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Research Article

STAGING OF IDIOPATHIC PULMONARY FIBROSIS

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A B S T R A C T

Idiopathic Pulmonary Fibrosis (IPF) is relentless progressive interstitial lung disease (ILD) of unknown etiology (1). Main pathogenesis is aberrant recovery of epithelial injury and collagen deposition (2). Majority of IPF patients have been elderly men with smokers (3).The older, the more often have IPF (4).

Clinical point of view, non-productive cough, and progressive exertional dyspnea are main symptoms. In addition, scalene muscle hypertrophy, fine crackles and finger clubbing key findings (5).Serum marker such as lactate dehydrogenase (LDH), Krebs van den Lungeng-6 (KL-6) are sensitive for ILD detection and activity. Pulmonary function test (PFT) and 6-minute walk test (6MWT) are quite meaningful physiological examination. International IPF guideline published recently and highlighted on the importance of high-resolution computed tomography (HRCT) findings. Key findings of IPF are honeycombing, traction bronchiectasis and subpleural reticular opacity. However, baseline clinical physiological status can predict future prognosis of IPF. Recently some composite index were proposed for mortality prediction of IPF patients.In management, two anti-fibrotic agents such as pirfenidone and nintedanib are available for prevention of progression of IPF. In this review, I focus on clinical characteristics, staging and real management of IPF including comorbidities.

INTRODUCTION

IPF is irreversible progressive interstitial lung disease of unknown etiology (1, 2). IPF occurs usually elderly people over 50 with smoking history (3, 4). For diagnosis, chronic nonproductive cough and progressive exertional dyspnea with typical HRCT and pathological usual interstitial pneumonia (UIP) are essential. International guideline especially insist on the importance of HRCT findings such as subpleural distribution and honeycombing recently (3, 4). The pathological point of view, UIP is associated with many clinical conditions (1,6). Therefore, multi-disciplinary discussion including clinicians, radiologists and pathologists is important for diagnosis of IPF (3).

Clinical manifestations

Symptoms

Non-productive cough and progressive exertional dyspnea are key symptoms in IPF. Cough sometimes worse both on exercise and at night (7).

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Understanding triggering situation is important. In addition, cough predict disease progression (OR 4.97, 95% CI: 1.25-19.80, P = 0.02) independent of disease severity, and may predict time to death or lung transplantation (HR 1.78, 95% CI: 0.94-3.35, P =0.08) (8). Cough is associated with quality of life in IPF (9). When patient report more cough and heartburn on supine, we suspect gastroesophageal reflux and IPF (10). Regarding dyspnea, we should evaluate modified Medical Research Council dyspnea scale (11). Tracing the grade of dyspnea over time is quite important for IPF patients.Sensation of change of dyspnea grade is associated with forced vital capacity (FVC) (12).

Physical findings

General appearance is important for evaluation of nutritional status and body mass index (BMI) is associated with breathing workload. Neck have much useful information of chronic lung disease. Patients with moderate to severe restrictive disorder which often have hypertrophy of scalene muscle. Use of scalene muscle is prominent when patient develop acute exacerbation (5). Typical auscultation bilateral fine crackles (13,14). Fine crackles are early findings of ILD before fibrotic changes are detected by CT scan (15, 16). If IPF progress, crackles are heard from base to upper zones

(17). Extent of fine crackles have often have positive correlation with area of fibrosis in HRCT. Squawk is short phase high-pitched mixed sound including musical and non-musical sound. It is often heard chronic hypersensitivity pneumonitis (CHP) (18) and combined pulmonary fibrosis and emphysema (CPFE). Finger clubbing means chronicity of disease process. Approximately one third to half of IPF patients have clubbing. For ruling out important differential diagnosis, such as connective tissue disease (CTD), we should check arthralgia, myalgia, mechanic's hand and specific rash such as heliotrope rash and Gottron sign.

