BMC Cancer

RESEARCH Open Access

Treatment rechallenge is safe and leads to better survival in pancreatic cancer patients with interstitial pneumonitis

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Abstract

Background and aims Interstitial pneumonitis is a potentially fatal complication of cancer-related therapy. However, data regarding the risk factors, prognosis and safety and benefit of rechallenge treatment are scarce.

Methods Patients diagnosed with pancreatic cancer were retrospectively enrolled, and those with pneumonitis were identified. We investigated the incidence and etiology of pneumonitis, potential risk factors, and impact of treatment rechallenge on clinical outcomes.

Results A total of 809 patients were diagnosed with pancreatic cancer, among whom 62 (7.7%) were diagnosed with interstitial pneumonitis. Risk factors identified through competing risk analysis included nab-paclitaxel, gemcitabine, erlotinib, and previous lung diseases such as pre-existing ILD, asthma, chronic obstructive pulmonary disease, tuberculosis, primary lung cancer, metastasis, or pneumonia. Among these patients, 33 experienced acute respiratory distress syndrome, resulting in 15 deaths during pneumonitis episodes. After rechallenge therapy in 33 patients, pneumonitis recurred in 3 (9%). The median overall survival was longer in patients with pneumonitis than in those without. Subgroup analysis further revealed that overall survival was significantly better in the rechallenge group.

Conclusions Most cases of pneumonitis are not directly induced by cancer therapy. Therefore, treatment rechallenge is considered a reasonable approach, potentially resulting in improved survival outcomes.

Keywords Interstitial pneumonitis, Rechallenge, Pancreatic cancer, Nab-paclitaxel, Gemcitabine, Erlotinib

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Background

Pancreatic adenocarcinoma is a life-threatening disease and ranks as the fourth leading cause of cancer-related death in the United States [1]. Several treatment regimens have demonstrated survival benefits, showing improvements in progression-free survival (PFS) and overall survival (OS) [2–4]. Unfortunately, cancer-related therapy is sometimes discontinued due to disease progression, severe adverse effects, or general clinical deterioration.

Interstitial lung disease (ILD) is an umbrella term to describe a heterogeneous group of lung disease characterized by inflammation and fibrosis of pulmonary interstitium, including interstitial pneumonitis. Interstitial

pneumonitis could be induced by several conditions, such as connective tissue disease, lung infection, or other etiologies. Drug-induced ILD is one of the possible causes of interstitial pneumonitis, a potentially fatal complication occurred during cancer treatment [5]. Over 350 medications, including gemcitabine [6], erlotinib [7, 8], and nanoparticle-albumin-bound-paclitaxel (nab-paclitaxel) [9–11], can cause ILD. Chest computed tomography (CT) and a multidisciplinary approach are necessary for a definite diagnosis and severity prediction of ILD [12]. Drug-induced ILD should be distinguished from other causes of pneumonitis by a comprehensive survey for other etiologies, such as infection, lymphatic carcinomatosis, pre-existing ILD exacerbation, or other etiologies. Once drug-induced ILD is suspected, potentially offending drugs should be promptly discontinued and appropriate management including steroid should be initiated immediately. Nevertheless, distinguishing drug-induced ILD from pneumonitis induced by other causes is still challenging due to the complexity of patients' comorbidities, and drug-induced ILD cannot be completely ruled out even if another etiology is identified [5, 13]. Naranjo Adverse Drug Reaction Probability Scale was used to evaluate the possibility of drug-induced adverse effects, including ILD, in previous studies [14].

Despite the potential life-threatening adverse effects of drug-induced ILD, the prognosis was better than that of nondrug-related ILD, with appropriate management [15]. Takeda et al. [11] also revealed no significant difference in the median OS between the ILD and non-ILD groups in patients with pancreatic cancer who received nab-paclitaxel and gemcitabine.

Generally, rechallenge is contraindicated in patients with drug-induced ILD [16]. However, several case reports have shown successful rechallenge after recovery from drug-induced ILD in non-small cell lung cancer patients, with better outcomes than in non-ILD patients [17]. Moreover, treatment options for patients with pancreatic adenocarcinoma are limited. Therefore, rechallenge treatment should be considered after recovery from previous interstitial pneumonitis.

In this study, we aimed to evaluate the incidence, etiology, risk factors, and outcomes of patients with pancreatic adenocarcinoma who developed interstitial pneumonitis during cancer-related therapy, as well as the outcomes of rechallenge treatment.

