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ORIGINAL RESEARCH

A retrospective analysis of safety and efficacy of weekly nab-paclitaxel as second-line chemotherapy in elderly patients with advanced squamous non-small-cell lung carcinoma

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Purpose: The aim of this retrospective study was to investigate the anticancer effect and toxicity of weekly administered nab-paclitaxel as a second-line chemotherapy in elderly patients with relapsed squamous non-small-cell lung cancer (NSCLC).

Patients and methods: We retrospectively reviewed the treatment of 42 elderly patients with relapsed squamous NSCLC, who received nab-paclitaxel monotherapy as a second-line treatment from January 2010 to March 2014. A dose of 100 mg/m^2 nab-paclitaxel was administered weekly on days 1, 8, and 15, followed by 1 week of rest. The protocol was maintained for at least two cycles.

Results: The overall response rate (ORR) and the disease control rate (DCR) were 21.43% (9/42) and 47.62% (20/42), respectively. The median progression-free survival (PFS) and overall survival (OS) were 6.6 and 10.9 months, respectively. In the subgroup analysis, there was no significant difference in ORR, DCR, PFS, and OS, accounting for the first-line therapy factors (taxane agent, radiotherapy, or surgery). There was a statistically significant difference in DCR for stages III and IV (62.96% vs 20%, P=0.008), but there was no such difference in either PFS or OS. The ORR of 29 patients receiving more than three cycles of treatment was higher than that of those receiving less than three cycles of treatment (31.03% vs 0%, P=0.038), and there was a significant difference in PFS (7.6 vs 4.9 months, P=0.004) and OS (11.7 vs 8.9 months, P=0.002). No hypersensitivity reactions or treatment-related grade 4 adverse events were reported.

Conclusion: Nab-paclitaxel monotherapy administered weekly at a dose of 100 mg/m^2 is shown to be an effective and safe regimen for elderly patients with relapsed squamous NSCLC, especially for patients with stage III disease or good performance status.

Keywords: nab-paclitaxel, squamous, non-small-cell lung cancer, second line, elderly

Introduction

Approximately 90% of all lung cancers are non-small-cell lung cancer (NSCLC), with ~25%–30% of NSCLC being of the squamous subtype.[1] To date, no agents have been specifically approved for the treatment of squamous NSCLC. Most patients with NSCLC present with advanced or metastatic disease at the time of diagnosis, and the 5-year survival for these patients is only 3.9%.[2] The primary therapy is palliative chemotherapy, for which platinum-based chemotherapy is the only option. Although cytotoxic chemotherapy as a first-line treatment may delay disease progression and prolong survival, almost all patients develop progressive disease and require additional therapies. Recently, substantial advances have been made in treating nonsquamous

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NSCLC, but there has been little progress in the treatment of the squamous subtype.

With increasing life expectancy worldwide, there has been a notable increase in the incidence of lung cancer owing to the associated cumulative increase in the risk of cancer with age. For all patients diagnosed in 1975–2010, the median age was 70 years.[2] In elderly patients with a good performance status (PS) of 0–1, doublet chemotherapy, including platinum, should not be excluded, especially for patients of age 70–75 years without comorbidities.[3] However, evidence suggests that patients >65 years old are likely to metabolize chemotherapeutic agents more slowly than do younger patients, resulting in higher drug exposure levels and more serious adverse events (AEs).[4] Concern about AEs may lead clinicians to reduce treatment dose or to interrupt treatment, which could in turn compromise efficacy. Therefore, more effective and better tolerated therapeutic options are needed for elderly patients with NSCLC.