Laboratory findings

Classically, serum LDH is useful marker for activity of IPF and helpful parameter of severity of acute exacerbation (AE) of IPF (19). During acute phase, LDH is more sensitive for treatment response.KL-6 is reported to be a sensitive marker for ILD activity recently. KL-6 is associated with fibrotic area of HRCT and future exacerbation of IPF (20,21). Other epithelial or macrophage-related proteins such as surfactant protein-A(SP-A), SP-D, chemokine ligand-18(CCL18) and matrixmetalloproteinase-7(MMP-7) are associated with reduced survival (22-25). SP-D often have positive association with extent of ground-glass opacity (GGO) and negative association with percent FVC. Combined product of KL-6 and SP-D was found to highly correlate with %VC and %TLC. And this product are good indicators of the presence of fibrotic lesion in emphysema patients (26).

Pulmonary function test

FVC is robust parameter for prediction of mortality of IPF and is used as primary endpoint of many clinical trials in IPF (11). FVC is reliable, reproducible important indicator of future prediction in IPF (27). Reduction of FVC over 6 months predicts 1-year mortality. Minimal clinically important difference (MCID) of FVC absolute change is 2-6%.In the meantime, absolute change of FVC is used. However, if we identify over 10% decline in FVC patients, choosing relative change is not different (28). Diffusing capacity for carbon monoxide (DLco) is another important physiological parameter for IPF. However, if patient's vital capacity under1500 ml, the value is not reliable with single breath method. In addition, it is affected by respiratory infections, anemia. Therefore, reproducibility is not enough. 6 Minute walk test (6MWT) is classic physiological test for chronic lung disease. It is weakly correlated with other physiological function. In addition, 24-week decline of greater than 50 m in 6 MWT distance predict mortality (29). The estimated MCID of 6 MWT distance is 24-45 m.

Radiological findings

Chest radiograph

It is useful for evaluation of disease distribution and serial change of volume loss especially in lower lung field. Comparison of previous film is important for decision to start aggressive treatment. Imaging based volume loss sometimes precedes decline of FVC. In addition, IPF patients often have pulmonary hypertension (PH) in advanced stage. In these status, change of cardio-thoracic ratio and prominence of bilateral hilum are important information.

HRCT findings

HRCT provide useful information about anatomical location of disease process and key findings of IPF such as reticular opacity, traction bronchiectasis and honeycombing (4, 30). Honeycombing is manifested on HRCT as clustered cystic airspaces, typically of comparable diameters on the order of 3-10 mm. It is usually located subpleural and characterized by well-defined walls (31). And both peripheral linear shadow in upper lung field and heterogeneity are important findings of IPF. When we see atypical findings, we consider alternative diagnosis or require pathology for definite diagnosis. Both micronodules and air trapping suggest CHP. Extensive GGO, peri-broncho vascular predominant distribution suggests nonspecific interstitial pneumonia (NSIP) and CTD-associated ILD. And multi-focal peripheral consolidation is associated with organizing pneumonia (OP). If we see undetermined pattern, HRCT provide adequate site for surgical lung biopsy for definitive diagnosis. Integration of clinical and imaging information contributes to final diagnosis.

Bronchoalveolar lavage (BAL)

BAL is helpful for ruling out infection, diagnosis of granulomatous lung disease and prediction of treatment response. It is quite useful especially in AE of IPF. Because advanced stage patients, it is very difficult to distinguish infection from AE with only clinical information. Bronchoalveolar lavage fluid (BALF) cellular analysis provide additive information for evaluation of ILD. In smokers, alveolar macrophages are predominant. In typical IPF patients, cell populations are usually normal or neutrophils predominant. When we see BALF lymphocytosis over 30% with similar presentation of IPF, we consider the possibility of CHP, NSIP, or fibrotic sarcoidosis (32,33). Regarding CD4/CD 8 ratio, acute HP is usually decreased. On the other hand that is elevated for CHP and sarcoidosis (34). In BALF eosinophilia, eosinophilic pneumonia or drug associated ILD is possible (35). BALF analyses have some limitations. However, when we see ILD patients. In AE of IPF, BALF biomarkers such as KL-6, thrombomodulin have potentials to predict mortality and treatment response (36).