Methods

Study design and participants

This retrospective study, conducted at Taipei Veterans General Hospital, a tertiary medical center in northern Taiwan, examined pancreatic cancer patients who developed pneumonitis during cancer therapy and control patients without pneumonitis from June 2012 to June 2020. When pneumonitis was impressed according to clinical symptoms and signs, chest radiograph or other clues, chest CT was performed for definite diagnosis, with or without high-resolution CT, just before treatment initiation. Broncho-alveolar lavage would be performed if the diagnosis was inconclusive, and the condition was not improved after initial treatment. The diagnosis of pneumonitis involved a multidisciplinary approach involving clinicians, radiologists, and/or pathologists. Once the diagnosis of pneumonitis was confirmed, the possibility of drug-induced ILD was calculated with the Naranjo Adverse Drug Reaction Probability Scale (supplementary materials 4). Baseline characteristics, including age, sex, smoking status, Eastern Cooperative Oncology Group performance status, underlying disease status, initial cancer status, treatment course, pneumonitis diagnosis date, pneumonitis severity, pathogen investigations, pneumonitis outcomes, treatment rechallenge date, pneumonitis recurrence status, final contact date, and final status, were collected.

Severity of pneumonitis

Pneumonitis severity was graded according to CTCAE, v5.0, with four groups established. The outpatient group included those with grade 1–2 pneumonitis (asymptomatic or limiting instrumental activities of daily living). Patients with grade 3 pneumonitis (severe symptoms, limited self-care activities of daily living, and the need for oxygen supplementation) were classified into the admission group. Grade 4 pneumonitis (life-threatening, with severe hypoxia requiring immediate intervention) was defined by a PaO2:FiO2 (P: F) ratio < 200 mmHg in arterial blood gas, akin to moderate to severe ARDS according to the Berlin definition [18]. Consequently, endotracheal tube intubation with mechanical ventilation was recommended. Grade 4 pneumonitis patients were further categorized into ARDS with ventilators and ARDS without ventilators groups based on their intubation status.

Etiology of pneumonitis

A thorough examination was conducted following the diagnosis of pneumonitis, including bacterial culture; atypical pathogen survey (*Mycoplasma/Chlamydophila* IgM and Legionella urine IgM); acid-fast stain; tuberculosis culture; virus survey, including cytomegalovirus (CMV), Epstein–Barr virus (EBV), herpes simplex virus (HSV), varicella-zoster virus; and fungal culture for sputum.

Risk factors for pneumonitis

The risk factors identified in previous studies were investigated, which included age, sex, smoking status, diabetes mellitus status, prior lung diseases (such as pre-existing

ILD, asthma, chronic obstructive pulmonary disease [COPD], tuberculosis, lung cancer or metastasis), prior radiotherapy, erlotinib and nab-paclitaxel use. Because of the poor outcomes of patients with pancreatic adenocarcinoma, a competing risk analysis of pneumonitis incidence with competing patient death events was performed to eliminate the effects of patient death on these relationships.

Treatment rechallenge after pneumonitis recovery

After surviving pneumonitis events, patients proceeded with further cancer treatment, choosing between rechallenging previous therapy, switching to a new regimen, or receiving supportive care. All patients were followed up until the final contact date and rechallenge and recurrence rates were calculated as percentages. Timelines from treatment initiation to pneumonitis events, hospitalization, ventilator use, and durations from pneumonitis events to rechallenge and recurrence were all summarized.

Clinical outcomes and survival analysis of the interstitial pneumonitis and non-pneumonitis groups

The best responses of the medicine when pneumonitis occurred were calculated. OS between the interstitial pneumonitis and non-pneumonitis groups was estimated. Further subgroup analyses of OS between the interstitial pneumonitis and non-pneumonitis groups were also performed to eliminate possible confounding factors: patients who had received nab-paclitaxel, those who never received nab-paclitaxel, and those diagnosed with metastatic pancreatic cancer after 2018. Another survival analysis was performed on patients separated into four groups: patients who successfully recovered from treatment after pneumonitis recovery, those who did not recover from treatment after pneumonitis recovery, those who died due to pneumonitis events, and those without pneumonitis events. In addition, a comparison of clinical outcomes in patients with pneumonitis and those without pneumonitis was also performed.

Statistical analysis

For the baseline characteristics, continuous variables are presented as medians (ranges), and categorical variables are described as absolute numbers (proportions). The $\chi 2$ test or Fisher's exact test was performed for categorical data. The risk factors identified in previous studies were investigated using competing risk analysis with the Fine–Gray model and cmprsk package in R version 4.2.2 (R Statistical Foundation for Computing, Vienna, Austria). Survival analysis was performed using the Kaplan–Meier method and the log-rank test. The collected data were analyzed using SPSS version 23.0 (IBM, Armonk, NY, USA) and the survival package in R. All variables were considered statistically significant at $P < 0.05$.

