Am J Transl Res 2026;18(9):8417-8429
www.ajtr.org /ISSN:1943-8141/AJTR0173866

Original Article

Intrapleural anti-PD-1 injection enhances T-cell immune responses and improves clinical outcomes in elderly patients with advanced lung cancer and malignant pleural effusion

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Received May 7, 2026; Accepted July 30, 2026; Epub September 15, 2026; Published September 30, 2026

Abstract: Objective: To investigate the efficacy of intrapleural anti-PD-1 therapy in elderly patients with advanced non-small cell lung cancer (NSCLC) complicated by malignant pleural effusion (MPE), and to assess its impact on T-cell subset dynamics. Methods: A total of 152 elderly patients (≥65 years) with advanced NSCLC and MPE were enrolled. All patients received a single intrapleural injection of anti-PD-1 antibody (Sintilimab, 100 mg) after thoracentesis and drainage. Clinical outcomes, adverse events, and quality-of-life measures were evaluated at baseline, 5 weeks, and 10 weeks after treatment. Concurrently, peripheral blood and pleural effusion T-cell subsets, as well as pleural effusion levels of lactate dehydrogenase (LDH), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) were also measured. Results: The pleural atresia rates at 5 and 10 weeks were 75.7% and 64.5%, respectively. The objective response rate (ORR) increased from 29.0% at 5 weeks to 38.2% at 10 weeks, and disease control rate (DCR) from 59.9% to 76.4%. Karnofsky Performance Status (KPS) score improved significantly from baseline (57.3 ± 9.6) to 5 weeks (66.5 ± 9.2) and 10 weeks (74.5 ± 8.3), Borg scores decreased from (6.1 ± 1.3) to (3.8 ± 0.9) and (3.1 ± 0.7), and Visual Analogue Scale (VAS) scores decreased from (4.5 ± 1.1) to (2.8 ± 0.5) and (2.2 ± 0.6) (all P<0.01). At 5 weeks, peripheral blood $CD3^+$, $CD4^+$, and $CD8^+$ T cells increased from baseline (53.3 ± 8.6%, 28.25 ± 5.64%, 20.5 ± 4.6%) to (60.5 ± 9.5%, 32.5 ± 7.2%, and 25.2 ± 6.3%), while the $CD4^+/CD8^+$ ratio decreased from (1.38 ± 0.11) to (1.29 ± 0.12) (all P<0.01); in pleural effusion, corresponding values rose to (69.5 ± 4.3%, 34.5 ± 6.4%, and 28.8 ± 7.7%), with the ratio falling to (1.19 ± 0.04) (P<0.01). By 10 weeks, peripheral values further increased to (68.7 ± 8.4%, 36.2 ± 6.9%, and 30.5 ± 5.2%), and the ratio dropped to (1.19 ± 0.06) (P<0.01); pleural effusion values reached 74.5 ± 7.4% ($CD3^+$), 37.1 ± 6.2% ($CD4^+$), and 32.9 ± 7.3% ($CD8^+$), with a ratio of 1.13 ± 0.05 (P<0.001). Pleural effusion levels of LDH, TNF-α, and IL-6 all declined from baseline (856.6 ± 130.2 U/L, 48.4 ± 2.3 pg/mL, 74.81 ± 9.17 pg/mL) to 5 weeks (512.5 ± 95.7 U/L, 32.3 ± 3.8 pg/mL, 52.8 ± 7.1 pg/mL) and 10 weeks (385.6 ± 74.8 U/L, 24.9 ± 2.6 pg/mL, 36.6 ± 5.4 pg/mL) (all P<0.01). Multivariable logistic regression identified that a higher baseline KPS score (OR = 1.18, 95% CI: 1.05-1.32, P<0.01) and a lower baseline pleural effusion LDH level (OR = 0.72, 95% CI: 0.58-0.89, P<0.01) were independent protective factors, while a higher baseline peripheral blood $CD4^+/CD8^+$ ratio (OR = 0.65, 95% CI: 0.48-0.88, P<0.01) was an independent negative predictor for 10-week DCR. Conclusion: Intrapleural administration of anti-PD-1 antibody is relatively safe and demonstrates effective control of MPE in elderly patients with advanced NSCLC. It improves performance status and quality of life, enhances both systemic and local T-cell immune responses, and reduces inflammatory cytokines and LDH levels in pleural effusion.

Keywords: Anti-PD-1, intrapleural injection, elderly advanced lung cancer, malignant pleural effusion, T cell subsets

Introduction

Among advanced lung cancers, malignant pleural effusion (MPE) is a common complication, particularly prevalent in non-small cell lung cancer (NSCLC) [1]. The development of MPE signifies tumor invasion of the pleura and is frequently accompanied by progressively worsening dyspnea, chest pain, and cough, symptoms that severely constrain daily activities and significantly diminish quality of life [2, 3]. Moreover, MPE generally portends a poor prog-

https://doi.org/10.62347/UKYY2328

nosis. Conventional treatments such as repeated thoracentesis and chemical pleurodesis, provide only temporary symptomatic relief and do not address the underlying persistent fluid accumulation [4, 5]. Therefore, exploring more effective local treatment strategies to improve outcomes for this patient population is of great clinical significance.

Elderly patients with advanced NSCLC and MPE display distinct clinical characteristics. With advancing age, the immune function naturally declines. At the same time, elderly patients often have a higher burden of comorbidities (e.g., hypertension, diabetes, chronic cardiopulmonary disorders) and reduced physiological reserve, all of which contribute to poor tolerance to systemic treatments [6, 7]. Although conventional systemic chemotherapy retains some efficacy, its use in the elderly is limited by increased incidence and severity of adverse reactions, including myelosuppression, cardiotoxicity, and nephrotoxicity [8, 9]. Even with the recent advent of intravenous immunotherapy as a breakthrough in lung cancer treatment [10], elderly patients still face a higher risk of immune-related adverse events (irAEs). Once severe irAEs occur, they are often difficult to manage and may become life-threatening. Therefore, there is an urgent need to identify a treatment that is both effective and safe for this vulnerable population.

