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Sintilimab Combined with Nanoparticle Albumin-Bound Paclitaxel-Based Chemotherapy in Severe Locally Advanced or Metastatic Squamous NSCLC Showed Good Efficacy and Safety: A Pilot Retrospective Analysis

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Introduction: Squamous non-small cell lung carcinoma (sqNSCLC) is associated with a poorer prognosis and limited treatment options. Sintilizumab combined with chemotherapy is used as first-line treatment for advanced sqNSCLC. However, the efficacy and safety of sintilimab combined with nanoparticle albumin-bound paclitaxel-based chemotherapy for severe squamous NSCLC remain to be unknown in clinical studies.

Methods: Patients with confirmed unresectable stage III/IV sqNSCLC were retrospectively collected between July 1st, 2019, and December 31st. According to performance status (PS) scores, these patients received first-line sintilimab plus nab-PTX-based chemotherapy were divided into severe (PS=2) and non-severe groups (PS=0–1). The treatment regimen was repeated every 3 weeks for a maximum of six cycles, or until unacceptable toxicity occurred. The primary endpoint of this study was to assess progression free survival (PFS), with secondary endpoints including the objective response rate (ORR), adverse events (AEs) and disease control rate (DCR).

Results: Among 367 patients with unresectable stage III/IV sqNSCLC, 28 male patients, with a median age of 65.5 years, received first-line sintilimab plus nab-PTX-based chemotherapy. These patients were divided into a severe group (11 patients) and a non-severe group (17 patients). The severe group had a significantly higher incidence of chronic obstructive pulmonary disease (COPD) compared to the non-severe group (54.5% vs 11.8%, p = 0.03). The two groups had a similar median number of treatment cycles and safety profiles. Although the severe group showed higher ORR (63.6% vs 47.1%) and DCR (100% vs 76.5%) than the non-severe group, these differences were not statistically significant. Median PFS and Kaplan-Meier curves were also comparable between the groups.

Conclusion: Sintilimab combined with nab-PTX-based chemotherapy was effective and well tolerated in a small sample of severe lung squamous cell carcinoma population. This combination may offer a potential treatment option for these patients.

Keywords: chemotherapy, immunotherapy, severe lung cancer, squamous non-small cell lung carcinoma

Introduction

Lung squamous cell carcinoma, a subtype of non-small cell lung carcinoma (NSCLC), has a poorer prognosis compared to other non-squamous subtypes.[1] The 1- and 5-year survival rates for this condition are 14.6% and 1.6%, respectively.[1–3] Treatment options for patients with squamous NSCLC (sqNSCLC) are limited. Immunotherapy,

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particularly those targeting programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1), offers a new treatment approach for sqNSCLC.[4–7] Combining immunotherapy with chemotherapy has shown a synergistic effect in NSCLC. Major NSCLC guidelines recommend the combination of PD-1/PD-L1 inhibitors and chemotherapy as a preferred treatment option for locally advanced or metastatic sqNSCLC without driver gene mutations, irrespective of PD-L1 expression.[3,8,9]

Severe lung cancer, a concept introduced by a global consensus group in 2021, refers to a condition where patients exhibit an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2–4 at certain stages due to various acute or chronic co-morbidities, the tumor itself, and/or treatment-related adverse events (AEs).[10] Despite this, there is a high likelihood of survival and/or improvement in the PS score through supportive care and anti-tumor treatment based on dynamic and precise testing. Unlike end-stage lung cancer, severe lung cancer allows for the possibility of survival through individualized treatment.[11,12] Patients with severe lung cancer typically have poor PS scores, leading to low tolerance to anti-tumor treatments. Consequently, treatments for these patients should have a relatively rapid onset to better address disease progression. Therefore, tailored, effective, and safe anti-tumor treatments are necessary, along with robust life support measures. For patients with severe locally advanced or metastatic sqNSCLC, which often lack driver gene mutations, combining immunotherapy with chemotherapy may represent a potential anti-tumor treatment approach.

Sintilimab is a fully human IgG4 monoclonal antibody designed to block the binding of PD-1. Preclinical data suggests that it has a higher binding affinity compared to nivolumab and pembrolizumab.[7,13] In the ORIENT-12 study, combining sintilimab with gemcitabine/platinum (GP) treatment resulted in a significant prolongation of progression-free survival (PFS) compared to GP alone as first-line treatment for locally advanced or metastatic sqNSCLC (5.5 months vs 4.9 months).[14] Another real-world study showed that combining sintilimab with paclitaxel/nanoparticle albumin-bound paclitaxel (nab-PTX) and platinum achieved a PFS of 13.9 months as first-line treatment for locally advanced or metastatic sqNSCLC.[15] Currently, sintilimab in combination with GP has been approved for the first-line treatment of sqNSCLC in China.

