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Risk factors and management of lung cancer in idiopathic pulmonary fibrosis: A comprehensive review

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Abstract. Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease. Lung cancer (LC) is among the most crucial comorbidity factors in patients with IPF. IPF patients that are diagnosed with LC have a reduced mean survival time. Therapeutic strategies for LC in patients with IPF need to be adapted according to the individual treatment risk. Life-threatening acute exacerbation (AE) of IPF may occur in association with cancer treatment, thereby severely restricting the therapeutic options for IPF-associated LC. Because LC and anticancer treatments can worsen the prognosis of IPF, the prevention of LC is as critical as managing patients with IPF.

Key words: idiopathic pulmonary fibrosis, lung cancer risk, fibrosis-associated lung cancer, management strategies, pulmonary fibrosis and cancer

Introduction

Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease that is characterized by progressive dyspnea and decrease in lung function. The delayed disease progression in IPF patients has led to an increased prevalence of comorbidities. Among the significant comorbidities in IPF patients is lung cancer (LC), with an incidence density of 25.2 cases per 1000 person-years (1). The links between pulmonary fibrosis and LC are based on the shared genetic, molecular, and cellular processes that connect both diseases. Management of IPF patients with LC need to be tailored based on individual risks and the prognosis of both LC and underlying IPF. It is important to note that life-threatening acute exacerbation (AE) of IPF may occur in association with cancer treatment. Given the known negative impact of LC and anticancer treatments on the prognosis of IPF, the prevention of LC is of utmost importance in managing patients with IPF. This review article aims to consolidate the current state of knowledge especially on the pathogenetic commonalities between IPF and LC. Additionally, it will focus on the therapeutic data pertaining to both diseases, providing a comprehensive overview of the interplay between IPF and LC.

Epidemiology

The incidence of LC in individuals with IPF is higher compared to the general population, with a relative risk ranging from 7 to 14 (2,3). A multicenter, retrospective study conducted across seven European countries identified 324 cases of LC among 3178 IPF patients, and the authors reported cumulative incidence rates of 5.5%, 11.4%, 14.1%, and 26.6% at 1, 3, 5, and 10 years, respectively (4). The estimated prevalence of LC in individuals with IPF was found to be 6.4% to 13.74% (4-6). Predisposing factors for the development of LC in individuals with IPF encompasses diverse features in different studies; high pack-years of smoking, concomitant emphysema, high % vital capacity (7), male gender,

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current smoking at the time of IPF diagnosis, rapid annual decline of 10% or more in forced vital capacity (FVC) (8). Lung cancer in IPF patients is closely related with short survival, the median survival time is reported to be 38.7 months (9). A recent study found that patients with IPF and LC had a higher risk of all-cause mortality compared to IPF patients without LC, with a hazard ratio (HR) of 1.51 ([95% CI: 1.22–1.86], $p < 0.0001$) (4). Not only the subgroup of ILD, but also presence of any interstitial lung abnormality (ILA) is a predictor for survival. Zhu et al. (10) reported 765 newly diagnosed non-small cell lung cancer (NSCLC) cases, 101 (13.2%) cases experienced ILA at the time of NSCLC diagnosis. Authors showed that the presence of ILA in NSCLC patients was significantly associated with a shorter overall survival (OS) period than those without ILA (751 days vs. 445 days, HR 0.6, $p = 0.001$) (10).

Pathogenesis

The pathogenesis of ILDs, specifically IPF, shares similarities with cancer development, a variety of genetic and epigentic alterations that promote aberrant activation of the same transduction pathways, such as Wnt/b-catenin and phosphoinositide 3-kinase/protein kinase B. They involve various factors such as abnormalities in epithelial cells ranging from metaplasia to carcinomatous transformation, alterations in cellular bioenergetics, release of soluble mediators, and aging-related processes including telomere attrition and aberrant activation of developmental pathways and alterations in several essential biological processes for cellular functions such as autophagy, endoplasmic reticulum (ER) stress/unfolded protein response (UPR) and apoptosis, that are also hallmarks of ageing (Figure 1).

In IPF an ongoing interaction between metaplastic epithelial cells with accumulated genetic alterations and activated mesenchymal cells triggers cancer initiation and progression, whereas cell transformations to mesenchymal phenotypes, including epithelial and endothelial to mesenchymal transition, significantly contribute to tumor metaplasia, invasion, and metastasis. Genetic factors play a role in both IPF and lung cancer, with certain genetic loci associated with both conditions. Mutations in surfactant protein genes (such as SFTPA2) have been identified in IPF and have been linked to impaired protein secretion, endoplasmic reticular stress, apoptosis, and the development of various lung cancer types, including bronchoalveolar cell carcinoma and adenocarcinoma. These mutations are often observed in cases of isolated IPF or IPF with atypical bronchiolar epithelial proliferation (11). Additionally, genetic alterations in microsatellites located in chromosomal regions 8p21.3-q11.1 and 17q11.2-q2 have been implicated in the genetic basis of IPF and are also frequently detected in cancer. These alterations may help explain the higher risk of tumorigenesis observed in IPF patients (12). Imbalances between oncogenes and tumor suppressor genes have also been observed in IPF. A study analyzing p53 gene mutations and expression in tumor tissues from LC-IPF patients found that p53 mutations were present in 57% of cancer cells and 26% of squamous metaplasia cells in the analyzed samples (13). It has been demonstrated that those mutations in p53 are associated with increased expression and apoptosis resistance in patients with IPF and in patients with lung cancer (14) (Figure 2).

It should be underlined that a low frequency of KRAS mutations in lung cancer which are otherwise known Tobacco-associated KRAS mutations characteristic of lung cancer, are detected with low frequency in IPF-lung cancer, despite the high percentage of smokers, therefore implying other, endogenous carcinogenic mechanisms linked to lung fibrosis (15). Advanced molecular techniques, including genome-wide association approaches, have identified two germline mutations (in TERT and CDKN1A genes) that are associated with increased risks of IPF in a majority of patients. This suggests the presence of common genetic factors that contribute to the development of both lung cancer and fibrosis (16). Telomerase, which plays a differential role in fibrosis and tumorigenesis, has been investigated. The expression of TERT and TERC genes, which are components of telomerase, was significantly lower in the lung tissue of IPF patients compared to non-small cell lung cancer (NSCLC) tissues and controls (17) (Figure 1). IPF and lung cancer have common environmental risk factors (ie, smoking, occupational and environmental exposures), and both are characterized not only by an accelerated aging process (18), but they exibit similar methylation profiles as well (19,20), with aberrant expression of certain noncoding RNAs such as miR-21, miR-29 and let-7d, that either up- or downregulated play an important role