Results

Patient characteristics

A total of 809 patients with pancreatic cancer who received cancer-related therapy between June 2012 and June 2020 were enrolled. Pneumonitis developed in 62 of these patients (7.7%). All these 62 patients were diagnosed with chest CT. Among these patients, 29 patients (47%) received HRCT just before treatment initiation. Broncho-alveolar lavage was performed for further differential diagnosis in 12 patients (19%). The incidence rates of interstitial pneumonitis in patients treated with gemcitabine, erlotinib and nab-paclitaxel were 3.8%, 7.8% and 10.1%, respectively. The baseline characteristics of patients with and without interstitial pneumonitis are summarized in Table 1. The results of Naranjo Adverse Drug Reaction Probability Scale were also summarized in Table 1, with most patients (98%) as possible drug-induced ILD.

Severity of pneumonitis

Among the patients who developed pneumonitis, 57 were admitted to the hospital for further management (Fig. 1). During hospitalization, 33 patients developed ARDS. Seventeen patients underwent endotracheal tube intubation with mechanical ventilation, and 13 survived with ventilator support and intensive care (Fig. 1). Of the 16 patients who refused intubation, only 5 survived. The mortality rate was 24.2% in all patients with interstitial pneumonitis and 45.5% in patients with ARDS. The mortality rate was 23.5% with and 68.8% without ventilator support ($P = 0.015$; Fig. 2).

Treatment for pneumonitis

In all patients diagnosed with pneumonitis, antibiotic therapy was administered because the possibility of pneumonia could not be ruled out initially. Steroid treatment was also initiated due to suspected drug-induced ILD. For patients with specific pathogens identified, appropriate medications targeting those pathogens were administered, if present.

Clinical course of pneumonitis and treatment rechallenge

The median duration of treatment initiation for pneumonitis events was 2.85 months (range from 7 days to 9.4 months). The median duration of hospitalization was 16 days (2–80 days), and the median duration of ventilator use was 10 days (4–20 days). Additionally, the median duration from pneumonitis to rechallenge was 3.71 months (13 days to 8.1 months), and the durations from rechallenge to recurrence were 10.6 months, 2.3 months,

Table 1 Baseline characteristics

	All patients	(*n* = 809)	Pneumonitis	(*n* = 62)	Non-pneumonitis	(*n* = 747)
Age, years	64	(20–93)	63	(20–86)	64	(23–93)
> 65 years old	410	50.7%	35	56.5%	375	50.2%
Sex (male)	454	56.1%	36	58.1%	418	56.0%
Initial ECOG PS (0–1)	770	95.2%	61	98.4%	709	94.9%
ABO type						
A	235	29.0%	15	24.2%	220	29.5%
B	206	25.5%	17	27.4%	189	25.3%
O	255	31.5%	26	41.9%	229	30.7%
AB	47	5.8%	2	3.2%	45	6.0%
Smoking	184	22.7%	18	29.0%	166	22.2%
Diabetes mellitus	274	33.9%	18	29.0%	256	34.3%
Previous lung diseases	116	14.3%	16	25.8%	100	13.4%
COPD	11	1.4%	2	3.2%	9	1.2%
Asthma	4	0.5%	3	4.8%	1	0.1%
Pre-existing ILD	2	0.2%	1	1.6%	1	0.1%
Lung cancer/Metastasis	26	3.2%	18	29.0%	8	1.1%
Tuberculosis	8	1.0%	2	3.2%	6	0.8%
Initial status						
Localized	293	36.2%	12	19.4%	281	37.6%
Metastatic	516	63.8%	50	80.6%	466	62.4%
Lines of treatment						
1st	701	86.7%	49	79.0%	652	87.3%
2nd or later	108	13.3%	13	21.0%	95	12.7%
Previous radiotherapy	164	20.3%	11	17.7%	153	20.5%
Therapies before pneumonitis*						
Gemcitabine	793	98.0%	62	100.0%	731	97.9%
Erlotinib	411	50.8%	33	53.2%	378	50.6%
Nab-paclitaxel	276	34.1%	31	50.0%	245	32.8%
Naranjo Scales						
1 (possible)			1	1.6%		
2 (possible)			24	38.7%		
3 (possible)			24	38.7%		
4 (possible)			12	19.4%		
5 (probable)			1	1.6%		
Therapies when pneumonitis						
Gemcitabine			30	48.4%		
Erlotinib			32	51.6%		
Nab-paclitaxel			28	45.2%		
FOLFIRINOX			1	1.6%		
Nal-IRI + 5-FU + LV			1	1.6%		
Pembrolizumab			1	1.6%		

* Therapies before ILD in the non-ILD arm indicate all therapies received during pancreatic cancer treatment. ILD = interstitial lung disease; COPD = chronic obstructive pulmonary disease; nab-paclitaxel = nanoparticle albumin-bound paclitaxel

and 2.1 months in these three patients with recurrent pneumonitis.