Nab-PTX is a nanoparticulate formulation of paclitaxel bound to human serum albumin.[16–18] Unlike solvent paclitaxel (sb-PTX), nab-PTX offers several advantages that make it a preferred chemotherapy agent for use in severe lung cancer.[16] Firstly, nab-PTX does not contain polyoxyethylene castor oil, the lipid-based solvent found in sb-PTX, which has been linked to allergic reactions. Consequently, nab-PTX does not necessitate corticosteroid pre-medication to prevent hypersensitivity reactions. Secondly, nab-PTX delivers significantly higher doses of paclitaxel over a shorter infusion time (0.5 hours vs 3 hours for sb-PTX).[19] Thirdly, numerous studies have demonstrated the efficacy and safety of nab-PTX in treating NSCLC, particularly in older patients.[17,18,20,21] Subgroup analysis in patients aged ≥ 70 years in a Phase III trial showed a significant improvement in median overall survival with nab-PTX, with better tolerability of adverse events compared to sb-PTX.[20]

Hence, the combination of sintilimab and nab-PTX-based chemotherapy holds promise as a potential regimen for treating sqNSCLC. Nonetheless, the efficacy and safety of this combination in patients with severe locally advanced or metastatic sqNSCLC remain largely unexplored. Therefore, the aim of this study was to conduct a preliminary investigation into the efficacy and safety of sintilimab and nab-PTX-based chemotherapy as a first-line treatment for patients with severe locally advanced or metastatic sqNSCLC.

Methods

Ethical Approval

This retrospective study was conducted at the Second Affiliated Hospital of Zhejiang University School of Medicine in China. Ethical approval was obtained from the Ethics Committee of the hospital (Approval number: 2021–0608). Given that the study was non-interventional and retrospective, it posed minimal risk to participants. Therefore, the Ethics Committee waived the requirement for informed consent. All procedures adhered to the ethical principles outlined in the Declaration of Helsinki, ensuring the privacy and confidentiality of patient data.

Patients

The medical records of consecutive patients diagnosed with locally advanced or metastatic sqNSCLC between July 1st, 2019, and December 31st, 2021, were retrospectively reviewed. Eligible patients were identified based on the following criteria: (1) histological confirmation of nonresectable stage IIIB and IIIC or stage IV sqNSCLC according to the 8th edition of the TNM classification for lung cancer; (2) receipt of sintilimab and nab-PTX-based chemotherapy as first-line treatment. Patients included in the study did not harbor sensitive epidermal growth factor receptor mutations or anaplastic lymphoma kinase rearrangements.

Severe Lung Cancer

Severe lung cancer was defined as previously described,[10] meeting the following criteria: (A) Eastern Cooperative Oncology Group performance status (ECOG PS) of 2–4; (B) presence of at least one of the following: (a) diagnosis of heart failure by cardiologists, (b) confirmation of chronic obstructive pulmonary disease (COPD) through spirometry, (c) diagnosis of interstitial lung disease (ILD) based on clinical features and findings from pretreatment chest high-resolution computed tomography (HRCT), (d) obesity with a body mass index (BMI) > 28, (e) extensive pleural effusion leading to lung collapse, (f) substantial pericardial effusion requiring pericardiocentesis, (g) significant tracheal or bronchial proximal stenosis, (h) venous thromboembolism (VTE), including deep vein thrombosis in the lower extremities and pulmonary embolism.

Treatment

Sintilimab at a dose of 200 mg was administered intravenously (IV) on day 1 of each treatment cycle, along with nab-PTX (130 mg/m2 IV on day 1 and 8, or 260 mg/m2 IV on day 1), and either nedaplatin (100 mg/m2 IV on day 1) or carboplatin (area under the concentration–time curve, 5 mg/mL/min IV on day 1). The ratio of each component in this product is Paclitaxel: albumin = 1:7–1:11. In cases of severe AEs, dose adjustments or interruptions were implemented at the discretion of the treating physicians. The treatment regimen was repeated every 3 weeks for a maximum of six cycles, or until unacceptable toxicity occurred, with the option for maintenance therapy with sintilimab left to the discretion of the physicians.

Evaluation of Response and AEs

Treatment response was assessed according to the response evaluation criteria in solid tumors version 1.1. Tumor size was evaluated using chest CT scans and B-scan ultrasonography of abdominal organs and lymph nodes every two treatment cycles. AEs were assessed based on medical records using the Common Terminology Criteria for Adverse Events, version 5.0.