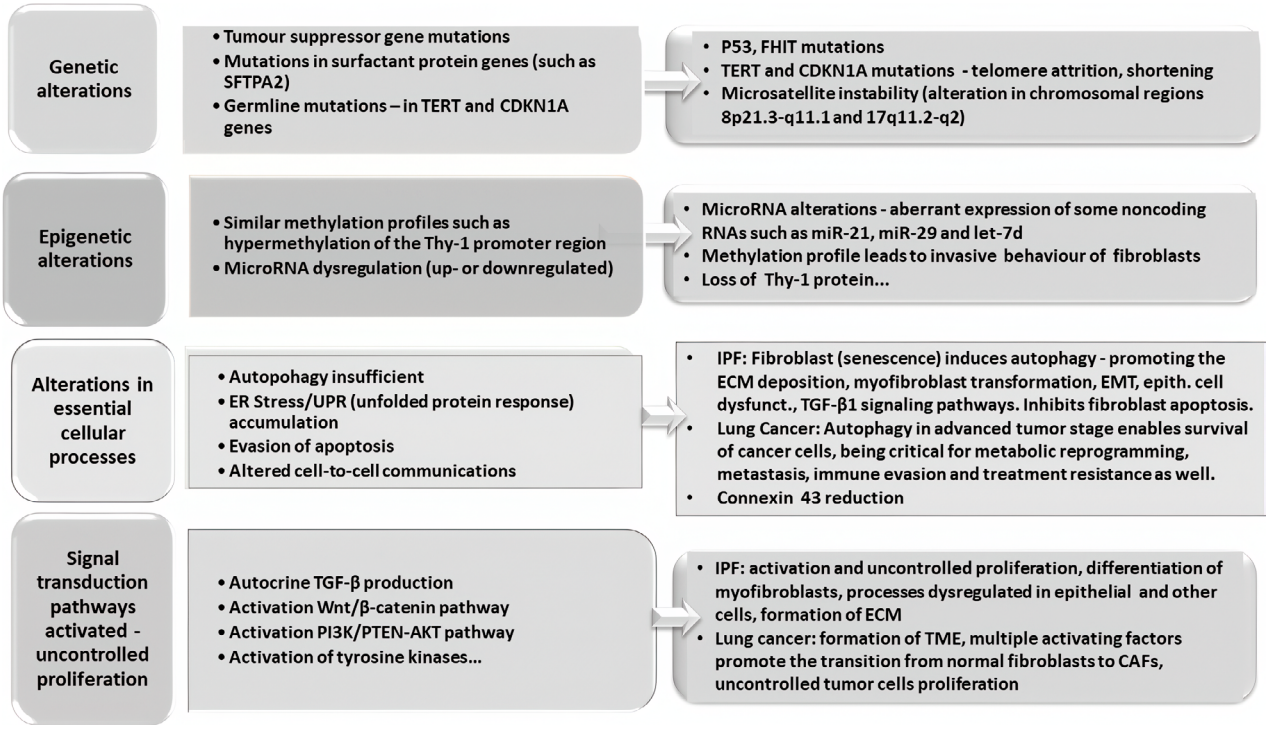

Figure 1. Pathogenetic similarities between IPF and cancer.

Common Genetic and Epigenetic Pathogenic Mechanisms between IPF and Lung

Genetics	
SFTPA2	Germline mutations in families with IPF and LC
SFTPA1	Germline mutation in families with IPF and LC
TERT	Germline mutation in patients with IPF-LC
p53	Mutant and upregulated in IPF and IPF-LC lung tissue
p21	Mutant in IPF and IPF-LC lung tissue
KRAS	Upregulated in IPF-LC lung tissue
CA125, CA 19-9	Increased expression in IPF lung tissue
FHIT	Loss of heterozygosity in *FHIT* chromosomal locus in IPF lung tissue and sputum
MET	Mutant in IPF-LC lung tissue
BRAF	Mutant in IPF-LC lung tissue

Epigenetics	
miR-21	Upregulated in IPF and LC tissue samples/association with poor clinical outcomes
let-7d	Downregulated in IPF/down- or upregulated in LC
miR-29	Downregulated in IPF and LC lung tissue and BAL cells

Figure 2. Common Genetic and Epigenetic Pathogenic Mechanisms between IPF and LC
Modified from Tzouvelekis A. et al. Common Pathogenic Mechanisms Between Idiopathic Pulmonary Fibrosis and Lung Cancer. CHEST 2019; 156(2):383-391.

in both, dvelopment of fibrosis and carcinogenesis (21,22). The most important cells that are common in pathogenetic processes of both IPF and LC are fibroblasts. Fibroblasts originate from different lung resident cell populations such as the interstitial lung fibroblasts, the lipofibroblasts, lung resident mesenchymal stromal cells (LR-MSCs), the perycites and mesothelial cells, aside from the contribution of both, epithelial cells in EMT and circulating fibrocytes (23,24). The stem-like 'universal' type of fibroblast cell, characterized by expression of peptidase inhibitor 16 (Pi16) and Col15a, have been found across normal tissues, having the ability to differentiate into specialized fibroblasts in the state of disease or injury where they change into highly activated fibroblasts (25). Fibroblasts display phenotypic divergence within the normal lung, while this heterogeneity is significantly more pronounced in diseases such as the IPF and (lung) cancer (26,27). There are prominent similarities between IPF fibroblast and cancer-associated fibroblasts (CAFs) (28,29). Myofibroblasts represent the key cells in IPF since their proliferation and activation under profibrotic trigger factors lead to the secretion and excessive deposition of extracellular matrix (ECM) proteins that increasingly cause stiffness of the lung parenchyma. Thus these cells become responsible for causing fibrosis (24,30). On the other hand, CAF are also key components of the tumor microenvironment (TME) that affects the biological features of the tumor, both favoring the tumour cells proliferation and dissemination as well as the resistance to systemic therapy. In both diseases, fibroblasts activated through inflammatory mediators and characterized by paracrine and autocrine signaling, play key role in development and progression (Figure 1). IPF is characterized by uncontrolled activation of fibroblasts, caused by increased inflammatory cytokines, (e.g. TNFα, IFNγ and IL-6) which are at the start secreted by inflammatory cells (e.g. macrophages). Activated IPF fibroblasts can secrete a variety of pro-fibrotic and pro-angiogenic signals that promote disease progression (31). Pro-fibrotic mediators secreted by activated fibroblasts continue to act on fibroblasts causing a positive feedback, and thus leading to production and deposition of ECM and myofibroblast differentiation (32). IPF fibroblast can activate healthy neighboring cells in IPF and this paracrine signaling in IPF fibroblasts is linked to overexpression of proinflammatory cytokine IL-6R, suppressor of cytokine signaling 3 (SOCS3), phospho-STAT3-Y705 and phospho-Smad3, while in addition fibroblasts proliferate faster, secrete more IL-6 and express higher levels of the soluble IL-6R. The IL-6/STAT3/Smad3 axis further ease cells' responses that could potentially promote fibrotic process. Interleukin-6 (IL-6) produced mostly by fibroblasts is elevated in lungs of IPF patients (33) and can foster fibrosis by governing chronic inflammation (34) and by activation of the TGFβ pathway (35-39), the most potent profibrotic cytokine, the key factor that promotes fibroblast differentiation into myofibroblasts (40) (Figure 3). It is worth noting that myofibroblasts