Etiology of pneumonitis

Infectious disease was identified in 28 of the 62 patients with interstitial pneumonitis (45.2%), and the pathogen results are summarized in Figure S1. Among these patients, CMV was observed in nine, fungus in six, *Mycoplasma* in one, *Chlamydophila* in three, tuberculosis in one, nontuberculous mycobacteria in four, EBV in one, HSV in one, coronavirus in one, and bacterial infection (methicillin-resistant *Staphylococcus aureus* and *Escherichia coli* in both blood culture and sputum culture) in one patient.

Risk factors for pneumonitis with competing risk analysis

The results of the competing risk analysis of the incidence of pneumonitis with competing events (patient deaths)

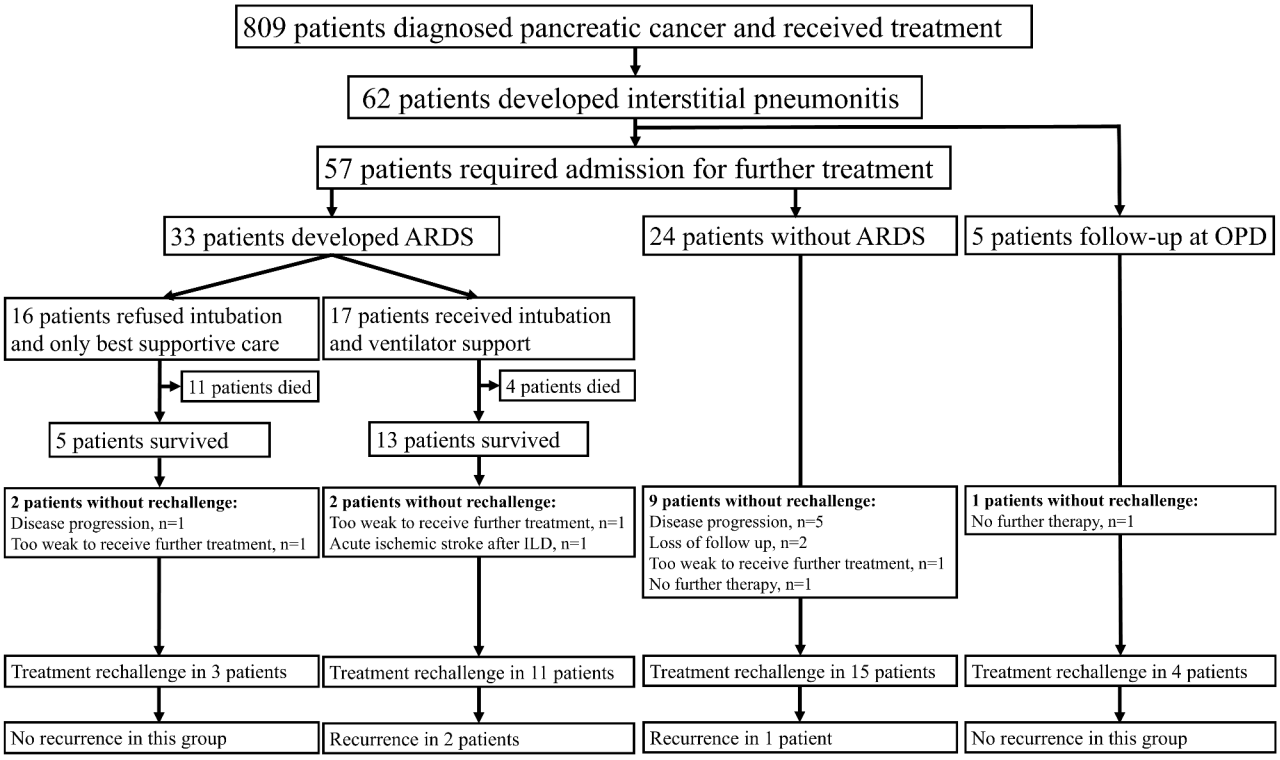

Fig. 1 Flow chart

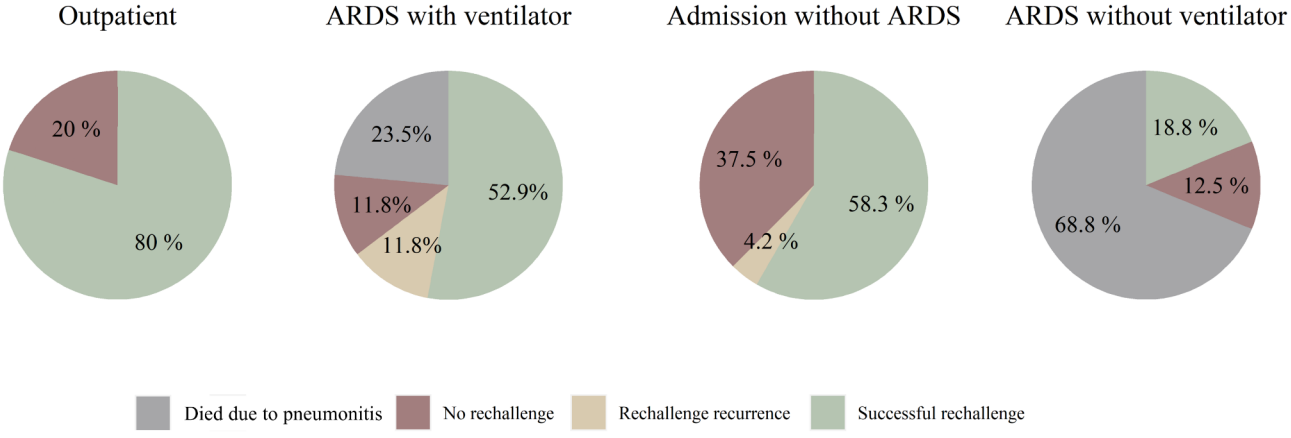

Fig. 2 Outcomes of ILD patients with different disease severities

are summarized in Table 2. The subdistribution hazard ratios of previous lung diseases, including pre-existing ILD, asthma, COPD, tuberculosis, lung cancer, metastasis, or pneumonia (hazard ratio [HR]: 2.56, 95% confidence interval [CI]: 1.49–4.63, $P=0.002$), gemcitabine (HR: 5.02, 95% CI: 1.82–13.83, $P=0.002$), nab-paclitaxel use (HR: 8.40, 95% CI: 2.98–23.72, $P<0.001$) and erlotinib (HR: 1.94, 95% CI: 1.15–3.28, $P=0.013$), were identified as independent risk factors.

Treatment rechallenge after pneumonitis recovery

Of the 47 patients who recovered from pneumonitis, 33 underwent cancer therapy rechallenge (Fig. 1). Among them, 4 patients were in the outpatient group, 15 were admitted, 11 were in the ARDS with ventilator group, and 3 were in the ARDS without ventilator group. Only 3 patients (9%) experienced another episode of pneumonitis, all with pathogens identified during their initial episode of pneumonitis.

Table 2 Analysis of competing risk factors for interstitial pneumonitis

	HR	95% CI	*P*
Age ≥ 65 years	1.31	0.74–2.30	0.36
Sex, male	0.98	0.57–1.68	0.93
ECOG Performance status 0–1	2.50	0.39–16.21	0.34
Smoking	1.28	0.69–2.36	0.43
Diabetes Mellitus	0.86	0.48–1.52	0.59
Previous lung diseases	2.56	1.49–4.63	0.002
Previous radiotherapy	0.67	0.35–1.26	0.21
Therapies when pneumonitis			