Statistical Analysis

The primary endpoint of this study was to assess PFS, with secondary endpoints including the objective response rate (ORR) and AEs. PFS was determined using the Kaplan–Meier method, calculated from the initiation of chemotherapy until disease progression, death from any cause, or the last follow-up date, whichever came first. ORR was defined as proportion of patients with best overall response of complete response or partial response based on applicable criteria. Data analysis was conducted using IBM SPSS Statistics 20. Continuous variables are expressed as mean with standard deviation (SD) or median with interquartile range (IQR), based on data distribution. Comparisons between variables were made using unpaired Student's *t*-test, Welch *t*-test, or Wilcoxon rank sum test with continuity correction, depending on data normality and variance homogeneity. Categorical data are presented as absolute values and percentages and analyzed using the chi-square test or Fisher's exact test as appropriate. Statistical significance was defined as $p < 0.05$.

Results

Patient Characteristics

Out of the 1316 patients diagnosed with sqNSCLC between July 1st, 2019, and December 31st, 2021, at the study hospital, 367 had unresectable stage III/IV disease. Among them, 28 patients received first-line treatment with sintilimab

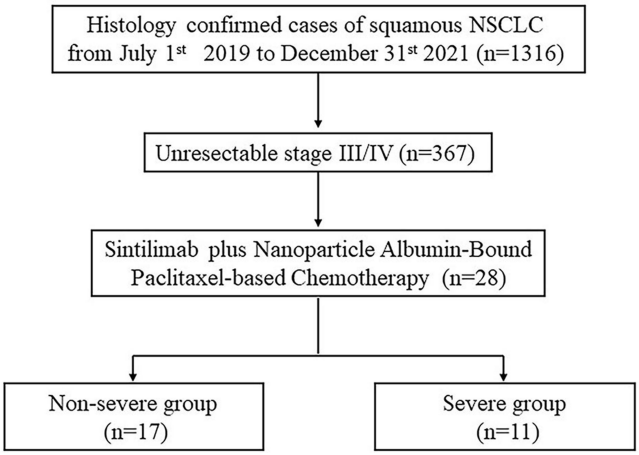

Figure 1 Flow chart of study population. NSCLC: non-small cell lung carcinoma.

and nab-PTX-based chemotherapy and were included in the analysis (Figure 1). Among these patients, 11 met the criteria for severe lung cancer and were categorized into the severe group. COPD and airway stenosis were the most common reasons for severe lung cancer (Table 1). The remaining 17 patients were classified into the non-severe group.

The baseline characteristics of the patients were documented (Table 2). The median age was 65.5 (range: 57.0 to 72.2) years for the severe group and 64.0 (range: 61.0 to 72.0) years for the non-severe group. All patients in both groups were male. Both groups exhibited similar BMI and smoking status, although there was a tendency for more former or current smokers in the severe group. Significantly more patients in the severe group had COPD compared to the non-severe group (54.5% vs 11.8%, $p = 0.03$). Additionally, the severe group had significantly lower FEV1/FVC ratios than the non-severe group (57.9% vs 72.0%, $p = 0.03$), which corresponded to the higher prevalence of COPD in the severe group. Other lung function test results were similar between the two groups.

The distribution of stage III and IV diseases was similar between the two groups (Table 3). The PD-L1 expression status was not evaluated in 63.6% of patients in the severe group and 88.2% of patients in the non-severe group, respectively. Among the assessed patients, all had positive PD-L1 expression. Blood test results were comparable between the two groups. Platinum was included in the chemotherapy regimens for all but one patient. Carboplatin was the most frequently used platinum agent in both groups, followed by nedaplatin.

Table 1 Causes of Severe Lung Cancer

Patients	HF	COPD	ILD	Obesity	Pleural effusion	Pericardial effusion	Airway stenosis	VTE
Patient 1	×	×	×	×	√	×	√	×
Patient 2	×	×	×	×	×	×	√	×
Patient 3	√	×	×	×	×	×	×	×
Patient 4	×	√	×	√	×	×	×	×
Patient 5	×	√	×	×	×	×	×	×
Patient 6	×	√	×	×	×	×	×	×
Patient 7	×	√	√	×	×	×	×	×
Patient 8	×	×	×	×	×	×	√	×
Patient 9	×	×	×	×	×	×	√	×
Patient 10	×	√	×	×	×	×	√	×
Patient 11	×	×	×	×	×	×	√	×

Abbreviations: HF, heart failure; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; VTE, Venous thromboembolism.

