitaxel as first-line chemotherapy at King Chulalongkorn Memorial Hospital. We obtained the corresponding archived tissue samples and performed immunohistochemical staining to determine the p53 expression in tumor tissues. We then compared the response rates and time to progression (TTP) between two regimens and p53 expression statuses.

Results: Of the 76 advanced NSCLC patients, we identified 40 (52.6%) patients with p53 overexpression, in which we showed better treatment outcomes with platinum-paclitaxel than with platinum-gemcitabine: the response rates were 42.1% vs 14.3% ($p = 0.053$) and TTPs were 5.3 [95%CI, 4.3–6.3] months vs 3.3 [95%CI, 1.3–5.2] months ($p = 0.067$). In the platinum-gemcitabine group, the response rate and TTP were better in normal expression of p53 subgroup compared to p53-overexpression subgroup (response rate 47.4% vs 14.3%, $p = 0.026$ and TTP 5.0 [95%CI, 4.4–5.5] months vs 3.3 [95%CI, 1.3–5.2] months, $p = 0.062$). These differences were not found in the platinum-paclitaxel group.

Conclusion: Our findings suggest that p53 expression is a potential predictive marker for the response to platinum-gemcitabine in advanced NSCLC. Consequently, platinum-paclitaxel would be favored over platinum-gemcitabine in patients with p53 overexpression.

Keywords: Advanced NSCLC, gemcitabine, paclitaxel, platinum, p53 expression

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer deaths worldwide [1]. More than half of NSCLC patients present with an advanced stage of the disease. Although some targeted agents are very effective in some particular subgroups, chemotherapy is still the main treatment for advanced NSCLC. The current standard first-line chemotherapies are the platinum doublets, which consist of a platinum drug and a third generation agents such as gemcitabine, paclitaxel, docetaxel, vinorelbine, or pemetrexed. Large randomized trials demonstrated similar efficacy of these regimens with the only difference being toxicity [2, 3]. With a low response rate and substantial toxicity, platinum doublets require an effective predictor which would allow for more personalized chemotherapy in advanced NSCLC.

p53, a tumor suppressor gene, plays a critical role in cellular response to DNA-damaging insults by blocking the cell cycle or leading to apoptosis. Abnormal p53, either p53 mutation or p53

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overexpression, is found in almost all cancer types, including about half of NSCLCs [1]. Both in vivo and in vitro studies have demonstrated that tumor with loss-of-function mutation in *p53* are resistant to many DNA-targeted chemotherapies, including platinum compounds and antimetabolites, but not to antimitotic agents [4, 5]. Many retrospective studies have demonstrated that patients with p53-overexpression NSCLC have a worse response to cisplatin-based chemotherapy than do patients with normal p53 expression NSCLC [6-8]. Abnormal p53 in NSCLC patients led to a worse response to gemcitabine (an antimetabolite), but did not affect their response to paclitaxel (an antimitotic agent) [9-12].

Currently, platinum-gemcitabine and platinum-paclitaxel are the two most commonly used chemotherapy regimens for advanced NSCLC. We hypothesized that p53 overexpression would predict a worse response to the platinum-gemcitabine regimen than to the platinum-paclitaxel regimen in advanced NCSLC patients. To test this hypothesis, we initiated a retrospective cohort study and used immunohistochemical staining to determine p53 expression in archived tissue samples. Instead of comparison between patient with or without p53 over expression as in previous studies, we specifically compared the treatment outcomes between these two regimens in advanced NSCLC patients with p53 over expression.