The National Comprehensive Cancer Network Guidelines authorize three drugs (docetaxel, pemetrexed, and erlotinib) for second-line therapy in patients with advanced NSCLC who have been previously treated with at least one line of a platinum-based combination chemotherapy. Docetaxel is considered more effective than pemetrexed and erlotinib for the second-line treatment of advanced or metastatic squamous NSCLC.[5,6] Despite the clinical activity, the use of docetaxel could be limited by significant toxicities observed in treated patients, such as hypersensitivity reactions and peripheral neuropathy.[7]

Nab-paclitaxel (Abraxane; Abraxis BioScience, Inc., Santa Monica, CA, USA) is a formulation of 130 nm albumin-bound paclitaxel particles. It was developed to improve the therapeutic index of paclitaxel, which as a single agent had exhibited promising efficacy and tolerability in Phase I/II studies in stage IV NSCLC.[8] The same result had been achieved in combination with carboplatin for elderly patients.[9] Furthermore, single-agent nab-paclitaxel as a second-line chemotherapy was approved for the treatment of metastatic breast cancer and was shown to be effective and well tolerated.[10] Nonetheless, little is known about the effect of nab-paclitaxel as a second-line therapy targeting squamous NSCLC at an advanced or metastatic stage.

Although there has been no clinical trial, specifically in elderly patients, of second-line therapy for squamous NSCLC, preliminary data indicate roles for nab-paclitaxel as a single agent for the first-line or third-line treatment of advanced or metastatic NSCLC.[11,12] The purpose of this retrospective study was to investigate the anticancer effect and toxicity of weekly administered nab-paclitaxel as a second-line chemotherapy in elderly patients with advanced or metastatic squamous NSCLC who had failed conventional therapy.

Materials and methods

All patients met the following inclusion criteria: 1) they had a histologic or cytologic diagnosis of stage III or IV squamous NSCLC, 2) they had previously received no less than two cycles of first-line platinum-based doublet chemotherapy without nab-paclitaxel, but the disease progressed, 3) they were older than 65 years, 4) they had an Eastern Cooperative Oncology Group PS ≤2, 5) they had not received third-line chemotherapy, and 6) they had measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST).[13] Patients were excluded if they had symptomatic brain metastases or preexisting peripheral neuropathy (grade 1 or higher). We could not evaluate elderly patients by comprehensive geriatric assessment due to some patients with unknown sociodemographic factors. Because this was a retrospective study, informed consent was not required. The Institutional Review Board of Shandong Cancer Hospital approved the study.

Nab-paclitaxel was administered weekly on days 1, 8, and 15, followed by 1 week of rest. Treatment was repeated every 4 weeks until disease progression or unacceptable toxicity. A dose of 100 mg/m^2 was administered for ~30 minutes without corticosteroid or antihistamine premedication. The protocol recommended that if patients experienced grade 3 or 4 neutropenia or thrombocytopenia during treatment, they should receive a subcutaneous injection of granulocyte colony-stimulating factor or interleukin-11 to address such hematological toxicities. This protocol was maintained for at least two cycles.

The primary efficacy end point was overall response rate (ORR), defined as the percentage of patients having either a complete response (CR) or a partial response (PR), determined according to the RECIST guidelines.[13] Secondary efficacy end points included disease control rate (DCR; defined as the percentage of patients with stable disease [SD] for 16 weeks and CR and PR), progression-free survival (PFS; defined as the time from treatment to the objective progression of disease), and overall survival (OS; defined as the time from treatment to death). Response assessments were performed every 8 weeks. All patients had a baseline computed tomography (CT) examination of the chest and a reassessment every two treatment cycles. Hematologic and imaging examinations were routinely performed during treatment with nab-paclitaxel. The safety end points were as follows: 1) the incidence of treatment-related AEs based on

National Cancer Institute Common Toxicity Criteria Version 2.0, 2) laboratory abnormalities, and 3) serious AEs.

All analyses were performed using the Statistical Package for the Social Sciences 20.0 software. Correlation between clinical features and curative effects was analyzed using a χ^2 test. PFS and OS were summarized descriptively, and two-sided 95% confidence intervals (CIs) were presented. PFS and OS were estimated using the Kaplan–Meier method. Differences were assumed to be significant when a *P*-value of <0.05 was achieved.