Programmed cell death-1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors block immune checkpoint pathways and restore T-cell- mediated tumor recognition and killing, and have become a standard-of-care for advanced lung cancer [11, 12]. However, intravenous administration leads to systemic drug distribution and off-target immune activation, which is a primary cause of irAEs [13]. Intrapleural injection of anti-PD-1 monoclonal antibodies offers an alternative approach: direct delivery into the pleural cavity achieves high local drug concentrations at the lesion site while limiting systemic exposure, theoretically enhancing local anti-tumor immune responses within the pleural and effusion microenvironment and reducing systemic toxicity [14-16]. Although several clinical studies have preliminarily confirmed the safety and feasibility of this route [17, 18], systematic data on its efficacy, safety, and specific effects on local and systemic T-cell subsets in elderly NSCLC patients with MPE remain lacking.

The innovations of this study are twofold: (1) it simultaneously longitudinally monitors T cell subsets in both peripheral blood and pleural effusion, providing direct immunological evidence for local immunomodulation; and (2) it explores associations between biochemical indicators in pleural effusion and immune responses, aiming to identify potential predictors of treatment benefit. Clinically, this study demonstrates that a single intrapleural anti-PD-1 injection can achieve favorable disease control, improve quality of life, and maintain manageable safety in elderly patients who may be unfit for systemic therapy. By restoring both local and systemic T-cell immunity, this convenient, low-toxicity local treatment fills an important evidence gap for this understudied population.

Against this background, we enrolled 152 elderly patients with advanced NSCLC and MPE. All patients received a single intrapleural injection of the anti-PD-1 antibody (Sintilimab, 100 mg) following thoracentesis and drainage. Through comparative assessments at multiple time points before and after treatment, we comprehensively evaluated the objective response rate (ORR), disease control rate (DCR), quality-of-life improvement, and adverse events. In addition, we measured T-cell subset proportions in both pleural effusion and peripheral blood, and analyzed their correlations with biochemical parameters in pleural effusion.

Materials and methods

Study design and patients

A total of 152 elderly NSCLC patients with MPE who were admitted to the First Dongguan Affiliated Hospital, Guangdong Medical University between January 2022 and June 2025 were screened from the electronic medical record system. This retrospective cohort study was approved by the Ethics Committee of the First Dongguan Affiliated Hospital (No. YS202309018). Given the retrospective design of this study, the requirement for written informed consent was waived by the ethics committee.

Inclusion criteria: (1) age ≥65 years; (2) histopathologically or cytologically confirmed NSCLC, stage IIIB-IV; (3) imaging evidence of moderate to large pleural effusion, with malignant cells confirmed by cytological examination

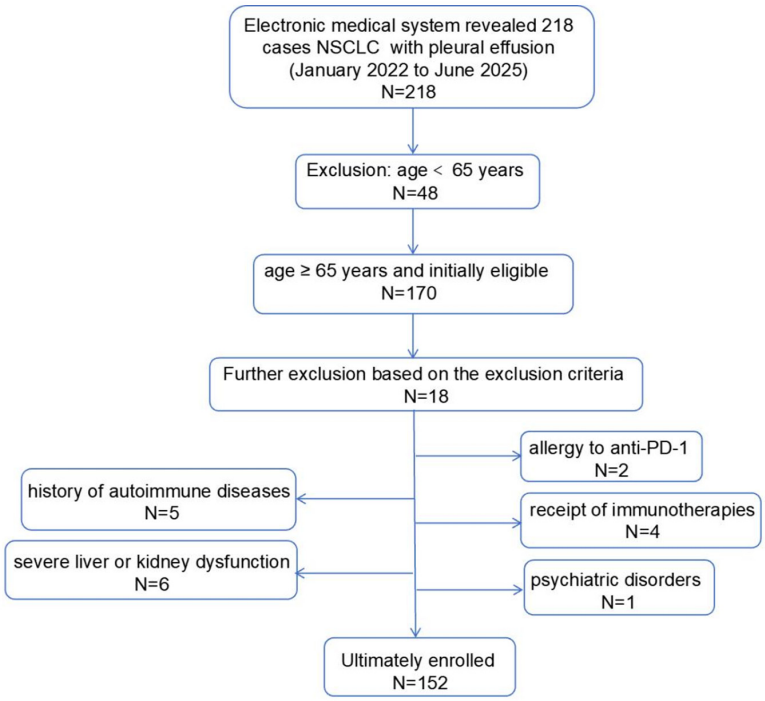


Figure 1. Flow chart showing patient inclusion process.

of the effusion; (4) no prior treatment with PD-1/PD-L1 inhibitors; (5) Karnofsky Performance Status (KPS) score ≥40; (6) expected survival ≥3 months. Exclusion criteria: (1) active infection or bleeding tendency; (2) severe hepatic or renal dysfunction; (3) history of autoimmune disease; (4) allergy to anti-PD-1 monoclonal antibodies; (5) prior receipt of other immunotherapies (e.g., CTLA-4 inhibitors, LAG-3 inhibitors); (6) other active malignancies within the past 5 years; (7) receipt of live vaccines within 4 weeks prior to enrollment; (8) presence of severe psychiatric disorders.

Data extraction

Initial screening of hospital electronic medical system identified 218 cases NSCLC patients with MPE between January 2022 and June 2025. Of these, 48 cases were excluded due to age <65 years. An additional 18 cases were excluded for the following reasons: history of autoimmune disease (5 cases), severe hepatic or renal dysfunction (6 cases), prior receipt of other immunotherapies (4 cases), psychiatric disorders (1 case), and allergy to anti-PD-1 (2 cases). The flowchart detailing patient disposition is shown in **Figure 1**.