Patients and methods

Patient selection

Patients with advanced NCLSC who had been treated with either platinum-gemcitabine or platinum-paclitaxel as first line chemotherapy at King Chulalongkorn Memorial Hospital between November 2002 and December 2008 were included in this study. The advanced NSCLC was defined as either stage IIIb with malignant pleural or pericardial effusion or stage IV. All patients had received two or more courses of our standard chemotherapy regimens for advanced NSCLC at 3 week intervals. The platinum-gemcitabine consisted of cisplatin (70mg/m^2) or carboplatin (area under the curve [AUC] at 5) on day 1 and gemcitabine (1,000 mg/m^2) on day 1 and 8, and the platinum-paclitaxel consisted of carboplatin (AUC at 5.5) and paclitaxel (175 mg/m^2). Radiographic evaluations had been periodically performed and responses had been categorized by Response Evaluation Criteria in Solid Tumors [13]. The objective responses included complete response and partial response. The protocol was approved by the Research Affairs Ethics Committee, Faculty of Medicine, at Chulalongkorn University.

Tissues preparation and immunohistochemical staining

We accessed eligible patients' archived tissue samples that contained adequate viable tumor cells. We cut 2 μm sections from paraffin-embedded tissue blocks and then allowed them to air dry. After specimen deparaffinization, we performed antigen retrieval and immunohistochemical staining, using Bench Mark LT (Ventana Medical Systems, Tucson, Arizona, USA) We used the mouse antihuman p53 monoclonal antibody, clone DO-7 (Dako, Glostrup, Denmark) and the "multimer" staining technique using an ultraView Universal DAB Detection Kit (Ventana Medical Systems).

Immunohistochemical slide interpretation

One pathologist (PC), who was blinded to the clinical data, independently evaluated the slides and reported the p53 expression in terms of percentage of p53-positive cells in the primary tumor. While the cutoff level for positivity of p53 immunohistochemistry is arbitrary and varies from 1% to 50% among different studies, our institution has no specific cutoff level for this protein. Because half of NSCLC patients have p53 abnormality, we used the median of the p53 expression as the cutoff for our study. However, we planned to pick the cutoff that resulted in the most powerful differentiation between the responses to the two regimens.

Statistical analysis

Our primary endpoint was the objective response rate to the two chemotherapeutic regimens in patients with advanced NSCLC with p53 overexpression and the secondary endpoint was time to progression (TTP) and overall survival (OS). We used a one-sided *p* value of .05 for each comparison. The study was designed to have 80% power to detect an odds ratio of 3.5 or better in the response rate for the platinum-paclitaxel group over the platinum-gemcitabine in patients with p53 overexpression. Based on the previous studies demonstrating a 15% response rate to platinum-based chemotherapy in NSCLC patients with p53 overexpression [7, 8], the expected response rates to platinum-gemcitabine and platinum-paclitaxel would be

15% and 38% in our patients with p53 overexpression. Therefore, we required 22 patients per group. Since the p53 overexpression occurs in about half of NSCLCs, we needed 88 patients for our study.

A χ^2 test or Fisher's exact test was used to analyze the difference in objective response rates between the two treatment groups in patients with p53 overexpression. As mentioned above, the objective response included only complete response and partial response. TTP was calculated as the period from the first day of treatment to the date of tumor progression, death from any cause, or the last follow-up, at which point data were censored. OS was calculated as the period from the first day of treatment until death from any cause or the date of the last follow-up, at which point data were censored. Both TTP and OS were estimated using the Kaplan–Meier method and compared using a log-rank test. Logistic and Cox regression models were used to determine the independent predictive and/or prognostic factors for response rates, and for TTP and OS, respectively. In addition to gender, pathology type and smoking status, we included p53 expression or chemotherapy (depending on analytic group) in these multivariate analysis models. The receiver operating characteristic (ROC) curve was used to determine the most powerful cutoff of p53 overexpression in terms of discrimination of response rate between these two regimens.

Results

For the 88 cases we initially identified, we are able to analyze 76 specimens by immunohistochemical staining; eight specimens were not available, and four specimens had inadequate tumor cells. Thus, we performed our analysis using these 76 patients. Forty patients received the platinum-gemcitabine regimen, and 36 patients received the platinum-paclitaxel regimen. The baseline demographic and characteristics of these patients are shown in **Table 1**. The platinum-paclitaxel arm had proportionally more adenocarcinomas, more nonsmokers, and younger age than did the platinum-gemcitabine group. In the platinum-gemcitabine group, 19 patients (47.5%) cisplatin-gemcitabine and 21 patients (52.5%) received carboplatin-gemcitabine.