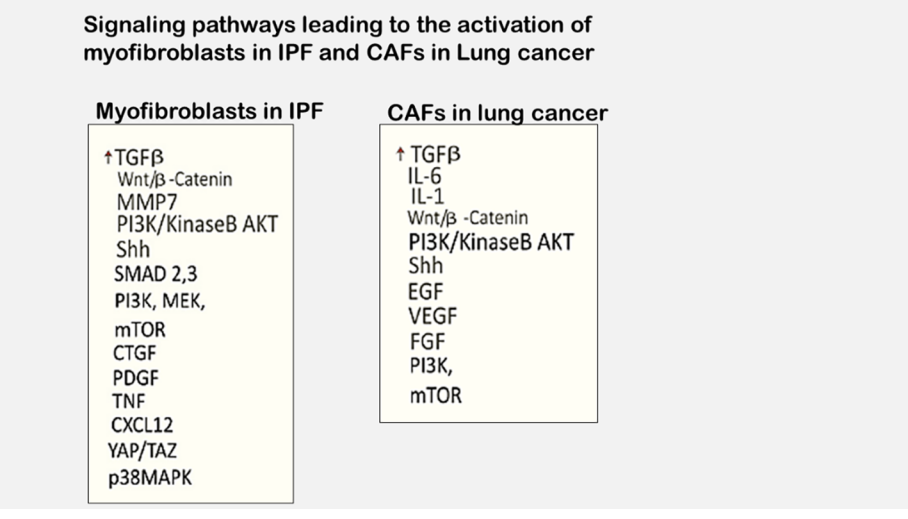

Figure 3. Signaling pathways that lead to activation of myofibroblasts in IPF and CAFs in lung cancer.

secrete more ECM than fibroblasts and are the main collagen-producing cells in the lung characterized by expression of contractile protein α-SMA and fibroblast activation protein (FAP), the latter essential for collagen remodeling (41). This interplay, IPF fibroblast interaction with the microenvironment, especially with the immune cells, has important role in the disease progression. The actively proliferating fibroblast foci contrast with neighboring areas of relatively normal parenchyma and over time move from subpleural regions towards central ones.

Cancer-associated fibroblasts, key cells of the TME, as are lung fibroblasts in IPF, represent a heterogeneous cell population originating from a variety of sources. Potential cellular origin of CAFs include local tissue resident stellate cells and normal fibroblasts and nonfibroblast lineage or recruited bone marrow-derived mesenchymal stem cells (MSCs) and macrophages. Tumor cells together with stromal cells trigger CAFs activation through inflammatory mediators such as transforming growth factor beta (TGF-ß1), interleukin (IL)-1, and interleukin (IL)-6 that play important roles in inflammation and carcinogenesis. In fact, multiple activating factors promote the transition from normal fibroblasts to CAFs in the tumor microenvironment (TME): tumor cell secreted growth factors (TGF-b, HGF, PDGF, EGF, CTGF, FGF), transcription factors (NF0kB, HSF-1), cytokines (interleukins), metalloproteinases, ROS/hypoxia, tumor cell-derived exosomes, microRNAs (23,24,42,43). Activation of CAFs can arise in response to damage-associated molecular patterns (DAMPs) released by damaged tissue or necrotic tumor cells, through pathways such as the NLRP3 inflammasome (44). Not only tumour cells, but endothelial, inflammatory and immune cells in the TME as well secrete mediators of fibroblast activation, whereas autocrine activation by activated fibroblasts production of factors and matrix occurs as well (45). A dynamic transformation of stromal fibroblasts in a context-dependent way occurs due to the plasticity of CAFs. They exibit different phenotypical and functional characteristics. Therefore, this phenotypic and functional diversity, and spatiotemporally dynamics of CAFs subtypes are regulated by complex molecular mechanisms, including genetic mediated by tumor cell-derived factors, epigenetic modulation by direct contact between tumor cells and CAFs, and metabolic reprogramming. These mechanisms can act independently or cooperate to define the structural and functional characteristics of stroma, which then result in tumor suppressive or tumor supporting effects of CAF subpopulations in a context-dependent way. As CAFs interact with cancer cells and other stromal cells, as noted above they are characterized by secretion of different kinds of cytokines and chemokines, growth factors and extracellular matrix proteins involved in cancer cell proliferation, invasion, metastasis and chemoresistance. Thus secretion of TGFβ, PDGF, IL-6 is important for cancer cell proliferation, EMT with ECM remodeling and secretion of HGF, IL-6, HIF-1 for invasion and metastasis, VEGF for tumour angiogenesis. Regarding chemoresistance CAFs may create physical milieu through ECM remodeling, ECM stifness and increased expression of collagen, hyaluronan, fibronectin, along with crosstalks with cancer cells leading to acquisition of stemness, inhibition of apoptosis and induction of EMT (46-56) (Figure 3). The main subsets of CAFs include myofibroblast-like CAFs (myCAFs), inflammatory CAFs (iCAFs) and recently characterized novel, antigen-presenting CAFs (apCAFs), all of them having diverse biological characteristics and leading to phenotypical diversity and functional heterogeneity in cancer development. Furthermore, the distinct subsets of CAFs have the ability to convert one into another via modulation of specific signaling, such as the conversion between iCAFs and myCAFs via the TGFβ or IL-6 signaling pathway of CAFs, reflecting their plasticity (57). MyCAFs characterized by myofibroblastic features and ECM remodeling express dual tumor-restraining and tumor promoting activities, dependent on the disease stage and the multiplex, complicated surrounding TME, whereas iCAFs are generally tumor-promoting by secreting of inflammatory cytokines and growth factors such as IL-6, IL-11, LIF, CHCLs (58), thus leading to proliferation, metastasis and chemoresistance of cancer cells (59). ApCAFs featured by the expression of major histocompatibility complex class II molecules that suggests their immunodulatory function of CAFs (60). Available data suggest context-dependent tumor-promoting or tumor-suppressive effects of apCAFs differing among specific tumour types. In lung cancer apCAFs have a role in T-cell immunity against lung tumors (61) (Figure 3). Recent studies have demonstrated the powerful immunosuppressive properties of stroma as a key mechanism by which stroma can foster tumor progression and cause