Dosage regimen

Patients with NSCLC complicated by MPE underwent thoracentesis and drainage under ultrasound or computed tomography (CT) guidance. After adequate drainage - defined as a daily output of <100 mL for two consecutive days - the pleural effusion was drained as completely as possible. Then, the anti-PD-1 antibody (Sintilimab, 100 mg; orb1694625, China) diluted in normal saline was administered through the drainage tube as a single injection.

Clinical specimen collection

(1) Pleural effusion specimens: Samples were collected at three time points: prior to intrapleural injection, and at 5 weeks and 10 weeks post-treatment. Collection was performed using 50-mL centrifuge tubes (Corning, USA) and a 50-mL syringe. After patient identification, ≥200 mL of pleural effusion was aspirated. The collected samples were centrifuged at 3,000 rpm for 10 minutes at 4°C to separate the supernatant and cell pellet within 2 hours. The supernatant was carefully aliquoted into 15-mL centrifuge tubes without disturbing the cell pellet, recentrifuged, and stored in 2-mL aliquots. Specimens were either immediately sent to the laboratory for subsequent analysis or stored long-term at -80°C (Thermo Fisher Scientific, USA).

(2) Peripheral blood samples: Blood samples were collected at the same three time points using sterile 10-mL ethylenediaminetetraacetic acid (EDTA) tubes (BD Vacutainer, USA) via a scalp vein set. After patient identification, 10 mL of peripheral blood was drawn. The tubes were gently inverted 4-6 times immediately after collection. Separation of plasma and cellular components was completed within 2 hours post-collection.

Primary indicators

Chest B-ultrasound was performed prior to intrapleural injection, and at 5 weeks and 10

weeks after treatment to evaluate pleural effusion response according to the following criteria: complete response (CR, disappearance of effusion lasting ≥4 weeks), partial response (PR, reduction of effusion ≥50%), stable disease (SD, reduction of effusion <50% or increase <25%), and progressive disease (PD, increase of effusion ≥25%). The ORR was calculated as (CR+PR)/total number of cases × 100%, and the DCR was calculated as (CR+PR+SD)/total number of cases × 100%.

Secondary indicators

Clinical symptom scores: Clinical assessments were performed prior to injection, and at 5 weeks and 10 weeks after treatment: KPS score (range 0-100) was used to assess patients' activities of daily living, with higher scores indicating better functional status; Borg Dyspnea Scale (range 0-10) was used to evaluate subjective dyspnea severity, with higher scores indicating more severe dyspnea; Visual Analogue Scale (VAS; range 0-10) was used to measure chest pain intensity, with higher score indicating more severe pain (0, no pain - 10, most severe pain).

Peripheral blood and pleural effusion lymphocyte subsets: (1) Isolation of human lymphocytes: At baseline, 5 weeks, and 10 weeks after treatment, collected pleural effusion and peripheral blood were centrifuged at 3,000 rpm for 10 min at 4°C. After removing the supernatant, the cell pellet was resuspended in a small volume of phosphate-buffered saline (PBS, Sigma-Aldrich, USA) and then gently layered along the tube wall onto lymphocyte separation medium (MP Biomedicals, USA) in a separation tube. Following centrifugation at 2,500 rpm for 15 min, the supernatant was carefully transferred to a clean 15-mL centrifuge tube. Cells were washed once with PBS and centrifuged (300×g, 5 min). Then, the pellet was treated with 2 mL of 1× red blood cell lysis buffer for 3 min, after which PBS was added to stop lysis. Following a further centrifugation step, the lymphocyte pellet was resuspended in PBS and washed. All procedures were performed under sterile conditions. Thereafter, in a laminar flow hood, cells were resuspended in approximately 3 mL of Roswell Park Memorial Institute (RPMI) 1640 medium (Gibco, USA) containing 10% fetal bovine serum (FBS, Gibco), transferred to a culture flask (Corning), gently mixed, and incubated overnight at 37°C with 5% CO_2.

(2) Flow cytometry analysis: Isolated lymphocytes were adjusted to a concentration of 1×10^7 cells/mL with PBS, confirmed by counting using a hemocytometer (Hausser Scientific, USA) under a microscope (Leica, Germany). A 100-μL aliquot of the cell suspension was prepared and stained with the following surface antibodies according to the recommended volumes: APC-Cy™7 anti-CD3 (300317, Biolegend, USA), FITC anti-CD8 (344704, Biolegend), FITC anti-CD4 (344604, Biolegend). The proportions of $CD3^+$, $CD4^+$, and $CD8^+$ T cells, and the $CD4^+/CD8^+$ ratio were detected by flow cytometry (FACS Canto II, BD Biosciences) at baseline, 5 weeks, and 10 weeks post-treatment.

Measurement of LDH, TNF-α, and IL-6 levels: Levels of LDH, TNF-α, and IL-6 in pleural effusion were measured using enzyme-linked immunosorbent assay (ELISA) kits (all from Elabscience, Wuhan, China) at baseline, 5 weeks, and 10 weeks post-treatment. Samples and standards were added to pre-coated plates and incubated with specific antibodies. Following washing, horseradish peroxidase (HRP)-conjugated secondary antibodies and substrate solution were added sequentially. Optical density (OD) was measured at 450 nm using a microplate reader. Concentrations of LDH, TNF-α, and IL-6 were calculated from standard curves and expressed in U/L or pg/mL. All measurements were performed in duplicate.

Statistical analysis

Statistical analyses were performed using SPSS 26.0 (IBM Corporation, Armonk, NY, USA). Continuous data with a normal distribution were expressed as means ± standard deviations (SD). One-way repeated-measures analysis of variance (ANOVA) was used for comparisons among multiple time points, followed by post-hoc pairwise comparisons using the Bonferroni correction. A two-sided *P*-value of <0.05 was considered statistically significant.