The median p53 expression level of the overall cohort was 30%. Using this cutoff, we found 40 (52.6%), 21 (52.5%), and 19 (52.8%) patients had p53 overexpression in the overall cohort, the platinum-gemcitabine group, and platinum-paclitaxel group, respectively. This cutoff also resulted in the most powerful discrimination of the responses to these two regimens among patient with p53 overexpression with the area under the ROC curve of 0.674.

The response rates relating to p53 expression for all patients, the platinum-gemcitabine group, and the platinum-paclitaxel group are summarized in **Table 2**. The overall cohort had objective response rate of 34.21%, with no difference in the two chemotherapy regimens or the status of p53 expression. However, among patients with p53 overexpression, the response rate for the platinum-gemcitabine regimen was lower than for the platinum-paclitaxel regimen (14.3% vs 42.1%), $p = 0.053$. The response to the platinum-gemcitabine regimen was significantly better in patients with normal p53 expression than in patients with p53 overexpression (47.4% vs 14.3%, $p = 0.026$).

The survival curves for TTP and the median TTP of each subgroup are shown in **Table 3** and **Figure 1**. The median TTP of the overall cohort was 5.2 months and we observed no differences in TTP for the two regimens or p53 expression statuses. In patients with p53 overexpression, TTP was longer in the platinum-paclitaxel group than it was in the platinum-gemcitabine group (5.2 vs 3.3 months, $p = 0.067$). In the platinum-gemcitabine group, patients with normal p53 expression had longer TTP than patients with p53 over expression group (5.0 vs 3.3 months, $p = 0.062$).

The OS of the overall group and the subgroups are shown in **Table 4**.The median OS of all patient was 15.8 months. In patients with p53 overexpression, the OS was 12.4 months in platinum-gemcitabine group and 18.4 months in platinum-paclitaxel group ($p = 0.339$).

In multiple logistic regression analysis, we included gender, pathology type, smoking status, and p53 expression or chemotherapy depending on analytic group. There was not any independently predictive factor for response in the total cohort of patients. In patients with p53 over expression, the chemotherapy regimen was the only independently predictive factor for response even with only borderline statistical significance ($p = 0.056$). The p53 expression status was the only independently predictive factor for response ($p = 0.039$) and TTP ($p = 0.030$) in platinum-gemcitabine group; this factor did not predict response or TTP in patients receiving platinum-paclitaxel, however. The female gender was the only independently prognostic factor for OS in our total cohort of patients ($p = 0.026$).

Table 1. Demographic data and disease characteristics for all patients and for patients categorized by two chemotherapy regimen groups

Characteristics	Total (n = 76)	Platinum-gemcitabine (n = 40)	Platinum-paclitaxel (n = 36)	*p*
Age, mean ± SD	57.8 ± 9.4	60.0 ± 10.1	55.6 ± 8.0	0.041
Gender, n (%)				
Female	42 (55.3)	20 (50.0)	22/36 (61.1)	0.331
Male	34 (44.7)	20 (50.0)	14/36 (38.9)	
Stage, n (%)				
IIIb	14 (18.4)	9 (22.5)	5 (13.9)	0.526
IV	59 (77.6)	29 (72.5)	30 (83.3)	
Recurrent disease	3 (3.9)	2 (5.0)	1 (2.8)	
Pathologic type, n (%)				
Adenocarcinoma	55 (72.4)	24 (60.0)	31 (86.1)	0.031
Squamous cell carcinoma	2 (2.6)	2 (5.0)	0	
NSCLC, unspecified	19 (25.0)	14 (35.0)	5 (13.8)	
Performance status, n (%)				
ECOG 1	67 (88.2)	36 (90.0)	31 (86.1)	0.728
ECOG 2	9 (11.8)	4 (10.0)	5 (13.8)	
Smoking status, n (%)				
No	39 (51.3)	17 (42.5)	22 (61.1)	0.049
Yes	28 (36.8)	19 (47.5)	9 (25.0)	
Unknown	9 (11.8)	4 (10.0)	5 (13.8)	
Weight loss, n (%)				
No	29 (38.2)	14 (35.0)	15 (41.7)	0.366
Yes	30 (39.5)	18 (45.0)	12 (33.3)	
Unknown	17 (22.4)	8 (20.0)	9 (25.0)	
Salvage therapy, n (%)	55 (72.4)	33 (82.50)	22 (66.67)	0.118
EGFR TKIs	26 (34.2)	16 (44.44)	10 (30.32)	0.226
P53 Overexpression, n (%)	40 (52.6)	21 (52.5)	19 (52.8)	0.981