resistance to immunotherapy, regulating cancer-associated inflammation and antitumor immunity, the latter due to the interactions between CAFs and immune cells. CAFs can influence immune cell infiltration either directly—via secreted cytokines and chemokines and cell surface proteins—or indirectly—through deposition of different ECM components and remodeling ECM on which immune cells functioning depend (42,62). Novel CAF subsets that vary in their functions have been discovered as well in diverse cancer types ocurring at different disease stages, and consequently having differing roles in cancer development (63). For example LRRC15+ CAFs, are the dominant CAF population under TGF-β signals over tumor ocurrence and progression exibiting the suppression of antitumor immunity of cytotoxic T cells (64), while CD10+ GPR77+ CAFs correlate with chemoresistance by sustaining cancer stemness potentially serving as a prognostic factor in lung cancer (65). There are other pathogenetic mechanisms that take part in both disease. In IPF, the compression force exerted during alveolar constriction (66) can lead to the shrinkage of intercellular space, creating an environment enriched with growth factors and cytokines that promote tumor growth (67). The mechanical stretch and increased stiffness of the extracellular matrix in IPF not only directly stimulate the proliferation signaling of local cancer cells but also awaken dormant cancer cells, potentially contributing to the progression of lung cancer (68).

IPF is also characterized by an increase in endothelial shear stress (69). Elevated circulatory shear stress levels have been shown to accelerate the expression of markers associated with epithelial-mesenchymal transition (EMT), such as TWIST1 and SNAI2, in lung cancer cells (70). In the context of lung cancer (LC), the interaction between the tumor and the surrounding stroma plays a significant role in tumor progression and metastasis. The stroma adjacent to the tumor shares common features with the fibrotic tissue observed in pulmonary fibrosis, which is characteristic of IPF. It has been reported that this peritumoral stroma facilitates the development of a mesenchymal phenotype in tumor cells, promoting their invasive capabilities (71). IPF and lung cancer share common characteristics in terms of aberrant activation of key signaling pathways involved in both diseases. One such pathway is the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway, which has been implicated in fibroproliferative disorders (72). The deregulation of PI3K can lead to the activation of various downstream profibrotic mediators, including TGF-b1 and platelet-derived growth factor. As a result, targeting PI3K has been suggested as a potential therapeutic approach for both IPF and lung cancer (73). Tumor transforming growth factor beta (TGFβ) has been implicated in the process of fibrogenesis. Under normal conditions, TGFβ exerts an anti-proliferative effect on epithelial cells while activating the Wnt/β-catenin signaling pathway, which transforms fibroblasts into myofibroblasts (74,75). Abnormal activation of the Wnt/β-catenin pathway has been observed in fibrotic areas of lung tissue samples obtained from IPF patients. TGF-b signaling is recognized as a key profibrotic pathway and mediator of the epithelial-mesenchymal transition, EMT, which is not only the major feature of IPF, but also been shown to be involved in cancer progression and its ability to metastasize (76). This GF represents one of key inflammatory mediators through which tumour and stromal cells trigger CAFs activation and is essential in cancer cells proliferation. Available data point that this pathway may also play a role in squamous dysplasia and the promotion of squamous carcinoma differentiation (77).

Management of IPF patients with LC

Although the relationship between LC and pulmonary fibrosis is well known, there is a significant lack of knowledge in the diagnosis and treatment management of patients with these two clinical entities. As noted in an international survey called DIAMORPHOS (Diagnosis and Management of Lung Cancer and Fibrosis), only five areas of interest reached consensus among participants, while 28% of participants reported no awareness (78). In ILD patients, the diagnostic approach for LC needs to be carefully considered due to the fragility of these individuals. Tzouvelekis et al. (79) proposed an algorithm that includes annual high-resolution computed tomography (HRCT) screening for LC in all IPF patients (Figure 4). For nodules with a diameter of ≥8 mm, PET-CT scan is highly recommended. If the PET-CT scan shows indications of tumor lesions, the authors suggested proceeding with minimally invasive diagnostic procedures such as transthoracic needle biopsy (TTNB) for peripheral lesions

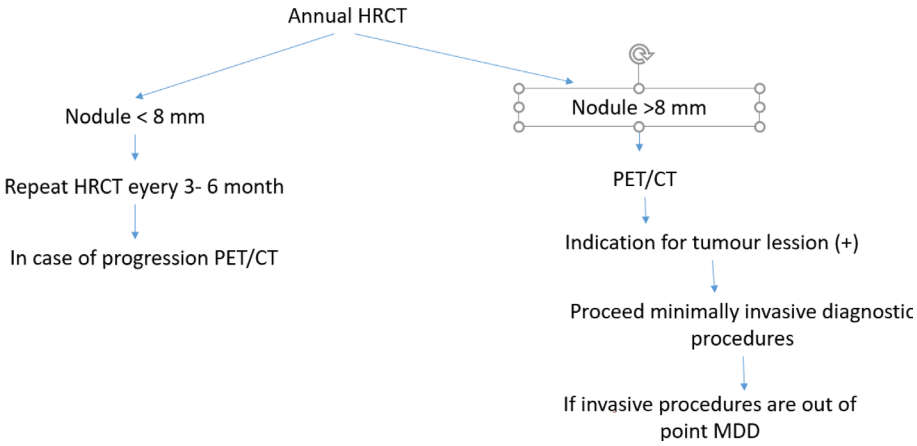

Figure 4. An algorithm for diagnostic approach for lung cancer in IPF patients (79).

or endobronchial ultrasound-guided transbronchial needle biopsy for pathological lymph nodes.

The treatment of LC in the context of ILD presents challenges, especially in elderly patients with reduced respiratory reserve. It is well recognized that idiopathic or treatment-induced AE can occur in patients with ILD, including those undergoing anticancer treatments. AE in IPF has significant prognostic implications, with approximately 40% of deaths in IPF being preceded by an AE (80). Risk factors for cancer treatment-related AE in idiopathic interstitial pneumonia (IIP) include the presence of usual interstitial pneumonia (UIP) pattern on chest CT and a decrease in FVC by 10% or more (81). In the same study, the incidence rates specific to different treatment modalities were reported as 7.5% for surgery (3 out of 40 patients), 10.0% for chemotherapy (5 out of 50 patients), and 7.7% for radiation therapy (2 out of 26 patients).