Results

Patients

We retrospectively reviewed 42 patients who received a second-line treatment of nab-paclitaxel for NSCLC from January 2010 to March 2014 in the Shandong Cancer Hospital and Institute, People's Republic of China. The baseline characteristics of patients are presented in Table 1. The median age was 71 years (range: 66–83 years) with 37 (88.1%) male and five (11.9%) female patients. The number of patients with a PS score 0–1 (considered good) was 38 (90.48%); 31 patients (73.81%) had a history of smoking.

Table 1 Baseline characteristics and previous therapy of 42 patients

Clinical feature	N	Percentage
Sex		
Male	37	88.1
Female	5	11.9
Age		
Median	71	
66–75 years	34	80.95
>75 years	8	19.05
ECOG PS		
0–1	38	90.48
2	4	9.52
Smoking status		
Current or former smoker	31	73.81
Never smoked	11	26.19
Clinical stage		
Stage III	27	64.29
Stage IIIA	11	26.19
Stage IIIB	16	38.10
Stage IV	15	35.71
Previous taxane		
Yes	17	40.48
No	25	59.52
Previous radiotherapy		
Yes	18	42.86
No	24	57.14
Previous surgery		
Yes	16	38.1
No	26	61.9

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status.

There were 27 (64.29%) cases of stage III disease, including eleven (26.19%) cases of IIIA and 16 (38.1%) cases of stage IIIB; there were 15 (35.71%) cases of stage IV disease. Seventeen (40.48%) patients had previously received a taxane agent, 18 (42.86%) had previously received radiotherapy, and 16 (38.1%) had previously undergone lung surgery. A total of 159 cycles of treatment were delivered overall, with a median of four cycles per patient (range: 2–6). In the treatment group that received less than three cycles, there were five (11.9%) patients who discontinued therapy for financial reasons.

Therapeutic outcome

Therapeutic effect was evaluated using the RECIST standard:

- CR was not experienced in any case.
- PR was experienced in nine cases.
- SD was experienced in eleven cases.
- Progressive disease was experienced in 22 cases.

The ORR (CR + PR) was 21.43% (95% CI =17.31%–24.21%), and the DCR (CR + PR + SD) was 47.62% (95% CI =43.52%–51.24%). There was no significant difference in either ORR or DCR for the prognostic factors of sex, age, Eastern Cooperative Oncology Group scores, or smoking status (Table 2). There were 27 cases of ORR (29.63%) and DCR (62.96%) in the patients with stage III disease, and there were 15 cases of ORR (6.67%) and DCR (20%) in the patients with stage IV disease. Notably, there was a significant difference in DCR for stage (*P*=0.008; Table 2). For the prognostic factors of related first-line therapy (taxane agent, radiotherapy, or surgery), there was no significant difference in ORR or DCR (Table 3). According to the analysis, the ORR of 29 patients receiving more than three cycles of treatment was higher than that of those receiving less than three cycles (31.03% vs 0%, *P*=0.038), but a similar result was not found in DCR (38.46% vs 51.72%, *P*=0.426; Table 4).

Among patients receiving second-line therapy, follow-up showed that the median PFS and OS was 6.6 months (95% CI =5.118–8.082; Figure 1A) and 10.9 months (95% CI =9.206–12.594 months; Figure 1B), respectively, and the 1-year survival rate was 35.71% (15/42). The median PFS of 17 patients who had previously received a taxane agent was 7.2 months (95% CI =4.108–10.292), and the median PFS of other patients was 6.4 months (95% CI =5.258–7.542). The median OS of patients who had previously received a taxane agent was 11.2 months (95% CI =8.78–13.62) and of those who had received a nontaxane agent was 10.9 months (95% CI =8.942–12.858). The median PFS of patients at

Table 2 Correlation between clinical feature and curative effect of nab-paclitaxel as a second-line treatment on lung squamous carcinoma