Gemcitabine	5.02	1.82–13.83	0.002
Nab-paclitaxel	8.40	2.98–23.72	< 0.001
Erlotinib	1.94	1.15–3.28	0.013
mFOLFIRINOX	0.96	0.11–8.30	0.97
S-1 (tegafur/gimeracil/oteracil)	0.60	0.17–2.19	0.44
Nal-IRI	1.09	0.13–9.51	0.94

HR = hazard ratio; CI = confidence interval; nab-paclitaxel = nanoparticle albumin-bound paclitaxel; nal-IRI = nanoliposomal irinotecan

Clinical outcomes and survival analysis

In all patients with unresectable diseases, the objective response rates were 26.5% and disease-control rate were 77.6%. The median OS was longer in patients with interstitial pneumonitis (pneumonitis vs. non-pneumonitis group: 11.3 vs. 8.3 months, $P < 0.001$; Fig. 3). Subgroup analysis also revealed survival benefits in all patients who received nab-paclitaxel therapy (median OS of pneumonitis vs. non-pneumonitis: 11.3 months vs. 10.0 months, $P = 0.02$; Figure S2A), those not treated with nab-paclitaxel (16.5 months vs. 7.7 months, $P < 0.001$; Supplementary Figure S2B), and all patients diagnosed with stage IV pancreatic cancer between 2018 and 2020 (11.3 vs. 5.9 months, $P = 0.02$; Supplementary Figure S2C). Further subgroup analysis was performed on the following four groups: treatment rechallenge, no rechallenge, pneumonitis-related death, and no pneumonitis. The patients who were rechallenged after recovery from pneumonitis had better OS than the other patients did (13.8, 8.6, 5.4, and 8.3 months, respectively; $P < 0.001$; Fig. 4).

Clinical outcomes and survival analysis according to etiology

Because the survival benefit may vary due to different etiologies, we further performed a clinical outcome and survival analysis for interstitial pneumonitis patients with or without an alternative etiology (summarized in Table S1). In interstitial pneumonitis without an alternative etiology, 29 patients were admitted, and 14 patients developed ARDS. Of these 14 patients, 8 refused endotracheal tube intubation, and 5 died during the pneumonitis episodes. Six patients received intubation and mechanical ventilator support, and none died during these episodes. Among the 34 patients with interstitial pneumonitis without an alternative etiology, 19 received treatment rechallenge, and none recurred (0%).