Surgery

The gold standard treatment for early-stage NSCLC is lobectomy and lymph node dissection. However, managing NSCLC in patients with underlying ILD, particularly IPF, poses challenges. In stage I-IIIA NSCLC patients with fibrosing interstitial lung disease (fILD), lobectomy or video-assisted thoracoscopic surgery (VATS), while without adjuvant chemotherapy is recommended as a standard therapeutic strategy only in stage IA disease (82). A recent study by Tane et al. (83) introduced an alternative procedure called the "simple deep wedge resection technique," which is a practical and fast stapler-based procedure that avoids dissecting vessels or bronchi in NSCLC patients with IPF. This technique, although not been regarded as radical operation for lung cancer, resulted in no cases of acute exacerbation.

The presence of IPF and ILA in patients with LC undergoing curative surgery are associated with increased complications and decreased survival (84). A systematic review reported 3-year overall survival rates of 31% to 75% for patients with ILD compared to 79% to 95% for patients without ILD following radical surgical resection (85). A recent study suggested that surgically treated patients with IPF and operable LC may have a survival benefit compared to patients who did not undergo surgical resection (4). So, early identification of these patients appears crucial to increase the percentage of patients diagnosed at an operable stage, underlying the importance of screening for lung cancer in IPF patients. Additionally standard adjuvant systemic therapy (either chemotherapy alone, or sequential chemo- and targeted or immunotherapy) or adjuvant radiation therapy, represent a distinct problem that needs to be considered by multidisciplinary team (MDT). Predicting the incidence of postoperative AE in IPF patients can be challenging. A large Japanese cohort study identified several risk factors for AE after lung cancer surgery (Table 1) (86).

Various supportive treatments, such as intraoperative fluid balance control, postoperative ulinastatin, preoperative methylprednisolone, and sivelestat, may prevent postoperative AE in IPF patients (87-89).

Table 1. Predictive factors for the postoperative AE in IPF patients (86).

Predictive factor
Low % vital capacity
History of AE
Surgical procedure
UIP pattern
Male gender
Steroid use
Elevated KL-6 concentration

Antifibrotic drugs, such as pirfenidone, have also been studied for their potential impact on the incidence of postoperative acute exacerbation in patients with IPF and NSCLC. The phase II PEOPLE study evaluated the safety and efficacy of perioperative pirfenidone treatment in reducing postoperative AE in LC patients with fibrosis. The study showed that the incidence of AE among patients treated with pirfenidone was significantly lower, and no serious adverse events caused by pirfenidone were observed (90).

Chemotherapy

In advanced stages of lung cancer, chemotherapy is often used as a treatment option, either as monotherapy or combined, along with targeted therapy in oncogene driven NSCLC and immunotherapy in non-oncogene driven NSCLC. However, the decision to use above listed systemic therapy in patients with IPF should be carefully considered by assessing the risk/benefit balance. Platinum-based cytotoxic chemotherapy is commonly used in NSCLC patients with IPF. A phase II trial involving 18 patients with advanced NSCLC and interstitial pneumonia, including some with IPF, showed that combination chemotherapy with carboplatin and paclitaxel had significant antitumor efficacy and an acceptable safety profile (91). Gemcitabine plus cisplatin can be considered an alternative treatment for patients with pulmonary squamous carcinoma and IPF (92). In cases of platinum-refractory advanced NSCLC (stage IIIB, IV, or relapse) with preexisting IPF, second-line docetaxel monotherapy may be an option (93). The addition of bevacizumab is recommended to be considered for fit nonsquamous NSCLC patients. Vinorelbine (for squamous histology) and pemetrexed (for adenocarcinoma histology) monotherapy are recommended as second-line treatment options in these patients (82). The standard systemic treatment for limited-stage (LS) involves systemic chemotherapy combined with radiotherapy, while for extended-stage (ES) SCLC chemotherapy in combination with immunotherapy. For decades carboplatin and etoposide given for four or six cycles are the established standards regimen of chemotherapy for SCLC (82). It is important to note that chemotherapy can induce AE of IPF, the incidence of such exacerbation has been reported to be 13.1% (94). Althugh rarely, chemotherapy can also lead to drug-induced interstitial pneumonitis by the cytostatic drugs administered in LC. A retrospective study reported that 7.2% of patients developed chemotherapy-induced ILD, and preexisting ILD was identified as a risk factor for this complication. The study also found that a UIP pattern and lower values of FVC were independent risk factors for chemotherapy-related ILD (95). Vinorelbine and paclitaxel are rarely associated with drug-induced ILD. Patients have similar AE incidence rates of 10% and 13%, respectively after cisplatin or carboplatin therapy. Docetaxel has a higher incidence of 28%, while etoposide is associated with a 24% incidence. On the other hand, paclitaxel has a lower incidence of 3% (96). PD-1/PD-L1 inhibitors have been linked to an increased risk of pneumonitis in different grades. The risk ratios (RR) for grade 1-5 and grade 3-5 pneumonitis are 5.17 (95% CI: 2.82–9.47, $p < 0.001$) and 4.14 (95% CI: 1.82–9.42, $p < 0.001$), respectively (97).

Several studies have reported response rates and outcomes of chemotherapy in patients with ILD and LC. A meta-analysis of seven studies involving 251 patients with stage IIIA, IIIB, or IV LC-ILD showed a response rate of 41.3% and a disease control rate of 77.7% with chemotherapy. The median progression-free survival (PFS) was 4.4 months, and the OS was 8.5 months in this study (98). Another study showed that ILD was a significantly unfavorable factor for PFS and OS in NSCLC patients receiving chemotherapy (99). Similar results were reported in SCLC patients, a study involving 75 patients with IPF and SCLC revealed that patients with IPF had significantly shorter median PFS and OS compared to those without ILD. Multivariate analysis identified poor performance status, extensive disease stage, and the presence of IPF as factors associated with shorter OS (100). Due to the detrimental impact of AEs on patient survival, several studies have been conducted to explore preventive procedures during chemotherapy. A recent study investigated the prophylactic effect of

pirfenidone in preventing chemotherapy-associated AE of IPF in NSCLC patients (101). The study included 14 patients with IPF and NSCLC who received pirfenidone in combination with carboplatin and nanoparticle albumin-bound paclitaxel as first-line chemotherapy. The progression-free survival for IPF was 447 days (95% CI: 286–indeterminate days), and the cumulative incidence of AE-IPF within one year was 18%. No AE-IPF associated with first-line chemotherapy was observed. The authors concluded that the combination of pirfenidone with carboplatin-based regimens or ICIs could potentially serve as a safe first-line systemic therapy approach for patients with IPF and NSCLC.