Clinical feature	Total (N)	PR	SD	PD	ORR (%)	*P*-value	DCR (%)	*P*-value
Sex								
Male	37	8	10	19	21.62	0.934	48.65	0.716
Female	5	1	1	3	20		40	
Age, years								
66–75	34	7	9	18	20.59	0.784	47.06	0.881
>75	8	2	2	4	25		50	
ECOG scores								
0–1	38	9	10	19	23.68	0.561	50	0.341
2	4	0	1	3	0		25	
Smoking status								
Current or former smoker	31	6	9	16	19.35	0.582	48.39	0.867
Nonsmoker	11	3	2	6	27.27		45.45	
Clinical stage								
Stage III	27	8	9	10	29.63	0.082	62.96	0.008
Stage IV	15	1	2	12	6.67		20	

Abbreviations: DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; PR, partial response; SD, stable disease; ORR, overall response rate.

Table 3 Correlation between previous therapy feature and curative effect of nab-paclitaxel as a second-line treatment on lung squamous carcinoma

Subgroup	Total (N)	PR	SD	PD	ORR (%)	*P*-value	DCR (%)	*P*-value
Previous taxane								
Yes	17	4	4	9	23.53	0.784	47.06	0.952
No	25	5	7	13	20		48	
Previous radiotherapy								
Yes	18	5	6	7	27.78	0.385	61.11	0.129
No	24	4	5	15	16.67		37.5	
Previous surgery								
Yes	16	4	4	8	25	0.658	50	0.808
No	26	5	7	14	19.23		46.15	

Abbreviations: DCR, disease control rate; PD, progressive disease; PR, partial response; SD, stable disease; ORR, overall response rate.

Table 4 Correlation between chemotherapy cycles and curative effect of nab-paclitaxel as a second-line treatment on lung squamous carcinoma

Cycles of SL chemotherapy	Total (N)	PR	SD	PD	ORR (%)	*P*-value	DCR (%)	*P*-value
<3	13	0	5	8	0	0.038	38.46	0.426
≥3	29	9	6	14	31.03		51.72	

Abbreviations: DCR, disease control rate; PD, progressive disease; PR, partial response; SD, stable disease; SL, second line; ORR, overall response rate.

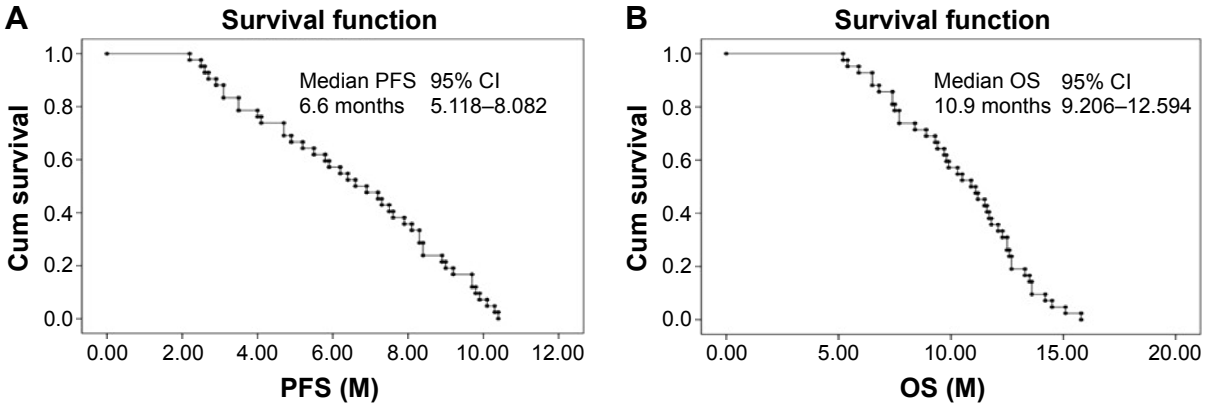

Figure 1 Kaplan–Meier curve for (**A**) PFS and (**B**) OS in the entire cohort of elderly patients with relapsed squamous non-small-cell lung carcinoma (n=42).
Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival; M, months.