In interstitial pneumonitis with an alternative etiology, 28 patients were admitted, and 19 developed ARDS.

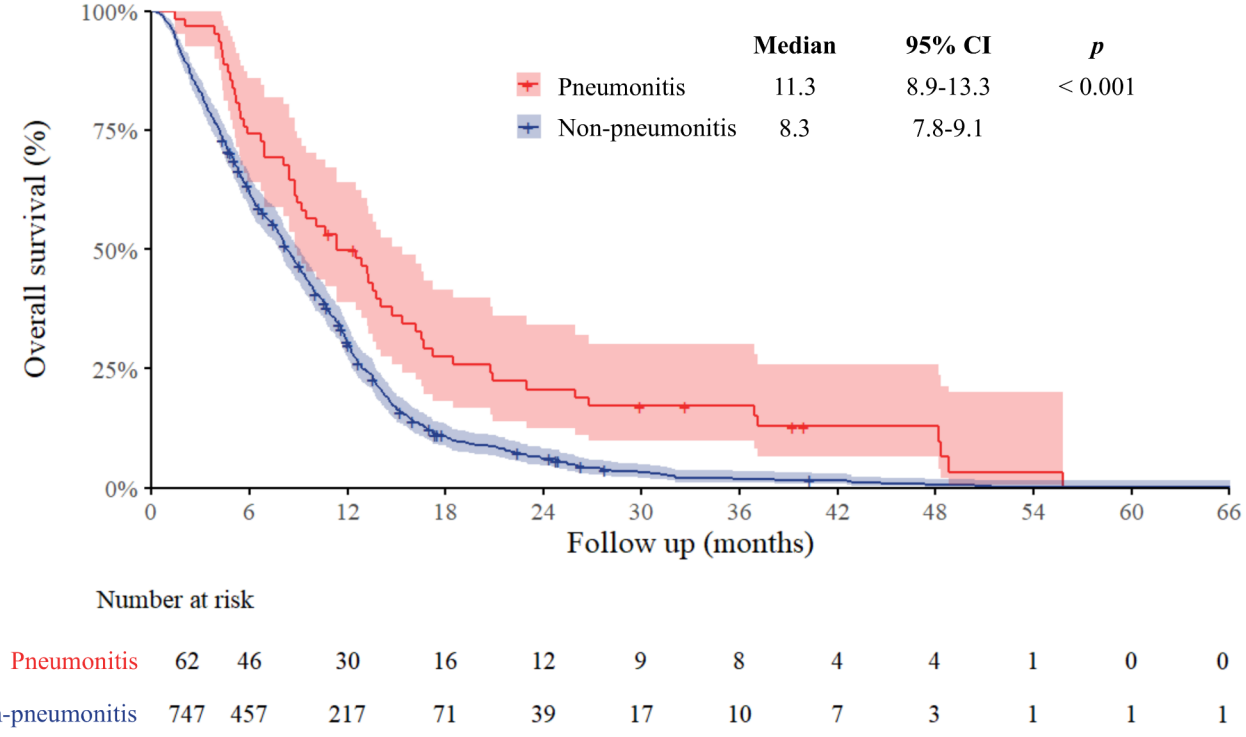

Fig. 3 Overall survival in patients with or without ILD

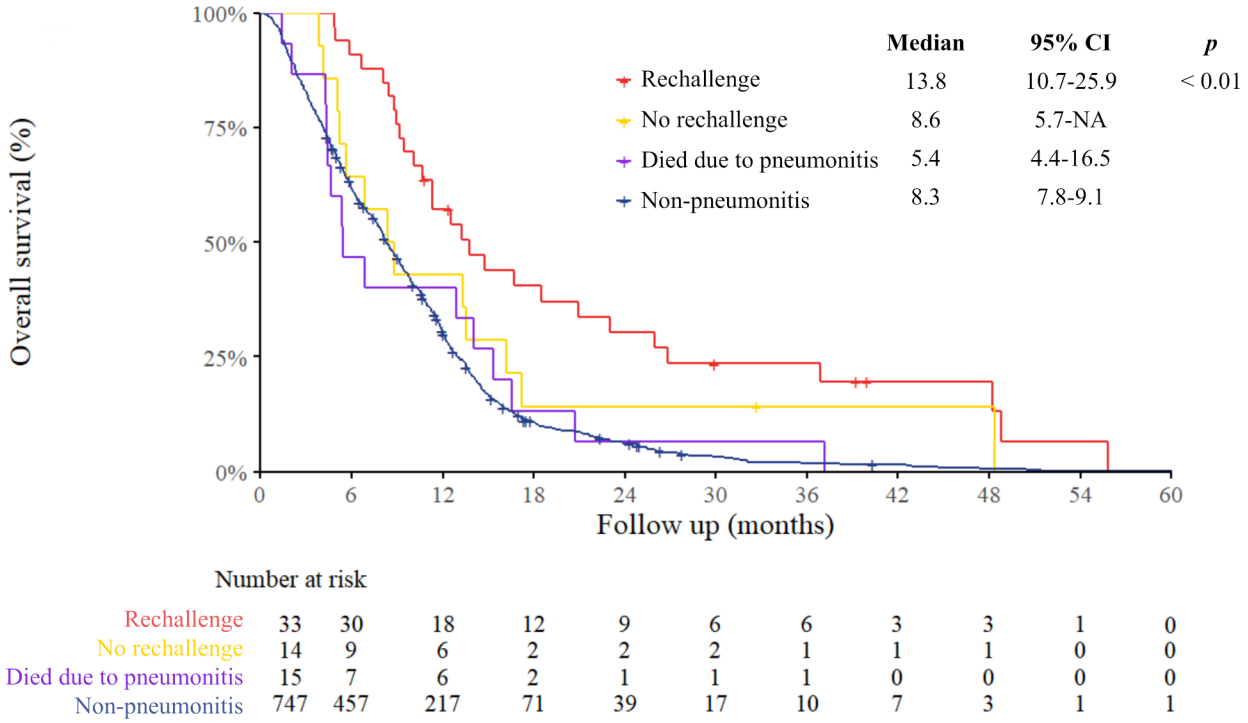

Fig. 4 Subgroup analysis for overall survival in patients who were rechallenged, without rechallenge, who died due to ILD, and who did not experience ILD events

Eight patients refused endotracheal tube intubation, and 6 died during these episodes. Eleven patients received intubation and mechanical ventilator support, and 4 died during these episodes. Of the 14 patients who received treatment rechallenge, three recurred (21.4%).

In the survival analysis, the median OS was longer in patients with interstitial pneumonitis without an alternative etiology, but there was no significant difference compared to pneumonitis with an alternative etiology: 13.3 vs. 10.1 months, $P = 0.61$ (Figure S3).

Discussion

In this retrospective study, we reviewed patients who received pancreatic cancer-related therapy at Taipei Veterans General Hospital and identified those who developed pneumonitis during treatment. Patients treated with nab-paclitaxel, gemcitabine and erlotinib had a greater risk of pneumonitis. Rechallenge is a feasible option because of rare pneumonitis recurrence, which can lead to a longer OS.

The diagnosis of drug-induced ILD was complicated because there was no single diagnostic examination. The Naranjo Adverse Drug Reaction Probability Scale was used to assess the possibility of drug-induced adverse effects [14]. However, several items could not be well-evaluated and may overestimate the probability. Besides, the recurrence and severity of ILD following rechallenge therapy cannot be predicted with this scale [5]. Therefore, this scale was not very useful to evaluate drug-induced ILD.