ECOG = Eastern cooperative oncology group, EGFR TKIs = Epidermal growth factor receptor tyrosine kinase inhibitors

Table 2. The comparison of objective response rate between two chemotherapeutic regimens related to p53 expression

	All patients	Platinum-gemcitabine group	Platinum-paclitaxel group	*p**
All patients	26/76 (34.21%)	12/40 (30.00%)	12/36 (33.33%)	0.415
P53 overexpression	11/40 (27.50%)	3/21 (14.29%)	8/19 (42.11%)	0.053
P53 normal expression	15/36 (41.67%)	9/19 (47.37%)	6/17 (35.29%)	0.463
p-value**	0.194	0.026	0.676	

*Comparison between the two chemotherapy regimens, **Comparison between the p53 normal expression and p53 over expression

Table 3. The median TTP (months) of the all patients and all subgroups

	All patients	Platinum-gemcitabine group	Platinum-paclitaxel group	*p**
All patients	5.2 [95%CI, 4.6–5.8]	4.67 [95%CI, 3.6–5.9]	5.30 [95%CI, 4.7–5.9]	0.148
P53 over expression	4.5 [95%CI, 3.4–5.5]	3.27 [95%CI, 1.3–5.2]	5.17 [95%CI, 4.3–6.3]	0.067
P53 normal expression	5.6 [95%CI, 3.7–7.4]	4.97 [95%CI, 4.4–5.5]	6.83 [95%CI, 4.2–9.4]	0.750
p-value**	0.258	0.062	0.855	

*Comparison between the two chemotherapy regimens, **Comparison between the p53 normal expression and p53 overexpression
Abbreviations: TTP = time to progression; CI = confidence interval.