Pathological findings

Among the IPF patients, approximately one-third of patients have atypical presentation both clinical symptoms and HRCT findings (37). In these cases, we think surgical lung biopsy for definite diagnosis (3, 38). When we perform video-assisted thoracic surgery, we should take at least two or three specimens from different lobes. Especially choosing less intense area is very crucial for prediction of disease activity. However, some patients have contraindication for surgery such as pulmonary hypertension, severe heart failure and advanced age. Or patient reject this procedure. Without surgical procedure in undetermined cases, clinicians should decide whether or not to do aggressive treatment based on disease behavior (38). International guideline showed main histological IPF/UIP pattern. These findings are as follows: honeycombing a predominantly subpleural or para-septal distribution, patchy involvement of lung parenchyma by fibrosis, presence of fibroblastic foci and absence of features against a diagnosis of UIP (38). When we see UIP pattern with lymphoid aggregates with germinal centers, extensive pleuritis, prominent plasmacytic infiltration and dense perivascular collagen, lung dominant CTD is possible (39). I In this situation, we carefully follow future development of CTD. If we see centrilobular fibrosis, bridging fibrosis,

bronchiolitis with granuloma, we should think about CHP (40). In NSIP usually show diffuse homogeneous fibrosis with temporal uniformity and preserve architecture. In addition, honeycombing is absent or scant, after obtained pathological information, multidisciplinary discussion is able to compensate for the weakness of each diagnostic process and lead to practical diagnosis with sharing key information (41).

Clinical staging

Chronic phase

Staging of IPF is useful for physicians and patients. Traditionally, clinical, radiographic, and physiologic (CRP) scoring system for IPF was proposed (42). High CRP score correlated significantly with the total pathology score including cellular and fibrotic score($r=0.61$. $p<0.001$). However, CRP score was derived from many variables such as dyspnea, chest radiograph, spirometry, lung volume, diffusion capacity, resting alveolar-arterial PaO2, and exercise O2 saturation (43). Therefore, this score is complicated and not applicable easily in real world. Staging should be simple and easy to use in clinical practice. Wells, *et al*. proposed composite physiologic index (CPI) especially for IPF with emphysema (44). CPI consists of only major PFT parameters such as %FVC, % DLco, and %FEV1. (45, 46). CPI reflect morphologic extent of emphysema (47, 48). High CPI index is associated with severity of fibrosis. Over 50 of CPI have positive relationship with mortality (49). Therefore, threshold 50 in CPI is useful for prediction of mortality of IPF. In addition, 5 point increase in CPI over 12 months predicts mortality similarly to declines of 10% in FVC or 15% in DLco. (HR 2.1, p=0.004) (50). Ley, *et al.* reported Gender-Age-Physiology (GAP) Index for staging of IPF recently. GAP Index includes gender, age, %FVC, and % DLco. They stratified three stages and showed significant difference of 1-year mortality (stages I, II, and III, 6%, 16%, and 39%, respectively) (51). These difference confirmed both derivation cohort and validation cohort.(Table 1) This index is simple and applicable not only tertiary center but also general hospital (52,53).And GAP index was valuable as a measure of IPF severity (54-59). Presence of Velcro Crackles is associated with high score of GAP in IPF (60). However, there was no significant difference in survival between Stages II and III, and the mortality rates in the patients classified into the GAP Stages I and II were underestimated in Japanese cohort (61,62). Homma, *et al*. reported usefulness of Japanese severity system of IPF (63). (Table 2) They showed clear difference of survival based on stage. In addition, baseline partial pressure of arterial oxygen, vital capacity, and diffusing capacity for carbon monoxide are highly correlated with survival and stage. According to this report, more severe stage, more often have acute exacerbation (AE). In IPF, FVC is robust predictor of mortality. Therefore, combined blood gas value and GAP index is interesting predictor of mortality in IPF patients.

Table 1 Staging of chronic phase of Idiopathic Pulmonary Fibrosis

Index	Variables	Advantage	Disadvantage	Easiness
JRS system	Pa02,6MWT, SpO2	Good relationship with survival	Slightly invasive	Rather complicated
CPI	%FVC,%DLco, %FEV1	Avoid effect of emphysema	Underestimate of obstructive disorder	Proper
GAP	Gender, Age, %FVC, %DLco	Simple	Underestimate of severe group	Easy

Definition of abbreviations: JRS=Japanese Respiratory Society; CPI= Composite Physiologic Index; GAP=Gender, Age, Physiology; PaO2= Partial pressure of arterial oxygen; 6MWT=6 minute walk test; SpO2=peripheral capillary oxygen saturation; FVC=forced vital capacity; DLco=diffusion capacity of the lung carbon monoxide; FEV1=forced expiratory volume I second.