Role of antifibrotics as a chemotherapeutic agent

Nintedanib, a triple tyrosine kinase inhibitor (FGFR, VEGFR, PDGFR inhibitor) is an agent known for its antifibrotic effects in IPF and its antitumor effects in malignant tumors as well. It targets receptor tyrosine kinases (RTKs) that are involved in various molecular pathways implicated in the development of LC and IPF. These RTKs, activated by growth factors, play a role in crucial cellular processes such as apoptosis, protein synthesis, metabolism, and the cell cycle. Dysregulation of these pathways has been associated with fibroproliferative disorders and cancer progression through the activation of profibrotic mediators like TGF-β1 and platelet-derived growth factor (102). Clinical trials, including phase I studies, have demonstrated the safety and tolerability of nintedanib in combination with chemotherapy for patients with advanced NSCLC (103,104). The efficacy of nintedanib in combination with cytotoxic chemotherapy was assessed in the LUME-Lung 1 and LUME-Lung 2 trials for the treatment of advanced NSCLC. In the randomized phase III trial (LUME-Lung 1) comparing docetaxel plus nintedanib with docetaxel plus placebo in previously treated NSCLC, it was found that PFS was significantly improved in the docetaxel plus nintedanib group (median 3.4 months vs. 2.7 months; hazard ratio [HR] 0.79, 95% CI 0.68-0.92) (105). Furthermore, overall survival was significantly improved in patients with adenocarcinoma histology in the docetaxel plus nintedanib group (median 12.6 months vs. 10.3 months; HR 0.83, 95% CI 0.70-0.99, p=0.0359). The LUME-Lung 2 trial investigated the efficacy and safety of nintedanib plus pemetrexed in patients with pretreated non-squamous NSCLC (106). Although recruitment was stopped prematurely, subsequent analysis showed a significant improvement in PFS favoring the nintedanib/pemetrexed group over the placebo/pemetrexed group (median 4.4 months vs. 3.6 months; HR 0.83, 95% CI 0.70-0.99, p=0.0435), with a manageable safety profile. While nintedanib has been reported as safe and tolerable in combination with chemotherapy for patients with advanced NSCLC, its efficacy and tolerability specifically in NSCLC patients with concurrent IPF have not been clearly defined. The J-SONIC study, a randomized phase 3 trial, was designed to compare the efficacy and safety of nintedanib plus chemotherapy (carboplatin plus nanoparticle albumin-bound paclitaxel) with chemotherapy alone in chemotherapy-naïve patients with advanced NSCLC and IPF (107). During the study, only a small proportion of patients (2.9%) experienced AE, and although the incidence was numerically higher in the nintedanib plus chemotherapy group, the difference between the two groups was not statistically significant. The low incidence of AE in this study may be attributed to the inclusion of patients at early stages of IPF and with better performance status. The overall response rate was higher in the nintedanib plus chemotherapy group compared to the chemotherapy group, and PFS was significantly improved with combination therapy. However, OS did not show a significant improvement in the overall population, although it was improved in patients with nonsquamous histology. No new safety concerns were observed, indicating that the presence of IPF did not exacerbate nonrespiratory adverse events. There are also case reports suggesting the potential efficacy of nintedanib monotherapy in NSCLC patients with IPF who are unable to tolerate cytotoxic chemotherapy. One case report involved an 82-year-old man with NSCLC and IPF treated solely with nintedanib (108). After nine months, a partial remission of the lung cancer was observed without exacerbation of IPF. This case highlights the possibility of nintedanib monotherapy in controlling lung cancer in patients with IPF. Another case involved an advanced NSCLC patient with IPF who showed disease progression after multiple lines of chemotherapy (109). The patient received the best supportive care and nintedanib was introduced to treat IPF. After one month, partial remissions of the primary tumor and pleural

dissemination were observed without severe adverse events. These cases suggest that nintedanib monotherapy could be an effective treatment option for NSCLC in patients with IPF who are unable to tolerate cytotoxic chemotherapy.

Pirfenidone (PFD) has been investigated for its potential preventive and treatment effects in LC, in addition to its recognized antifibrotic properties. In an experimental study, it was observed that pirfenidone monotherapy attenuated tumor growth and induced a T-cell inflammatory signature in tumors (110). Furthermore, when pirfenidone was combined with PD-L1 blockade, there was a significant delay in tumor growth and improved survival compared to either treatment alone. These findings suggest that pirfenidone may act as an adjuvant to immunotherapy in the treatment of cancer, particularly in lung cancer patients with preexisting IPF (110). One of the underlying therapeutic strategies for lung cancer is inhibiting epithelial-to-mesenchymal transition (EMT), which is a fundamental process where epithelial cells lose their polarity and acquire a mesenchymal phenotype. Pirfenidone exhibits broad anti-fibrotic effects, including the suppression of multiple cytokines and growth factors, such as transforming growth factor β (TGF-β), TGF-β is a potent inducer of EMT (111). In an experimental study conducted using NSCLC cell lines in vitro and in vivo, it was found that pirfenidone significantly inhibited TGF-β1-induced EMT. Although pirfenidone alone did not inhibit tumor progression in the in vivo examination, its combination with carboplatin significantly reduced tumor growth. This suggests that pirfenidone may hold promise as a therapeutic agent for the treatment of NSCLC by regulating EMT (112). In a study investigating the effects of pirfenidone in the tumor microenvironment, researchers demonstrated that pirfenidone induced apoptotic cell death in lung CAFs at a high concentration (113). Additionally, the combination of cisplatin and pirfenidone in NSCLC cells led to increased apoptosis and synergistic cell death. These findings suggest that the combination of cisplatin and pirfenidone may have activity in preclinical models of NSCLC, indicating a potential new therapeutic approach for this disease.

Pirfenidone has also been shown to attenuate the expression of collagen triple helix repeat containing 1 (CTHRC1), which is overexpressed in NSCLC and is involved in the Wnt/β-catenin signaling pathway implicated in carcinogenesis. This suppression of CTHRC1 may contribute to the anti-tumor effects of pirfenidone in patients with IPF who have concomitant LC (114). These mechanisms provide further insight into how pirfenidone may suppress LC in individuals with IPF.