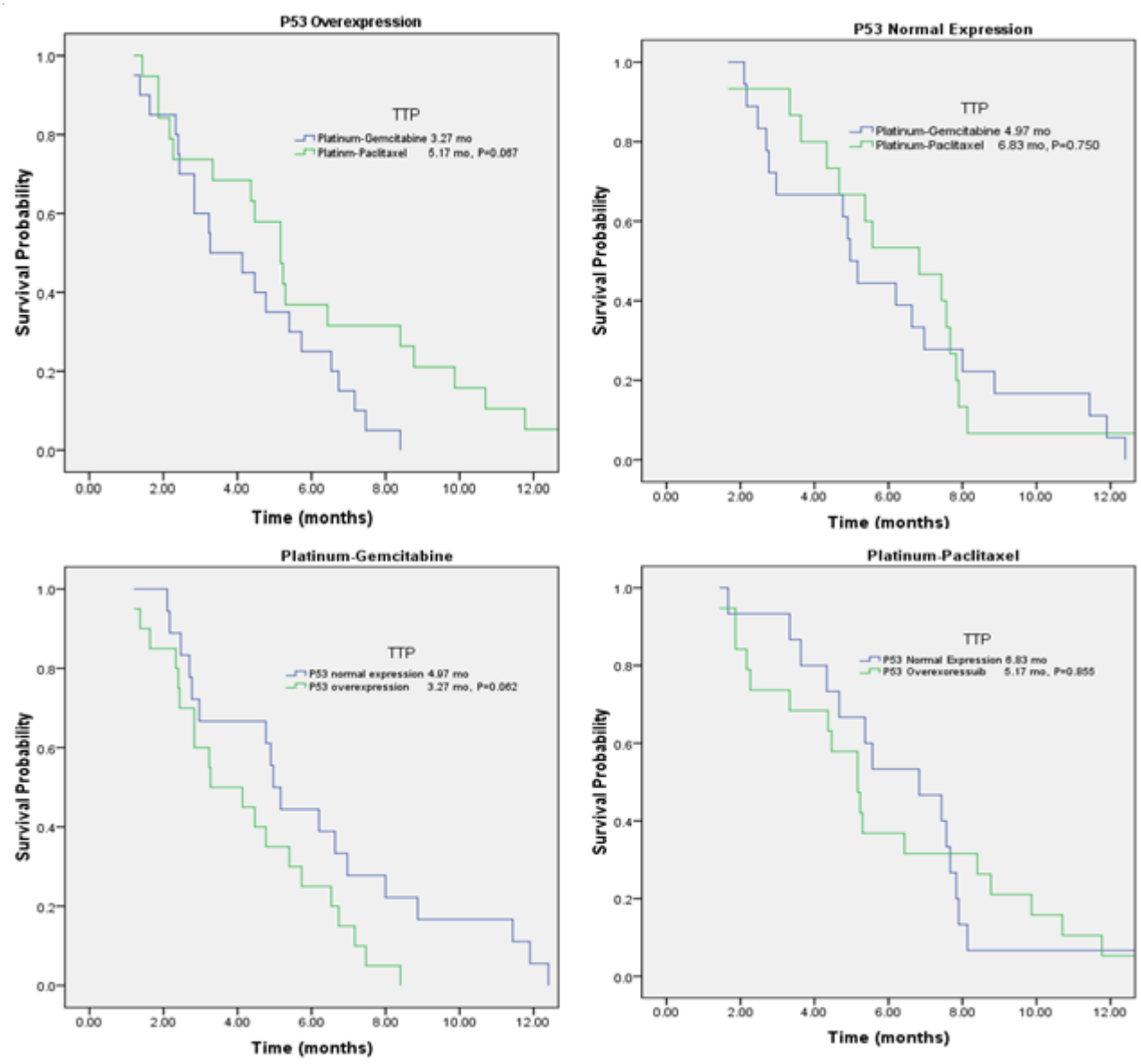

Figure 1. The survival curves for time to progression (TTP)

Table 4. The median OS (months) of the all patients and all subgroups

	All patients	Platinum-gemcitabine group	Platinum-paclitaxel group	*p**
All patients	15.8 [95%CI, 13.6–18.06]	14.5 [95%CI, 10.3–18.7]	18.0 [95%CI, 14.1–21.9]	.667
P53 over expression	14.6 [95%CI, 7.22–22.12]	12.4 [95%CI, 7.3–17.6]	18.4 [95%CI, 16.8–20.1]	0.339
P53 normal expression	16.2 [95%CI, 14.24–18.10]	16.2 [95%CI, 11.2–21.1]	15.8 [95%CI, 13.3–18.4]	0.689
p-value**	0.273	0.119	0.859	

*Comparison between the two chemotherapy regimens, **Comparison between the p53 normal expression and p53 overexpression. OS = overall survival, CI = confidence interval

Discussion

We hypothesized that patients with advanced NSCLC and p53 overexpression would have better response to the platinum-paclitaxel than to the platinum-gemcitabine regimen and our findings supported our hypothesis. We showed a trend toward better response to the platinum-paclitaxel regimen than to the platinum-gemcitabine regimen in patients with p53 overexpression.