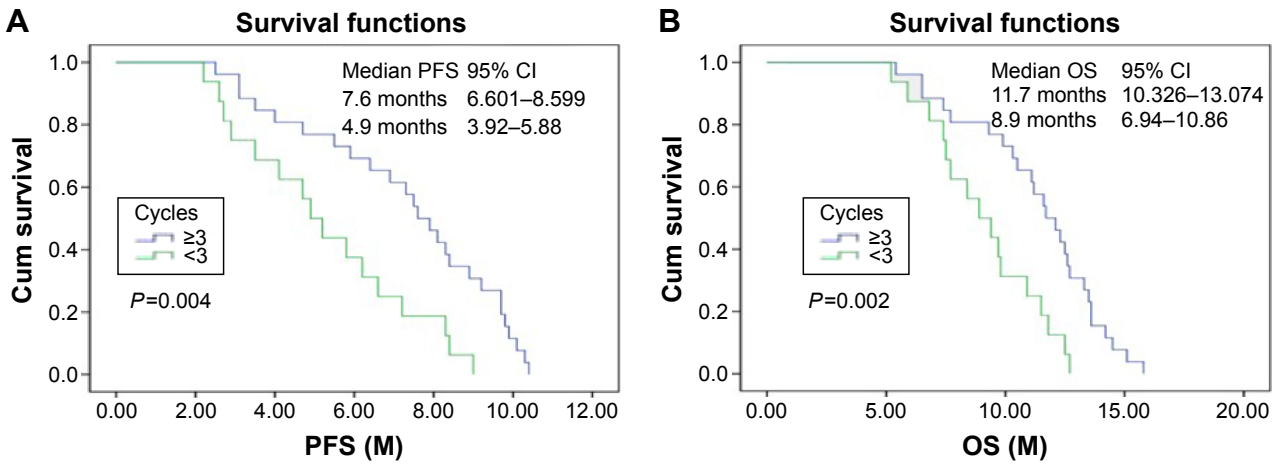

Figure 2 Kaplan–Meier curve for (**A**) PFS and (**B**) OS of the patients according to cycles of nab-paclitaxel monotherapy.
Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival; M, months.

stage III was 7.2 months (95% CI =5.165–9.235) and of those at stage IV was 6.2 months (95% CI =2.287–10.113), and the median OS of patients at stage III was 11.5 months (95% CI =10.313–12.687) and at stage IV was 9.4 months (95% CI =6.749–12.051). The median PFS and the median OS of patients who had previously received radiotherapy were 7.5 months (95% CI =6.007–8.993) and 11.7 months (95% CI =10.705–12.695), respectively. The median PFS and the median OS of patients who had previously received nonradiotherapy were 6.2 months (95% CI =3.852–8.548) and 10.3 months (95% CI =8.578–12.022), respectively. There was a significant difference in PFS and OS for the cycles of treatment (P=0.004 and P=0.002, respectively; Figure 2A and B). The median PFS of patients receiving less than three cycles was 4.9 months (95% CI =3.92–5.88; Figure 2A) and of those receiving more than three cycles was 7.6 months (95% CI =6.601–8.599; Figure 2A). The median OS of patients receiving less than three cycles was 8.9 months (95% CI =6.94–10.86; Figure 2B) and of those receiving more than three cycles was 11.7 months (95% CI =10.326–13.074; Figure 2B).