Radiation therapy

Radiation therapy (RT), particularly stereotactic body radiation therapy (SBRT), is the standard treatment option for early-stage NSCLC in patients who are either not suitable for surgery, or refuse operation. However, guidelines from the European Organisation for Research and Treatment of Cancer recommend avoiding conventional radiotherapy in patients with lung cancer-associated interstitial lung disease (115). One of the most significant complications of RT is radiation pneumonitis (RP), an inflammation of the lung tissue caused by radiation, which if not timely treated, leads to definitive fibrosis. In a retrospective study of 101 patients with IPF and LC who underwent SBRT, RP occurred in 18% of patients (116). The extent of ILD involving more than 10% of lung parenchyma was identified as an independent risk factor for RP. Subclinical ILD was also found to be significantly associated with grade 2 to 5 RP in patients treated with SBRT (117). Another retrospective study of 242 patients with ILD and early-stage lung cancer receiving SBRT reported a severe RP rate of 12.4% and a mortality rate of 6.9%. Risk factors for poor outcomes included low FVC, more than 10% of normal lung receiving radiation, poor performance status, presence of squamous cell carcinoma, clinical stage T2, and regular use of steroids before SBRT (118). FDG PET/CT imaging can be useful in predicting the risk of RP. In a retrospective study of NSCLC patients, it was found that patients were 6.9 times more likely to experience at least grade 2 RP if their pretreatment FDG PET/CT showed a standardized uptake value $(SUV)_{95}$ greater than 1.5 for all lung parenchyma (119). Proton beam therapy (PBT) is an alternative option for patients requiring radiation therapy. PBT offers a rapid dose fall-off, which may minimize radiation exposure to normal tissues, making it an appealing option for patients with IPF. In a retrospective study comparing PBT and SBRT in 30 patients with early-stage NSCLC and IPF, severe treatment-related pulmonary complications were less common with PBT

(12.5% vs. 40.9%), and 1-year OS was better with PBT (50% vs. 26%) (120). However, another study reported an RP rate of 19.8% in NSCLC patients treated with PBT, including one case of grade 5 pneumonitis (121). Percutaneous image-guided thermal ablation (IGTA), using modalities such as radiofrequency ablation (RFA), microwave ablation (MWA), or cryoablation, is a minimally invasive treatment option for early-stage NSCLC. Local control with IGTA is comparable to sublobar resection and radiation therapy in the general population (122). However, in patients with preexisting ILD, there may be higher risks associated with IGTA. A retrospective analysis of ILD patients undergoing RFA reported a 7.1% mortality rate due to ILD-associated adverse events (123). In a systematic review of inoperable patients with early-stage NSCLC treated with RFA, mortality was 8.7% and ILD-specific toxicity was 25%, with lower mortality compared to SBRT (85). Percutaneous cryoablation may be an appealing option for NSCLC in patients with IPF, as it has shown lower morbidity compared to RFA and MWA (124). There is evidence from an experimental study that suggests the therapeutic potential of pirfenidone in treating radiation-induced pulmonary fibrosis. In a study conducted on mice that received thoracic radiation, treatment with pirfenidone resulted in an extended median survival time and reduced collagen accumulation and fibrosis in lung tissues compared to mice that did not receive pirfenidone (125). These findings suggest that pirfenidone may have a promising role in treating or minimizing radiation-induced pulmonary fibrosis.

Immunotherapy

It is known that immune checkpoint inhibitors (ICIs) can improve overall survival in advanced cancer (126). However, it is also known that ICIs have significant side effects, one of which is ICI-related pneumonitis that can be fatal in some patients (127). The incidence of pneumonitis related with drugs targeting the PD-1/PD-L1 axis has been reported as 11.8% (128). In a study that included 915 patients receiving anti-PD-1/PD-L1 mAbs treatment, the pneumonitis rate was given as 5%. Authors reported that 72% of those who developed pneumonitis were grade 1-2, and 86% of the patients who developed pneumonitis resolved with holding the drug or immunosuppressive treatment (127). It has been reported that toxicity may increase, especially when immunotherapy is given after radiotherapy, and ICIs may cause the development of radiation recall pneumonitis (129). Although pneumonitis is a well-known side effect of ICIs, no relationship has been found between the time of onset of pneumonitis and the severity of ILD. Moreover, no risk factors are known between patients with grades 1–2 ILD versus grades 3–5 ILD (130). Kato et al. defined some risk factors in their study, which included 111 patients who were started on nivolumab due to advanced stage NSCLC. The ILD development rate was given as 7.2% and it was stated that all patients who had ILD were older (>65), male, and had a smoking history (131). Moreover, combination ICI therapy, and tumor histologic type (squamous cell carcinoma) are also defined as risk factors for the development of pneumonitis (132). In a recent study, medical records of LC patients who received nivolumab, pembrolizumab, or combination ipilimumab and nivolumab reviewed, and authors concluded that independent factors associated with the development of pneumonitis were the presence of fibrosis on baseline CT (adjusted OR [aOR], 6.61; 95% CI, 2.48-17.7), a composite measure of obstructive lung disease (aOR, 2.79; 95% CI, 1.07-7.29), and treatment with pembrolizumab (aOR, 2.57; 95% CI, 1.08-6.11) (133). It is known that approximately 10% of advanced stage NSCLC patients have IP (134). Data regarding the use of ICIs in patients with ILD are conflicting. Some studies have reported that ILD patients are more prone to developing ICI-related pneumonitis (135,136). Shibaki et al (135**)** reported that the incidence of pneumonitis was higher in patients with pre-existing IP than in those without pre-existing IP (29% versus 10%). Yamaguchi et al (136) retrospectively reviewed data from 123 NSCLC patients with pre-existing pulmonary fibrosis who were treated with anti-PD-1 antibodies (nivolumab or pembrolizumab), and showed that anti-PD-1-related pneumonitis was observed in 18 patients (14.6%), and 3% of whom were ≥ grade 3. They reported that the only risk factor in the development of pneumonitis was a fibrosis score ≥1. Dobre et al. (137) reported similar results, they evaluated the clinical and radiologic outcomes of cancer patients (41 patients who were given pembrolizumab or nivolumab) with ILD. After treatment with ICIs, hypoxemic respiratory failure developed due to ILD or ICI-related pneumonitis in 3 patients (2 of the 3 cases were patients with a