Table 2 Japanese severity system of Idiopathic Pulmonary Fibrosis

Stage	Definition
Ⅰ	PaO2≧ 80mmHg without desaturation<90% in 6MWT
Ⅱ	70≦ PaO2<80mmHg or PaO2>80mmHg with desaturation <90% in 6MWT
Ⅲ	60≦ PaO2<70mmHg or PaO2>70mmHg with desaturation <90% in 6MWT
Ⅳ	PaO2<60mmHg

Definition of abbreviations: PaO2= Partial pressure of arterial oxygen; 6MWT=6 minute walk test

Acute phase

In AE of IPF patients, Akira proposed radiological staging. They reviewed 64 episodes of 58 patients with IPF. A semi-quantitative analysis of overall extent of parenchymal abnormalities, extent of alveolar opacity (ground-glass attenuation and consolidation), and extent of fibrotic opacity (reticulation and honeycombing) on CT was performed. They included 34 patients of peripheral pattern, 8 of multifocal pattern, and 16 of diffuse pattern. On multivariate analysis, the strongest correlations were observed between CT patterns (combined diffuse and multifocal versus peripheral) and survival (odds ratio, 4.629; 95% confidence interval, 1.900-11.278; P = 0.001) (64). Kishaba, *et al*. reported clinical staging of AE of IPF. They observed 58 episodes of AE in IPF. They showed extensive stage had poor prognosis compared to limited stage with variables of serum LDH, KL-6, ratio of partial pressure of oxygen and fraction of inspiratory oxygen, and total extent of abnormal findings on HRCT of the chest (19). (Table 3)

Management

Clinical trials

We had the result of three important clinical trials recently. First, phase III trial of pirfenidone showed there was a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10 percentage points or more in the percentage of the predicted FVC or who died over 52 weeks (P<0.001) (65). In addition, pirfenidone had significant effect on reduction for death from any cause (P=0.01) and from IPF

Table 3 Staging of acute exacerbation of Idiopathic Pulmonary Fibrosis

Staging	Variables	Advantage	Disadvantage	Easiness
Akira staging	HRCT, peripheral, multi-focal, diffuse	Non-invasive	Without clinical information	Training required
Kishaba Staging	LDH, P/F ratio, HRCT extent	Positive relationship with survival	Slightly complicated	Practical

Definition of abbreviations: HRCT=High resolution computed tomography; LDH=Lactate dehydrogenase; P/F ratio=Ratio of arterial oxygen partial pressure to fractional inspired oxygen.

(P=0.006). Obstructive component was strictly excluded and target population were mild to moderate restrictive disorder in this study. In terms of adverse effect, nausea and rash were common. Both UV exposure and smoking should be avoided.

Second, the result of phase Ⅲ two trial of nintedanib which is named INPULSIS-1 and INPULSIS-2were available. In this study, the adjusted annual rate of change in FVC was −114.7 ml with nintedanib versus −239.9 ml with placebo (difference, 125.3 ml; 95% confidence interval [CI], 77.7 to 172.8; P<0.001) in INPULSIS-1 and 113.6ml with nintedanib versus −207.3 ml with placebo (difference, 93.7 ml per year; 95% CI, 44.8 to 142.7; P<0.001) in INPULSIS-2. And INPULSIS-2, there was a significant benefit with nintedanib versus placebo about AE (hazard ratio, 0.38; 95% CI, 0.19 to 0.77; P=0.005) (66). The most frequent adverse effect of nintedanib was diarrhea. However, majority of patients were controllable with anti-diarrhea drug or dose reduction. Third, N-acetylcysteine treatment of IPF patients showed no significant difference in the change in FVC between the N-acetylcysteine group and the placebo group (−0.18 liters and −0.19 liters, respectively over 60 weeks; P=0.77) (67). If both pirfenidone and nintedanib cannot be used due to adverse effect, N-acetylcysteine may play a role for IPF. Based on recent reports, treatment with pirfenidone for 1 year resulted in clinically meaningful reductions in disease progression in patients with IPF (68). For long-term usage of pirfenidone, Bando, *et al*. reported that pirfenidone treatment lasted for two years or longer in 111 cases (22.1%). The mean change in FVC was -30±224 (SD) mL in the first year of treatment, -158±258 mL in the second year, and -201±367 mL in the third year. The FVC improved in only a small percentage of patients who received pirfenidone treatment for a long period of time. So, which patients should be received pirfenidone for a long time remains unknown.