Toxicities

In general, treatment-related toxicities from weekly nab-paclitaxel at the dose of 100 mg/m^2 were mild to moderate, and no patient experienced a treatment-related death, a dose reduction, or a therapy discontinuation because of nab-paclitaxel-associated toxicities. Treatment-related AEs are presented in Table 5. No hypersensitivity reactions or treatment-related grade 4 AEs were reported. The major grade 3 toxicities were leukopenia (5%), neutropenia (2%), fatigue (10%), and sensory neuropathy (7%). Other treatment-related toxicities, including anemia, thrombocytopenia, febrile neutropenia, alopecia, anorexia, nausea, myalgia, and arthralgia, were well tolerated and easily managed.

Discussion

This is the first article to evaluate the anticancer effect and toxicity of weekly administered nab-paclitaxel as a second-line chemotherapy in treating elderly patients with advanced or metastatic squamous NSCLC. In this study, we retrospectively reviewed 42 elderly patients with relapsed NSCLC. Nab-paclitaxel was administered on days 1, 8, and 15 followed by 1 week of rest. This treatment protocol prolonged patient survival, with a median PFS of 6.6 months and a median OS of 10.9 months. The exact mechanisms behind the efficacy of nab-paclitaxel monotherapy are unknown. It is speculated that the improved survival is related to the

Table 5 Adverse effects of nab-paclitaxel monotherapy of 42 patients, n (%)

Adverse effects	Maximum grade				
	All	1	2	3	4
Hematologic					
Anemia	16 (38)	14 (33)	2 (5)	0	0
Leukopenia	20 (48)	7 (17)	11 (26)	2 (5)	0
Neutropenia	16 (38)	7 (17)	8 (19)	1 (2)	0
Thrombocytopenia	5 (11)	5 (11)	0	0	0
Febrile neutropenia	4 (10)	2 (5)	2 (5)	0	0
Nonhematologic					
Alopecia	28 (67)	12 (29)	16 (38)	0	0
Fatigue	24 (58)	10 (24)	10 (24)	4 (10)	0
Sensory neuropathy	25 (59)	16 (38)	6 (14)	3 (7)	0
Anorexia	12 (29)	8 (19)	4 (10)	0	0
Nausea	15 (36)	13 (31)	2 (5)	0	0
Myalgia	8 (19)	6 (14)	2 (5)	0	0
Arthralgia	11 (26)	8 (19)	3 (7)	0	0
Hypersensitivity	0	0	0	0	0

fact that nab-paclitaxel drug levels increase with age. Similar results were found in a clinical trail of nab-paclitaxel in combination with carboplatin; in this study, the median OS for the subpopulation aged 70 years or older was prolonged compared with the median OS for younger patients.[14] Another hypothesis is that the higher PFS and OS are related to the character and treatment protocol of nab-paclitaxel. Studies show that nab-paclitaxel utilizes albumin to deliver paclitaxel, resulting in a higher concentration relative to solvent-based paclitaxel.[15] Another possible contributing factor to the finding that nab-paclitaxel accumulates in the tumor is the prevalence of albumin-binding proteins, such as secreted protein, near the tumors that are acidic and rich in cysteine.[16] An obvious advantage to weekly regimens is close monitoring and an improved safety profile on average.[17] Another study of elderly patients with metastatic breast cancer similarly found that weekly nab-paclitaxel is safe and more efficacious than a every-3-week schedule.[10] Furthermore, a meta-analysis revealed that weekly paclitaxel regimens show a more favorable toxicity profile than every-3-week paclitaxel administration.[18] Because so few toxicities were experienced, the elderly patients in these studies showed better compliance, resulting in better PFS and OS. However, we cannot demonstrate that the schedule is effective for patients with poor PS owing to few patients (9.52%).