Results

Patient baseline characteristics

The clinicopathological characteristics of the 152 patients are summarized in **Table 1**. There

Table 1. Patient baseline characteristics

Clinical data	Number of patients (n)	Percentage (%)
Age (years)		
Range	65-84	
Median	71.5	
Sex		
Male	95	62.5
Female	57	37.5
Alcohol consumption rate [n (%)]	58	38.2
Smoking rate [n (%)]	32	21.1
Histological type [n (%)]		
Adenocarcinoma	116	76.3
Squamous carcinoma	36	23.7
ECOG score [n (%)]		
1	142	93.4
2	10	6.6
Extra-pleural metastasis [n (%)]	72	47.4
5-week pleural atresia rate [n (%)]	115	75.7
10-week pleural atresia rate [n (%)]	98	64.5

Notes: ECOG, electrocorticography.

were 95 males (62.5%) and 57 females (37.5%), with ages ranging from 65 to 84 years (median: 71.5 years). Adenocarcinoma was the predominant histology, accounting for 116 patients (76.3%), while squamous cell carcinoma was identified in 36 patients (23.7%). The pleural atresia rate at 5 weeks post-treatment was 75.7% (115/152), declining to 64.5% (98/152) at 10 weeks.

Adverse events

Constipation was the most commonly observed event (46.1%), with all cases being grade I. Grade III adverse events were also observed, including anemia (7.2%), decreased lymphocyte count (8.6%), hypoalbuminemia (5.9%), elevated liver enzymes (5.9%), and drug-related dermatitis (7.9%). No grade IV adverse events were observed in any patient. Detailed information is shown in **Table 2**.

Improvement in ORR and DCR

Chest ultrasonography was performed at 5 and 10 weeks after treatment evaluate pleural effusion control. According to imaging response evaluation criteria, the numbers of patients achieving CR, PR, SD, and PD were recorded, and ORR and DCR were calculated (**Table 3**).

At 5 weeks after treatment, the ORR was 29.0% (44/152), including 12 cases (7.9%) of CR and 32 cases (21.1%) of PR. The DCR was 59.9% (91/152), with 47 cases (30.9%) of SD. At 10 weeks after treatment, the ORR increased to 38.2% (58/152), including 17 cases (11.2%) of CR and 41 cases (27.0%) of PR. The DCR rose to 76.4% (116/152), with 58 cases (38.2%) classified as SD.

Improvement in performance status and quality-of-life measures

As shown in **Table 4**, at 5 weeks after treatment, the patients' KPS score increased significantly from baseline (57.3 ± 9.6) to (66.5 ± 9.2) ($P<0.01$). Concurrently, the Borg dyspnea score decreased from (6.1 ± 1.3) to (3.8 ± 0.9) ($P<0.01$), and the VAS chest pain score decreased from (4.5 ± 1.1) to (2.8 ± 0.5) ($P<0.01$). At 10 weeks after treatment, further improvements were observed: KPS score rose to (74.5 ± 8.3) ($P<0.01$), Borg dyspnea score decreased to (3.1 ± 0.7) ($P<0.01$), and the VAS score dropped to (2.2 ± 0.6) ($P<0.01$).

Changes in peripheral blood T-cell subsets

As shown in **Table 5** and **Figure 2**, at 5 weeks after treatment, the proportion of peripheral blood $CD3^+$ T cells increased from (53.3 ± 8.6%) at baseline to (60.5 ± 9.5%) ($P<0.01$); $CD4^+$ T cells increased from (28.25 ± 5.64%) to (32.5 ± 7.2%) ($P<0.01$); $CD8^+$ T cells increased from (20.5 ± 4.6%) to (25.2 ± 6.3%) ($P<0.01$); and the $CD4^+/CD8^+$ ratio decreased from (1.38 ± 0.11) to (1.29 ± 0.12) ($P<0.01$). At 10 weeks after treatment, these trends continued: $CD3^+$, $CD4^+$, and $CD8^+$ T-cell proportions further increased to (68.7 ± 8.4%), (36.2 ± 6.9%) and (30.5 ± 5.2%), respectively, while the $CD4^+/CD8^+$ ratio further decreased to (1.19 ± 0.06) (all $P<0.01$).

Changes in pleural effusion T-cell subsets

As shown in **Table 6** and **Figure 3**, at 5 weeks after treatment, the proportion of $CD3^+$ T cells in pleural effusion increased to (69.5 ± 4.3%),

Table 2. Distribution of adverse events

	NCI-CTC 4.0					Grade
	0°	I°	II°	III°	IV°	III°/IV° (%)
Hematological toxicity						
Anemia	103	35	3	11	0	7.2
Leukocytopenia	102	20	28	2	0	1.3
Neutropenia	99	43	10	0	0	0
Lymphocytopenia	99	23	17	13	0	8.6
Thrombocytopenia	122	20	10	0	0	0
Febrile neutropenia	124	6	16	6	0	3.9
Non-hematological toxicity						
Constipation	82	70	0	0	0	0
Infection	126	15	11	0	0	0
Dermatitis medicamentosa	127	7	6	12	0	7.9
Hypoalbuminemia	111	14	18	9	0	5.9
Liver enzymes (ALT/AST)	79	44	20	9	0	5.9
Bilirubin	128	20	4	0	0	0
Uric acid	128	15	9	0	0	0

Notes: NCI-CTC, National Cancer Institute-Common Toxicity Criteria; ALT/AST, alanine aminotransferase/aspartate aminotransferase.