Table 2 Baseline Demographics

Variables	All patients (n=28)	Non-severe group (n=17)	Severe group (n=11)	p#
Age	65.5 (61.0, 68.5)	64.0 (61.0, 72.0)	65.5 (57.0, 72.2)	0.474
Male	28 (100.0%)	17 (100.0%)	11 (100.0%)	1
BMI	21.5 ± 3.1	20.9 ± 2.7	22.7 ± 4.4	0.971
Smoking status				0.361
Former smoker	6 (21.4%)	2 (11.8%)	3 (27.3%)	
Current smoker	17 (60.7%)	10 (58.8%)	7 (63.6%)	
Never smoker	5 (17.9%)	5 (29.4%)	1 (9.1%)	
Comorbidities				
COPD	8 (28.6%)	2 (11.8%)	6 (54.5%)	0.03
Asthma	0	0	0	
ILD	1 (3.6%)	0	1 (9.1%)	0.393
Coronary heart disease	0	0	0	
Hypertension	7 (25.0%)	6 (35.3%)	1 (9.1%)	0.191
Diabetes mellitus	0	0	0	
Liver disease	2 (7.1%)	1 (5.9%)	1 (9.1%)	1
History of other malignancy	2 (7.1%)	1 (5.9%)	1 (9.1%)	1
Lung function test				
FEV1	2.1 ± 0.4	2.1 ± 0.5	2.1 ± 0.4	0.442
FEV1% predicted	76.9% ± 15.0%	78.9% ± 17.0%	72.8% ± 9.9%	0.273
FVC	3.2 ± 0.6	3.1 ± 0.7	3.3 ± 0.6	0.719
FVC % predicted	90.4% ± 19.5%	91.1% ± 21.1%	89.0% ± 17.4%	0.757
FEV1/FVC	67.3% ± 14.7%	72.0% ± 12.1%	57.9% ± 15.8%	0.029
DLCO % predicted	66.1% ± 5.5%	66.1% ± 5.7%	66.1% ± 5.4%	0.787
No spirometry performed	10 (55.6%)	5 (29.4%)	5 (45.5%)	

Notes: All data are presented as No. (%), median (interquartile range), or mean (standard deviation). #Variables were compared between non-severe group and severe group.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DLCO, carbon monoxide diffusing capacity.

Efficacy

The median number of treatment cycles was comparable between the two groups, with 5.0 (4.0, 6.0) cycles for the severe group and 4.0 (3.0, 5.0) cycles for the non-severe group (Table 4). Although the severe group exhibited higher ORR and disease control rate (DCR) compared to the non-severe group (ORR: 63.6% vs 47.1%; DCR: 100% vs 76.5%), these differences did not reach statistical significance.

At the time of data cutoff, disease progression was observed in 19 patients (66.7%). The overall median PFS was 8.7 months (95% CI, 7.4–9.9 months) (Figure 2). The median PFS values were similar between the two groups, with 13.3 months (95% CI, 0.1–26.5 months) for the severe group and 8.7 months (95% CI, 5.0–12.3 months) for the non-severe group. Kaplan–Meier curves indicated no significant difference between the two groups (log rank: p = 0.583) (Figure 3).

Tumor size was evaluated using chest CT scans and B-scan ultrasonography of abdominal organs and lymph nodes every two treatment cycles in our study. Two patient's CT images were retrieved from clinical stations and compared before treatments and after 2 cycles treatments.

Patient 1, a 59-year-old male, was diagnosed with right upper lung squamous cell carcinoma T4N2bM0 stage IIIB complicated with superior vena cava obstruction with a PS score of 2. He was treated with sintilimab + carboplatin + nab-PTX for 2 cycles on February 5, 2020 and February 26, 2020, respectively. Chest CT enhancement indicated PR on March 5, 2020 and PS score was 1 (Figure 4).

Patient 2, male, was diagnosed with right lower lung squamous cell carcinoma T4N2M0 stage IIIB with PS score of 1. He was treated with sintilimab + carboplatin + nab-PTX for 2 cycles on July 11, 2020 and August 4, 2020, respectively. Chest CT enhancement assessment PR was reviewed on August 25, 2020 (Figure 5).