Although many retrospective studies have demonstrated platinum resistance in NSCLC patients with aberrant p53 [6-9], other studies had conflicting results [14-17]. These inconsistent results could be attributable to several factors such as different methods to evaluate p53, sample size, or the retrospective study design. The chemotherapy regimen was another important factor in that all previous studies relied only on platinum resistance despite their use of combination regimens. By contrast, we focused on the combination agents, gemcitabine and paclitaxel, in this study. When all patients were included without prespecified characteristics, we did not find any prognostic or predictive values of p53 expression in our cohort. However, when patients were grouped accordingly to the chemotherapy regimen, p53 expression was the only predictor for response and TTP in the platinum-gemcitabine group. However, it was not predictive in the platinum-paclitaxel group. Recently, Joerger and colleagues have reported that p53 expression did not predict the response to platinum-gemcitabine regimen in advanced NSCLC patients [18]. Though, this data should be carefully considered because of the unusual high prevalence of p53 over expression (approximately 70%), which might be a reason for the different study results.

Likewise, we demonstrated that TTP results could be predicted accordingly to the p53 expression and chemotherapy regimen. Although, there was a trend toward shorter TTP in p53 over expression group compared to p53 normal expression group among the overall patients, it was clear that p53 over expression predicted poor TTP only in platinum-gemcitabine group, not platinum-paclitaxel group, suggesting p53 as a predictive factor rather than a prognostic factor. However, p53 did not influence OS outcomes, which could be explained by wide differences in accessibility to EGFR tyrosine kinase inhibitors among Thai patients. When we included EGFR tyrosine kinase inhibitor in the multivariate analysis model, it was the only independently prognostic factor for OS in our patient cohort (data not shown). Unfortunately, only one third of our patients received this treatment. Our cohort was conceivable to have a high prevalence of EGFR mutations because of the ethnicity and high proportion of adenocarcinoma, but there was no EGFR mutational analysis data in our studied patients.

Although, there were more favorable prognostic factors including younger age, adenocarcinoma and nonsmoking status in the platinum-paclitaxel group than in the platinum-gemcitabine group, we did not find any significantly different outcomes between these two groups unless p53 expression was considered. To evaluate the effects of these imbalance characteristics, we performed a multivariate analysis that identified the chemotherapy regimen as the only independent predictor for response among patients with p53 overexpression (even though it was borderline significance). Therefore, the difference in response rate between platinum-gemcitabine group and platinum-paclitaxel group in patients with p53 overexpression less likely resulted from these imbalance characteristics.

To evaluate p53 status, we can perform either a *p53* mutation test or a p53 expression test. The wild-type p53 protein's half-life is very short, while most

mutated p53 proteins [19, 20] are more stable and detectable by immunohistochemical staining. Therefore p53 expression can imply the *p53* gene mutation, but cannot identify all mutation types. Both tests for p53 status were used in several NSCLC studies with some studies showing the imperfect correlation between them [21, 22]. We decided to use only immunohistochemical staining because of its simplicity, economy, and wide availability. However, we were aware the technical issues of immunohistochemical staining, which could be a reason for the inconsistency of the results compared with previous studies [6, 8, 14, 15]. Using our institute routine immunohistochemical staining method might reduce this potential bias by the available quality control system.

We accept that there are limitations of our study including small sample size, retrospective design, more favorable clinical characteristics in platinum-paclitaxel group, and pathologist dependence on immunohistochemistry interpretation.

Our hypothesis needs to be confirmed in a large well-controlled study (a prospective or larger retrospective study). Also the mutational testing might be a better approach with which to evaluate p53 status compared with immunohistochemical staining. Our hypothesis based on the different mechanisms of action that paclitaxel, but not gemcitabine, may be the counterpart of the platinum resistance in patients with p53 aberrant NSCLC. To our knowledge, this is the first study demonstrating p53 as a potential biomarker differentiating the outcome of these two commonly used chemotherapies in advanced NSCLC. However, we realized that a single biomarker has limited power as a predictive factor in this highly complex disease. Our results emphasize the need to consider p53 pathway proteins as a set of biomarkers able to predict chemotherapy outcomes in NSCLC.

Conclusions

Our findings support p53 expression as a potential predictive marker for the response to platinum-gemcitabine in patients with advanced NSCLC; thus a platinum-paclitaxel regimen would appear to be preferred to a platinum-gemcitabine regimen in patients with p53 overexpression. These results need to be confirmed in a large retrospective study or a prospective study.

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