Table 3. Distribution of ORR and DCR at 5 weeks and 10 weeks post-treatment

Efficacy Grade	After 5-week treatment		After 10-week treatment	
	Number of Cases (n)	Percentage (%)	Number of Cases (n)	Percentage
CR	12	7.9%	17	11.2
PR	32	21.1%	41	27.0
SD	47	30.9%	58	38.2
PD	61	40.1%	36	23.6
Total	152	100%	152	100

Notes: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

$CD4^+$ and $CD8^+$ T cells increased to (34.5 ± 6.4%) and (28.8 ± 7.7%), respectively, and the $CD4^+/CD8^+$ ratio decreased to (1.19 ± 0.04) (all P<0.01). At 10 weeks, $CD3^+$ T cells in the pleural effusion further increased to (74.5 ± 7.4%) (P<0.01), $CD4^+$ and $CD8^+$ T cells increased to (37.1 ± 6.2%) and (32.9 ± 7.3%) (P<0.01 and P<0.001), respectively; and the $CD4^+/CD8^+$ ratio decreased to (1.13 ± 0.05) (P<0.001).

Changes in pleural effusion biochemical markers

As detailed in **Table 7**, at 5 weeks after treatment, the LDH level in pleural effusion decreased from (856.6 ± 130.2 U/L) at baseline to (512.5 ± 95.7 U/L) (P<0.01). The levels of TNF-α declined from (48.4 ± 2.3 pg/mL) to (32.3 ± 3.8 pg/mL) (P< 0.01), and IL-6 decreased from (74.81 ± 9.17 pg/mL) to (52.8 ± 7.1 pg/mL) (P<0.01). At 10 weeks, LDH levels further decreased to (385.6 ± 74.8 U/L), while TNF-α and IL-6 levels further reduced to (24.9 ± 2.6 pg/mL) and (36.6 ± 5.4 pg/mL), respectively (P<0.01).

Multivariate regression analysis of factors associated with DCR and pleural atresia

To identify independent predictors of 10-week DCR and pleural atresia, binary logistic regression analyses were performed (**Table 8**). Variables in the multivariate model included age, sex, histological type, baseline KPS score, baseline pleural effusion LDH level, baseline peripheral blood $CD4^+/CD8^+$ ratio, and baseline pleural effusion TNF-α level.

For 10-week DCR: Multivariate analysis revealed that a higher baseline KPS score (OR = 1.18, 95% CI: 1.05-1.32, P<0.01) and a lower baseline pleural effusion LDH level (OR = 0.72, 95% CI: 0.58-0.89, P<0.01) were independent protective factors for achieving DCR. Conversely, a higher baseline peripheral blood $CD4^+/CD8^+$ ratio was identified as an indepen-

Table 4. Comparison of KPS, Borg and VAS scores at baseline, 5 weeks and 10 weeks post-treatment among the three groups

Indicators	Pre-treatment	After 5-week treatment	After 10-week treatment	F	P
KPS score	57.3 ± 9.6	66.5 ± 9.2	74.5 ± 8.3	12.93	<0.01[a,b]
Borg score	6.1 ± 1.3	3.8 ± 0.9	3.1 ± 0.7	16.54	<0.01[a,b]
VAS score	4.5 ± 1.1	2.8 ± 0.5	2.2 ± 0.6	7.41	<0.01[a,b]

Notes: KPS, Karnofsky Performance Status; VAS, Visual Analogue Scale. [a]indicates the overall significant differences among the three time points; [b]indicates the significant differences between pre-treatment and after 5-week treatment, as well as between pre-treatment and 10-week treatment.

Table 5. Comparison of peripheral blood T-cell subsets at baseline, 5 weeks and 10 weeks post-treatment among the three groups

Indicators	Pre-treatment	After 5-week treatment	After 10-week treatment	F	P
$CD3^+T$ (%)	53.3 ± 8.6	60.5 ± 9.5	68.7 ± 8.4	24.35	<0.01[a,b]
$CD3^+CD4^+T$ (%)	28.25 ± 5.64	32.5 ± 7.2	36.2 ± 6.9	30.42	<0.01[a,b]
$CD3^+CD8^+T$ (%)	20.5 ± 4.6	25.2 ± 6.3	30.5 ± 5.2	37.79	<0.01[a,b]
$CD4^+/CD8^+$	1.38 ± 0.11	1.29 ± 0.12	1.19 ± 0.06	11.65	<0.01[a,b]

Notes: [a]indicates the overall significant differences among the three time points; [b]indicates the significant differences between pre-treatment and after 5-week treatment, as well as between pre-treatment and 10-week treatment.

dent negative predictor (OR = 0.65, 95% CI: 0.48-0.88, P<0.01). Histological type and sex showed no significant independent associations with DCR (both P>0.05).

For 10-week pleural atresia: A lower baseline pleural effusion TNF-α levels (OR = 0.80, 95% CI: 0.68-0.94, P<0.01) was independently associated with successful pleural atresia.

Discussion

MPE is a common complication during the progression of various malignant tumors. Despite continuous advances in molecular medicine and the consequent improvement in overall survival of cancer patients, the development of MPE often signifies a poor prognosis and remains a challenging clinical issue that respiratory physicians, thoracic surgeons, and other specialties must urgently address [19, 20]. Beyond conventional treatments, local therapy, particularly intrapleural drug administration, has become an important strategy for controlling MPE-related symptoms and potentially prolonging survival [21]. In the present study, we administered a single intrapleural injection of the anti-PD-1 antibody Sintilimab (100 mg) to 152 elderly patients with advanced NSCLC complicated by MPE. Our results showed favorable pleural effusion control with acceptable safety. The pleural atresia rates were 75.7% at 5 weeks and 64.5% at 10 weeks; the ORR increased from 29.0% at 5 weeks to 38.2% at 10 weeks, and the DCR rose from 59.9% to 76.4% over the same period. These data suggest that local immune checkpoint inhibitor therapy not only promotes pleural adhesion but may also induce durable antitumor effects, with some patients achieving disease remission even after treatment discontinuation.