Previous studies have linked pancreatic adenocarcinoma therapies such as nab-paclitaxel, erlotinib, and gemcitabine to drug-induced ILD. Our analysis confirms these associations. Compared with other therapies, nab-paclitaxel treatment was associated with a greater incidence of pneumonitis (10.1%), consistent with previous findings ranging from 2.2–18.9% [3, 9, 11]. Despite these lower rates, gemcitabine and erlotinib remained significant risk factors for pneumonitis.

Various studies have explored additional risk factors for drug-induced ILD in cancer therapies. Umemura et al. [6] reported that prior thoracic radiotherapy and preexisting pulmonary fibrosis were independent risk factors for ILD in patients who received gemcitabine therapy. Other studies have also shown that gemcitabine combination therapy with paclitaxel, docetaxel, S-1 (tegafur/gimeracil/oteracil) or erlotinib increases the risk of ILD [6, 19, 20]. In a postmarketing surveillance study of gemcitabine combined with erlotinib, previous or concurrent lung disease and metastasis to three or more organs were identified as significant risk factors [10]. Another study identified ABO blood type B as an independent risk factor for gemcitabine- and nab-paclitaxel therapy-induced ILD [11]. However, in the present study, in addition to cancer-related therapy, only prior lung disease, including COPD, asthma, pre-existing ILD, lung cancer, lung

metastases, and tuberculosis, was an independent risk factor for pneumonitis.

When pneumonitis occurred, more than half of the patients experienced severe hypoxia with ARDS within days. Despite the high mortality rate in patients with ARDS (45.5%), intubation with ventilator support was recommended because the mortality rate was significantly lower in patients with intubation and ventilator support who had a better prognosis.