Table 3 Baseline Disease Characteristics

Variables	All patients (n=28)	Non-severe group (n=17)	Severe group (n=11)	p#
ECOG PS	1 (1, 2)	1 (1, 1)	2 (2, 2)	<0.001
Disease stage, n (%)				0.46
III	13 (46.4%)	9 (52.9%)	4 (36.4%)	
IV	15 (53.6%)	8 (47.1%)	7 (63.6%)	
PD-L1 expression status				1
Positive*	6 (21.4%)	2 (11.8%)	4 (36.4%)	
Negative	0	0	0	
Not assessed	22 (78.6%)	15 (88.2%)	7 (63.6%)	
Blood test results				
CRP	12.0 (2.7, 39.2)	5.9 (2.2, 28.8)	28.9 (2.7, 97.2)	0.144
D-dimer	520.0 (310.0, 1170.0)	450.0 (302.5, 1167.5)	520.0 (380.0, 1260.0)	0.526
Albumin	36.4 (34.3, 38.7)	37.3 (35.8, 40.2)	35.1 (33.7, 37.6)	0.937
White blood cell count	7.4 (5.7, 8.3)	7.4 (5.7, 7.9)	7.5 (5.6, 8.5)	0.874
Neutrophil count	5.0 (4.0, 6.0)	5.1 (3.8, 5.9)	4.7 (4.0, 6.0)	0.888
Lymphocyte count	1.3 (0.9, 1.7)	1.5 (1.0, 1.7)	1.2 (0.8, 1.7)	0.219
Hemoglobin	131.0 (113.0, 149.0)	131.5 (117.5, 147.8)	124.0 (108.0, 149.0)	0.561
Platelets count	250.0 (202.0, 310.0)	236.0 (192.2, 301.0)	283.0 (202.0, 311.0)	0.159
Platinum choice, n (%)				0.463
No platinum	1 (3.1%)	0	1 (9.1%)	
Carboplatin	21 (75.0%)	14 (82.4%)	7 (63.6%)	
Nedaplatin	6 (21.4%)	3 (17.6%)	3 (27.3%)	

Notes: All data are presented as No. (%), median (interquartile range), or mean (standard deviation). *If PD-L1 expression was > 1%. #Variables were compared between non-severe group and severe group.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status; PD-L1, programmed cell death-ligand 1; CRP, C-reactive protein.

Table 4 Response to Treatment

Variables	All patients (n=28)	Non-severe group (n=17)	Severe group (n=11)	p#
Cycles	4.0(3.0, 5.8)	4.0(3.0, 5.0)	5.0(4.0, 6.0)	0.152
Best overall response				0.285
Complete response	0	0	0	
Partial response	15(53.6%)	8(47.1%)	7(63.6%)	
Stable disease	9(32.1%)	5(29.4%)	4(36.4%)	
Progressive disease	4(14.3%)	4(23.5%)	0	
Objective response rate	15(53.6%)	8(47.1%)	7(63.6%)	
Disease control rate	24(85.7%)	13(76.5%)	11(100.0%)	

Notes: All data are presented as No. (%). #Variables were compared between non-severe group and severe group.

Safety Profile

The predominant AEs in both groups were hematological, such as leukopenia, neutropenia, and anemia. Liver dysfunction, rash, and renal insufficiency were the most common non-hematological AEs (Table 5). In the severe group, a total of 19 AEs, with 2 AEs graded as 3 or higher (1 case of rash and 1 case of Thrombocytopenia), were recorded. Conversely, the non-severe group experienced a total of 47 AEs, including 13 graded as 3 or higher (3 cases of leukopenia, 4 cases of neutropenia, 1 case of anemia, 1 case of thrombocytopenia, 1 case of arrhythmia, 1 case of renal insufficiency and 2 cases of tuberculosis) (Table 5). Notably, two patients in the non-severe group contracted tuberculosis (TB), leading to discontinuation of anti-tumor treatment.

Discussions

To our understanding, this was the first such study to explore the preliminary efficacy and safety of sintilimab combined with nab-PTX-based chemotherapy as an initial treatment for 11 cases of severe locally advanced or metastatic

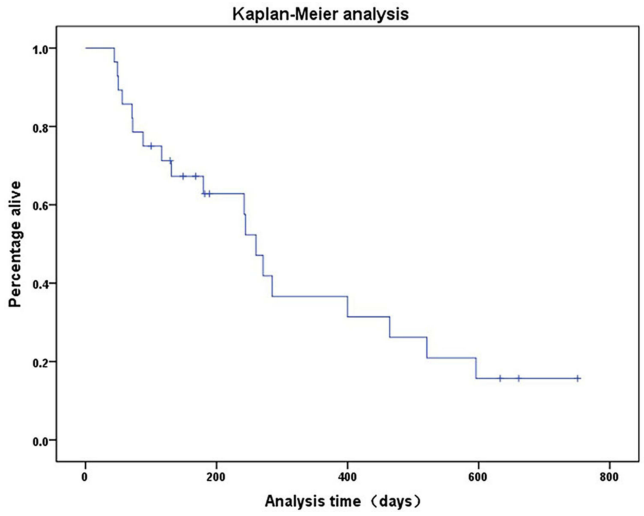

Figure 2 Kaplan-Meier survival analysis of study population.Disease progression was observed in 19 patients (66.7%). The overall median PFS was 8.7 months (95% CI, 7.4–9.9 months).