Elderly patients with advanced NSCLC often present with poor general conditions, multiple comorbidities, and compromised immune function, making them poorly tolerant of systemic immunotherapy or chemotherapy [22, 23]. Multiple clinical studies have confirmed that blockade of the PD-1/PD-L1 pathway markedly extends survival in patient with malignant tumors, with benefits surpassing those of traditional platinum-based chemotherapy [24-26]. Sintilimab, a fully human anti-PD-1 monoclonal antibody, has demonstrated high binding affinity and biological activity against PD-1 in preclinical studies [27]. Against this background, we adopted an intrapleural administration route to achieve high local drug concentrations in the pleural cavity while minimizing adverse events related to systemic absorption. Our results showed that no grade ≥3 immune-related adverse events were reported during the treatment period, and patients' quality of life (KPS score), dyspnea (Borg score), and pain

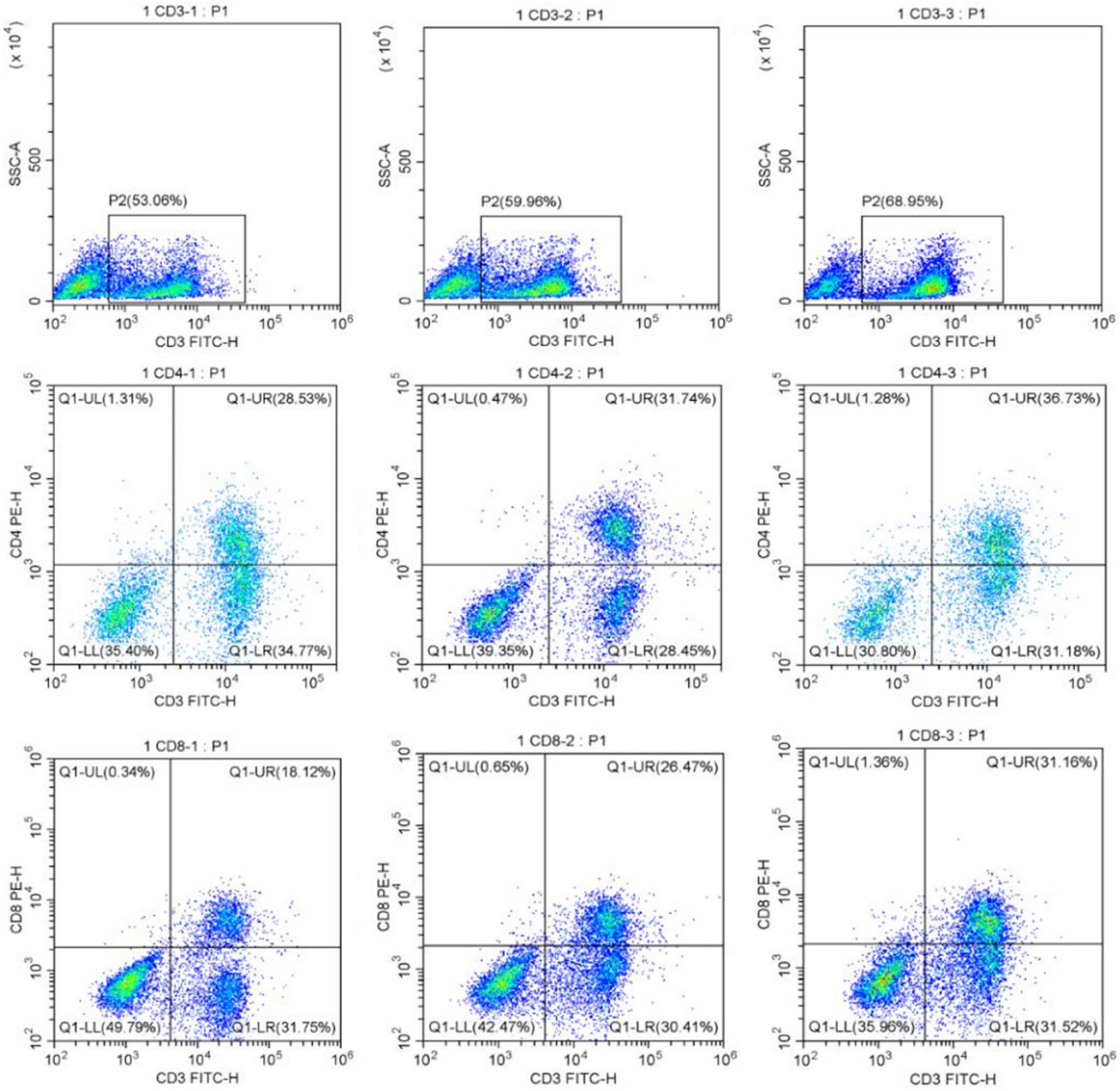


Figure 2. Representative images of peripheral blood T cell subsets. The proportions of $CD3^+$, $CD4^+$, and $CD8^+$ T cells in peripheral blood were measured by flow cytometry at baseline, and at 5 and 10 weeks post-treatment.

Table 6. Comparison of local T-cell subsets in pleural effusion at baseline, 5 weeks and 10 weeks post-treatment among the three groups

Indicators	Pre-treatment	After 5-week treatment	After 10-week treatment	F	P
$CD3^+$T (%)	58.5 ± 3.4	69.5 ± 4.3	74.5 ± 7.4	13.28	<0.01[a,b]
$CD3^+CD4^+$T (%)	30.5 ± 2.5	34.5 ± 6.4	37.1 ± 6.2	6.23	<0.01[a,b]
$CD3^+CD8^+$T (%)	24.2 ± 2.4	28.8 ± 7.7	32.9 ± 7.3	17.45	<0.001[a,b]
$CD4^+/CD8^+$	1.26 ± 0.10	1.19 ± 0.04	1.13 ± 0.05	26.4	<0.001[a,b]

Notes: [a]indicates the overall significant differences among the three time points; [b]indicates the significant differences between pre-treatment and after 5-week treatment, as well as between pre-treatment and 10-week treatment.

(VAS score) all significantly improved, indicating that this regimen is both feasible and safe in the elderly population.