In the two-replicate randomized Phase III INPULSIStrials in patients with IPF, Of the treated patients, 322 were Asian (nintedanib n=194; placebo n=128) and 608 were White (nintedanib n=360; placebo n=248). The treatment effect of nintedanib on the annual rate of decline in FVC in Asian and White patients was similar (treatment-by-subgroup interaction P=0.72) and consistent with the overall population. Race did not influence the effect of nintedanib on disease progression (69). And Seven hundred twenty-three (68.1%) patients had honeycombing and/or biopsy, and 338 (31.9%) patients had no honeycombing or biopsy. In these subgroups, respectively, the adjusted annual rate of decline in FVC in patients treated with placebo was -225.7 and -221.0 ml/yr, and the nintedanib versus placebo difference in the adjusted annual rate of decline in FVC was 117.0 ml/yr (95% confidence interval, 76.3-157.8) and 98.9 ml/yr (95% confidence interval, 36.4-161.5) in INPULSIS trials. Raghu, *et al*. reported that patients with IPF who had possible UIP with traction bronchiectasis on HRCT and had not undergone surgical lung biopsy had disease that progressed in a similar way, and responded similarly to nintedanib, to that of patients with honeycombing on HRCT and/or confirmation of UIP by biopsy (70).

Real management

Both pirfenidone and nintedanib are reasonable choice for mild to moderate IPF. And pirfenidone have anti-inflammatory effect. Therefore, when we see IPF with inflammation component, pirfenidone is an option. In progressive deteriorating group, first three months trend of vital capacity is predictive of mortality (71). Pirfenidone may be effective for such progressive patients. Nintedanib showed definite reduction of AE of IPF. So, when we manage IPF patients who have risk factors of AE such as reduced FVC and never smoking, nintedanib is a strong candidate. Nintedanib is also used for active patients because of absence of photosensitivity. (Table 4)

Table 4 Management of Idiopathic Pulmonary Fibrosis

Drug	Indication	Adverse effect
Pirfenidone	50%≦%FVC, disease progression, inflammation component	Photosensitivity Liver dysfunction
Nintedanib	50%≦%FVC, Risk factor of AE such as reduced FVC, never smoker	Diarrhea Liver dysfunction,

Definition of abbreviations: FVC=forced vital capacity; AE=Acute exacerbation.

Comorbidity

Finally, we check comorbidity such as obstructive sleep apnea(OSA), pulmonary arterial hypertension(PAH).IPF patients more often have OSA and apnea-hypopnea index have negative relationship with total lung capacity (72). OSA is manageable with nasal continuous positive airway pressure (n-CPAP). More severe IPF patients have high incidence of PAH (73). Currently, PAH-specific drugs are not approved for IPF with PAH. Therefore, we think lung transplantation in case of young age or PAH-specific drug such as sildenafil is an option for elderly patients. Collard, *et al*. described pulmonary infection is important comorbidity in IPF (74). And bacterial burden contributes disease progression based on recent report. IPF and cardiovascular disease such as ischemic heart disease have same risk factor including smoking. Venous thrombosis is also sometimes seen in IPF patients. So, if IPF patients undertake orthopedic or pelvic surgery, prevention of deep vein thrombosis is crucial. Gastro-esophageal reflux disease (GERD) may contribute to disease progression and acute exacerbation of IPF. And unilateral fibrosis have association with microaspiration due to GERD. However, no significant relationship between GERD and IPF based on meta-analysis. There remains controversy issue of these two diseases (75). IPF patients often have lung cancer especially adjacent fibrotic tissue and most common histology is squamous cell carcinoma. IPF with lung cancer tend to have poor prognosis because of limitation of management of discovery of advanced stage. Therefore, early detection of cancer is required. In conclusion, IPF consists of heterogeneous patients. We can decide to treat depend on clinical staging. And clinicians should monitor trend of clinical parameters, imaging findings, physiological items carefully.

Compliance with Ethical Standards

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Conflict of Interest: Tomoo Kishaba declares that I am no conflict of interest. Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study of this review.

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