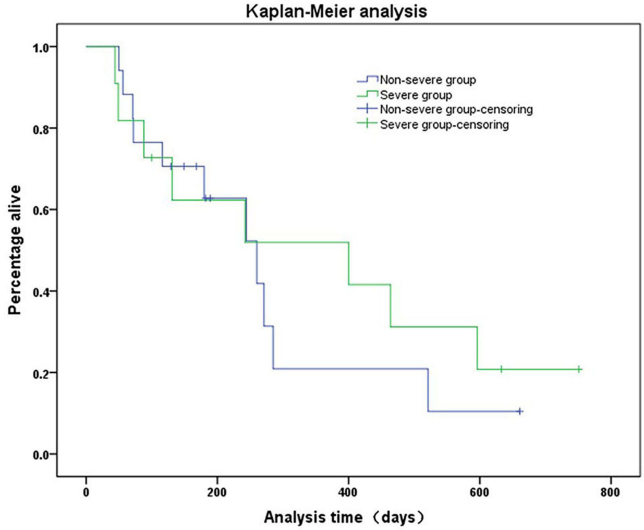

Figure 3 Kaplan-Meier survival analysis between two groups. The median PFS values was 13.3 months (95% CI, 0.1–26.5 months) in severe group and 8.7 months (95% CI, 5.0–12.3 months) in the non-severe group. The Kaplan–Meier curves showed no significantly difference between two groups (log rank: p=0.583).

sqNSCLC. Employing real-world data, our study suggested that this regimen could be a viable, well-tolerated, and efficacious option for these patients instead of best supportive treatment. Given the challenges of conducting prospective studies in this patient population, real-world evidence such as this study provided valuable insights for clinical management. Therefore, sintilimab and nab-PTX-based chemotherapy might offer a promising therapeutic approach for some patients with severe locally advanced or metastatic sqNSCLC.

Severe lung cancer represents a novel concept intricately linked with elevated PS scores.[10] Clinical trials typically focus on patients with PS scores ranging from 0 to 1, often excluding those with higher scores of 2 to 4.[5,6,14] Consequently, there is a lack of robust evidence guiding the management of this particular population, with supportive care frequently recommended for those with PS scores of 3 to 4 according to prominent lung cancer guidelines.[3,8,9] However, it's noteworthy that PS scores are stage-specific and can be reversed with effective treatment. In real-world scenarios, approximately a quarter of patients present with PS scores of 3 to 4, and it's observed that a subset of these

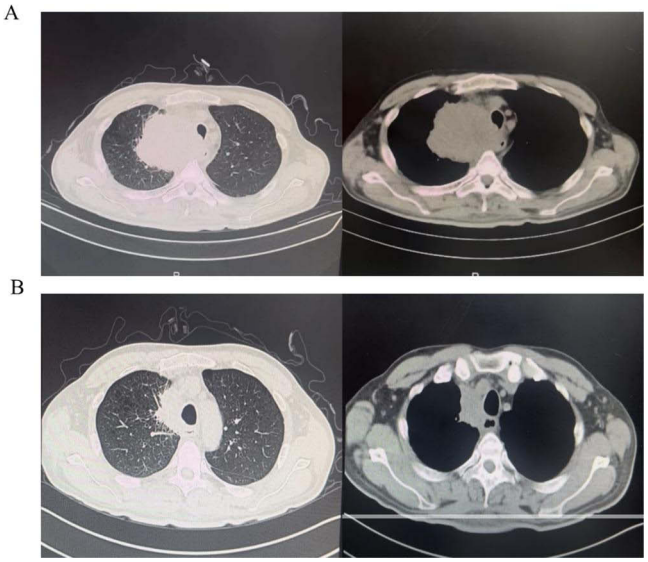

Figure 4 CT images compared before treatments and after 2 cycles treatments of patient 1. (**A**) Before treatment (on February 5 2020); (**B**) After treatment (on March 25 2020).