Compared with historical data from systemic anti-PD-1 treatment, our intrapleural approach achieved a substantially higher pleural effusion

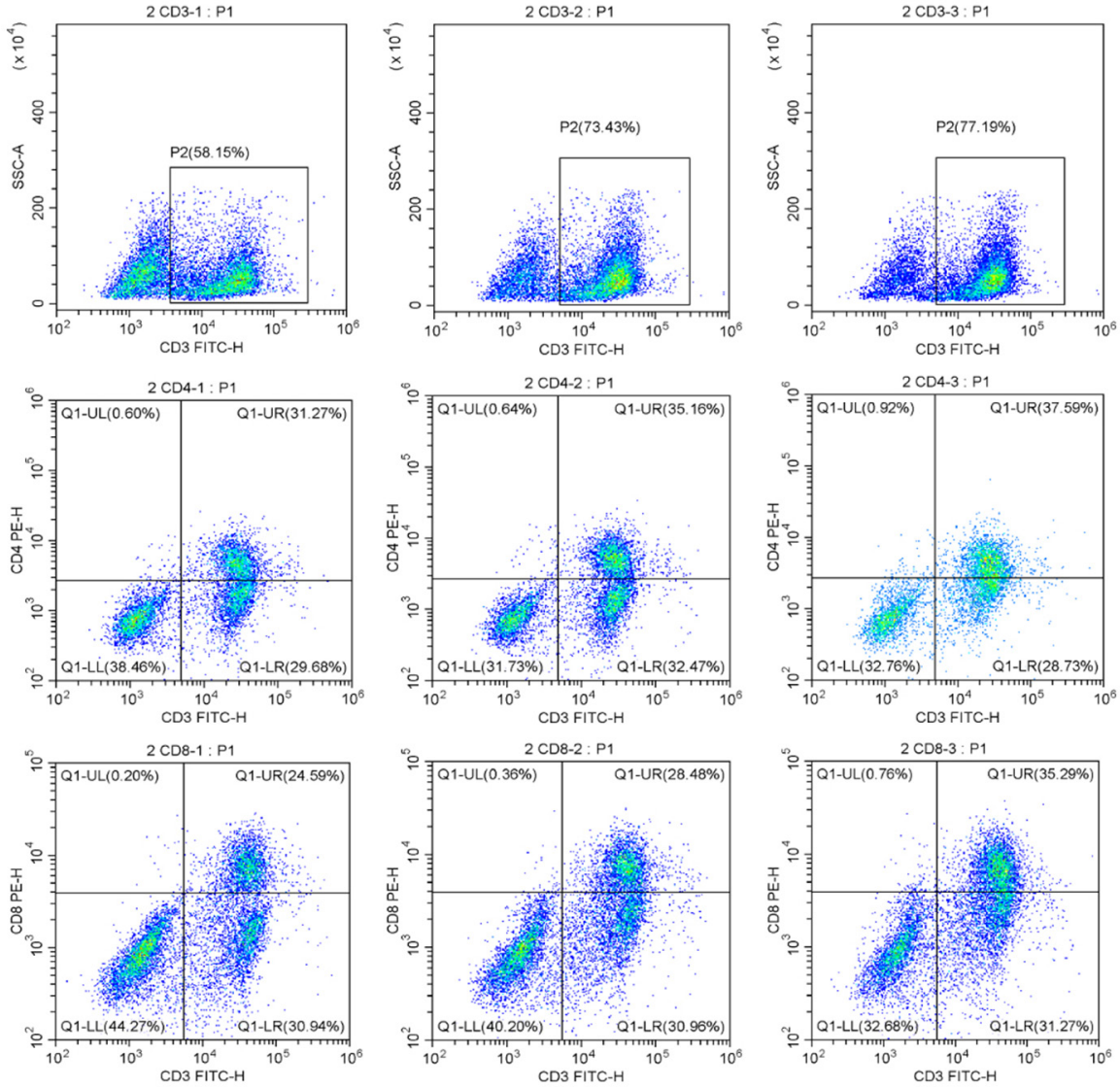


Figure 3. Representative images of local T cell subsets in pleural effusion. The proportions of $CD3^+$, $CD4^+$, and $CD8^+$ T cells in pleural effusion were measured by flow cytometry at baseline, and at 5 and 10 weeks post-treatment.

Table 7. Comparison of pleural effusion LDH, TNF-α and IL-6 levels at baseline, 5 weeks and 10 weeks post-treatment among the three groups

Indicators	Pre-treatment	After 5-week treatment	After 10-week treatment	F	P
LDH (U/L)	856.6 ± 130.2	512.5 ± 95.7	385.6 ± 74.8	32.45	<0.01[a,b]
TNF-α (pg/mL)	48.4 ± 2.3	32.3 ± 3.8	24.9 ± 2.6	11.65	<0.01[a,b]
IL-6 (pg/mL)	74.81 ± 9.17	52.8 ± 7.1	36.6 ± 5.4	16.48	<0.01[a,b]

Notes: LDH, lactate dehydrogenase; TNF-α, tumor necrosis factor α; IL-6, interleukin-6. [a]indicates the overall significant differences among the three time points; [b]indicates the significant differences between pre-treatment and after 5-week treatment, as well as between pre-treatment and 10-week treatment.

control rate in elderly MPE patients, with a more rapid onset of effect. For instance, prior studies using intravenous pembrolizumab or nivolumab in NSCLC-associated MPE reported pleural response rates of approximately 45-55% at similar time points [28], whereas our 5-week atresia rate of 75.7% markedly exceeds these data. This difference underscores the

Table 8. Multivariate logistic regression analysis of factors associated with 10-week DCR and pleural atresia