Although cancer-related therapies can trigger interstitial pneumonitis, it is essential to explore other potential causes. Our study conducted a thorough investigation into etiologies among hospitalized patients, revealing infectious diseases in 49.1% of cases and highlighting their role in pneumonitis during cancer therapy. Rechallenge therapy, although useful for diagnosing drug-induced ILD, carries risks of recurrence, which can be life-threatening. Despite some caution against nab-paclitaxel rechallenge, given its association with ILD recurrence [16], we cautiously reintroduced cancer therapy after pneumonitis recovery, with patient consent, regardless of the identified etiology. Most patients tolerated chemotherapy without pneumonitis recurrence. All pneumonitis patients without an alternative etiology didn't experience pneumonitis recurrence. Only three individuals with pathogens identified in the first pneumonitis episode experienced recurrence, with two cases linked to specific pathogens identified during the pneumonitis episodes. Despite one fatality due to pneumonitis recurrence resulting from infection, rechallenging cancer therapy after full recovery appears generally safe, with necessary precautions against pathogens during treatment.

This study revealed that patients with pneumonitis had longer OS than those without pneumonitis, regardless of whether they had received nab-paclitaxel treatment. This study also revealed a great disease control rate (77.6%), which is comparable to previous studies and clinical trials. Further subgroup analysis of patients with stage IV pancreatic cancer between 2018 and 2020 to eliminate the heterogeneity of cancer status revealed that those with pneumonitis had better OS than those without pneumonitis. Additionally, another subgroup analysis revealed that patients who underwent rechallenge after pneumonitis had longer OS than did those who did not, those who died due to pneumonitis, and those without pneumonitis. Therefore, this study suggested that the survival benefit in patients with pneumonitis is linked to treatment rechallenge, which extends the use of effective treatments.

This study has several limitations. First, its retrospective nature may have led to recall bias and could have led to missed patients with mild pneumonitis. Second, many individuals with mild symptoms treated as outpatients were not thoroughly evaluated for pneumonitis causes, potentially underestimating the incidence of infectious disease. Third, not all patients underwent treatment rechallenge, which may have resulted in selection bias. Nevertheless, the findings of this study support the use of cancer-related rechallenge therapy in these patients. Additionally, the assessment of patients with different disease statuses together may have influenced the results due to heterogeneity. Nevertheless, subgroup analyses indicated better OS in patients who underwent rechallenge treatment. Further prospective studies are necessary to explore the relationship between pneumonitis and survival.

Conclusions

Most pneumonitis was not directly induced by cancer-related therapy, and self-protection from possible infection was recommended. Treatment rechallenge after an pneumonitis episode during pancreatic cancer therapy is a viable approach since pneumonitis recurrence is uncommon, not only in patients with an alternative etiology, but also in patients without an alternative etiology, which may be diagnosed of drug-induced ILD. Treatment rechallenge could extend the use of effective medicine, resulting in better OS. However, treatment rechallenge should be performed under strict monitoring because pneumonitis recurrence is still a potentially fatal complication.

Abbreviations

CI	Confidence interval
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
EBV	Epstein–Barr virus
HR	Hazard ratio
HSV	Herpes simplex virus
ILD	Intestinal lung disease
nab-paclitaxel	Nanoparticle-albumin-bound-paclitaxel
OS	Overall survival
PFS	Progression-free survival
P:F	PaO2:FiO2

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13896-5.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Acknowledgements

Part of the study data is based on the Cancer Registry Data Base, Taipei Veterans General Hospital. We also thank the Clinical Research Core Laboratory

and Medical Science & Technology Building of Taipei Veterans General Hospital for providing experimental space and facilities.

Author contributions
HY Yu helped to perform statistical analysis and write this manuscript. CY Lee helped to collect data and statistical analysis. YC Hu helped to collect data and formal analysis. LG Lin helped to collect data and data curation. Y Chao supervised this study and helped to review this manuscript. CP Li designed this study and helped to review the manuscript.

Funding
This work was supported by grants from the Taipei Veterans General Hospital (V110C-087, V111C-164, V112EA-007, V113C-154, V113EA-010, and VGHUST113-G6-2-2), Ministry of Science and Technology (MOST 109-2314-B-075-030, MOST 111-2410-H-075-002), VGHUST113-G6-2-2, snd Yin Shu-Tien Foundation Taipei Veterans General Hospital-National Yang Ming Chiao Tung University Excellent Physician Scientists Cultivation Program, No. 113-V-B-062.

Data availability
Data is provided within the manuscript and supplementary information files.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declarations of Helsinki and Istanbul and approved by the Institutional Review Board (IRB) of Taipei Veterans General Hospital (approval number 2019-09-001AC). The need for consent to participate was waived by the IRB of Taipei Veterans General Hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 1 July 2024 / Accepted: 10 March 2025
Published online: 19 March 2025

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