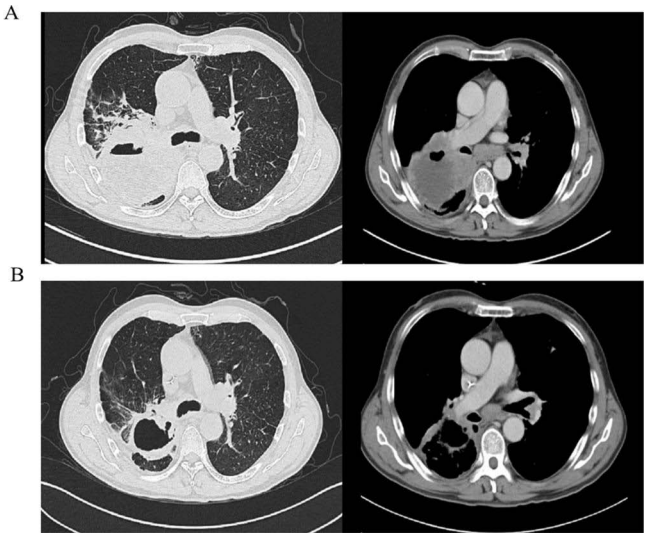

Figure 5 CT images compared before treatments and after 2 cycles treatments of patient 2. (**A**) Before treatment (on July 2 2020); (**B**) After treatment (on August 25 2020).

patients may experience survival benefits or improvements in PS scores following supportive care and effective anti-tumor treatment.[11,12,22] Hence, the concept of severe lung cancer has emerged to delineate this subgroup of patients.

For individuals with locally advanced or metastatic sqNSCLC lacking driver gene mutations, the combination of immunotherapy and chemotherapy has become the standard of care.[3,9] Despite the common occurrence of immunotherapy-related toxicities, it is generally better tolerated than chemotherapy, rendering it feasible for patients with severe lung cancer.[23] Among chemotherapy agents, nab-PTX stands out due to its notable tolerance and efficacy.[16] Nab-PTX is a solvent-free formulation of paclitaxel bound to albumin. Compared to conventional paclitaxel, nab-PTX carries a reduced risk of hypersensitivity reactions and blood toxicity associated with organic solvents. Moreover, nab-PTX exhibits enhanced antitumor activity owing to increased intratumoral concentrations. In a phase III trial, patients with sqNSCLC treated with nab-PTX/carboplatin demonstrated a significantly higher ORR compared to those receiving paclitaxel/carboplatin (41% vs 24%).[21] Additionally, in patients who were over 70 years of age, median overall survival

Table 5 Treatment-Related Adverse Events

Event	All patients (n=28)		Non-severe group (n=17)		Severe group (n=11)	
	Any grade	Grade≥3	Any grade	Grade≥3	Any grade	Grade≥3
Hematological AEs						
Leukopenia	13 (46.4%)	3 (10.74%)	9 (52.9%)	3 (17.6%)	4 (36.4%)	0
Neutropenia	6 (21.4%)	4 (21.4%)	5 (29.4%)	4 (23.5%)	1 (9.1%)	0
Anemia	11 (39.3%)	1 (3.6%)	7 (41.2%)	1 (5.9%)	4 (36.4%)	0
Thrombocytopenia	5 (17.9%)	2 (7.1%)	4 (23.5%)	1 (5.9%)	1 (9.1%)	1 (9.1%)
Nonhematological AEs						
Liver dysfunction	7 (25.0%)	0	3 (17.6%)	0	4 (36.4%)	0
Fever	3 (10.74%)	0	3 (17.6%)	0	0	0
Hyperthyroidism	1 (3.6%)	0	1 (5.9%)	0	0	0
Hypothyroidism	2 (7.1%)	0	2 (11.8%)	0	0	0
Elevated cardiac enzymes	3 (10.7%)	0	2 (11.8%)	0	1 (9.1%)	0
Rash	4 (21.4%)	1 (3.6%)	2 (11.8%)	0	2 (18.2%)	1 (9.1%)
Numbness	2 (7.1%)	0	0	0	2 (18.2%)	0
Arrhythmia	1 (3.6%)	1 (3.6%)	1 (5.9%)	1 (5.9%)	0	0
Renal insufficiency	4 (21.4%)	1 (3.6%)	4 (23.5%)	1 (5.9%)	0	0
ILD	1 (3.6%)	0	1 (5.9%)	0	0	0
Diarrhea	1 (3.6%)	0	1 (5.9%)	0	0	0
Tuberculosis	2 (7.1%)	2 (7.1%)	2 (11.8%)	2 (11.8%)	0	0
Total	66	15	47	13	19	2

Notes: All data are presented as No. (%).
Abbreviations: AEs, adverse events; ILD, interstitial lung disease.

(OS) was notably prolonged with nab-PTX/carboplatin compared to paclitaxel/carboplatin (19.9 vs 10.4 months). Thus, the remarkable tolerability and efficacy of nab-PTX position it as an ideal chemotherapy option for individuals with severe lung cancer.