Variables	10-Week DCR (n = 152)	*P* value	10-Week Pleural Atresia (n = 152)	*P* value
	OR (95% CI)		OR (95% CI)	
Age (≥75 vs. <75)	0.87 (0.45-1.68)	0.68	1.02 (0.53-1.96)	0.95
Sex (Male vs. Female)	1.12 (0.58-2.16)	0.73	0.91 (0.49-1.69)	0.77
Cancer type (SCC vs. ADC)	0.92 (0.51-1.66)	0.78	1.15 (0.61-2.17)	0.66
Baseline KPS score (per 1-unit increase)	1.18 (1.05-1.32)	<0.01	1.09 (0.98-1.21)	0.10
Baseline LDH in PE (per 10 U/L increase)	0.72 (0.58-0.89)	<0.01	0.88 (0.75-1.03)	0.11
Baseline $CD4^+/CD8^+$ ratio in peripheral blood	0.65 (0.48-0.88)	<0.01	0.77 (0.56-1.06)	0.12
Baseline TNF-α in PE (per pg/mL increase)	0.91 (0.79-1.05)	0.20	0.80 (0.68-0.94)	<0.01

Notes: OR, odds ratio; CI, confidence interval; SCC, squamous cell carcinoma; ADC, adenocarcinoma; PE, pleural effusion; KPS, Karnofsky Performance Status; LDH, lactate dehydrogenase; TNF-α, tumor necrosis factor α.

potential pharmacokinetic and pharmacodynamic advantages of direct intrapleural delivery, which may be attributable to higher local drug concentration, avoidance of peripheral immune exhaustion, and the unique immune microenvironment of the pleural cavity [29]. However, the pleural adhesion rate in our study declined from 75.7% at 5 weeks to 64.5% at 10 weeks, suggesting that some patients experience delayed pleural effusion recurrence. Potential mechanisms include acquired resistance (e.g., upregulation of alternative checkpoints such as TIM-3 and LAG-3, loss of tumor neoantigens, or emergence of immunosuppressive myeloid cells within the pleural space [30]) and incomplete pleural fibrosis resulting from insufficient local drug exposure over time or interindividual variability in fibrotic responses. These hypotheses warrant investigation in future translational studies with extended follow-up and mechanistic exploration.

$CD4^+$ and $CD8^+$ T cells are known to play critical roles in shaping and regulating immune responses in both cancer and immune related diseases, a finding that has translated into significant clinical benefits [31]. Notably, this study dynamically monitored changes in T-cell subsets in both peripheral blood and pleural effusion. At 5 and 10 weeks post-treatment, the percentages of $CD3^+$, $CD4^+$, and $CD8^+$ T cells were all significantly increased compared with baseline, while the $CD4^+/CD8^+$ ratio decreased. This pattern likely reflects the reactivation of local and systemic cellular immunity by anti-PD-1 antibodies: activated T cells migrate to the peripheral circulation, and the expansion of $CD8^+$ cytotoxic T cells outpaces that of $CD4^+$ helper T cells, resulting in a decreased ratio. Previous studies have confirmed that intrapleural immunotherapy can induce an "in situ vaccination" effect, promoting tumor antigen presentation and T cell priming [32, 33]. The results of this study provide clinical evidence supporting this mechanism. The concurrent rise in both peripheral and local T-cell counts, coupled with the declining CD4/CD8 ratio, indicates a systemic redistribution of effector T cells originating from the pleural compartment. This pattern aligns with the concept that local checkpoint blockade not only activates regional immunity but also generates a systemic antitumor response, which may explain the sustained disease control observed even after treatment cessation. In addition, pleural effusion levels of LDH, TNF-α, and IL-6 all significantly decreased after treatment. LDH is a marker of tumor burden and cellular damage, and its reduction indicates a decrease in malignant cells within MPE [34]; TNF-α and IL-6 are pro-inflammatory cytokines that promote vascular permeability and pleural effusion accumulation [35]. These findings indicate that anti-PD-1 treatment may exert its effect not only through immune-mediated tumor killing but also by down-regulating the inflammatory microenvironment, thereby synergistically controlling effusion. Future randomized, double-blind, placebo-controlled trials are warranted to confirm our preliminary findings.

This study has several limitations. First, the sample size was relatively small, and the study employed a single-center, non-randomized design without a comparison arm (e.g., systemic therapy or intrapleural chemotherapy).

Second, the definition of "elderly" was based solely on age (≥65 years), without a thorough assessment of functional age or comorbidity burden, which may limit the generalizability of our findings. Third, our T-cell subset analysis did not include Tregs or exhaustion markers, constraining our ability to fully characterize the magnitude and quality of the immune response. Fourth, biomarkers such as circulating tumor DNA or pleural effusion exosomes were not detected, making it difficult to identify molecular predictors of therapeutic efficacy. Fifth, we did not perform sequential pleural biopsies or thoracoscopic examinations; consequently, we lack histological evidence of local immune infiltration, fibrotic changes, or resistance-related alterations in the tumor microenvironment. Sixth, the short follow-up period (10 weeks) precludes assessment of the long-term durability of effusion control and its impact on overall survival. These inherent limitations collectively urge caution in interpreting the efficacy results and highlight the need for more rigorous, biomarker-driven trials.

Conclusion

Intrathoracic administration of anti-PD-1 antibodies represents a safe and effective option for elderly patients with advanced NSCLC and MPE. This approach significantly controls pleural effusion, improves quality of life and functional status, enhances both systemic and local T-cell immune responses, and reduces the local inflammatory burden. Future multi-center clinical trials are necessary to compare this approach with standard thoracic perfusion therapy, and to explore the potential of combined treatments (e.g., low-dose radiotherapy or chemotherapy). Additionally, developing efficacy prediction models based on the pleural fluid immune microenvironment will facilitate individualized treatment decisions.

Acknowledgements

This work was supported by the Dongguan Science and Technology of Social Development Program (Grant No. 20231800937362) and the Talent Development Foundation of The First Dongguan Affiliated Hospital of Guangdong Medical University (Grant No. PF100-2-08). We thank the patients and clinical staff who participated in this study.

Disclosure of conflict of interest

None.

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