UIP pattern), and all deaths owing to hypoxemic respiratory failure were in the UIP group. Moreover, they showed that the rates of ILD progression based on CT follow-up were higher in the UIP group (33.0%) compared with all other radiologic patterns (17.2%). They concluded that the presence of a UIP pattern may be a risk factor for increased cancer-related mortality such these patients. Another study, which included advanced NSCLC patients with chronic fibrotic idiopathic IP and given atezolizumab, was terminated early due to the high incidence of pneumonitis (29.4%) (138). The risk of ICIs related pneuminitis in patients with ILD may not warrant depriving patients of this treatment. A recently published meta-analysis, which included 179 patients with ILD-LC who received ICIs, reported that the overall response rate (ORR) rate was higher in patients with ILD (139). Similarly, in a study that included NSCLC patients, given nivolumab or pembrolizumab, grouped according to the presence of ILD, it was reported that the response rates, disease control rate, PFS and OS were similar in both groups (140). In a previous phase II clinical trial, the efficacy and safety of nivolumab in previously-treated, inoperable NSCLC patients with mild IIP was investigated (141). In this study, which included 18 patients, the 6-month PFS rate was reported as 56%, the response rate was 39%, and the disease control rate was 72%. Moreover, pneumonitis was observed in only 2 patients, and the authors commented that nivolumab may be an effective treatment for NSCLC patients with mild IIPs. There are data reporting that ICIs treatment is not only effective but also safe. In a study including 1836 cancer patients given ICIs, it was reported that only 1 patient had IPF before treatment, the time to development of ILD in this patient after 2 anti-PD1 infusions was 3 weeks, and improved rapidly after steroid treatment (130). Tan et al. (142) reported two combined pulmonary fibrosis and emphysema (CPFE)+LC patients who underwent surgical resections and received immunotherapy after progression of lung cancer. One patient suffered AE of ILD after immunotherapy and developed a progressive-fibrosing phenotype, but the other patient had no progression of the CPFE fibrosis. In another case report, Khunger et al. (143) reported that nivolumab was started in an IPF patient due to a diagnosis of squamous cell lung cancer, and the patient tolerated nivolimab treatment well, and his exercise tolerance, and oxygen reqirement improved after nivolumab. In the study examining 6 cases of IPF and LC who treated with PD1 inhibitors, authors reported that no patient developed ICIs-associated pneumonitis (144). It is known that IPF and LC share common bio-molecular characteristics, and the PD-1/PD-L1 axis is one of the common pathways between them. So, ICIs may play a role not only in cancer treatment but also in the treatment of pulmonary fibrosis. Animal studies have reported that inhibition of the PD-1 axis may have beneficial effects on pulmonary fibrosis (145). Abnormal PD-1 or PD-L1 expression in lung tissues of patients with IPF or pulmonary fibrosis murine models is known (146-148). It is also known that PD-1+ CD4+ T cells (mainly Th17 subsets) promote pulmonary fibrosis in IPF patients and murine specimens via signal transducer and activator of transcription 3 (STAT3)-mediated IL-17A and TGF-b production (145). Moreover, elevated concentrations of sPD-L1 in the serum of IPF patients have found when compared with healthy control group (146). Habiel et al. (147) showed higher levels of PD-1 proteins in humanized NSG mice. The results of this study demonstrated that IPF CD28null T cells may promote lung fibrosis but the immune checkpoint proteins, CTLA-4 and PD-1, appears to limit this effect. In a novel pulmonary fibrosis model in humanized mice study, authors demonstrated that PD-1/PD-L1 pathway–mediated immunosuppression contributed to the attenuation of pulmonary fibrosis by human mesenchymal stem cells (MSCs) (148). Another humanized IPF model in mice showed upregulation of immune checkpoint ligand CD274 (also known as PD-L1) on invasive lung fibroblasts (149). Authors showed that activating CD274 in IPF fibroblasts promoted invasion in vitro and pulmonary fibrosis in vivo, suggesting that CD274 may be a novel therapeutic target in IPF. So, it may be suggested that PD-L1 thus seems to be a promising target to pursue in the quest for new therapeutic options in IPF. These studies show that ICIs may be effective on fibrosis, so what effect may occur when ICIs is used together with antifibrotics? Qin et al. (150), investigated whether pirfenidone had a synergistic effect in lung cancer patients with comorbid IPF. They reported that PD-L1 blockade together with pirfenidone delayed tumor growth and extended the survival time. They also showed a benefit of combination therapy in alleviating the pulmonary fibrosis and reducing the tumor growth. Therefore, combining

anti-fibrotic agents with ICIs may bring potential benefits for IPF. There are also data reporting that antifibrotics may protect the development of ICIs related pneumonitis. In a case report, a 78-year-old man with squamous cell lung carcinoma + IPF underwent treatment with atezolizumab as 4th-line chemotherapy (151). After 1 cycle atezolizumab, pneumonitis developed. Authors prescribed prednisolone, and nintedanib was started as additional therapy. After three cycles atezolizumab, he remained stable without exacerbation of drug-induced pneumonitis. Authors concluded that addition of nintedanib to ICI therapy might prevent drug-induced pneumonitis or acute exacerbation of IPF. It is known that nintedanib is a VEGF inhibitor, and it exerts its immunosuppressive effect by inhibiting dendritic cell maturation and function, and increasing PD-L1 expression from dendritic cells. Therefore, nintedanib may prevent the development of ICI-associated pneumonitis by targeting the VEGF pathway. As a conclusion, all these data suggest that ICIs should not be uniformly withheld in patients with ILD and that a thorough risk–benefit analysis that includes pneumonitis risk must be conducted and tailored to the individual patient. Clinicians should be cautious when using ICIs in patients with preexisting ILD.

Prevention of lung cancer in IPF patients

The prevention of LC in patients with IPF is crucial due to the potential negative impact of LC and anticancer treatments on the prognosis of IPF. Studies have investigated the potential benefits of antifibrotic therapy in preventing lung cancer development in IPF patients. One study conducted by Miura et al. (7) compared the incidence of lung cancer in IPF patients with and without pirfenidone administration. The results showed a significantly lower incidence of LC in the group of patients treated with pirfenidone compared to those not receiving pirfenidone. Another retrospective study reviewed a cohort of 378 consecutive patients with IPF and classified them into two groups: IPF-antifibrotic therapy (+) and IPF-antifibrotic therapy (-) (152). During the observation period, a total of 35 patients developed lung cancer. The study found that the incidence and prevalence of LC development were significantly lower in the IPF-antifibrotic therapy (+) group compared to the IPF-antifibrotic therapy (-) group. The cumulative incidence of LC development was also lower in patients treated with antifibrotic therapy. Additionally, the mortality rate related to LC was lower in patients who received antifibrotic therapy. The study concluded that antifibrotic therapy was an independent low-risk factor for the development of LC in IPF patients.

Conclusion

In conclusion, IPF is a significant risk factor for the development of LC, and patients with IPF who develop LC have poorer survival outcomes. The diagnosis and treatment of LC in IPF patients are challenging due to the increased incidence of severe complications and the limited treatment options available. The management of LC in IPF follows similar approaches as in the general population, including chemotherapy, radiation therapy, and surgical intervention.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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