The study found that sintilimab and nab-PTX-based chemotherapy demonstrated good efficacy in patients with severe lung cancer. The PFS, which was the primary endpoint, was found to be comparable to findings from previous studies. Specifically, the median PFS was 13.3 months for the severe group and 8.7 months for the non-severe group in our study. These results align with a real-world study investigating sintilimab plus paclitaxel/nab-PTX and platinum as first-line treatment for locally advanced or metastatic sqNSCLC, which reported a median PFS of 13.9 months.[15] Furthermore, our observed PFS rates were consistent with those reported in pivotal trials such as KEYNOTE-407 (median PFS, 6.4 months), IMpower131 (median PFS, 6.3 months), RATIONALE 307 (median PFS, 7.6 months), and CameL-Sq (median PFS, 8.5 months).[5,6,24,25]

Sintilimab and nab-PTX-based chemotherapy demonstrated favorable tolerability in patients with severe lung cancer, as evidenced by a low incidence of grade 3 or higher AEs. Most AEs were either resolved or improved and were manageable. Interestingly, the severe group exhibited a lower frequency of AEs of any grade and grade 3 or higher AEs compared to the non-severe group. Common AEs observed in both groups included leukopenia, neutropenia, and anemia, which aligns with findings from previous studies.[24,25] These hematological AEs were attributed to the chemotherapy regimen. Notably, two patients in the non-severe group, who had no prior history of TB, developed active TB during treatment. TB reactivation associated with PD-1/PD-L1 inhibitors has been reported previously, highlighting a significant risk to patients.[26] In our study, the occurrence of active TB necessitated discontinuation of anti-tumor treatment. However, some studies have indicated that combining PD-1/PD-L1 inhibitors with anti-TB therapy is well-tolerated and does not result in significant unexpected toxic effects.[27,28]

Through the comparison of pre- and post-treatment imaging findings in these two patients, it is evident that the combination of Sintilimab and nab-PTX-based chemotherapy demonstrates significant efficacy in the treatment of squamous non-small cell lung cancer (SqNSCLC). This therapeutic regimen not only substantially reduces tumor size

but also alleviates related symptoms and improves patients' quality of life. These imaging changes provide strong evidence for the effectiveness of this combined therapy in SqNSCLC. Furthermore, these results underscore the importance of further investigating the potential of this treatment regimen to bring clinical benefits to a larger patient population.

Several limitations were noted in this study. Firstly, its retrospective nature and small sample size restricted the statistical power of the analysis. Therefore, larger prospective cohort studies are warranted to validate these findings comprehensively.

Another limitation was the variability in chemotherapy agent dosages, which were adjusted at the discretion of attending physicians rather than following a standardized protocol. Additionally, there was a lack of data on PD-L1 expression and tumor mutation burden for most of the patients, precluding evaluation of these factors as potential biomarkers.

Conclusions

The findings of this study suggested that sintilimab combined with nab-PTX-based chemotherapy show good efficacy and safety in patients with some severe locally advanced or metastatic sqNSCLC. This regimen might be an alternative treatment option and need more larger sample sizes research to support this conclusion in further.

Highlights

1. This was the first study to investigate the combination of sintilimab with nanoparticle albumin-bound paclitaxel (nab-PTX)/platinum in treating severe squamous NSCLC.

2. The combination of sintilimab with nab-PTX/platinum demonstrated good efficacy and safety in a small sample of severe lung squamous cell carcinoma population.

Abbreviations

NSCLC, non-small cell lung carcinoma; sqNSCLC, squamous non-small cell lung carcinoma; nab-PTX, nanoparticle albumin-bound paclitaxel-based; sb-PTX, solvent paclitaxel; PS, performance status; COPD, chronic obstructive pulmonary disease; ORR, objective response rate; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; OS, Overall survival; AEs, adverse events; GP, gemcitabine/platinum; PFS, progression-free survival; ILD, interstitial lung disease; HRCT, high resolution computed tomography; BMI, body mass index; VTE, venous thromboembolism; IV, intravenously; SD, stand deviation; IQR, interquartile range; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DLCO, carbon monoxide diffusing capacity; PD-L1, programmed cell death-ligand 1; CRP, C-reactive protein; TB, tuberculosis.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available due patients' individual privacy could be compromised, but are available from the corresponding author on reasonable request.

Ethical Approval

This retrospective study was conducted at the Second Affiliated Hospital of Zhejiang University School of Medicine in China. Ethical approval was obtained from the Ethics Committee of Linping Campus, The Second Affiliated Hospital, Zhejiang University School of Medicine (Approval number: 2021-0608). Given that the study was non-interventional and retrospective, it posed minimal risk to participants. Therefore, the Ethics Committee waived the requirement for informed consent. All procedures adhered to the ethical principles outlined in the Declaration of Helsinki, ensuring the privacy and confidentiality of patient data.

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Disclosure

The authors report no conflicts of interest in this work.

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