In the subgroup analysis, there was no significant difference in efficacy if the patient had previously received a taxane agent. The exact reasons are unclear, though a possible explanation is that the first-line therapy failed owing to platinum resistance or taxane agent-sensitive relapse. The previous study had similar results in that the previous use of paclitaxel had no impact on the response or survival to subsequent docetaxel therapy.[19] Although this difference in PFS and OS was not statistically significant for patients regardless of whether they had previously received radiotherapy, the median PFS and the median OS of these previously treated patients were prolonged by 1.3 and 1.4 months, respectively. A study revealed that nab-paclitaxel improved radiotherapy in a supra-additive manner,[20] but no trail has evaluated the role of nab-paclitaxel after radiotherapy. Based on our results, patients with stage III were more likely to benefit from the schedule. On the one hand, the patients who received radiotherapy were mainly patients with stage III disease who had better OS. On the other hand, the previous radiotherapy alleviated the tumor burden and strengthened the control of local tumor so that second-line agents produced superior efficacy. Patients with stage IV disease were apt to select the best support treatment other than the second-line chemotherapy when the first-line chemotherapy failed. Therefore, patients with stage IV disease were fewer than those with stage III disease in this study. In this retrospective study, there was no significant difference in survival from the previous surgery. The study found that surgery history was not an important factor for survival.

In the present retrospective analysis, the survival of patients receiving less than three cycles of treatment was worse than that of those receiving more than three cycles of treatment. There was no patient who had CR or PR, but SD was higher (38.46% vs 20.69%). In contrast, nine patients receiving more than three cycles of monotherapy had PR. These results suggest that the efficacy of nab-paclitaxel is related to drug accumulation, such that partly SD may later lead to PR with prolonged treatment. Therefore, an evaluation of the anticancer effect of at least three cycles of treatment was warranted.

In terms of treatment-related toxicities, no severe hypersensitivity reactions or grade 4 AEs occurred. The common AEs were anemia, leukopenia, neutropenia, alopecia, fatigue, sensory neuropathy, nausea, anorexia, arthralgia, and arthralgia. Grade 3 AEs were leukopenia, neutropenia, fatigue, and sensory neuropathy. No patients were compelled to reduce their dose or delay treatment because of treatment-related toxicities, which is consistent with the findings in published literature on this subject.[19] Even nab-paclitaxel proved beneficial and tolerable in patients with advanced NSCLC and mild and moderate renal impairment.[21] Except for the medicinal properties of nab-paclitaxel,[22] the benefit and tolerability of this line of therapy may be related to a smaller dose of each individual administration. On the whole, the treatment-related AEs experienced with the weekly schedule were relatively mild and controllable in elderly patients with squamous NSCLC.

As the treatment of advanced NSCLC has evolved over the past decade, advances in the treatment of squamous NSCLC have lagged. Currently, there is no special drug for the treatment of elderly patients with refractory advanced or metastatic squamous NSCLC. Several recently concluded trials of antiangiogenic agents and other biologically targeted treatments could represent the way to improve survival expectancy for these patients. A prospective Phase III trial with a combination arm of ramucirumab (a human IgG1 monoclonal antibody) and docetaxel and a single-agent arm of docetaxel alone revealed a significantly higher ORR (23% and 14%, $P<0.001$) and longer survival (9.5 vs 8.2 months) for relapsed stage IV squamous NSCLC.[23] The other Phase II, single-arm trial of nivolumab (a fully human IgG4 PD-1 immune checkpoint inhibitor antibody) showed promising ORR (14.5%) and median OS (8.2 months) for those patients whose median age was 65 years.[24] Although therapies with

the new drugs have achieved higher OS than others, they are currently not administered clinically because of their relative high cost and indefinite activity. The efficacy and safety of these new drugs require further study.

Conclusion

Treatment options for patients with relapsed squamous NSCLC are limited, and elderly patients are often undertreated owing to toxicity concerns. Our study finds that weekly administered nab-paclitaxel monotherapy is an effective and safe regimen for this population, especially for patients with stage III disease or good PS. From our single-institution analysis, we find that the efficacy of nab-paclitaxel is related to drug accumulation. Therefore, the anticancer effect can be evaluated after at least three cycles of treatment. Because our retrospective analysis had a small sample size, however, a prospective, large sample, multicenter clinical study is needed to verify these results.

Disclosure

The authors report no conflicts of interest in this work.

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